



2018

# Glycemic Control and Type 1 Diabetes Mellitus: Current Standard Treatment vs. Closed-Loop Insulin Pumps

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*Physician Assistant Scholarly Project Papers*. 10.  
<https://commons.und.edu/pas-grad-papers/10>

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Glycemic Control and Type 1 Diabetes Mellitus: Current Standard Treatment  
vs. Closed-Loop Insulin Pumps

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A Scholarly Project

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May

2018

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**ACKNOWLEDGMENTS**

I would like to give a very special thank you to Dr. Marilyn Klug, Barb West, RN-CDE, Professor Daryl Sieg, Dawn Hackman, and the UND writing center for all their hard work and dedication in helping me to develop and proficiently write this scholarly project. Your time, help and expertise is greatly appreciated, and has not went unnoticed. I also would like to take time to thank the UND Physician Assistant program faculty for their commitment to providing me a quality education and for providing exceptional guidance throughout my endeavors in the PA program.

**ABSTRACT**

As of 2015, 9.4% of the US population had a diagnosis of Diabetes Mellitus (DM). Although most of the data sets studied encompass type 1 (T1) and type 2 (T2) DM data in all ages of patients, the focus of this project will be primarily on T1DM patients. A thorough review of the current literature reveals that there are effective methods currently available for the management of T1DM patients. These methods include: closed-loop insulin pumps that integrate a continuous glucose monitor (CGM) and insulin pump into one effective system that calculates the needed insulin doses through complicated algorithms, CGM with self-blood glucose monitoring calibrations (SBGM) and insulin administration, and SBGM with insulin administration. Even though these individual methods have their associated challenges, the literature reveals that closed-loop insulin pumps have the potential to provide better disease management and improved disease outcomes for those patients who are motivated to use them as directed and find them a desirable option. When patients can effectively manage their blood glucose, and practice healthy lifestyle and dietary choices, they can avoid unnecessary hospitalizations and long-term diabetic complications. This will simultaneously reduce healthcare-related costs, increase longevity and can improve the patient's quality of life.

## INTRODUCTION

Diabetes Mellitus (DM) is a chronic, complex disease that can involve multiple body organ systems. According to the Center for Disease Control and Prevention (CDC), DM affects an estimated 30.3 million people in the United States alone, and five percent of those cases are estimated to be Type 1 Diabetes Mellitus (T1DM). The incidence of DM is steadily increasing with an estimated 1.5 million new cases of diabetes diagnosed in 2015 (Center for disease control and prevention, 2017). If left untreated, DM will likely cause multiple end-organ damage which can result in: chronic kidney disease (CKD), lower limb amputation, coronary artery disease (CAD), and stroke.

There are numerous methods available for insulin delivery in the management of the T1DM patient, and there are many great clinical recommendations with many years of research to help validate them. The purpose of this scholarly project is to outline the history of DM management and determine which methods provide the most effective insulin delivery system, glycemic control, and describe each method's benefits and challenges.

Current medical treatment for DM patients requires SBGM-done by needle sticks to the fingers, medications-provided by oral tablets, insulin injections, non-insulin injectables, or by insulin pumps, combined with healthy eating habits and physical activity. CGM is another option for blood glucose monitoring. Insulin injections are administered by the patient using vials and syringes, insulin pen devices, insulin pumps that allow calculation of insulin dosage by the patient, or by hybrid closed-loop pumps that automatically calculate basal insulin dose; but all these modalities are dependent on the patients' ability to count carbs accurately for adequate dose calculation.

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The intent of this project was not to describe the different types of insulin on the market, the different brands of CGM devices on the market, or the different brands of closed-loop systems currently available; but instead, strongly make the suggestion that it is up to the discretion of the provider and patient to choose whatever type of insulin, CGM, insulin pump, and/or a closed-loop system that they are able to use safely and effectively. The purpose of this project was to find answers to the following questions: Will closed-loop insulin pumps provide better efficacy by monitoring glycemic control according to patient's blood glucose levels and glycosylated hemoglobin levels (HgbA1C) and decrease the incidence of hypoglycemic episodes, as compared to the current standard treatment of insulin pump therapy in patients with T1DM? What are the unique benefits of the different effective T1DM management methods? What are the challenges of these management methods and how will they affect their actual use-effectiveness?

## LITERATURE REVIEW

A search of peer reviewed journal articles was performed utilizing several electronic databases. These databases included AccessMedicine, ClinicalKey, PubMed, UpToDate, DynaMed PLUS, and ScienceDirect. A combination of key words and subject headings included: Type 1 Diabetes Mellitus, pathophysiology, continuous glucose monitoring, closed loop insulin delivery, artificial pancreas, glycemic control, hypoglycemia, insulin dependent, and diabetes control and complications trial (DCCT). Many of these keywords were combined using the Boolean operator “AND” to limit the search. Several complete articles were retrieved and reviewed including those that describe the pathophysiology behind DM, current pharmacologic therapy used to treat DM, studies that examine modifying risk factors for DM (i.e. diet, exercise), creating a unified database to compile relevant research information on clinical trials aimed at preventing and treating DM, and the role of the primary care provider in utilizing these approaches. Types of studies that were excluded from the research pertained to: studies with the sole focus of T2DM management, DM management that did not require the use of insulin, among others.

Additionally, pathophysiology textbooks were used to supplement information on the pathophysiology of DM. All sources used have been reviewed and published within the past ten years, apart from the DCCT trial which was completed in 1993. The DCCT is the basis for clinical management of T1DM to this day, that includes older adults at risk for, or who have been diagnosed with DM. The articles reviewed include systematic reviews, randomized control trials, cohort, and observational studies. Research found varies in participant populations into the thousands to no less than ~30 study participants.



### **Pathophysiology, prevalence, environmental factors and clinical manifestations in the development of DM**

DM is described as a metabolic disease that includes hyperglycemia due to insulin secretion defects, insulin action, or a combination of both. Insulin plays an important role in glucagon control; if there is too much glucagon, the blood glucose levels will remain high, which will result in hyperglycemia. Insulin counteracts glucagon and lowers blood glucose levels by suppressing the secretion of glucagon. Due to this metabolic dysfunction, DM may manifest in many ways. McCance and Huether (2014) outline some of these clinical manifestations as follows:

<b>Polydipsia</b>	Due to elevated blood glucose levels, water is osmotically attracted from body cells, resulting in intracellular dehydration and hypothalamic stimulation of thirst.
<b>Polyuria</b>	Hyperglycemia acts as an osmotic diuretic; the amount of glucose filtered by the glomeruli of the kidneys exceeds the amount that can be reabsorbed by the renal tubules; glycosuria results, accompanied by large amounts of water lost in the urine.
<b>Polyphagia</b>	Depletion of cellular stores of carbohydrates, fats, and protein results in cellular starvation and a corresponding increase in hunger.
<b>Weight Loss</b>	Weight loss occurs due to fluid loss in osmotic diuresis and the loss of body tissue as fat and proteins are used for energy because of the effects of insulin deficiency.
<b>Fatigue</b>	Metabolic changes result in poor use of food products, contributing to lethargy and fatigue; sleep loss from severe nocturia also contributes to fatigue.

