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Medical Policy Manual

Topic: Continuous Monitoring of Glucose in the Interstitial Fluid

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NOTE: This policy has been revised. The revised policy will be effective January 1, 2015. To view the revised policy, click here.

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Maintenance of a target blood glucose and target glycated hemoglobin (HgA1c < 7%), a marker which is used as a proxy for average blood glucose, is now considered standard of care for diabetic patients. Also known as tight diabetic control, this strategy is intended to prevent severe hypoglycemic events and lower the risk of cardiovascular disease mortality associated with uncontrolled glycemia.[1] The strategy involves frequent home blood glucose checks (fingersticks) several times each day (i.e., before meals and at bedtime). Measurement of blood glucose at such specific points in time may not reveal trends in blood glucose, particularly those associated with nighttime sleep.

Continuous glucose monitor (CGM) devices, which take measurements of glucose in the interstitial fluid have been developed as an adjunct to traditional blood glucose monitors to help achieve tight glucose control. CGM devices work through the use of a subcutaneously placed sensor which continuously measures glucose levels in the interstitial fluid. Some devices are also designed to be used with an insulin pump.

Also, under development is an artificial pancreas or artificial pancreas device system (APDS). The proposed artificial pancreas is a series of devices e.g., a CGM, blood glucose device and an insulin pump, plus a computer algorithm that communicates with all of the devices. The goal of the APDS is to automatically monitor glucose levels and adjust insulin levels. These systems are also called closed-loop

systems or autonomous systems for glucose control. One technology associated with artificial pancreas development is a "low glucose suspend (LGS)" feature included with an insulin pump. The LGS feature is designed to suspend insulin delivery when plasma glucose levels fall below a pre-specified threshold.

Regulatory Status

According to U.S. Food and Drug Administration (FDA) labeling, none of the CGM devices are intended to be an alternative to traditional self-monitoring of blood glucose with a home glucose monitor, but rather serve as an adjunct, supplying additional information on glucose trends that are not available from self-monitoring. Fingerstick confirmations of the readings are still recommended.

Several continuous glucose monitoring systems have been approved by the FDA through the premarket approval (PMA) process.

Recently, the MiniMed® 530G System by Medtronic©, an artificial pancreas device system with a "low glucose suspend" feature, received PMA approval from the FDA.[2] According to the FDA PMA summary,

> "The MiniMed 530G System is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. The MiniMed 530G System is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the Threshold Suspend alarm to take measures to prevent or treat hypoglycemia himself. Therapy to prevent or treat hypoglycemia should be administered according to the recommendations of the user's Health Care Provider."

Notes:

- In addition to stand-alone continuous glucose monitors, several insulin pump systems include a built-in CGM. This policy addresses continuous glucose monitoring devices, not the insulin pump portion of these systems.
- Also, this policy only addresses c*ontinuous* monitoring of glucose in the interstitial fluid. *Intermittent* monitoring of glucose in the interstitial fluid for up to 72 hours may be considered medically necessary.

MEDICAL POLICY CRITERIA

I. Continuous monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring, including real-time monitoring, may be considered **medically necessary** when the following criteria (A, B, and C) are met:

   A. The patient has diabetes requiring treatment with insulin; and

   B. There is documentation the patient uses best practices, including compliance with a regimen including 4 or more blood glucose tests ("fingersticks") per day and adjustment of insulin; and

   C. One of the following 2 criteria are met:

1. The patient is pregnant with poorly controlled diabetes. Poorly controlled diabetes includes unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia, or recurrent diabetic ketoacidosis; or
2. There is documentation of two or more episodes of unexplained severe hypoglycemia that puts the patient or others at risk. Severe hypoglycemia is generally associated with blood glucose levels less than 50 mg/dl or an event which requires the assistance of another person (to administer carbohydrates, glucagon, or to take other resuscitative actions). Measurement of low glucose levels may be by self-monitor blood glucose test ("fingerstick") and/or by intermittent monitoring of glucose in the interstitial fluid.

II. Other uses of continuous monitoring of glucose levels in interstitial fluid in patients with diabetes, including real-time monitoring, are considered **not medically necessary**. Uses in conditions other than diabetes are considered **investigational**.

III. Use of an artificial pancreas system, including but not limited to closed-loop monitoring devices with low-glucose suspend (LGS) features, are considered **investigational**.

SCIENTIFIC EVIDENCE

The key clinical outcomes regarding the clinical utility of interstitial measurements of glucose relate to their ability to provide either additional information on glucose levels leading to improved glucose control, or to improve the morbidity/mortality associated with clinically significant severe and acute hypoglycemia or hyperglycemic events. Because diabetic control encompasses numerous variables including diabetic regimen and patient self-management, randomized, controlled trials are important to isolate the contribution of interstitial glucose measurements to the overall diabetic management.

Literature Appraisal

There is a large and growing body of published literature on the outcomes associated with the use of continuous glucose monitor (CGM) devices compared with home self-monitoring of blood glucose (SMBG). The focus of this literature appraisal is on technology assessments, systematic reviews, and prospective randomized controlled trials.

