DEFINING SUCCESS: REEVALUATING DISEASE MANAGEMENT METRICS IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES

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A thesis submitted to Johns Hopkins University in conformity with the requirements for

the degree of Master of Science in Research Administration

Baltimore, Maryland
April 2020

Abstract

Despite advancements in diabetes devices and management technologies, pediatric patients with type 1 diabetes (T1D) are still struggling to meet standards for glycemic goals. With the inability to appropriately control glucose levels, studies have shown that there are definite increases in diabetes-related complications and potentially life-threatening consequences. Currently, diabetes success is measured by having a hemoglobin A1c (HbA1c) value that is less than or equal to the national target of 7.5%. Recognizing that a disappointing percentage of patients are actually meeting these glycemic targets, researchers have attempted to narrow the gap between patients achieving and not achieving metabolic control. While it has been suggested that the glycemic profile is not being evaluated in its entirety, this thesis project examined the need to integrate other metrics when evaluating a patient's actual degree of glycemic control and resultant diabetes success.

The project focus was directed to time in range values, rather than HbA1c levels, as a defining outcome of glycemic control. Data was collected on pediatric patients with type 1 diabetes who were using continuous glucose monitoring (CGM). Parameters such as HbA1c levels, time in range, average sensor glucose, scored levels of compliance to six specific self-management behaviors, along with basic demographic information were included in the final data set. The primary relationship between the effect adherence to six self-management habits had on time in range values was closely analyzed.

A final sample size of 654 T1D pediatric patients using CGM were included for review. Results from regression analyses indicated that patients who performed the self-management habits were more likely to have higher time in range values. As patients increased their adherence to the six habits by performing more than one behavior, time in range values also

increased. In spite of the promising relationship identified between these two variables, still only 18.8% of the CGM cohort met the current goals for time in range (≥60%). In the same cohort, only 32.9% of patients met the standard HbA1c target. Disproportionate access to CGM may play a role in the statistical findings of this cohort with regard to meeting glycemic targets, as time in range is most easily retrieved from CGM devices when evaluating metabolic control.

Discovering a correlation between time in range and self-management habits is only one of many steps to reevaluate how diabetes success is defined. Combining time in range information with current HbA1c testing could facilitate the development of more realistic management plans for patients with type 1 diabetes. Introducing the importance of time in range and its positive associations with reduced disease-related complications and improved glycemic control is vital to initiate a more encompassing review of diabetes success. Future research is still needed to further investigate the relationship between time in range and compliance with self-management behaviors in a larger population of patients with type 1 diabetes. Having scientific data to support other metrics and methods to aid in disease management could offer patients with type 1 diabetes a new hope for success.

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Abbreviations

A1c	*Hemoglobin A1c*
ADA	*American Diabetes Association*
BGMF	*Blood Glucose Monitoring Frequency*
CDE	*Certified Diabetes Educator*
CGM	*Continuous Glucose Monitoring*
HCL	*Hybrid Closed-Loop*
JHU	*Johns Hopkins University*
PHI	*Protected Health Information*
QI	*Quality Improvement*
SMBG	*Self-Monitoring of Blood Glucose*
T1D	*Type 1 Diabetes*
TIR	*Time in Range*
UM	*University of Michigan*

Glossary

Blood Glucose Monitoring Frequency: at-home testing of blood glucose levels to monitor for and prevent asymptomatic hypoglycemia.

Capillary glucose: concentration of glucose in the blood.

Continuous Glucose Monitoring: advanced way for people living with diabetes to check glucose readings in real-time or monitor glucose readings over a period of time using a device.

Glucose Counterregulation: the sum of processes that protect against development of hypoglycemia and that restore normal glycemia if hypoglycemia should occur

Glucose Variation (GV): the acute excursions of glucose around a mean value

HCL: also known as the artificial pancreas, the hybrid closed-loop system combines a continuous glucose monitor and an insulin pump to regulate a user's insulin with minimal interaction required from the patient.

Hemoglobin A1c (HbA1c): a form of hemoglobin (a blood pigment that carries oxygen) that is bound to glucose.