McCance and Huether (2014) also states that there are two well-defined types of T1DM: autoimmune and nonimmune. In autoimmune-mediated DM (type 1A), environmental-genetic factors are thought to trigger T-cell mediated destruction of pancreatic beta cells. Nonimmune is

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far less common and arises secondary to other disease processes, such as pancreatitis, or to a more acute and severe disorder termed idiopathic diabetes (type 1B). However, type 1B DM occurs more commonly in people of Asian or African descent and affected individuals that have varying degrees of insulin deficiency. As stated previously, an individual develops T1DM most commonly due to the autoimmune destruction of the insulin-producing pancreatic beta cells in the islet of Langerhans. McCance and Huether (2014) describe the progressive destruction of beta cells in the following two steps:

1. Lymphocyte and macrophage infiltration of the islets resulting in inflammation (insulinitis) and islet beta-cell death. Autoantigens are expressed on the surface of pancreatic islet cells and circulate in the bloodstream and lymphatics. Circulating autoantigens are ingested by antigen-presenting cells that activate T helper 1 (Th1) lymphocytes. The activated Th lymphocytes secrete interleukin-2 (IL-2) that activates beta-cell autoantigen-specific T cytotoxic lymphocytes, causing them to proliferate and attack islet cells through secretion of toxic perforins and granzymes. T helper lymphocytes also secrete interferon that activates macrophages and stimulates the release of inflammatory cytokines (including IL-1) and tumor necrosis factor [TNF]), which cause further beta-cell destruction and apoptosis.
2. Production of autoantibodies against islet cells, insulin, glutamic acid decarboxylase (GAD), and other cytoplasmic proteins. Activated T helper 2 (Th2) lymphocytes produce IL-4, which stimulates B lymphocytes to proliferate and produce antibodies. Islet cell autoantibodies (ICAs) precede evidence of beta-cell deficiency and can be found in the serum years before symptoms occur. Anti-glutamic acid decarboxylase (antiGAD) antibodies, which is an enzyme in beta cells that is involved in

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coordinating insulin release, are more persistent. This makes them clinically useful in differentiating the etiology of diabetes in a specific individual. Autoantibodies against insulin [IAAs] also have been noted. It is likely that IAAs may form during the process of active islet cell and beta-cell destruction. Finally, another IAA in T1DM can now be measured in the serum. It is called the zinc transporter 8 (Znt8) protein and is associated with variation in disease progression.

Pietropaolo (2016) characterizes T1DM as a slow-progressing, autoimmune, T cell-mediated disease that occurs in genetically susceptible individuals. The lifelong risk of T1DM being markedly increased in close relatives of patients that have a first-degree relative with T1DM, averaging approximately six percent in offspring, five percent in siblings, and fifty percent in identical twins (versus 0.4% in subjects with no family history).

As the clinical manifestations and pathophysiology of DM were outlined above, we will now discuss some of the general risk factors that are associated with the development of DM. The National Diabetes Statistics Report provided by the CDC (2017) included multiple data that pertains to some of these factors, those of which are outlined in Table 1 below:

### *Common Risk Factors for Diabetic Complications*

*2011-2014, US adults >18 years of age with diagnosed diabetes, [95% CI]*

<b>Smoking</b>	15.9% were current smokers and 34.5% had quit smoking but had a history of smoking at least 100 cigarettes in their lifetime.
<b>BMI</b>	87.5% were overweight or obese, defined as a BMI of 25 or greater; 26.1% having a BMI of 25-30, 43.5% having a BMI of 30-40, and 17.8% with a BMI of 40 or higher.

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- Physical Inactivity** 40.8% of adults got less than 10 minutes/week of moderate to vigorous activity in either work, leisure, or transportation.
- Hypertension** 73.6% had systolic BP of 140mmHg or higher and diastolic BP of 90mmHg or higher, or they were already on BP controlling medications.
- High Cholesterol** 58.2% over age 21 with no self-reported CV disease who were eligible for statin therapy and were on a lipid-lowering medication. 66.9% over age 21 with self-reported CV disease who were eligible for statin therapy and were on a lipid-lowering medication.
- Hyperglycemia** 15.6% of adults had a HgbA1C value higher than 9%.

The CDC (2017) also states:

In 2014, a total of 7.2 million hospital discharges and 14.2 million emergency department visits were reported with diabetes being listed as any kind of diagnosis among US adults aged 18 years or older. The total direct and indirect estimated cost of diagnosed diabetes in the US in 2012 was \$245 billion; with an average of \$13,700/year/person being medical expenditures related to diabetes. This is around 2.3 times higher than expenditures for people without diabetes. It is also important to note that DM was the seventh leading cause of death in the US in 2015.

## **Diagnosis of DM, importance of glycemic control in DM and recommended disease management of DM**

In patients that are suspected to have DM, there are four diagnostic criteria. Only one out of the four needs to be met for a diagnosis of DM. DynaMed (2017) establishes the diagnostic criteria for DM as:

- fasting plasma glucose  $\geq 126$  mg/dL (7 mmol/L) (after no caloric intake for  $\geq 8$  hours)
- symptoms of hyperglycemia with random plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L)
- 2-hour plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L) during a 75g oral glucose tolerance test (OGTT)
- HbA1c  $\geq 6.5\%$  (HbA1c may not be accurate for diagnosis if pregnancy, hemoglobinopathy, certain anemias, or abnormal erythrocyte loss or replacement)

Regarding patients that have a diagnosis of T1DM, DynaMed (2017) states there is a strong recommendation to use HgbA1C to monitor glycemic control, and it should be checked four times per year or more frequently if needed. HgbA1C reflects the glycemic effect on hemoglobin over the preceding three months, and it can be converted to an estimate average blood glucose range that may be easier for patients to understand. Other strong recommendations for T1DM patients include: SBGM before meals, snacks, and at bedtime, or the use of real-time CGM in adults and adolescents.

The Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study are in their 30<sup>th</sup> and 20<sup>th</sup> year of application, respectively, since the reporting of the DCCT primary results. It is because of these two studies that our understanding the relationship between metabolic control and long-term complications and the treatment of T1DM, has been transformed.

The Diabetes Control and Complications Trial (DCCT)

The DCCT performed by Nathan, D. M., Bayless, M., Cleary, P., Glenuth, S., Gubitosi-Klug, R., Lachin, J. M., ... Zinman, B. (2013) began in 1983 and ended in 1993 and was designed as a parallel-arm randomized clinical trial (RCT) that compared: the “standard” or conventional therapy and the “experimental” or intensive therapy in male and female T1DM patients aged 13-39 years of age with a diabetes duration of one to five years. The study sought to answer the following two questions: For primary prevention, will an intensive treatment program designed to achieve glycemic control as close to the nondiabetic range as safely as possible prevent or delay the appearance of early background retinopathy? And for secondary intervention, will such an intervention prevent the progression of early retinopathy to more advanced forms of retinopathy? Power calculations required 700 subjects, 350 for each treatment arm of primary prevention, to detect a significant difference. They ultimately ended up with 1,441 randomized participants, 11 of whom died during DCCT and only eight of the 1,430 survivors failed out of the trial.

