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The Effect of Continuous Glucose Monitoring on Glycemic Control

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By

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Introduction

Advances in research and technology foster a constant evolution to the recommended management of serious medical conditions. The new studies and improvements in treatment contribute to the innovation and success of the medical field. One prominent advancement is that of continuous glucose monitoring (CGM) in the management of Diabetes Mellitus (DM).

Diabetes is a disease characterized by the body's inability to produce or properly use insulin.[1] Various medications and non-pharmacologic therapies are available to diabetic patients to combat this issue; yet, all diabetic populations share the requirement of regularly checking blood sugar.

Diabetes is an extremely prevalent and deadly disease. It was the seventh leading cause of death and 30.3 million Americans were reported to have the disease in 2015.[1] Consequently, DM is frequently managed in primary care. Although management is precarious, good control is pertinent as diabetes not only carries its own burden but also increases the risk of other grave health conditions. A diabetic patient is more likely to suffer from a cerebrovascular accident, myocardial infarction, amputation, blindness, or kidney failure.[1] Diabetes is a complicating factor in the treatment of many other conditions, thereby making appropriate and accurate management important for healthcare providers and patients alike.

Countless studies have focused on determining the best medication, exercise and diet regimen to control blood sugar; nevertheless, management starts one step before blood glucose control. Clinicians and patients must have accurate data about blood glucose levels in order to appropriately adjust treatment.

Background

The current standard of care and conventional way to monitor sugars is by self-monitoring of blood glucose (SMBG). SMBG uses a glucometer and finger prick blood sample to calculate the blood sugar level at a single point in time. Currently, the American Diabetes Association recommends obtaining readings at least three times a day; however, monitoring is often only prompted by symptoms.[2,3] There are many limitations to successful utilization of SMBG, but the unappealing finger stick is one of the biggest barriers.

Continuous glucose monitors are the newest alternative to SMBG. CGMs are subcutaneous sensors worn by patients that measure and convert interstitial glucose levels to clinically useful blood glucose values.[3-6] In addition to the sensor, a CGM system contains a transmitter and receiver to display data to the wearer.[4] These monitors provide patients with immediate information regarding current glucose levels and prediction of trends.[6]

There are three different types of CGMs: real-time (rt-CGM), intermittently scanned (is-CGM), and retrospective continuous glucose monitors (r-CGM).[3,5] Although information provided by the monitors is similar, the method of receiving the information varies. Real-time CGMs transmit constant (approximately every five minutes) data visible to the user including glucose levels, trends, and alarms at certain sugar levels.[3,6-7] Conversely, r-CGMs do not show readings in real time but provide information from the past few days to be analyzed for trends. Is-CGMs require the user to intentionally scan the monitor to view data.[3-5]

Rt-CGMs offer immediately-available and accurate data for patients plus information clinicians can analyze in order to predict impending glucose excursions, recognize nocturnal hypoglycemic events, and evaluate individual glucose trends and profiles.[3,5-7] This invaluable information is used to adjust treatment resulting in improved glycemic control.[2-4,6-7] Numerous studies, including the Diabetes Control and Complications Trial, have proven these repetitive readings are imperative to management success, reporting strong correlations between glucose control and frequency of SMBG.[2-4]

Accurately monitoring blood glucose levels is the cornerstone to developing an appropriate DM treatment plan. Consequently, CGMs have become the standard of care for type 1 diabetics over the past decade and have prompted continued investigation on the efficacy of CGMs.[3]

Hyper and Hypoglycemia

Serious complications are associated with blood glucose excursions; therefore, quality glucose monitoring is pertinent to diabetic health. Some dangers linked to elevated blood glucose include retinopathy, neuropathy, nephropathy, poor healing, ketoacidosis, and death.[8] According to the World Health Organization, in 2016 there were 1.6 million deaths caused by diabetes and an estimated 2.2 million deaths specifically associated with high blood sugar.[8]

Low blood glucose is often even more detrimental to well-being. Significant consequences associated with hypoglycemia include impaired brain functioning, seizure, coma, and death.[9] The IN CONTROL study of type 1 diabetics found severe hypoglycemia requiring third party assistance occurred 0.2-3.2 times per subject per year.[10] Although drops in blood sugar levels can happen any time of the day, these excursions frequently occur unnoticed at night.[11] CGMs can help recognize these otherwise overlooked fluctuations in glucose.