Hyperglycemia: a condition caused by a very high level of blood sugar (glucose)

Hypoglycemia: a condition caused by a very low level of blood sugar (glucose)

Interstitial glucose: glucose measured from the fluid that surrounds the cells of tissue below the skin.

SMBG: an approach whereby people with diabetes measure their blood sugar themselves using a glucose meter.

Time in range (TIR): the percentage of time that a person spends with their blood glucose levels in a target range.

Chapter 1. Introduction

1.1 Background

Type 1 diabetes (T1D) is an autoimmune disorder in which the pancreas produces little or no insulin.[1] "It is generally thought to be precipitated by an immune-associate, if not directly immune-mediated, destruction of the insulin-producing pancreatic beta cells resulting in the presence of autoantibodies." [2] This means that in patients with type 1 diabetes, the immune system, which normally fights infection, attacks and destroys the cells in the pancreas that are responsible for making insulin. Insulin is a hormone necessary to convert food into energy that fuels the body. Without insulin, other organs in the body struggle to function properly, which leads to serious complications.[3] This decrease in available insulin causes blood sugar levels to rise. As a result, people with T1D need to take insulin every day in order to stay alive. The exact cause of this chronic condition is unknown, but it is believed that several factors may contribute to the onset of disease. Genetics and exposure to viruses and other environmental elements that may trigger the body's immune response are possible causes.

The American Diabetes Association (ADA) reports that an average of 1.5 million people are diagnosed with diabetes every year; 5% of which have type 1 diabetes.[4,5] The risk to develop

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[1] National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). (2017). Type 1 Diabetes. Retrieved from https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-1-diabetes#diagnose

[2] Bluestone, J. A., Herold, K., & Eisenbarth, G. (2010). Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature, 464, 1293-1300. doi:10.1038/nature08933

[3] American Diabetes Association. (2019, June 10). Access to Continuous Glucose Monitors in Pediatric Diabetes Populations Improves Glycemic Control, Reduces Hypoglycemia and Improves Satisfaction with Diabetes Care and Technology Use. San Francisco, CA, USA. Retrieved from https://www.diabetes.org/newsroom/press-releases/2019/access-to-continuous-glucose

[4] Diabetes Research Institute Foundation. (2020). What is Diabetes? Retrieved from https://www.diabetesresearch.org/what-is-diabetes

[5] American Diabetes Association. (2020). Statistics About Diabetes. Retrieved from https://www.diabetes.org/resources/statistics/statistics-about-diabetes

type 1 diabetes for people in the general population is about 1 in 300. For those who have a family member with T1D, the risk increases to 1 in 20, or 15 times greater than that of the general population.[6] Common symptoms of type 1 diabetes include increased thirst, increased urination, extreme hunger, blurred vision, weakness, fatigue, rapid and unexplained weight loss, unusual irritability, nausea, vomiting, abdominal pain, unpleasant breath odor, and itchy skin.[6]

The primary treatment for patients with types 1 diabetes is insulin therapy. The ADA recommends that pediatric patients with T1D should be treated with intensive insulin therapy and should self-monitor blood glucose (SMBG) levels multiple times a day.[7] While the ADA does not provide a concrete number of times one should check blood sugars daily, they do recognize and emphasize the fact that SMBG is crucial in T1D control. Despite these management recommendations, treatment challenges continue to center around knowing how much or how little insulin to administer to correct blood sugars that are outside of a normal range. While there are methods to make educated calculations based on information utilizing carbohydrate ratios, the body's varying response to physiological changes can still make accurately dosing insulin a guessing game.

Complications resulting from uncontrolled diabetes will vary depending on the type of glucose excursions. Extended periods of elevated blood glucose levels, known as hyperglycemia, result in long-term complications and can be life-threatening. Consistently high blood glucose levels can lead to other health problems such as heart disease, stroke, kidney failure, dental

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[6] Type 1 Diabetes TrialNet. (2020). T1D Facts. Retrieved from https://www.trialnet.org/t1d-facts