CGM Devices: Technology Assessments, Meta-Analysis, Systematic and Cochrane Reviews

- A 2003 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment reviewed the published controlled clinical trials and concluded the available evidence was insufficient to permit conclusions on the effect of using interstitial fluid glucose monitoring on health outcomes.[3]

- In 2011, the Washington State Health Care Authority published a health technology assessment (HTA) regarding glucose monitoring[4] of individuals who are insulin dependent and 18 years or younger. Four studies were selected which compared CGM (in conjunction with SMBG) with SMBG alone. Authors of the HTA made the following conclusions:

  "Overall, these studies provide inconclusive evidence for the efficacy of CGM (in conjunction with SMBG) over SMBG alone with respect to reduction of mean A1C up to 26 weeks, or for reducing acute episodes of hypoglycemia or hyperglycemia. However, there is limited evidence

that a greater percentage of participants who used CGM achieved A1C targets compared with those using SMBG alone. These changes were achieved without significant difference in hypoglycemic events. No differences in quality of life measures were found."

- A recent Cochrane review and meta-analysis published in 2012 identified 22 randomized controlled trials which studied the use of CGM devices for improved glycemic control, quality of life, frequency of adverse events and diabetes-related morbidity and mortality.[5] When comparing CGM to self-monitoring of blood glucose (SMBG), a statistically significant average difference in HbA1c among CGM-users was observed (-0.2%, 95%CI: -0.4% to 0.1%), although this difference is not widely accepted as clinically relevant (≥0.4%).[5] No changes in severe hypoglycemia or ketoacidosis were observed. Neither were outcomes such as diabetes-related morbidity or mortality, or patient quality of life or satisfaction with the device widely reported. The review concluded that this technology may yet hold promise among patients who can adhere to treatment with a high compliance, although, "There is limited evidence for the effectiveness of real-time continuous glucose monitoring (CGM) use in children, adults and patients with poorly controlled diabetes." Other results of the meta-analysis are limited by the inclusion of studies where CGM devices paired with sensor augmented insulin pump therapy were compared with multiple daily injections of insulin. Because the effect of the CGM device cannot be isolated from that of integrated insulin pump therapy, these studies cannot be directly equated to studies assessing the independent impact of CGM devices studied without an insulin pump, therefore limiting interpretation of the meta-analysis.

- In 2012, the Agency for Healthcare Research and Quality (AHRQ) partnered with the Evidence-based Practice Center at Johns Hopkins University to conduct a systematic review of 41 studies to evaluate continuous subcutaneous insulin infusion (CSII) vs. multiple daily injections (MDI) and real-time continuous glucose monitoring (rt-CGM) vs. self-monitoring of blood glucose (SMBG).[6] The review found that rt-CGM appeared superior to SMBG in lowering HbA1c in non-pregnant patients with type 1 diabetes; however, authors note that pre-study adherence data was not reported and positive study findings may be related to poor historical adherence to treatment. Overall, analysis of the body of evidence regarding CGM was limited by small sample size (largest study, N=322), heterogeneous definitions of study measures, long-term outcomes, and exclusion of patients with existing comorbidities. The authors note:

  "These shortcomings highlight the need for future large, well-designed studies with participants of all ages and from diverse ethnic groups, standard outcome measures including measures of vascular complications and quality of life, and long follow-up duration and for studies in pregnant women with pre-existing type 1 or type 2 diabetes."

- Several meta-analyses of RCTs have been published; they focused on slightly different populations, e.g., age and/or type of diabetes and different study designs, e.g., by length of follow-up. In 2011, Gandhi and colleagues conducted a systematic review and meta-analysis of RCTs evaluating continuous glucose monitoring that included adults or children and individuals with type 1 or type 2 diabetes.[7] To be eligible, studies needed to have at least 8 weeks follow-up and be conducted in the outpatient setting. Both studies of real-time and non-real-time CGM devices were included; control groups needed to utilize SMBG. Nineteen trials met eligibility criteria and provided data for meta-analysis. Mean baseline HbA1c was at least 7.0% in all studies but one, in which the mean baseline HbA1c was 6.4%. Overall, compared with self-monitoring of blood glucose, CGM was associated with a statistically significant reduction in mean HbA1c [weighted mean difference (WMD) = -0.27%, 95% CI= -0.44 to -0.10%]. When

stratified by age and type of diabetes, there was a statistically significant reduction in HbA1c in adults with both type 1 and type 2 diabetes, but not in studies of children and adolescents with type 1 diabetes. However, this study contained several methodological limitations which preclude conclusion concerning the validity of the reported reduction in HbA1c levels in patients using CGM devices. Overall studies used in the analysis were limited by small sample size and differed in monitor type, follow-up, patient population, frequency of CGM use, and self-monitoring requirements. In addition, authors indicated that the effect of the statistical improvement in HbAc1 levels did not translate into an improvement in hypoglycemia incidence. The authors concluded:

"Larger trials with longer follow-up are needed to assess the efficacy of CGM in reducing patient-important complications without significantly increasing the burden of care for patients with diabetes."

- Another meta-analysis of RCTs on continuous glucose monitoring published in 2011 included trials conducted in adults and children with type 1 diabetes who were on an intensive insulin regimen (studies of type 2 diabetes were not included).[8] This meta-analysis found a statistically significant reduction in HbA1c with CGM compared to self-monitoring of blood glucose. However, similar limitations which were found in the Gandhi and the AHRQ studies were also present in this meta-analysis.