The standard therapy (CONV group) consisted of one or two daily insulin injections, daily urine or SBGM testing, diabetes education, and quarterly HgbA1C levels. The experimental therapy (INT group) consisted of at least three injections of insulin per day or treatment with continuous subcutaneous insulin infusion (CSII) that included dose adjustment guided by four or more SBGM tests per day, meal size and content, and anticipated exercise and specific glycemic targets. The goals of the trial were absence of symptoms of hyperglycemia or avoidance of severe episodes of hypoglycemia. The study demonstrated such dramatic positive results that it was recommended to be stopped one year short of its end date because the major questions had been answered.

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The DCCT showed an improvement in the INT group with the following outcomes:

**HgbA1C** - by three to six months to a level of 6.9% from the initial 9.1%

**Microvascular** – results found were consistent, significant, and clinically meaningful

**Cardiovascular** – the patient population was generally too young and healthy to experience major CVD events ( $p= 0.059$ ) INT group with three events in three subjects vs. CONV with twenty-one events in nine subjects

**Beta cell preservation** – INT group slowed the rate of loss of C-peptide responsiveness by ~50%.

The DCCT also demonstrated that the clinical benefit of persistent C-peptide secretion included significantly lower HgbA1C levels with lower insulin doses, fewer hypoglycemic episodes and lowered retinopathy risk.

The major adverse outcomes were hypoglycemia, which was defined as an episode of  $<50\text{mg/dL}$  that responded to intravenous glucose, glucagon, or oral carbohydrates, and weight gain of an average of 4.6kg. Although 20% of subjects in the INT and CONV groups reported a decrease in quality of life, there was a nonsignificant difference between the groups. These studies show the prudence of a strict insulin regimen and stringent glyceemic control regarding complications and reducing hyper- and hypoglycemic events in patients with T1DM. These results are what guide ADA recommendations for best diabetes care management. It is important to note that some of the limitations listed were the lack of patient adherence to these recommendations, limited time that clinicians have with patients, and societal, behavioral, or other psychological barriers that may affect clinical outcomes. Also, this study reported no relevant conflicts of interest as they may pertain to this article.

The Epidemiology of Diabetes Interventions and Complications (EDIC) study

The EDIC study performed by Nathan, et al. (2013) was started in 1994 and was an observational follow-up to the DCCT in which individuals from both groups (INT and CONV) that agreed to continue with observation were all subjected to the experimental INT therapy. The major goal was to see if the original DCCT INT therapy regimen would have a longer-term effect on the more advanced stages of DM microvascular complications and their clinical consequence on CVD. The EDIC was started with 1,394 subjects, and it is still ongoing with the last data at 2012 with 1,284 subjects. The differences in treatment quickly leveled out as the individuals' care was returned to their PCP, and it is important to note that differences in insurance may have skewed some outcomes. The HgbA1C of the former INT group raised by  $\sim 0.8$  and fell by  $\sim 1.0$  for the individuals that were in the CONV group. Five years into the EDIC, there was no statistical difference in HgbA1C and has stayed that way for the past 20 years. By 2012, in the 19<sup>th</sup> year of the EDIC, it was found that the risk of severe retinal outcomes had been reduced by 48% with the former DCCT INT group vs. former CONV group. It is also important to note that severe renal impairment decreased by  $\sim 50\%$  as well in the former INT vs. CONV group. This demonstrates the need for earlier intervention to reduce long-term diabetic complications.

It took 18 years of follow-up in the EDIC to show a statistical difference in the reduction in risk of primary CVD outcomes such as major nonfatal and fatal CVD events, angina or revascularization in the INT group by 42%. Fatal and nonfatal myocardial infarction and stroke risk was reduced by 58%. It is important to note that the quality of life decrease mentioned in the DCCT was due to the increase of fingersticks, and associated increase in time to manage their disease process at home and at clinic. A drawback of these studies includes them not listing the CI or some p values of their statistics to add validity to their studies.



**Evolution of SBGM into current therapy for T1DM CGM and efficacy**

Insulin administration is a mainstay of T1DM treatment, with its goal to attain a normal blood glucose level. It is prudent that patients and care-providers are given the option to choose the optimal insulin regimen that most fits their needs and lifestyle, and stress the importance of making sure the selected insulin regimen is an intensive one to achieve better glycemic control. Intensive regimens provide insulin in a more physiologic manner by maintaining a more level basal insulin baseline and by providing a bolus of insulin at meal times to account for carbohydrate content. It is also important to note that the use of an insulin pump is also considered an intensive regimen.

According to McCulloch (2017) on UpToDate, controlled trials of insulin pump therapy in children or adolescents generally suggest that it is similar to or somewhat better than multiple daily injections (MDIs) of insulin at achieving glycemic control and avoiding hypoglycemic episodes. McCulloch (2017) also states that insulin pump therapy is often preferred by children and their families, as MDI regimens can require as many as six to seven injections per day, which may hinder adherence to intensive therapy. The cost of the insulin pumps and associated supplies must also be accounted for, as well as complications of pump therapy, such as infusion pump failure, superficial infection, and dermatologic changes such as scars or nodules at the catheter site.

With MDI and insulin pump therapy there is still a requirement for SBGM, counting dietary carbohydrates, impact of exercise on insulin requirements, and having to make the appropriate adjustments to insulin infusion rates. This requires a level of commitment and will only be effective if the patient and caregivers will devote time to do so. CGM has the potential to improve glycemic control while decreasing hypoglycemic events. When compared to the

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improvement in glycemic control provided by SBGM, the outcomes are variable at best. As stated previously for CGM therapy to be effective, SBGM with fingersticks is still a requirement.

In a meta-analysis cited by McCulloch (2017) from individual patient data from six trials (N=892) that compared CGM with SBGM patients with T1DM, the overall mean difference in HgbA1C was 0.3%, which favored the use of CGM over SBGM. CGM can be expensive, with the author listing initial costs varying from ~\$1000 to \$2000 with monthly costs for supplies roughly between \$350 to \$450. It is important to note that insurance companies are improving reimbursement over the last few years. McCulloch (2017) outlined that some studies may have the potential for bias due to: patient adherence; or lack of, and patient motivation, which may account for a skewed sampling even in a RCT.

According to Olczuk and Preifer (2017) CGM was available for use by people diagnosed with DM. These monitors have the capability to take glucose readings every five minutes. This allows the patients and medical providers to have more in-depth knowledge about blood glucose trends that each patient experiences throughout the day and night. Olczuk and Preifer (2017) also outline that the newer models of CGM have the capability to detect hypo- or hyperglycemic episodes and alert the user of the CGM. This function may help improve quality-of-life and reduce the cost burden of diabetes in U.S. healthcare system. This article outlines six of the major devices on the market for CGM that are approved by the FDA. It is prudent for patients and medical providers to choose a device that they have the knowledge and capacity to use effectively.