[7] American Diabetes Association. (2018). Children and Adolescents. Sec. 12. In Standards of Medical Care in Diabetes. Diabetes Care, 41(Supplement 1), S126-S136. doi:10.2337/dc18-S012

diseases, nerve damage, depression, sleep apnea, and vision problems.[8] If high levels of blood glucose are left untreated, there can be further damage to the eyes, kidneys, nerves, heart, which can lead to coma and death.[9] Low levels of blood glucose, or hypoglycemia, can result in other serious conditions and can also quickly become life-threatening. Hypoglycemia can result in many clinically relevant occurrences such as an increased risk of subsequent severe hypoglycemia, defective glucose counterregulation/impaired hypoglycemia awareness, impairment in cognitive function, increase in cardiac arrhythmias, reduced work productivity, and impacts on sleep and quality of life.[10,11,12,13,14,15] For these reasons alone, uncontrolled diabetes is not a viable option.

The current clinical guideline to determine if a pediatric patient is in control of their

[8] National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). (2017). Type 1 Diabetes. Retrieved from https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-1-diabetes#diagnose

[9] If high levels of blood glucose are left untreated, there can be damage to the eyes, kidneys, nerves, and the heart, and can also lead to coma and death.

[10] Brod, M., Christensen, T., Thomsen, T. L., & Bushnell, D. M. (2011). The Impact of Non-Severe Hypoglycemic Events on Work Productivity and Diabetes Management. Value in Health, 14(5), 665-671. doi:10.1016/j.jval.2011.02.001

[11] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. (2011). Factors Predictive of Severe Hypoglycemia in Type 1 Diabetes. Diabetes Care, 34, 586-590. doi:10.2337/dc10-1111

[12] Brod, M., Pohlman, B., Wolden, M., & Christensen, T. (2013). Non-severe nocturnal hypoglycemic events: experience and impacts on patient functioning and well-being. Quality of Life Research, 22, 997-1004. doi:10.1007/s11136-012-0234-3

[13] Seaquist, E. R., Anderson, J., Childs, B., Cryer, P., Dagogo-Jack, S., Fish, L., . . . Vigersky, R. (2013). Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. The Journal of Clinical Endocrinology & Metabolism, 98(5), 1845–1859. doi:10.1210/jc.2012-4127

[14] International Hypoglycaemia Study Group. (2017). Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, 40(1), 155-157. doi:10.2337/dc16-2215

[15] Fawdry, R. A., Novodvorsky, P., Bernjak, A., Chow, E., Iqbal, A., Sellors, L., . . . Heller, S. R. (2017). Diurnal Differences in Risk of Cardiac Arrhythmias During Spontaneous Hypoglycemia in Young People With Type 1 Diabetes. Diabetes Care, 40(5), 655-662. doi:10.2337/dc16-2177

diabetes, set by the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes, is maintenance of a hemoglobin A1C (HbA1c) value less than 7.5%.[16] Most children with type 1 diabetes have HbA1c values well above target levels. There appears to be increasing support in declaring that glycemic goals may not be universal and that goals customized to each case may be more appropriate. "In those individuals with diabetes who are at risk for iatrogenic hypoglycemia because of treatment with insulin or other glucose lowering medications, a reasonable glycemic goal should be the lowest HbA1c that does not cause severe hypoglycemia at any given stage in the evolution of the individual's diabetes".[17] A range of acceptable HbA1c values, rather than one specified value, may be a better approach to using HbA1c as a metric to define diabetes success. Furthermore, there are known limitations to HbA1c testing that may interfere with accurate depictions of the glycemic profile and play a role in defining a patient's level of control of their disease.

Aside from striving to continually meet glycemic targets, patients with type 1 diabetes and their care providers face many challenges related to disease management. Given the complexity of the condition, patients and providers must be mindful of proper nutrition, levels of exercise, dedication to self-monitoring and accurate reporting, continuing education for devices, adherence to management plans, attending regular clinic visits, and the ongoing issues related to insurance coverage and affordability of necessary medications and supplies.[18] "The management

[16] Miller, K. M., Foster, N. C., Beck, R. W., Bergenstal, R. M., DuBose, S. N., DiMeglio, L. A., . . . Tamborlane, W. V. (2015). Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry. Diabetes Care, 38(6), 971-978. doi:10.2337/dc15-0078