- A systematic review published in 2011 identified 9 randomized controlled trials comparing CGM devices to SMBG and retained the 7 studies with commercially available devices for analysis.[9] Positive effects (ranging from a 0.3-0.7% mean decrease in HbA1c) were observed in the CGM groups in 6 of 7 studies, although no significant improvements were observed in hypoglycemic events. Although the review stated that this may be explained because, "the size of effect [observed in the treatment group] may be underestimated by better-than-average results in the control group, as self-monitoring blood glucose measurements are carried out more frequently [among patients in research studies] than in usual clinical practice," the authors cited lack of a standard definition of a hypoglycemic event, understanding of long-term patient compliance, adequate patient and provider training on the use of CGM devices, and sound study design (with appropriate blinding and comparative groups) as factors limiting conclusions regarding the use of these devices. A subsequent systematic review, published in late 2011 by a different research group, but which included many of the same studies, reported similar results.[10]

- A systematic review of randomized studies published in 2008 identified 7 studies with 335 patients that fulfilled their inclusion criteria.[11] Study duration varied from 12 to 24 weeks. This review concluded that compared with self-monitoring, CGMS was associated with a non-significant reduction in HbA1c levels, and that evidence is not sufficient to support the use of CGMS over self-monitoring for HbA1c reduction. There was some indication from this review of improved detection of asymptomatic nocturnal hypoglycemia in the CGMS group.

- Type 2 diabetes patients were the focus of a systematic review published in 2012, which evaluated the current literature on the topic, none of which studied device-usage for longer than 3 months.[12] Studies of longer duration are needed to evaluate long-term effectiveness of this technology among patients with type 2 diabetes.

<u>CGM Devices: Randomized Controlled Trials (RCTs)</u>

Several randomized trials have been published since publication of the 2003 TEC Assessment.

- In 2012, Battelino and colleagues published findings of a multicenter crossover study conducted in several European countries that included 153 children and adults with type 1 diabetes.[13] The study used the MiniMed Paradigm REAL-Time system, which integrates a CGM device and an insulin pump system. Patients were randomized to use of the system for 6 months with the sensor on and 6 months with the sensor off, in random order, with a washout period of 4 months between interventions. Baseline HbA1c ranged from 7.5-9.5%. After treatment, mean HbA1c was 8.04% in the Sensor On arm and 8.47% in the Sensor Off arm. The mean difference in HbA1c between groups was -0.43% (95% CI: -0.32% to -0.55%), p<0.001. Although this is a statistically significant finding, it is unclear if the difference between the groups is clinically significant and would result in overall improved health outcomes. In addition, this trial was limited by a lack of blinding and a comparison of continuous to intermittent use of CGM was not evaluated.

- In 2011, Battelino and colleagues published results from a trial of 120 patients ages 10 and older with type 1 diabetes, an HbA1c level of less than 7.5%, and daily insulin therapy who were contacted based upon membership in local diabetes registries and were enrolled in order of response.[14] Upon enrollment, patients were stratified by age and randomly assigned home glucose monitoring with use of a masked CGM device, the Freestyle Navigator, for 5 days every other week (control group) or 5 days per week use of an unmasked CMG device (experimental group), along with SMBG. The Freestyle Navigator has since been permanently discontinued for use within the US. Patients in the experimental group were not given specific instructions how to alter therapy based upon CGM device results. After a 1-month run-in, patients were followed for 26 weeks. The primary outcome was amount of time per day in hypoglycemia, defined as blood glucose concentration of <63 mg/dL. Secondary outcomes included the number of hypoglycemic events (>10 minutes with blood glucose <55 mg/dL or <63 mg/dL) per day and per night, and the mean difference in HbA1c between treatment groups. Although the amount of time spent with blood glucose <63 mg/dL was significantly shorter in the experimental group (average difference per day of 29 minutes, p<.03), according to the ADA, this is not a primary health outcome when studying the impact of a novel technology on hypoglycemia.[15] Therefore, interpretation of this finding was unclear. The hypoglycemic event rate (number of events lasting at least 10 minutes at <55 mg/dL or <63 mg/dL per 24 hours/day) did not differ between groups, although a comparison of nightly event rates did reach statistical significance (albeit with overlapping confidence intervals of estimated mean differences). A third outcome measured the difference from baseline to week 26 in average HbA1c between treatment groups (0.27%, p=0.008), although interpretation of this difference was limited by a the lack of discussion regarding clinical significance (elsewhere proposed to be closer to 0.4%)[5]. Limitations of this study include patient selection criteria which favored highly motivated individuals who demonstrated tight glucose control prior to the study initiation. Because the effectiveness of CGM devices is dependent upon their regular and consistent use,[16] results from a highly motivated study population may not be applicable to other patient populations.

- In 2011, Mauras and colleagues published an analysis from the Diabetes Research in Children Network (DirecNet) Study Group that evaluated CGM in the management of young children aged 4 to less than 10 years with type 1 diabetes.[17] A total of 146 children (mean age 7.5 years) were randomized to CGM or usual care. At baseline, 30 children (42%) had an HbA1c of at least 8%. The primary outcome was clinical success as defined as reduction in HbA1c by at least 0.5% without the occurrence of severe hypoglycemia at 26 weeks. Clinical success was attained by

19% in the CGM group and 28% in the usual care group; p=0.17. Mean change in HbA1c, a secondary outcome, did not differ significantly between groups (-0.1 in each group, p=0.79). In this rather large study of an important treatment group (children), use of CGM was not associated with any improved health outcomes.