Olczuk and Preifer (2017) outlined some of the limitations to CGM devices and the continued fingersticks for device calibration and lag time of the devices when using a sensor which can be anywhere from four to twenty-seven minutes. This accounts for the change in

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blood glucose vs. the interstitial fluid in the subcutaneous tissue where the sensor is mounted. Olczuk and Priefer (2017) stated “it is clear, however, that any research aimed at predicting or decreasing the lag between CGM glucose readings and blood glucose level readings must take into consideration both the intrinsic lag of the device and the physiological lag”. They suggested that SBGM should still be performed before any interventions were administered to account for the lag possibility. The lag times may help account for either the over- or underestimation of glucose intake or insulin injections. It is important to note that certain CGM devices are FDA approved for patients two years of age and older. Although this article outlined many different brands of CGM and SBGM devices, it was not the intent of this project to specify which brand may or may not be better, but to outline only the clinical outcomes of CGM and SBGM. Olczuk and Priefer (2017) also noted that there were no conflicts of interest in their study, and that they did receive funding from Western New England University-College of Pharmacy.

### The DIAMOND clinical trial

The DIAMOND randomized clinical trial, performed by Beck, R. W., Riddlesworth, T., Ruedy, K., Ahmann, A., Bergenstal, R., Haller, S., ... Price, D. (2017) sought to answer the following question: For adults with T1DM who are using multi-dose injections, does CGM improve HgbA1c levels compared with SBGM? The trial included 158 adult (aged 25 years or older) subjects with a random 2:1 assignment (n=105) in the CGM group and (n=53) in the “usual care” or control group. This study was conducted between October 2014 and May 2016, which is a somewhat short duration to be able to prove a clinical significance. The mean age of the participants was 48 years of age (SD,13); 44% were women and 56% were men, with a HgbA1c baseline of 8.6% (SD 0.6%) and median diabetes duration of 19 years (IQR 10-31 years). It is safe to say that the results of this study can be applied to adults with insulin

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dependent DM that have had the disease for many years. It would be difficult to conclude the effectiveness of the results in a newly diagnosed or younger DM patient because of the inclusion criteria. Of the 158 participants, 98% or 155 subjects were able to complete the study.

In the CGM group, 93% used CGM six days/week or more in month six of the trial. Mean HgbA1C reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% at 12 weeks and 0.4% at 24 weeks in the control group in a repeated-measure model with  $p < .001$ . At 24 weeks, the adjusted treatment-group difference in mean change in HbA<sub>1c</sub> level from baseline was  $-0.6%$  (95% CI,  $-0.8%$  to  $-0.3%$ ;  $p < .001$ ). Median duration of hypoglycemia at less than  $<70$  mg/dL was 43 min/d (IQR, 27-69) in the CGM group vs 80 min/d (IQR, 36-111) in the control group ( $p = 0.002$ ). Severe hypoglycemia events occurred in two participants in each group.

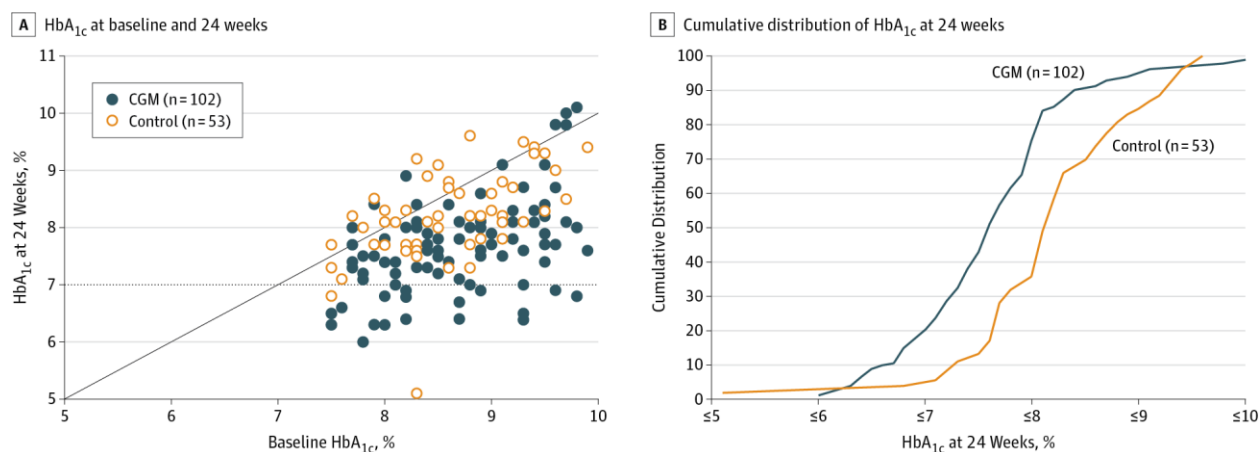


Table 2 adapted from Beck, et al, 2017 <https://doi.org/doi:10.1001/jama.2016.19975>

With this data, we can see that CGM as compared to the usual care of SBGM and insulin injections resulted in a greater decrease in HgbA1C levels over the 24 weeks that the trial was performed. Because the data comes from a newer form of technology, it was stated that further research is needed for long-term use effectiveness, clinical outcomes and possible adverse side effects. It is important to note that the authors of the study believe that the 0.4% mean

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improvement in HgbA1C in the control group was likely due to a study effect and a more structured training in using blood glucose monitoring and adjusting insulin regimens than was occurring for the control group individual before the study started. The study states its limitations as: the results may not be applicable to T1DM patients that are younger than 26 years of age, those that have HgbA1C levels outside the range of 7.5% to 9.9% and should also not be applied to individuals with T2DM who receive MDI of insulin. Beck, et al (2017) disclosed multiple parties that received funding or had interest in major companies, they stated that the study itself was funded by Dexcom©. Although the study was funded by a company that manufactures CGM devices, we can see that the statistics found are in fact significant in nature and that clinicians should be able to utilize them and feel confident that they will be effective to provide better disease management.

**Closed-loop monitoring systems for T1DM and efficacy**

Uduku and Oliver (2017) state that:

The enduring goal in DM care is to develop a safe mode of insulin delivery that closely mimics human body physiology and optimizes HgbA1C, without associated hypoglycemia. Recent advances in DM technology have provided clinicians with the chance to utilize closed-loop monitoring systems, also known as artificial pancreases, for T1DM patients. Closed-loop insulin delivery integrates an insulin pump and a CGM, combined with a glucose control algorithm. These algorithms are a set of pre-programmed rules which allow the glucose controller to perform the role of a normal pancreas and make automated insulin adjustments based on real-time CGM data.

Uduku and Oliver (2017) outline the two different available algorithms as follows:

**Model Predictive Control (MPC)** – this method proactively anticipates future glucose levels based on current blood glucose concentrations.

**Proportional Integral Derivative (PID)** – this is a reactive control algorithm that responds to deviations from target glucose level and the rate of glucose level change.

In a head to head comparison, both algorithms demonstrated safe glycemetic control; although MPC significantly demonstrated more time within target glycemetic range, and lower mean glucose overall and five hours after an unannounced 65g carbohydrate meal.

The article made it clear that there are pharmacological barriers to the closed-loop system, because there are no stable long-term glucagon analogues to be able to counteract the effects of insulin, as a non-diabetic pancreas would do, and that there is no long-term safety data like there is available for insulin. Some of the other barriers addressed was that the user needs to input meal and exercise events for the system to work properly.