[17] Cryer, P. E. (2014). Glycemic Goals in Diabetes: Trade-off Between Glycemic Control and Iatrogenic Hypoglycemia. Diabetes, 63(7), 2188-2195. doi:10.2337/db14-0059

[18] Iyengar, J., Thomas, I. H., & Soleimanpour, S. A. (2019). Transition from pediatric to adult care in emerging adults with type 1 diabetes: a blueprint for effective receivership. Clinical Diabetes and Endocrinology, 5(3), 1-7. doi:10.1186/s40842-019-0078-7

of pediatric type 1 diabetes requires the daily execution of a complex and demanding set of health behaviors, including but not limited to the coordination of the amount and timing of insulin administration with results of blood glucose monitoring, the amount and type of dietary intake, and the frequency and intensity of physical activity."[19] Patients with T1D cannot avoid disease-related complications by using exogenous insulin alone. Because of this, management plans often include the use of devices such as insulin pumps, hybrid closed loop systems (HCL), and other types of glucose meters to aid with optimal metabolic control.[20]

One device system in particular, continuous glucose monitoring (CGM), is able to overcome limitations of traditional blood glucose checks by providing a real-time picture of the glucose profile which grants T1D patients an opportunity to intervene when necessary to make immediate adjustments in order to prevent extreme glycemic events.[21] "CGM measures interstitial glucose (which correlates well with plasma glucose) and includes sophisticated alarms for hypo- and hyperglycemic excursions."[22] The system uses glucose sensors that are inserted subcutaneously with the attached device being worn externally by the patient. CGM allows for constant observations of glycemic events which can provide the opportunity for patients to make treatment adjustments in real-time. This type of monitoring can identify patterns and glucose variability, in addition to providing valuable information on not only current glucose levels but

[19] Vesco, A. T., Anderson, B. J., Laffel, L. M., Dolan, L. M., Ingerski, L. M., & Hood, K. K. (2010). Responsibility Sharing between Adolescents with Type 1 Diabetes and Their Caregivers: Importance of Adolescent Perceptions on Diabetes Management and Control. Journal of Pediatric Psychology, 35(10), 1168–1177. doi:10.1093/jpepsy/jsq038

[20] Aatkinson, M., Seisenbarth, G., & Wmichels, A. (2014). Type 1 diabetes. The Lancet, 383(9911), 69-82. doi:10.1016/S0140-6736(13)60591-7

[21] Alarcon-Casas Wright, L., & Hirsch, I. B. (2017). Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapeutics, 19(Supplement 2), S16-S26. doi:10.1089/dia.2017.0029

[22] American Diabetes Association. (2017). Glycemic targets. Sec. 6. In Standards of Medical Care. Diabetes Care, 40(Supplement 1), S48-S56. doi:10.2337/dc17-S009

also rates of change in those levels and associated trends.[23] "CGM profiles provide far more information than just the mean glucose variations. They identify patterns of hyperglycemia and hypoglycemia as well as potentially dangerous high or low glucose concentrations that are often missed with self-monitoring blood glucose (SMBG) checks."[24] Studies have shown that CGM systems can decrease the amount of time spent in hypoglycemia stages and lower HbA1c levels, and are considered to be very effective devices to regulate glucose levels, as long as patients are willing to wear them and maintain them properly.[25]

In 2017, roughly 11% of the type 1 diabetes community were using CGMs, but the rate is still slowly increasing.[26] CGM is becoming more popular because of the system's ability to rapidly aid in decision making regarding insulin dosing. Another added benefit is the utilization of convenient alarm features that provide early warning of abnormal glucose levels which helps limit the potential for more severe glycemic events. More recently, CGM has been advantageous to new clinical uses to close loops between insulin pumps. "CGM profiles provide opportunities to develop measures of glycemic control that provide clinically beneficial information beyond that provided by a HbA1c value and periodic self-testing of capillary glucose."[27] Such metrics

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[23] Battelino, T., Danne, T., Bergenstal, R. M., Amiel, S. A., Beck, R., Biester, T., . . . Phillip, M. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. doi:10.2337/dci19-0028