- Deiss reported on a 3-month study of 81 children and 81 adults with stable type 1 diabetes who had HbA1c levels of 8.1% or greater.[18] Patients were randomized to continuous real-time monitoring, continuous monitoring for 3 days every 2 weeks, or self-monitoring of blood glucose. At 3 months, 50% of patients with continuous real-time monitoring had a decrease in HbA1c of at least 1% compared with 37% of those with intermittent continuous monitoring, and 15% of controls. These results suggest that CGM may have potential for improving control in patients with diabetes; however, as the authors note, additional work is needed to determine long-term efficacy, clinical feasibility in patients with varying levels of glycemic control, and effect on rates of hypoglycemia.

- The Juvenile Diabetes Research Foundation (JDRF) has published several articles reporting on sub-groups of a single study with 451 children and adults with type 1 diabetes randomized to CGM or SMBG.

    - In 2011, the JDRF published results on 436 of 451 patients enrolled in the original JDRF study.[19] Patients were randomized to CGM or self-monitoring for 6 months, at which point the control group was also assigned CGM and both groups were followed for another 6 months. Using per protocol analysis, differences in average rates of severe hypoglycemic events between groups were not significant: 17.9 events per 100 person-years versus 18.7 events per 100 person-years comparing the CGM group to the control group. An additional analysis compared the predictive value of CGM for hypoglycemic events and found a positive predictive value (PPV) of ~5% and a false alarm rate of ~95%. Subsequent univariate and multivariate analyses failed to identify factors beyond previous history of severe hypoglycemia (within last 6 months) and gender, which improved CGM-aided prediction of future hypoglycemic events. The authors suggest that device measurement error may have been a factor for the low accuracy estimates. Although limited by the per-protocol analysis, the majority of patients (97%) were included in the final analysis, which concluded that CGM was not associated with a decrease in rates of hypoglycemic events.

    - In 2008, the JDRF published results on 322 adults and children with type I diabetes and HbA1c between 7% to 10% to CGM or self (home) monitoring.[20] With HbA1c as the primary outcome measure, there was a significant difference among patients 25 years of age or older that favored continuous monitoring (mean HbA1c difference 0.53%), while the difference between groups was not statistically significant for those age 15 to 24 years or 8 to 14 years. Unlike many prior studies, this study was sufficiently large to detect a meaningful change in HbA1c levels between groups. The population in this study had relatively well-controlled diabetes in that entry criterion was glycated Hb of 7% to 10% but about 70% had levels between 7% and 8%. In addition, over 70% of patients were using an insulin pump. No significant differences were noted in rates of hypoglycemic events, but the study was likely not sufficiently large to detect potential differences. The authors also reported that monitor use was greatest in those patients age 25 or older where 83% of patients used the monitor 6 or more days per week.

- JDRF subsequently conducted a follow-up study using the control group from the 2008 analysis.[21] The objective was to determine whether CGM was effective in the management of type 1 diabetes when it was implemented in a manner that more closely resembled clinical practice among patients who had used standard home blood glucose monitoring for the previous 6 months. The primary outcome was change in HbA1c at 6 months for those with levels ≥7.0%. Participants were provided with a CGM device and had an outpatient training session, 2 follow-up telephone calls, and outpatient visits at 1, 4, 13, and 26 weeks. There was a significant decrease in HbA1c in patients 25 or older ($p<0.001$), but not in those age 15 to 24 years or 8 to 14 years ($p=0.95$ and $p=0.85$, respectively). Severe hypoglycemic events decreased between the first and second trial, but the decrease was not significant ($p= 0.08$). The authors concluded that frequent use of CGM in a clinical care setting may improve HbA1C levels. Technology must evolve to make the benefits more applicable in clinical practice.

- In 2009, the JDRF published results on the potential benefits of CGM in the management of adults and children with well-controlled type 1 diabetes (HbA1c <7.0%).[22] In this study, 129 adults and children with intensively treated type 1 diabetes (age range 8-69 years) were randomly assigned to either continuous or standard glucose monitoring for 26 weeks. The main study outcomes were time with glucose level at or below 70 mg/dl, HbA1c level, and the proportion of study groups experiencing severe hypoglycemic events. At 26 weeks, biochemical hypoglycemia (at or below 70 mg/dl) was less frequent in the CGM group than in the control group (median 54 vs. 91 min/day), but the difference was not statistically significant ($p= 0.16$). Time out of range (< or =70 or >180 mg/dl) was significantly lower in the CGM group than in the control group (377 vs. 491 min/day, $p= 0.003$). There was a significant treatment group difference favoring the CGM group in mean HbA1c at 26 weeks adjusted for baseline values. One or more severe hypoglycemic events occurred in 10% and 11% of the 2 groups, respectively ($p= 1.0$). The authors concluded that the weight of evidence suggests that CGM is beneficial for individuals with type 1 diabetes who have already achieved excellent control with HbA1c <7.0%. This is a relatively small study with somewhat uncertain clinical significance of major outcomes. In addition, the source population, by virtue of the inclusion criteria, consisted of patients with well-controlled diabetes (as indicated by their HbA1c levels). Although the study of these devices may be warranted in that population, these results cannot be generalized to patients with poorly-controlled diabetes, a population of interest for use of these devices.[5]

- In a 6 month extension study, 80 pediatric (ages 8-17) patients included in the previous analysis[22] were followed for an additional 6 months (12 months total study time) to study overall use of the device, in addition to severe hypoglycemic event rates and HbA1c levels.[23] Although rates of severe hypoglycemic events were low, and therefore differences between groups not significant, significantly lower HbA1c levels were associated with near daily use of the CGM device (≥6 days/week) compared with any other level of use (0.8% vs. 0.1%, $p<.001$), although only 17 patients out of 80 achieved the top usage rate. Results from this study hint at a dose-response rate for CGM devices and improved health outcomes, although the observational nature of the study design precludes any conclusions about causality. In addition, findings from this study are limited by the small study sample, which may not have been large enough to find differences in other outcomes (such as severe hypoglycemic event rate).