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Klonoff, Ahn, and Andjela (2017) characterizes some drawbacks to CGM as: over-calibration of the monitor, which may lead to instrument error, or if a blood glucose reading was entered at a time of rapid change; like after a meal or exercise. This article also states that CGM provides usefulness in a wide range of T1DM patients such as: patients who regularly and frequently perform SBGM, those who have frequent hypoglycemia episodes with hypoglycemic unawareness, those with clinically significant glycemic variability, those with HgbA1C levels above goal, those whose SBGM values do not match their corresponding HgbA1C values, and those who are participating in sports or high-risk occupations and need to avoid hypoglycemia. This article states that sensor augmented pumps (open-loop control) are continuous monitors that display data and allows the user to act based on the glucose reading. A sensor integrated pump (closed-loop control) uses the CGM to determine the needed dose and adjust insulin delivery.

According to Devries (2017), report results from a randomized crossover trial comparing day-and-night closed-loop insulin delivery with usual pump therapy (four weeks each) in 29 adults with well controlled T1DM (HgbA1C <7.5%). A closed-loop system was used, in which the participant determined the amount of insulin administered before each meal. Participants had sensor glucose concentration in target range (3.9–10.0 mmol/L) 65.6% (SD 8.1) of the time during usual pump therapy and 76.2% (SD 6.4) of the time during closed-loop delivery which showed that the closed-loop system increased the proportion of time when glucose concentration was in target range by 10.5 percentage points (95% CI 7.6–13.4;  $p < 0.001$ ). Compared with usual pump therapy, closed-loop delivery reduced mean glucose concentration by 0.4 mmol/L (0.1–0.7,  $p = 0.0226$ ); the proportion of time with glucose concentration above 10.0 mmol/L by 6.9 percentage points (3.5–10.2;  $p = 0.0003$ ) and below 3.9 mmol/L by 50% (37–59,  $p < 0.001$ ); and glycemic dispersion (ie, SD of glucose concentration) by 0.5 mmol/L (0.3–0.7,  $p < 0.001$ ). It is

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important to note that this article also stated the need for larger controlled trials and stated that there are a few trials; NCT02985866 and NCT02748018 that are underway and are in the recruiting stage with the aim to assess the closed-loop interventions in 240-1500 patients for a duration of six months. There were some instances where CI was not reported or could not be found whereas other information was readily available. As with previous studies, clinicians would be able to put more confidence in the research if CI was more readily available.

Battelino, Omladic, and Phillip (2015) performed a meta-analysis and outlined data from 22 different studies that included the data from 518 subjects that met the following criteria: timeline between January 2004 to September 2014 that contained the words ‘closed loop’, ‘artificial pancreases’, and ‘type 1 diabetes’. Other criteria for inclusion were RCTs comparing closed-loop insulin delivery and combined CGM with CSII or with sensor augmented insulin pump (SAP), in participants with T1DM. The primary result focus was stressed upon: mean glucose levels or time within target range, time spent in hypoglycemia, or time spent in severe hypoglycemia.



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The following data show the results of the studies that met the above criteria:

Overview of Randomized Controlled Trials on Use of Closed loop in type 1 diabetes by years (CL – closed loop; SAP – sensor augmented pump; any insulin pump coupled with any sensor for continuous glucose monitoring).

Year	Study author (reference number)	Number of patients	Mean age	Study duration	Intervention	Primary study end point	Outcome: intervention vs control
2010	Hovorka [33]	21	13.5	2–5 days	CL vs SAP	Time in target glycaemic range; time in hypoglycaemia	20% ( $p = 0.00225$ ); –2 ( $p = 0.0304$ )
2011	Hovorka [40]	24	37.5	2–7 days	CL vs SAP	Time in target glycaemic range	15% ( $p = 0.002$ , eating in); 28% ( $p = 0.01$ , eating out)
2011	Murphy [54]	12	32.9	48 h	CL vs SAP	Time in target glycaemic range; time in hypoglycaemia	81% vs 81% ( $p = 0.75$ ); 0.0 vs 0.03 ( $p = 0.04$ )
2012	Breton [41]	38	41 (adults), 14.5 (adolescent)	22 h	CL vs SAP	Time in near normoglycaemia, time in tight glycaemic range, time in hypoglycaemia	12.9% ( $p = 0.01$ ), –2.5% ( $p = 0.66$ ), –2.7 ( $p = 0.01$ )
2013	Haidar [31]	15	/	30 h	Dual-hormone CL vs SAP	Time in target glycaemic range; time in hypoglycaemia	13.4% ( $p = 0.003$ ), 10.2% ( $p = 0.01$ )
2013	Elleri [38]	12	15.0	36 h	CL vs SAP	Time in target glycaemic range, mean plasma glucose level	35% ( $p = 0.02$ ), –37 mg/dl ( $p = 0.02$ )
2013	Sherr [37]	12	16.8	96 h	CL vs SAP	Night hypoglycaemia, time in target glycaemic range	–2.5% (sedentary), –6% (exercise) ( $p = 0.04$ ), 30% (sedentary), 14% (exercise) ( $p < 0.0001$ )
2013	Schmidt [42]	6	45	2 nights	CL vs SAP	Time in target glycaemic range, mean glucose, hypoglycaemic events	12.9% ( $p = 0.08$ ), 18 mg/dl ( $p = 0.38$ ), –3.7% ( $p = 0.22$ )
2013	Philip [39]	56	13.8	2 nights	CL vs SAP	Number of hypoglycaemic events, time spent in hypoglycaemia, mean overnight glucose level, time in target range	–15 ( $p = 0.003$ ), 0 ( $p = 0.02$ ), –14 mg/dl, 1.4 ( $p < 0.05$ )
2013	Nimri [47]	15	19	8 nights	CL vs SAP	Time in hypoglycaemia, percentage of nights with mean glucose in target range	–44.9 min ( $p = 0.0034$ ), 17% ( $p = 0.0034$ ), –5.3% ( $p = 0.377$ ), –4.3% ( $p = 0.001$ ), 18 mg/dl ( $p = 0.001$ )
2013	Luijf [48]	48	41.5	72 h	CL vs SAP	Time in target glycaemic range, mean glucose level, time in hypoglycaemia	2.1 h ( $p = 0.12$ ), –0.04 h ( $p = 0.86$ )
2013	Dauber [36]	10	5.1	2 nights	CL vs SAP	Time in target glycaemic range, time in hypoglycaemia	29.5% ( $p < 0.05$ ), –4.2% ( $p < 0.05$ )
2014	Capel [43]	10	46.7	2 nights	CL vs SAP	Time in target glycaemic range, time in hypoglycaemia	15% ( $p < 0.001$ ), –14 mg/dl ( $p < 0.001$ ), –7% ( $p < 0.01$ )
2014	Hovorka [46]	16	/	6 weeks	CL vs SAP	Time in target glycaemic range, mean overnight glucose, time in hypoglycaemia	–4.6% ( $p > 0.1$ ), 0.64 ( $p = 0.003$ ), 1.2 ( $p < 0.02$ ), 9 mg/dl ( $p < 0.04$ ), –0.55% ( $p > 0.1$ )
2014	Kovatchev [49]	20	/	80 h	CL vs SAP	Time in target glycaemic range, LGBI, hypoglycaemic events, mean BG, time in hypoglycaemia	13% ( $p = 0.005$ ), –12.6 mg/dl ( $p = 0.027$ ), –1.3% ( $p = 0.339$ )
2014	Leelarathna [50]	17	34	16 days	CL vs SAP	Time in target range, mean BG, time spent in hypoglycaemia	7% ( $p = 0.233$ )
2014	Iy [35]	20	/	106 nights	CL vs SAP	Time in target glycaemic range	–2.13% ( $p = 0.02$ ), 10.95% ( $p = 0.003$ )
2014	Nimri [44]	24	28.6	2 nights	CL vs SAP	Time in hypoglycaemia, time in target glycaemic range	–2.8% ( $p = 0.443$ ), 4.8% ( $p = 0.207$ )
2014	Oron [34]	37	12.4	2 weeks	CL vs SAP	Nocturnal hypoglycaemia episodes, time in target range	–26 mg/dl (adults, $p < 0.001$ ), –16 mg/dl (adolescent, $p = 0.004$ ); –3.2% (adults, $p = 0.01$ ), –1.8% (adolescents, $p = 0.05$ )
2014	Russell [51]	52	40 (adults), 16 (adolescents)	5 days	Bihormonal CL vs SAP	Mean plasma glucose level; time in hypoglycaemia	6.4% ( $p = 0.0016$ )
2014	Thabit [45]	25	43	11–12 weeks	CL vs SAP	Time in target glycaemic range	