[24] Beck, R. W., Connor, C. G., Mullen, D. M., Wesley, D. M., & Bergenstal, R. M. (2017). The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care, 40(8), 994-999. doi:10.2337/dc17-0636

[25] Aatkinson, M., Seisenbarth, G., & Wmichels, A. (2014). Type 1 diabetes. The Lancet, 383(9911), 69-82. doi:10.1016/S0140-6736(13)60591-7

[26] Agiostratidou, G., Anhalt, H., Ball, D., Blonde, L., Gourgari, E., Harriman, K. N., . . . Weinzimer, S. A. (2017). Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endo. Diabetes Care, 40(12), 1622-1630. doi:10.2337/dc17-1624

[27] Riddle, M. C., Gerstein, H. C., & Cefalu, W. T. (2017). Maturation of CGM and Glycemic Measurements Beyond HbA1c—A Turning Point in Research and Clinical Decisions. Diabetes Care, 40(12), 1611-1613.

are glucose exposure, glucose variation (GV), standard deviation (SD) round mean glucose, and time in range (TIR). CGMs are ideal and more accurate for reporting time in range because they collect constant measurements (usually every five minutes) that portray the full picture of precisely how many hours each day are spent within target glycemic ranges.[28] Ideally, CGM data is collected for "at least 14 days immediately preceding the measurement of HbA1c during a period when diabetes treatment and glycemic control are reasonably stable."[29]

1.2 Statement of the Problem

Because patients with diabetes are not meeting their glycemic goals, attention is being redirected to the use of quality improvement (QI) methods for not only improving clinical care but also patient outcomes. Previous research conducted using data from registries has shown that compliance with self-management habits aids in improving glycemic outcomes. This thesis project aims to transition a similar type of attention to a clinical setting. As diabetes treatment technologies advance, more information related to glucose metrics is becoming available. It is clear that HbA1c testing as a means to evaluate diabetes control may not be as widely accepted anymore, as there are limitations to the test itself that may not fully reflect a patient's typical glucose profile. One of the most concerning limitations of HbA1c measurements is the inability for the test to detect low blood glucose levels.[30] Low blood glucose, or hypoglycemia, can result

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doi:10.2337/dci17-0049

[28] diaTribe Foundation. (2020). Time in Range. Retrieved from https://diatribe.org/time-range

[29] Xing, D., Kollman, C., Beck, R. W., Tamborlane, W. V., Laffel, L., Buckingham, B. A., . . . Ruedy, K. J. (2011). Optimal Sampling Intervals to Assess Long-Term Glycemic Control Using Continuous Glucose Monitoring. Diabetes Technology & Therapeutics, 13(3), 351-358. doi:10.1089/dia.2010.0156

[30] Runge, A. S., Kennedy, L., Brown, A. S., Dove, A., Levine, B. J., Koontz, S., . . . Wood, R. (2018). Does Time-in-Range Matter? Perspectives From People With Diabetes on the Success of Current Therapies and the Drivers of Improved Outcomes. Clinical Diabetes, 36(2), 112-119. doi:10.2337/cd17-0094

in many clinically relevant occurrences and have a negative impact on one's quality of life. Given the limitations of HbA1c testing, other diabetes metrics should be considered when defining optimal glucose control for pediatric patients with type 1 diabetes.

One such metric coming to the forefront of gauging successful diabetes is time in range (TIR). TIR is the percentage of time that a person spends with their blood glucose levels in a specified target range. TIR more accurately presents profiles for individuals who have blood glucose levels rarely outside of their defined thresholds. Patients who have glucose levels more in range are less likely to experience short-term or long-term health effects than those who have more frequent blood glucose excursions.[31] A more accurate review of glucose profiles will allow clinicians to make appropriate adjustments in the diabetes management plan resulting in better glycemic control and quality of life for patients suffering from type 1 diabetes. Research is needed to evaluate relationships between TIR and compliance with self-management habits to ensure that the associations between TIR and self-management behaviors are similar enough to HbA1c and self-management behaviors for comparative outcomes of diabetes success.