- In a similar, 6-month extension study of participants in two previous JDRF studies,[20,22] Bode and colleagues reported on device-usage rates, and primary health outcomes associated with device-usage among 86 adults randomized to the experimental (CGM device) groups.[24] Primary outcomes included rate of device usage at 12 months, along with change in HbA1c, and rate of severe hypoglycemic events. Median device usage remained high (6.8 days/week), and little change was seen in the HbA1c reductions observed in the first 6 months of subject study participation. Nevertheless, the lack of comparison treatment group limits interpretation of the findings. Even when aggregated, the results from this extension study cannot be clearly applied to other study populations as they represent a heterogeneous group of patients in regard to baseline glucose control. Additionally, the researchers excluded patients who chose not to continue with device usage and evaluated the remainder of study participants (83 of 86 patients – a large majority) using a per-protocol analysis.

- In a randomized study of 132 adults and children from France, Raccah and colleagues reported improved HbA1c levels (change in A1c of 0.96% vs. 0.55%) in patients who were fully protocol compliant for use of an insulin pump integrated with CGMS compared to those using a pump with standard glucose self-monitoring.[25] This study is limited by its small sample size and also by lack of comparison to intermittent use of CGMS.

- The Minimally Invasive Technology Role and Evaluation (MITRE) trial was conducted to evaluate whether the additional information provided by use of minimally invasive glucose monitors resulted in improved glucose control in patients with poorly controlled insulin-requiring diabetes.[26] This was a 4-arm randomized controlled trial conducted at secondary care diabetes clinics in 4 hospitals in England. In this study, 404 people aged over 18 years with insulin-treated diabetes mellitus (types 1 or 2) for at least 6 months and 2 HbA1c values of at least 7.5% in the 15 months prior to entry, who were receiving 2 or more injections of insulin daily, were eligible. Two of the 4 groups received minimally invasive glucose monitoring devices (GlucoWatch Biographer or MiniMed CGMS); the CGMS was performed over several days at various points in the study. The GlucoWatch Biographer system has since been discontinued by the manufacturer for use within the US. These groups were compared with an attention control group (standard treatment with nurse feedback sessions at the same frequency as those in the device groups) and a standard control group (reflecting common practice in the clinical management of diabetes). Change in HbA1c from baseline to 3, 6, 12 and 18 months was the primary indicator of short- to long-term efficacy in this study. At 18 months, all groups demonstrated a decline in HbA1c levels from baseline. Mean percentage changes in HbA1c were -1.4 for the GlucoWatch group, -4.2 for the CGMS group, -5.1 for the attention control group and -4.9 for the standard care control group. In the intent-to-treat analysis, no significant differences were found between any of the groups at any of the assessment times. There was no evidence that the additional information provided by the devices resulted in any change in the number or nature of treatment recommendations offered by the nurses. Use and acceptability questions indicated a decline in use of both devices, which was most marked in the GlucoWatch group by 18 months (20% still using GlucoWatch versus 57% still using the CGMS). In this study of unselected patients, use of continuous glucose monitors (CGMS on an intermittent basis) did not lead to improved clinical outcomes.

- In 2006, Garg and colleagues published results of a randomized trial of the DexCom STS System in 91 insulin dependent patients, conducted for 9 days.[27] However, results from this trial are limited by the very short follow-up period.

- Tanenberg and colleagues reported on a study of 128 patients randomized to insulin therapy adjustments using data from either the continuous glucose monitoring system (CGMS) or self-monitoring of blood glucose (SMBG) using a home glucose monitor over a 12-week period.[28] At 12 weeks, there was no statistical difference in HbA1c levels and hyperglycemic event frequency and duration among the treatment groups. However, at 12 weeks, events of hypoglycemia (glucose equal to or less than 60 mg/dL) were found to be significantly shorter in the CGMS group than the SMBG group (49.4 +/- 40.8 vs. 81.0 +/- 61.1 minutes per event, p=0.009). The authors concluded durations of hypoglycemia can be further reduced by adjusting insulin therapy with data from the CGMS rather than using SMBG data alone. Nevertheless, the biochemically-defined measurements of hypoglycemia (without accompanying evidence of symptoms and/or a clinically significant hypoglycemic event) are not compelling outcomes. The clinical significance of these test results has not been established; i.e., there is insufficient evidence showing the link between increased duration of asymptomatic hypoglycemia and subsequent clinical outcomes.