Although type 1 diabetics most often utilize continuous glucose monitors, type 2 diabetics are now also employing CGMs.[3,5] According to the CDC, the applicability of CGMs in type 2 diabetic management increases the number of potential benefiters from the estimated 1.5 million type 1 diabetics to all 30 million diabetics in the United States.[12] As CGMs are becoming a globally applicable tool, continued research and analysis is necessary to determine whether CGM or SMBG is more effective at improving glycemic control measured by Hemoglobin A1c (HbA1c) and frequency of hypoglycemic events.

Discussion

Reduction of HbA1c

HbA1c is a numeric representation of the average amount of glucose attached to hemoglobin over the past three months. HbA1c is the current standard for diagnosing and monitoring control of diabetes.[1-2] It is considered the most important tool in assessing management success, and therefore one of the most studied benefits of CGMs.

Considering HbA1c is the most widely accepted measurement of diabetes control, there is no better support for CGMs than their ability to reduce A1c as reported harmoniously in several types of studies. Numerous recent articles found HbA1c was significantly reduced 3, 6, and 12 months after CGM device placement.[6,13-16] Interestingly, a study even reported HbA1c levels reverted back to baseline during a washout period when participants stopped wearing CGMs.[16]One cohort study explored the impact of rt-CGM financial reimbursement and reported a marked reduction in HbA1c after 12 months.[15]

The same results were reported in a randomized control trial (RCT) where no instructions or recommendations were given to the CGM intervention group. Despite the lack of direction, more than half of participants wearing CGMs had a reduction in HbA1c levels with a mean of 0.43% less than the control group.[6,16]

Continued research has shown the ability of CGMs to reduce HbA1c depends on many factors. Cohort studies found regular use of rt-CGMs to be one of the most important determinants of their efficacy.[6,14-15] One study reported the reduction in HbA1c was only significant in participants who wore CGMs >5 days per week.[14] This is consistent with results concluding participants who wore monitors more than 70% of study time had a significantly greater reduction in their A1c than those who wore CGMs intermittently or <70% of the time.[6,15-16] Charleer and colleagues even required CGMs be worn >70% of study time as part of the inclusion criteria for their cohort study.[15] The ability of CGMs to reduce HbA1c has a strong correlation with the amount of time the sensor is worn.

The extent to which CGMs can reduce HbA1c also depends upon the motivation for beginning continuous monitoring. Patients start using CGMs at different points in their diabetic journeys and for various reasons, both of which impact CGM efficacy. A pediatric RCT revealed the reduction in HbA1c was most significant in patients who started with an elevated A1c >8.0%.[13] Similarly, one cohort study of adult participants reported the average reduction in HbA1c was 0.4% greater in participants who began wearing CGMs because of poor glycemic control compared to subjects who started wearing monitors for reasons such as hypoglycemia or pregnancy.[15]

Age is another determinant in the usefulness of CGMs to decrease HbA1c. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group only found a significant reduction in HbA1c after CGM use in a specific subset of their 322 subjects.

Participants aged 25 years and older had a mean reduction in HbA1c of 0.53%, whereas participants aged 15-24 and 8-14 had less significant improvements.[7] There is an apparent correlation between patient maturity and the efficacy of CGMs.

While many studies have found CGMs to be instrumental in the reduction of HbA1c, simply wearing monitors is not enough to improve glucose control. The information obtained from CGMs must be appropriately interpreted and applied in order to adjust treatment. A recent study of type 1 diabetics discovered when adjustments were made to insulin and diet regimens as recommended by CGMs, the average HbA1c was reduced by 0.40% and 0.43% at three and six months of use, respectively.[17] Additionally, the improvement was sustained when reevaluated a year later. Researchers concluded the improvement was due to behavior and therapy modifications based on CGM data recommendations and not CGM use alone.[17] The therapy modifications suggested by CGMs, specifically to insulin regimens, can improve HbA1c and metabolic control.