1.3 Research Question

Studies have demonstrated that self-management habits such as frequent self-monitoring of blood glucose, using devices such as continuous glucose monitoring and insulin pumps, frequent insulin bolusing, and reviewing diabetes data are associated with improved glycemic

[31] Agiostratidou, G., Anhalt, H., Ball, D., Blonde, L., Gourgari, E., Harriman, K. N., . . . Weinzimer, S. A. (2017). Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endo. Diabetes Care, 40(12), 1622-1630. doi:10.2337/dc17-1624

outcomes.[32,33,34,35] As more attention within the diabetes community becomes focused on discovering better metrics for defining successful diabetes management, the concentration for this thesis project resided in investigating a more elementary question to that argument: *In pediatric patients with type 1 diabetes who use a continuous glucose monitor, is there a relationship between adherence to self-management behaviors and attaining time in range targets?*

1.4 Research Objectives

The objective of this study was to evaluate the relationship of six specific self-management habits performed by people with type 1 diabetes and to assess the association with optimal glycemic outcomes as measured by time in range values. The primary outcome was initially to identify a positive relationship between time in range values and several key adherence behaviors which would be used to suggest that TIR is another glycemic metric that should be more seriously considered when evaluating the status of a patient's level of metabolic control.

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[32] Rausch, J. R., Hood, K. K., Delamater, A., Pendley, J. S., Rohan, J. M., Reeves, G., . . . Drotar, D. (2012). Changes in Treatment Adherence and Glycemic Control During the Transition to Adolescence in Type 1 Diabetes. Diabetes Care, 35, 1219-1224.

[33] McNally, K., Rohan, J., Shroff Pendley, J., Delamater, A., & Drotar, D. (2010). Executive Functioning, Treatment Adherence, and Glycemic Control in Children With Type 1 Diabetes. Diabetes Care, 33(6), 1159-1162. doi:10.2337/dc09-2116

[34] Hilliard, M. E., Wu, Y. P., Rausch, J., Dolan, L. M., & Hood, K. K. (2013). Predictors of Deteriorations in Diabetes Management and Control in Adolescents With Type 1 Diabetes. Journal of Adolescent Health, 52(1), 28-34. doi:10.1016/j.jadohealth.2012.05.009

[35] Ziegler, R., Heidtmann, B., Hilgard, D., Hofer, S., Rosenbauer, J., & Holl, R. (2011). Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatric Diabetes, 12(1), 11-17. doi:10.1111/j.1399-5448.2010.00650.x

1.5 Significance

If time in range proves to be a valid measure of glycemic control, recommendations could be made to modify the types of data collected from patients with diabetes. For instance, rather than basing management decisions solely on HbA1c data, patients and providers could efficiently review time in range and other metrics available from diabetes devices to more accurately make adjustments to treatment and behavior regimens. To take things one step further, one might even go as far to imply that time in range not only be used as a complementary method to HbA1c when evaluating diabetes control, but rather that it should be used as a primary metric for assessing diabetes success. The way in which glycemic profiles are presented and reviewed by patients and their care teams could be impacted if data supports expanding the metrics used to evaluate success with diabetes management.

Chapter 2. Literature Review

2.1 Overview

Online searches for publications via PubMed and Google Scholar through access provided by the University of Michigan was the principal method utilized for the literature review. Both databases house millions of scholarly sources for biomedical texts. Primary searches involved key words such as type 1 diabetes, time in range, metrics, hemoglobin HbA1c, glycemic control, glycemic targets, and continuous glucose monitors. Information was gathered from sources that reviewed any combination of the main search criteria. Results were restricted to articles published within the last ten years. Studies that reported relationships between diabetes metrics, glycemic targets, management behaviors, and/or limitations to current metrics and testing were included for review. Additional searches were performed from reference lists when appropriate. Less structured searches related to general diabetes knowledge were also performed.

In general, the literature highlighted five major topics concerning glycemic control in pediatric patients with type 1 diabetes. Self-management habits and the use of diabetes devices, HbA1c and its limitations, benefits of incorporating time in range, relationships between various behaviors and glycemic metrics, and issues surrounding the inability to meet standardized glycemic targets were among the discussions. With this final factor highlighting concerns among clinicians and researchers that comprehensive glycemic profiles should be considered rather than snapshots of a T1D patient's spectrum, it seemed fitting for this project to investigate the potential of introducing new metrics for evaluating a patient's level of glucose control and successful disease management.