CL, closed loop; SAP, sensor augmented insulin pump.

Table 3 adapted from Battelino, Omladic, and Phillip 2015 from <https://doi.org/10.1016/j.beem.2015.03.001>

It is important to note that most of the studies available for closed-loop therapy have very small patient sample sizes and short durations.

## DISCUSSION

Based on a thorough review of the literature, closed-loop systems were found to provide an effective decrease in the subjects' HgbA1C levels, and effectively reduce hypoglycemic events. Although current standard methods to provide glycemic control and reduce hypoglycemic events such as SBGM with insulin injections and CGM with insulin injections are proven to be efficacious as well. Historical studies show that an intensive insulin regimen along with strict monitoring of blood glucose and HgbA1C levels provide patients with less long-term microvascular side effects of retinopathy, neuropathy, and nephropathy, as well as the macrovascular side effects of cardiovascular, peripheral vascular and cerebrovascular disease.

Initial management of a T1DM patient should include basic disease education, demonstration of SBGM, insulin administration, how to recognize and treat a hypoglycemic episode, and how to measure either blood or urine ketone concentration. This will require a multidisciplinary team that should ideally include an endocrinologist, a certified nurse educator, dietitian, and possibly a mental-health professional to provide support if the need should arise. As the patient and family members become more comfortable with the ability to successfully initially manage their disease process, they must progress into further understanding DM. Separate sessions with the individual team members may provide a more in-depth education and care that is directed towards glycemic control. During these individual sessions the concepts are taught and reinforced and a management regimen designed for each specific patient should be adhered to, to achieve the best possible glycemic control. The need for strict glycemic control should also be reinforced at these sessions, so that the patient is aware of the long-term benefits of preventing the complications caused by uncontrolled high blood glucose levels. The need for

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an age-specific management plan should be dependent on the patient's age, cognitive ability, and emotional maturity for the patient to be able to participate in the self-management of DM.

SBGM is done primarily by fingersticks and should be performed at least four times a day, before meals and at bedtime in the fasting state. As one can see this could be very cumbersome even though newer technology in lancets provide ultrafine gauge needles. CGM is also another acceptable form of blood glucose monitoring. CGM is useful for optimizing glycemic control in patients motivated to use them and in patients that have hypoglycemia unawareness. There are several different types of CGM devices that have been developed: CGM without real-time feedback that is commonly used in physician's offices, CGM with real-time feedback, sensor-augmented insulin pumps with or without threshold-suspend, and automated closed-loop insulin pumps.

For these interventions to be effective patients need to be motivated to use them appropriately, demonstrate healthy eating habits, and should include a reasonable physical activity regimen. Patients need to keep in mind that lifestyle choices may either increase or decrease their risk of long-term side effects as well. If patients can practice healthy lifestyle choices, they can in turn lower their associated healthcare cost by decreasing the time that may need to spend in the hospital. It is important to note that newer technology is, in fact, more expensive initially than the tried and true methods that have been around for decades; but the newer technology like CGM and closed-loop systems help decrease the overall cost of patient's disease management by providing them with more time in target glycemic range and by reducing hypoglycemic events that may require hospitalizations. Because closed-loop systems are newer technology; there is less long-term data available and limited patient data from which to gather

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results, but if past patterns ring true, clinicians can expect better patient outcomes as more data becomes available.

### **What are the unique benefits of the different T1DM management methods?**

Historical effective methods of T1DM include SBGM with multiple daily insulin injections, SBGM with continuous subcutaneous insulin infusion (CSII) via insulin pumps, CGM with subcutaneous insulin injections (open-loop systems) or CGM with CSII (closed-loop systems). While each method has been proven to out-perform its predecessor; there are still uses for each method. SBGM allows the T1DM patient to accurately monitor their blood glucose concentration at any given moment with a simple fingerstick and a small sample of blood. In a discussion with Barb West, RN-CDE, I learned that SBGM is relatively inexpensive and is easy to use for almost any person, with an average monthly cost of ~\$18 for test strips, ~\$2 for 100ct box of lancets that can be changed weekly (this is a patient preference measure, however) and around \$15-20 for a meter. It is also important to note that these costs are with insurance.

CGM allows the patient to be able to monitor their blood glucose levels at any moment, but also analyze the trends that are saved on the machine to help direct their disease management course without having to keep a paper diary with blood glucose concentrations. CGM allows the patient to be able to accurately manage their T1DM with fewer fingersticks, and this is a device that has one site with one needle that is inserted in the subcutaneous tissue. Insulin pumps allow the patient to have less injections as compared to insulin vials with needles. CGM with CSII will provide the patients with one system to be able to manage their disease, while requiring them to do minor things for the unit to work effectively. These include actions like being able to accurately count carbs, being able to manually bolus for food and increase in blood glucose, so the machines can provide adequate basal insulin doses.

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The DCCT and EDIC trials performed by Nathan, et al. (2013) set the stage for today's common practices when dealing with T1DM patients and their medical management. The trials proved that when T1DM patients utilize a combination of at least three injections of insulin per day or treatment with continuous subcutaneous insulin infusion (CSII) that included dose adjustment guided by four or more SBGM tests per day, meal size and content, and anticipated exercise and specific glycemic targets, they could significantly reduce their long-term risk of adverse events. The DCCT performed by Nathan, et al. (2013) demonstrated a drop of nearly ~2.5% in HgbA1C and a slowed rate of loss in C-peptide responsiveness in Beta cell preservation. The EDIC performed by Nathan, et al. (2013) demonstrated the need for earlier intervention in T1DM by showing that it can reduce severe renal impairment by ~50%, risk of primary CVD outcomes by 42%, and nonfatal MI or stroke by 58%.