Similarly, a RCT of pediatric patients supported the utilization of CGMs as tools for treatment adjustment. After three days of sensor wear, data was analyzed and reviewed with the patient and parent to adjust the current treatment regimen. Nine possible recommendations were made based on CGM data including changes to basal or bolus insulin dose or timing, treatment algorithms, exercise, mealtime injections, and referrals for counseling. The results revealed 87% of participants needed to change their basal insulin dose, 70% their bolus insulin dose, and 32% needed to increase the insulin used to correct hyperglycemic readings.[13] Considering the positive outcomes post-treatment, the study concluded alterations to management constructed from CGM information is an effective method for decreasing HbA1c.[13]

The majority of CGM research focuses on type 1 diabetics, but with further investigation studies also include type 2 participants. It is important to note a meta-analysis of type 2 diabetic RCTs found HbA1c levels were significantly lower in rt-CGM groups compared to SMBG groups.[5]

Detection of Hypoglycemic Events

While HbA1c is the most widely used instrument for diabetes diagnosis and treatment adjustment, it is not the only indicator of appropriate diabetes management. The frequency of glucose excursions to levels of hyperglycemia and hypoglycemia are also valuable indicators of glycemic control and effective management.

A noteworthy difference between CGMs and SMBG is the ability of continuous sensors to detect more glycemic excursions to unhealthy ranges than the intermittent finger pricks of SMBG. It is easy to understand why infrequent monitoring would miss such readings unless accompanied by symptoms. A study done to observe the limitations of SMBG reported only about one-third of hypoglycemic events detected by CGMs were accompanied by hypoglycemic symptoms.[11] Numerous supporting studies have reported high rates of hypoglycemia unawareness in diabetics who do not utilize SMBG frequently.[2,11,13]

Recent studies have repeatedly found a dramatic decrease in the number of hypoglycemic events that occur after participants wear CGMs for any length of time when compared to participants utilizing SMBG.[3,9-10] Furthermore, continued research supports a significant reduction in severe hypoglycemic events, especially in patients with problematic hypoglycemia.[3]

Weber et al. described in their cohort study that type 2 diabetics also benefitted from CGM use in the detection of hypoglycemia. After three days of CGM wear, a physician discussed individual sensor data with all 31 participants and made treatment adjustments as necessary. All subjects had significantly fewer episodes of hypoglycemia with a total of 23 fewer events following the changes.[18] Although HbA1c levels were not significantly reduced in this particular study, the CGMs provided valuable information about the frequency of hypoglycemia in a 24 hour period that could not be detected by infrequent, daytime SMBG alone.[18]

A substantial benefit of CGMs over SMBG is the detection of asymptomatic nocturnal hypoglycemia. One cohort study explored this fact to find asymptomatic nocturnal hypoglycemia in 67% of their subjects, yet only one patient was actually awoken from sleep by symptoms.[11] Similarly, a RCT with 47 subjects reported an average of 1.7 episodes of asymptomatic hypoglycemia while asleep, even in patients who checked their sugar by glucometer prior to going to bed.[13] Moreover, 22% of the participants had rebound hyperglycemia in the early morning known as the dawn phenomenon which was not apparent by SMBG.[13] The identification of such episodes of glycemic excursion prompted adjustment to basal or evening doses of insulin, thereby reducing future episodes of hypoglycemia.

The increased recognition of low glucose readings with sensor-wear undoubtedly prompts corrections in management, therefore concluding, without question, the conventional method of self-monitoring fails to detect important day-to-day excursions that CGMs would otherwise recognize.

Reduction of Time in Hypoglycemia

The negative consequences of hypoglycemia, defined as glucose <70mg/dL, are both serious and widely known. It is because of these harmful implications that continual research is performed to determine how to reduce the amount of time spent in hypoglycemia.

When comparing the time spent in hypoglycemia between groups monitoring glucose by means of CGM or SMBG, several studies agreed increased time was spent in the range of normoglycemia with CGM.[3-5,16,18] Researchers strive for methods to reduce time spent in hypoglycemia as it closely correlates with increased treatment satisfaction and reduced risk of adverse events.[3-5] The ability of CGMs to predict trends and warn users of impending hypoglycemia is the crucial factor in reducing time spent with concentrations of glucose below 70mg/dL.[4] RCTs in 2018 found as much as a 43% reduction of time spent in hypoglycemia with CGM.[3] Several more trials with type 1 diabetic subjects have since confirmed CGM intervention shortens time spent in hypoglycemia to such an extent that benefits can be applied practically in type 2 patients.[5]

The cohort study by Weber et al. attempted to determine if treatment adjustments after three days of CGM use would change the length of each hypoglycemic event. The average duration of each episode of hypoglycemia dropped from a staggering 70 minutes to 26 minutes per patient eight weeks later.[18] The significant reduction of time in hypoglycemia and frequency of hypoglycemic events directly reduces the risk of associated adverse events.