2.2 Details of Review

Diabetes is known to be a chronic and potentially disabling disorder that represents a major clinical and public health concern. Constantly attempting to regulate blood glucose levels in order to prevent serious complications is critical to patients with type 1 diabetes. Research has shown that there are ways for patients to actively participate in the daily management of their diabetes by performing several behavioral habits. The American Diabetes Association's recommendation of at least four blood glucose checks daily is supported by Hillard's findings that patients who met their glycemic targets completed 1-2 more glucose checks per day than patients who were out of target ranges.[36] Blood glucose checks often consist of a finger poke, which provides a small sample of blood that can be tested using at-home glucometers. "The frequency of blood glucose monitoring, which is readily available information to clinicians, offers a powerful tool for targeted management of type 1 diabetes, especially when combined with data concerning recent trajectories of glycemic control".[37]

Adherence to this portion of a treatment plan can be affected by a variety of factors, such as an individual's social situation, access to resources, levels of stress or diabetes-related distress, etc. Non-adherence with self-monitored blood glucose checking often occurs by way of the reduced frequency of checks or misreporting blood glucose values, either verbally or via logbooks submitted to care teams.[38] Misreporting of self-monitored blood glucose (SMBG) often

[36] Hilliard, M. E., Wu, Y. P., Rausch, J., Dolan, L. M., & Hood, K. K. (2013). Predictors of Deteriorations in Diabetes Management and Control in Adolescents With Type 1 Diabetes. Journal of Adolescent Health, 52(1), 28-34. doi:10.1016/j.jadohealth.2012.05.009

[37] Rausch, J. R., Hood, K. K., Delamater, A., Pendley, J. S., Rohan, J. M., Reeves, G., . . . Drotar, D. (2012). Changes in Treatment Adherence and Glycemic Control During the Transition to Adolescence in Type 1 Diabetes. Diabetes Care, 35, 1219-1224.

[38] Blackwell, M., & Wheeler, B. J. (2017). Clinical review: the misreporting of logbook, download, and verbal self-measured blood glucose in adults and children with type I diabetes. Acta Diabetol, 54(1), 1-8. doi:10.1007/s00592-016-0907-4

occurs to present a more favorable management profile. Studies have shown that 75% of patients misreport their blood glucose levels by documenting lower values than actually recorded by the glucometer.[39]

Not only do T1D patients have to perform SMBG, they also need to respond to the displayed results accordingly. It has been reported that patients with T1D who check blood glucose levels at least once per day do not always make adjustments to their management habits when levels are extremely high or too low.[40] Patients need to be educated in knowing when to intervene and what action is most appropriate depending in the reading from their glucometer.

Although there is substantial support presented by Rausch and colleagues for blood glucose monitoring frequency (BGMF) being used as an objective measure for treatment adherence in pediatric type 1 diabetes, they go on to propose that BGMF may not fully capture the multidimensional nature of treatment adherence.[41] In an effort to collect more comprehensive data related to treatment adherence, this thesis project focused on six behavioral self-management habits instead of just BGMF alone. Becoming more open to newer trends and updated approaches to manage type 1 diabetes is the first step in making positive changes to achieve glycemic targets.[42] The literature suggested that patients can use CGM information to

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[39] Blackwell, M., & Wheeler, B. J. (2017). Clinical review: the misreporting of logbook, download, and verbal self-measured blood glucose in adults and children with type I diabetes. Acta Diabetol, 54(1), 1-8. doi:10.1007/s00592-016-0907-4

[40] American Diabetes Association. (2017). Glycemic targets. Sec. 6. In Standards of Medical Care. Diabetes Care, 40(Supplement 1), S48-S56. doi:10.2337/dc17-S009

[41] Rausch, J. R., Hood, K. K., Delamater, A., Pendley, J. S., Rohan, J. M., Reeves, G., . . . Drotar, D. (2012). Changes in Treatment Adherence and Glycemic Control During the Transition to Adolescence in Type 1 Diabetes. Diabetes Care, 35, 1219-1224.