### **What are the challenges of these management methods and how will they affect their actual use effectiveness?**

Clinicians must consider the needs of every patient that they manage. With insulin administration being the mainstay of T1DM care, we must consider if the patient can understand the methods needed to be able to effectively manage their disease, and provide them with the means to do so. It is important for patients to have a good support structure to deal with the demands of insulin management. SBGM and injectable insulin therapy is a cost-effective alternative for patients that wish to manage their disease in this manner, however monitoring blood glucose levels should be performed at a frequency of four times per day to provide adequate disease monitoring and management. Along with the four needlesticks that are preferred for management, the patient must administer insulin which may account for as many as four or more injections per day as well.

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CGM therapy with insulin injections still need to be calibrated two-four times per day via fingersticks to keep the CGM running. It is also a disadvantage that CGM devices have a physiological lag due to subcutaneous monitoring vs the capillary monitoring provided by SBGM. Once the blood glucose reading is confirmed by SBGM, the patient will need to then administer an insulin injection; or if the patient has an insulin pump- they can input the data so that the pump can provide an adequate insulin dose for the SBGM reading. As outlined by McCulloch (2017) CGM devices can cost roughly ~\$1000 to \$4000, so it is important to note that clinicians will likely need to consider associated costs and insurance coverage for each specific patient, along with their education and level of understanding to be able to use the device effectively.

Closed-loop therapy incorporates a CGM with CSII and a complicated algorithm to predict needed basal insulin doses. Due to these devices being relatively new, the cost is quite high, and their long-term effectiveness is hard to adequately assess because of the limited data available regarding their use. These units still require that the patient count and input carb values at meal times to provide accurate insulin dosing. Furthermore, the ADA recommends that CSII be used primarily for well-educated and motivated patients who are unable to achieve optimal glycemic control with MDII. Some of the other limitations include: pump failure, infection at insertion site and dermatologic changes at insertion sites.

**Will closed-loop insulin pumps provide better efficacy by monitoring glycemic control according to patient's blood glucose levels and HgbA1C and decrease the incidence of hypoglycemic events, as compared to the current standard treatment of insulin pump therapy in patients with T1DM?**

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Clinicians should strive to develop a safe mode of insulin delivery that most closely mimics physiologic insulin delivery, optimizes HgbA1C, and decreases hypo- and hyperglycemic events. Closed-loop insulin delivery systems have proven themselves to have better efficacy in providing glycemic control. An article by Devries (2017) reports results from a trial that compared day and night closed-loop therapy, but had smaller patient samples and short duration times. Even with the short duration and small sample; the group in which the closed-loop system was used demonstrated being in their target glucose concentration 76.2% (SD 6.4) of the time vs the usual therapy group only being in target range 65.6% (SD 8.1) of the time. This result showed that the subjects using closed-loop therapy increased the proportion of time spent in target glucose concentration by 10.5% (7.6-13.4,  $p < 0.001$ ). With larger, longer trials underway, it is hopeful that clinicians can expect even better results and be able to apply them with confidence, based on the results from the smaller trials.

A meta-analysis published by Battelino, Omladic, and Phillip (2015) that included results from 22 different studies from data collected from 518 patients also provided hopeful results for closed-loop systems vs sensor augmented insulin pumps. Out of the 22 studies outlined, only three RCTs demonstrated no significant difference -- with two of the three trials showing increased time in target glucose concentration range; but just not a significant one. The results show that of the 22 trials studied, 16 demonstrated a significantly less time spent in hypoglycemia. The data available to clinicians now suggest that use of closed-loop systems in the management of T1DM is safe and efficient, and have the possibility to significantly decrease the risk of hypoglycemia and increase the time spent in the target glycemic range. It is hopeful that the closed-loop systems will alleviate the burden of managing T1DM.

### APPLICABILITY TO CLINICAL PRACTICE

Closed-loop insulin pumps are effective in lowering HgbA1C and blood glucose readings decreasing the number of hypoglycemic episodes when compared to current standard treatment of insulin pump therapy in patients with T1DM. By decreasing hypoglycemic incidents, we can lower the healthcare cost burden on our patients and our healthcare systems, by reducing the time that T1DM patients need hospitalization. However, the newer closed-loop systems are more expensive than current standard therapy, and represent their own unique challenges. Closed-loop systems are well suited for a variety of patients that may include: patients that are having a hard time controlling their blood glucose levels and HgbA1C even with following clinicians' orders, and patients with hypoglycemia unawareness. Patients need to be motivated to use these systems correctly and safely, and although there are no major differences between which rapid-acting insulin is used in a pump, the delivery method is an important aspect to think about when considering what is best for our patients.

When patients cannot control their blood glucose, they subject themselves to more fingersticks or blood draws to monitor those levels, this burdens them; not only with the pain of the associated needles, but by having to take the extra time and cost to do so as well. This may also put them at a higher risk of having a hypo-or hyperglycemic event that may require hospitalization. Closed-loop systems provide a way for patients to be able to control their disease more efficiently. However, they will need to be able to account for the carbs that they will intake throughout the day, also they need to be able to count carbs effectively and need to know how to enter them into the system correctly as well. This can be an attractive option for T1DM patients that do not want to have to “fuss” over things related to their diabetes care. This may seem like a



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simple solution to T1DM management, but it can be quite a daunting task to be able to perform all these actions correctly, so that the patient will receive the best disease management possible.

Although the methods available for T1DM management have all been proven clinically effective; they still have positive and negative attributes associated with each aspect. We, as clinicians must consider our patient's lifestyle, education level, cognition, desire for disease control, and socioeconomic status to adequately make a choice for their T1DM management regimen. Closed-loop systems are the more expensive options for initiation. Although limited long-term data has shown a significant decrease in hypoglycemic events and a significant increase in target blood glucose range, this translates to more time spent out of the hospital and decreased healthcare related costs as well. Lifelong T1DM management requires multiple insulin injections per day and as many as four fingersticks per day which can leave a lot of room for user error or neglect.

Closed-loop systems have proven themselves effective; and can lessen disease burden on the patient's lifestyle. They are appropriate to prescribe for use in patients that can manage them efficiently and are motivated to do so. Closed-loop systems should be strongly considered as a long-term management method in patients with T1DM.