An industry-sponsored RCT was identified that evaluated intermittent use of a CGM device in 100 patients with type 2 diabetes who were not on prandial insulin; findings were first published in 2011.[29] Eligible participants were 18 or older, had type 2 diabetes for at least 3 months and had an initial HbA1c of at least 7% but not more than 12%. The study compared real-time continuous monitoring with the DexCom device used for four 2-week cycles (2 weeks on/ 1 week off) to SMBG. The primary efficacy outcome was mean change in HbA1c. The mean decline from baseline in HbA1c in the CGM versus the SMBG group was 1.0% versus 0.5% at 12 week, 1.2% versus 0.5% at 24 weeks, 0.8% versus 0.5% at 38 weeks and 0.8% versus 0.2% at 1 year, respectively. Over the course of the study, the reduction in HbA1c was significantly greater than in the SMBG group (p=0.04). After adjusting for potential confounding variables including age, sex, baseline therapy and whether the individual started taking insulin during the study, the difference between groups over time remained statistically significant (p<0.0001).

Pregnant Women With Diabetes

- In 2013, a RCT was published evaluating CGM for use by women with diabetes during pregnancy.[30] In this study, Secher and colleagues in Denmark randomized 154 women to real-time CGM in addition to routine pregnancy care (n=79) or routine pregnancy care alone (n=75). There were 123 women with type 1 diabetes and 31 with type 2 diabetes. Patients in the CGM group were instructed to use the CGM device for 6 days prior to each of 5 study visits. These patients were then encouraged to use the device as much as possible during their entire pregnancy, although this was not a mandatory requirement. Participants in both groups were instructed to perform 8 daily self-monitored plasma glucose measurements for 6 days before each visit. Baseline mean HbA1c was 6.6% in the CGM group and 6.8% in the routine care group. The 154 pregnancies resulted in 149 live births and 5 miscarriages. The prevalence of large-for-gestational age infants (at least 90th percentile), the primary study outcome, was 45% in the CGM group and 34% in the routine care group. The difference between groups was not statistically significant, p=0.19. In addition, no statistically significant differences were found between-groups for secondary outcomes, including the prevalence of preterm delivery and the prevalence of severe neonatal hypoglycemia. Women in this study had low baseline HbA1c, which might help explain the lack of impact of CGM on outcomes. Other factors potentially contributing to the negative findings include the intensive SMBG routine in both groups and the

relatively low compliance rate (64%) in the CGM group with the instruction of use the CGM devices for 6 days before each of 5 study visits.

- Murphy and colleagues reported outcomes from an open-label randomized controlled trial comparing a small patient population of pregnant women with diabetes who received standard antenatal care or antenatal care plus CGM.[31] No significant differences between the groups were noted in the first or second trimesters. However, in the third trimester, HbA1c levels were significantly better in the CBGM group.

CGM Devices: Conclusion

Multiple assessments, systematic reviews, meta-analyses and randomized controlled trials have been published on the use of CGM devices for the control of hypoglycemic events in a variety of patient populations with diabetes. However, where associations were seen between CGM usage and decreased average HbA1c, interpretation of results was limited by lack of discussion of clinical relevance. In addition, most studies were limited by small sample sizes, and data on long-term (≥12 months) use of these devices, as an adjunct to standard home blood glucose monitoring, has not been widely reported.

Artificial Pancreas Device Systems (APDS), Including Low Glucose Suspend (LGS) Technology

Artificial pancreas systems consist of a series of devices including a CGM, insulin pump and blood glucose device, controlled by a computer algorithm to automatically monitor glucose levels and adjust insulin doses.

- Garg and colleagues, published a study which used a CGM device integrated with Paradigm® VEO™ insulin pump and evaluated a feature to suspend insulin delivery when glucose levels fell below a pre-specified threshold, known as a "low glucose suspend (LGS)" feature.[32] This randomized, crossover trial included 50 patients with type 1 diabetes who had at least 3 months experience with an insulin pump system. After a 2-week run-in period to verify and optimize basal rates, patients underwent 2 in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was turned on in one session and off in the other session, in random order. When on, the LGS feature was set to suspend insulin delivery for 2 hours when levels reached 70 mg/dL or less. The goal of the study was to evaluate whether the severity and duration of hypoglycemia was reduced when the LGS feature was used. The study protocol called for patients to start exercise with a glucose level of 100-140 mg/dL, and to use a treadmill or stationary bicycle until their plasma glucose level was 85 mg/dL or less. The study outcome, duration of hypoglycemia, was defined as the period of time glucose values were lower than 70 mg/dL and above 50 mg/dL, and hypoglycemia severity was defined as the lowest observed glucose value. A successful session was defined as an observation period of 3-4 hours and with glucose levels above 50 mg/dL. Patients who did not attain success could repeat the experiment up to 3 times.

  The 50 patients attempted 134 exercise sessions; 98 of these were successful. Duration of hypoglycemia was significantly less during the LGS-on sessions (mean: 138.5 minutes, SD: 68 minutes) than the LGS-off sessions (mean: 170.7 minutes, SD:91): p=0.006. Hypoglycemia severity was significantly lower in the LGS-on group. The mean lowest glucose level was 59.5 mg/dL (SD: 72) in the LGS-on group and 57.6 mg/dL (SD: 5.7) in the LGS-off group, p=0.015. The Garg study evaluated the LGS feature in a research setting and over a short time period.

- In collaboration with the ASPIRE study authors, Bergenstal and colleagues evaluated the LGS feature in 247 patients with type 1 diabetes, randomly assigned to receive sensor-augmented insulin-pump therapy with (n=121) or without (n=126) the suspend feature over a 3 month period.[33] Primary outcomes were change in glycate hemoglobin level and area under the curve (AUC) for nocturnal hypoglycemic events. Changes in glycate hemoglobin levels were similar between groups. The mean AUC for nocturnal hypoglycemic events was significantly lower in the LGS group than in the control group (37.5%, P<0.001) and nocturnal hypoglycemic events were significantly reduced in the LGS group compared to the control group (31.8% less, p<0.001). In addition, percentages of nocturnal sensor glucose values were also significantly less in the LGS group compared to the control group (p<0.001, for all ranges). Four patients in the control group had a severe hypoglycemic event and no events of ketoacidosis were reported in either group.