Decreased Fear of Hypoglycemic Events

While the numbers associated with glucose control are important in efficacious management of diabetes, the patient is central to successful therapy. Patients often admit to altering treatment regimens due to fear of hypoglycemic events. Recent studies concluded that in addition to reducing HbA1c and hypoglycemic events, CGMs have a significant impact on glycemic control by reducing patient fear of a hypoglycemic event occurring.[3,10,15]

Although CGMs have not been found to completely prevent hypoglycemic events, they reduce the degree and depth of hypoglycemia, thereby lessening patient concern. The IN CONTROL trial concluded CGMs fostered significantly less worry about hypoglycemic events in all 52 subjects.[10]

A similar cohort study investigating the relationship between CGMs and quality of life (QOL) found continuous monitoring significantly improved QOL in addition to reducing fear of hypoglycemia.[15] The total population of the study reported by survey a better QOL and lessened fear of hypoglycemia, with the greatest improvement noted in those who began wearing rt-CGMs due to prior issues with hypoglycemia.[15] The results likely suggest a reduced fear of hypoglycemia fosters an increased perception of QOL. Regardless, this study upholds the real-life benefit of CGMs.

Barriers to Use

The advantages of CGM might seem clear, but the question remains: Why, then, are not all diabetics utilizing continuous glucose monitoring? As with SMBG, there are both pros and cons to CGM.

Many researchers have been eager to unveil limitations and determine why CGM use has not grown as quickly as predicted. A meta-analysis of articles supporting CGMs found wearing the monitor to be one of the most significant barriers. One sensor can last anywhere from 6-180 days before it has to be replaced, and longer-lasting devices require an in-office placement procedure. Each new monitor necessitates a skin puncture and patients find it quite cumbersome to have a device attached to them.[3,19] Wearers also report localized skin reactions, malfunction of sensors and sensors falling off due to adhesives and sweating.[19]

The frequency of required calibration is additionally bothersome to patients.[3] Most models recommend a confirmatory SMBG reading when CGM readings do not match symptoms, as well as for calibration. The concurrent requirement of finger prick measurements is a burden.

As with any new medical treatment or device, cost is among the greatest barriers to patient use.[19] CGM costs, systems, and accessibility vary greatly depending on type of diabetes, patient age, and insurance. If CGMs are not affordable, no one is motivated to try them.

As new CGM devices are introduced, the accuracy of measurements varies.[3,19] Patients in the aforementioned meta-analysis reported lack of direction on how to modify treatment based on data and complained of limited ability to personalize the user interface of devices.[19] The lack of consistently accurate data and instruction discourages patients from continuing CGM use.

Although many of the limitations might seem minimal to an outsider, the devices are unfamiliar and cumbersome to those who have not previously used them. Most patients realize the benefit of continuous monitoring after some time but initiating CGM intervention can be intimidating.

Conclusion

As CGMs are relatively new devices in diabetes management, research must be done to determine long-term effects of their use. Further investigation about the generalizability of

CGM efficacy in geriatric, pregnant, and pediatric populations would also be valuable. The majority of information in the trials discussed above is applicable to type 2 diabetics, but continued research should attempt to prove the importance of CGM use in this ever-growing population. Ongoing research about the efficacy of CGMs in all diabetic subsets is imperative for CGM to become the standard of care in managing not only type 1 diabetes, but all other diabetic populations as well.

The power of CGM to change the way diabetes is managed is equally exciting and groundbreaking. The ability for clinicians and patients to make pertinent adjustments to pharmacologic and nonpharmacologic management using invaluable information from CGMs is revolutionary. The most recent evidence about diabetes control supports the efficacy of CGM in reducing HbA1c as well as length and frequency of hypoglycemic events. There is no question that both SMBG and CGM have advantages and disadvantages, but research is clear that CGMs are more successful at improving glycemic control.

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