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## Appendix

**Table 1**

*Common Risk Factors for Diabetic Complications*

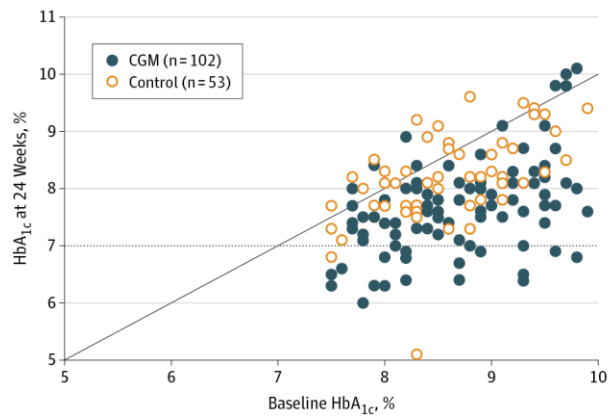
*2011-2014, US adults >18 years of age with diagnosed diabetes, [95% CI]*

<b>Smoking</b>	15.9% were current smokers and 34.5% had quit smoking but had a history of smoking at least 100 cigarettes in their lifetime.
<b>BMI</b>	87.5% were overweight or obese, defined as a BMI of 25 or greater; 26.1% having a BMI of 25-30, 43.5% having a BMI of 30-40, and 17.8% with a BMI of 40 or higher.
<b>Physical Inactivity</b>	40.8% of adults got less than 10 minutes/week of moderate to vigorous activity in either work, leisure, or transportation.
<b>Hypertension</b>	73.6% had systolic BP of 140mmHg or higher and diastolic BP of 90mmHg or higher, or they were already on BP controlling medications.
<b>High Cholesterol</b>	58.2% over age 21 with no self-reported CV disease who were eligible for statin therapy and were on a lipid-lowering medication. 66.9% over age 21 with self-reported CV disease who were eligible for statin therapy and were on a lipid-lowering medication.
<b>Hyperglycemia</b>	15.6% of adults had a HgbA1C value higher than 9%.

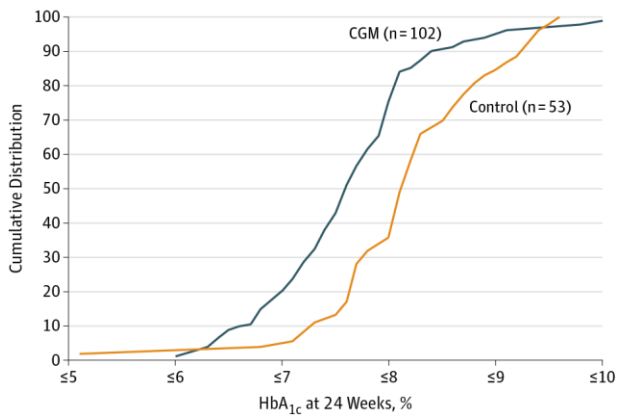
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**Table 2**

**A** HbA<sub>1c</sub> at baseline and 24 weeks



**B** Cumulative distribution of HbA<sub>1c</sub> at 24 weeks



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Table 3

Overview of Randomized Controlled Trials on Use of Closed loop in type 1 diabetes by years (CL – closed loop; SAP – sensor augmented pump; any insulin pump coupled with any sensor for continuous glucose monitoring).

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2011	Murphy [54]	12	32.9	48 h	CL vs SAP	Time in target glycaemic range; time in hypoglycaemia	81% vs 81% ( $p = 0.75$ ); 0.0 vs 0.03 ( $p = 0.04$ )
2012	Breton [41]	38	41 (adults), 14.5 (adolescent)	22 h	CL vs SAP	Time in near normoglycaemia, time in tight glycaemic range, time in hypoglycaemia	12.9% ( $p = 0.01$ ), –2.5% ( $p = 0.66$ ), –2.7 ( $p = 0.01$ )
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2013	Elleri [38]	12	15.0	36 h	CL vs SAP	Time in target glycaemic range, mean plasma glucose level	35% ( $p = 0.02$ ), –37 mg/dl ( $p = 0.02$ )
2013	Sherr [37]	12	16.8	96 h	CL vs SAP	Night hypoglycaemia, time in target glycaemic range	–2.5% (sedentary), –6% (exercise) ( $p = 0.04$ ), 30% (sedentary), 14% (exercise) ( $p < 0.0001$ )
2013	Schmidt [42]	6	45	2 nights	CL vs SAP	Time in target glycaemic range, mean glucose, hypoglycaemic events	12.5% ( $p = 0.08$ ), 18 mg/dl ( $p = 0.38$ ), –3.7% ( $p = 0.22$ )
2013	Philip [39]	56	13.8	2 nights	CL vs SAP	Number of hypoglycaemic events, time spent in hypoglycaemia, mean overnight glucose level, time in target range	–15 ( $p = 0.003$ ), 0 ( $p = 0.02$ ), –14 mg/dl, 1.4 ( $p < 0.05$ )
2013	Nimri [47]	15	19	8 nights	CL vs SAP		
2013	Luijf [48]	48	41.5	72 h	CL vs SAP	Time in hypoglycaemia, percentage of nights with mean glucose in target range	–44.9 min ( $p = 0.0034$ ), 17% ( $p = 0.5692$ )
2013	Dauber [36]	10	5.1	2 nights	CL vs SAP	Time in target glycaemic range, mean glucose level, time in hypoglycaemia	–5.3% ( $p = 0.377$ ), –4.3% ( $p = 0.001$ ), 18 mg/dl ( $p = 0.001$ )
2014	Capel [43]	10	46.7	2 nights	CL vs SAP	Time in target glycaemic range, time in hypoglycaemia	2.1 h ( $p = 0.12$ ), –0.04 h ( $p = 0.86$ )
2014	Hovorka [46]	16	/	6 weeks	CL vs SAP	Time in target glycaemic range, time in hypoglycaemia	29.5% ( $p < 0.05$ ), –4.2% ( $p < 0.05$ )
2014	Kovatchev [49]	20	/	80 h	CL vs SAP	Time in target glycaemic range, mean overnight glucose, time in hypoglycaemia	15% ( $p < 0.001$ ), –14 mg/dl ( $p < 0.001$ ), –7% ( $p < 0.01$ )
2014	Leelarathna [50]	17	34	16 days	CL vs SAP	Time in target glycaemic range, LGBI, hypoglycaemic events, mean BG, time in hypoglycaemia	–4.6% ( $p > 0.1$ ), 0.64 ( $p = 0.003$ ), 1.2 ( $p < 0.02$ ), 9 mg/dl ( $p < 0.04$ ), –0.55% ( $p > 0.1$ )
2014	Ly [35]	20	/	106 nights	CL vs SAP	Time in target range, mean BG, time spent in hypoglycaemia	13% ( $p = 0.005$ ), –12.6 mg/dl ( $p = 0.027$ ), –1.3% ( $p = 0.339$ )
2014	Nimri [44]	24	28.6	2 nights	CL vs SAP	Time in target glycaemic range	7% ( $p = 0.233$ )
2014	Oron [34]	37	12.4	2 weeks	CL vs SAP	Nocturnal hypoglycaemia episodes, time in target range	–2.13% ( $p = 0.02$ ), 10.95% ( $p = 0.003$ )
2014	Russell [51]	52	40 (adults), 16 (adolescents)	5 days	Bihormonal CL vs SAP	Mean plasma glucose level; time in hypoglycaemia	–2.8% ( $p = 0.443$ ), 4.8% ( $p = 0.207$ ) –26 mg/dl (adults, $p < 0.001$ ), –16 mg/dl (adolescent, $p = 0.004$ ); –3.2% (adults, $p = 0.01$ ), –1.8% (adolescents, $p = 0.05$ )
2014	Thabit [45]	25	43	11–12 weeks	CL vs SAP	Time in target glycaemic range	6.4% ( $p = 0.0016$ )

CL, closed loop; SAP, sensor augmented insulin pump.