  In a subsequent review of the Bergenstal study, authors questioned why the number of nocturnal hypoglycemic events were not similar between groups, given that the LGS feature was triggered by the onset of a hypoglycemic event and not if an event was imminent.[34] In response, Bergenstal and colleagues indicated that the LGS feature led not only to a decrease in second and subsequent hypoglycemic events but also to a decrease in initial hypoglycemic events as well.

  In another review, several limitations of the Bergenstal study were discussed.[35] The review author pointed out that the study lacked long-term follow-up and the benefit of the LGS feature in other populations, such as adolescent, young adult or geriatric patients could not be extrapolated from study results as these populations were not included in the original study. Lastly, the review author noted that, "we don't know how the threshold suspend with [sensor augmented pump (SAP)] would fare in a population prone to hypoglycemia but with significantly higher A1C levels. This is an important population, as significant numbers of patients with high A1C levels using [continuous subcutaneous insulin infusion (CSII)] have high rates of severe hypoglycemia." Overall, the review author concluded that although the Bergenstal study results appear promising, research into the efficacy and clinical utility of the artificial pancreas was still in its infancy, and additional long-term RCTs which focus on differing populations were needed.

- Another RCT evaluating a low-glucose suspend device was performed by the Diabetes Wireless Artificial Pancreas Consortium, using the MD-Logic Artificial Pancreas System.[36] The study included 56, 10-18 years old, type I diabetics who were attending a diabetes camp, and had used an insulin pump for at least 3 months. The study was done over two consecutive nights, during which each patient received an artificial pancreas one night and a continuous glucose monitor the other night, in random order. The primary endpoints were the number of hypoglycemic episodes (defined as glucose <63mg/dl for at least 10 minutes), the total time that glucose levels were <60mg/dl, and the mean overnight glucose levels.

  There were fewer episodes of hypoglycemia recorded in the artificial pancreas group compared to the CGM group (7 versus 22, p=0.003). The median time that patients had a Hgb <60 was 0 minutes in both groups, but the time was significantly less in the artificial pancreas group (p=0.02). However, there was no significant difference in the mean glucose level in the artificial pancreas group compared to the CGM group (126.4mg/dl versus 140.4mg/dl).

- In 2013, Ly and colleagues published a study evaluating the incidence of severe to moderate hypoglycemia with low-glucose suspension compared with standard pump therapy, in 95 patients

with type 1 diabetes.[37] The mean patient age was 18.6 years (SD ±11.8 years) with duration of diabetes of 11 years (SD ±8.9 years) and duration of pump therapy of 4.1 years (SD ±3.4 years). The baseline rate of moderate to severe hypoglycemic events was far less in the pump-only group compared to the suspension group (20.7 vs. 129.6 events per 100 patient months). Hypoglycemic unawareness was assessed using a modified Clarke questionnaire and a minimum score of 4 was required, which suggested impaired hypoglycemic unawareness. As with other RCTs assessing the artificial pancreas, patients could not be blinded to the intervention. At 6 months, the event rates decreased from 28 to 16 in the pump-only group versus 175 to 35 in the low-glucose suspension group. Authors then adjusted the incidence rate per 100 patient months and reported the pump-only group had an estimated 34.2 (95% CI, 22.0-53.3) events compared to the suspension group which had an estimated 9.5 (95% CI, 5.2-17.4) events (incidence ratio of 3.6; P <.001). No changes in glycated hemoglobin or counterregulatory hormone responses to hypoglycemia were reported in either group. Considering patients were randomized to either the pump-only or suspension group, it is unclear how patients with significantly more hypoglycemic events were disproportionally represented in the suspension group. Additional studies are required which demonstrate the benefits of the artificial pancreas over a longer duration of time, in study populations based on specific age and with similar baseline levels of hypoglycemia, hyperglycemia and glucose variability.

APDS Conclusion

Research regarding use of an artificial pancreas device to reduce hypoglycemic episodes is in its infancy. Current publications are limited in number and by small sample size and short-term follow-up. Conclusions regarding the clinical impact artificial pancreas devices will have in improving the over-all health of diabetic patients cannot be made.

Clinical Practice Guidelines

Currently, no evidence-based clinical practice guidelines recommend the use of the artificial pancreas, including the use of the low glucose suspend feature, for management of diabetic symptoms. One evidence-based and two consensus-based clinical practice guidelines recommending the use of CGM are presented below.

American Diabetes Association

The American Diabetes Association made the following consensus-based recommendations concerning CGM in its 2011 standards of medical care in diabetes:[38]

- "Continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower A1c in selected adults (age ≥25 years) with type 1 diabetes (Level of Evidence A).
- Although the evidence for A1c lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. (Level of Evidence C)
- CGM may be a supplemental tool to SMBG [self-monitoring of blood glucose] in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. (Level of Evidence E)"

Endocrine Society

In 2011, the Endocrine Society published a clinical practice guideline based on consensus opinion and evidence. Although evidence grades were assigned, the methodology for selecting the studies included in the review were not defined, nor were the included studies critically appraised.[39] The following recommendations were made regarding continuous glucose monitoring:

- RT-CGM (real-time continuous glucose monitoring) is recommended for all people with type 1 diabetes above the age of 8 years in the outpatient setting, although use among those with HbA1c levels above 7.0% should be restricted to patients "who are able to use these devices on a nearly daily basis".
- The use of RT-CGM in the intensive care unit or operating room is not recommended.
- There is no recommendation regarding the use of CGM within patients younger than 8.

Of note, 7 of the authors of this clinical practice guideline reported receiving financial remuneration from CGM device manufacturers.

The guideline recommendations were also based, in part, on the results of a commissioned systematic review. The review concluded that CGM devices, "improve glycemic control in adults" with type I and II diabetes in research settings. However, the authors call attention to shortcomings in the current body of research, such as device study design which may offer more support and training to the interventional group than that received in the real world, and therefore which may limit the applicability and translation of this evidence to real-world use of these devices.

Several published studies[14,18,22-24,40] were also specifically cited by the Endocrine Society's clinical practice guideline, although their conclusions are limited by the following:

- Lack of study of primary health outcomes directly associated with CGM devices,[18,40] or impact on rate of glycemic events,[14] which may limit interpretation of significant findings.
- Insignificant differences in primary health outcomes (such as a difference in the proportion of participants experiencing hypoglycemic events).[14,22,23]
- Short (≤3 months) study period,[18,40] which does not allow for an understanding of long-term efficacy.
- Non-standard statistical analysis, including *post-hoc* and per-protocol analysis,[14,24] which is likely to overestimate any association under study.
- Lack of comparison treatment group for duration of the study,[24] which may not allow for identification of treatment effect over and beyond that conferred by standard medical care.
- Small sample size,[18,23,40] which may have limited the ability to control for bias, or to find real differences between treatment groups where they truly existed.
- Very low long-term device compliance rate.[23]

American Association of Clinical Endocrinologists

In 2010, the American Association of Clinical Endocrinologists published a panel consensus statement on the use of CGM. [41] The consensus panel recommends the use of CGMs for patients with type 1 diabetes, who meet specific criteria, often in the absence of documented hypoglycemia. This recommendation, however, is not based upon a complete, reproducible systematic review of all the evidence. The AACE recommendations are primarily based upon expert opinion. In addition, 7 of the 10 authors of the consensus statement are affiliated in some way with a major manufacturer of CGM devices. These relationships pose a potential conflict of interest and raise concerns regarding bias.

Summary

In summary, the available studies demonstrate that intermittent glucose monitoring provides a different type of data than results from fingerstick glucose levels. In addition to providing more data points, it also provides information about trends (direction) in glucose levels. This additional information is most likely to benefit those patients with type I diabetes that do not have adequate control of their blood glucose. Therefore, continuous monitoring can be considered medically necessary to provide additional data for management of those who have recurrent, unexplained, severe hypoglycemia, despite use of current best practices.

However, data regarding the impact of long-term continuous glucose monitoring on primary health outcomes are still limited. Studies such as those conducted by the Juvenile Diabetes Research Foundation suggest that more frequent use of continuous glucose monitors may result in improved HbA1c, but this finding is not consistent across all available studies, and does not directly address the impact on diabetes-related morbidity and mortality. In addition, some believe that HbA1c may not be the most appropriate measure of glycemic control as patients with large variability in glucose levels, including severe hypo or hyperglycemic episodes may not have HbA1c values outside the normal range.[9] Due to these issues and the lack of understanding of device feasibility and patient compliance with long-term use of these devices (>12 months), the impact of CGM for the general diabetic population is uncertain. Therefore, CGM is considered investigational for the purpose of improving glucose control in the general diabetic population.

Evidence regarding use of an artificial pancreas device to reduce hypoglycemic episodes appears promising; however, current data is limited by small sample size and short term follow-up. Evidence from larger, long-term, randomized controlled trials, which demonstrate how artificial pancreas devices may be used to reduce initial and secondary hypoglycemic events and improve the overall health outcome of diabetic patient, is needed. Therefore, artificial pancreas devices are considered investigational for the purpose of improving glucose control or controlling nocturnal hypoglycemia in the general diabetic population.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	None	
HCPCS	A9276	Sensor; invasive (eg, subcutaneous), disposable, for use with interstitial continuous glucose monitoring system, 1 unit = 1 day supply
	A9277	Transmitter; external, for use with interstitial continuous glucose monitoring system
	A9278	Receiver (monitor); external, for use with interstitial continuous glucose monitoring system
	E1399	Durable medical equipment, miscellaneous
	S1030	Continuous noninvasive glucose monitoring device, purchase for physician interpretation of data, use CPT code)
	S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (for physician interpretation of data use CPT code)
	S1034	Artificial Pancreas Device System (eg, Low Glucose Suspend [LGS] Feature) Including Continuous Glucose Monitor, Blood Glucose Device, Insulin Pump And Computer Algorithm That Communicates With All Of The Devices
	S1035	Sensor; Invasive (eg, Subcutaneous), Disposable, For Use With Artificial

CODES	NUMBER	DESCRIPTION
		Pancreas Device System
	S1036	Transmitter; External, For Use With Artificial Pancreas Device System
	S1037	Receiver (Monitor); External, For Use With Artificial Pancreas Device System