[42] Juvenile Diabetes Research Foundation. (2018). Type 1 diabetes management: is HbA1c an out-of-date measure? Retrieved from https://jdrf.org.uk/stories/type-1-diabetes-management-hba1c-date-measure/

better detect patterns and make appropriate adjustments to their treatment plans.[43]

"Continuous glucose monitoring (CGM) is a method of continuously following glucose levels in the interstitial fluid as a basis for improving metabolic control".[44] CGM reported in a standardized way has the potential to help clinicians empower patients and decrease the burden of living with diabetes and its complications.[45] This method of monitoring blood glucose levels is also less cumbersome to the patient since they are not required to perform independent finger checks as often given the CGM's built-in capability of frequent interstitial testing which relays information to other synchronized devices. This constant observation of blood glucose levels allows CGMs to easily determine if an HbA1c value is over-or-underestimating the actual level of glycemic control.[46]

Rates for CGM usage have been steadily increasing. "Use of CGM increased from 7% in 2010–2012 to 30% in 2016–2018, with an exponential increase in use beginning between years 2013 and 2014. Children had a >10-fold increase in CGM use (4%–51% in children <6 years old and 3%–37% in children 6–12 years old)".[47] However, despite its usefulness in managing

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[43] Battelino, T., Danne, T., Bergenstal, R. M., Amiel, S. A., Beck, R., Biester, T., . . . Phillip, M. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. doi:10.2337/dci19-0028

[44] Petrie, J. R., Peters, A. L., Bergenstal, R. M., Holl, R. W., Fleming, G. A., & Heinemann, L. (2017). Improving the Clinical Value and Utility of CGM Systems: Issues and Recommendations. Diabetes Care, 40(12), 1614-1621. doi:10.2337/dci17-0043

[45] Alarcon-Casas Wright, L., & Hirsch, I. B. (2017). Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapeutics, 19(Supplement 2), S16-S26. doi:10.1089/dia.2017.0029

[46] Beck, R. W., Connor, C. G., Mullen, D. M., Wesley, D. M., & Bergenstal, R. M. (2017). The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care, 40(8), 994-999. doi:10.2337/dc17-0636

[47] Foster, N. C., Beck, R. W., Miller, K. M., Clements, M. A., Rickels, M. R., DiMeglio, L. A., . . . Garg, S. K. (2019). State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016–2018. Diabetes Technol Ther, 21(2), 66-72. doi:10.1089/dia.2018.0384

diabetes, research continues to show that CGMs are still widely underused.[48] As with many things, there are limitations to CGM usability. Limitations may include but are not limited to: issues related to technology (calibrations, sensor expiration), user compliance (patients must actually wear the devices, avoidance of skin puncture), safety (skin reactions, devices becoming detached, losing transmitter/receiver), and costs (not covered by all insurance companies, some require prior approval/paperwork, out-of-pocket costs associated with supplies/replacements/repairs).[49] It is important to note that research still needs to be conducted to assess the full range of efficacy of diabetes therapies, like CGM, given the limitations to the availability and usage of certain devices.[50] Until more data is available, hemoglobin A1c (HbA1c) remains the current standard for glycemic control.

Discovered in 1968, hemoglobin A1c was first used for clinical care in the early 1980s.[51] "Hemoglobin A1c became the gold-standard for assessing glycemic management after the landmark Diabetes Control and Complications Trial (DCCT) demonstrated the strong association between HbA1c levels and the risk of chronic diabetic vascular complications. Laboratory methods were soon developed so that HbA1c levels could be readily measured with a reasonable

[48] Alarcon-Casas Wright, L., & Hirsch, I. B. (2017). Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapeutics, 19(Supplement 2), S16-S26. doi:10.1089/dia.2017.0029

[49] Petrie, J. R., Peters, A. L., Bergenstal, R. M., Holl, R. W., Fleming, G. A., & Heinemann, L. (2017). Improving the Clinical Value and Utility of CGM Systems: Issues and Recommendations. Diabetes Care, 40(12), 1614-1621. doi:10.2337/dci17-0043

[50] Aleppo, G., Ruedy, K. J., Riddlesworth, T. D., Kruger, D. F., Peters, A. L., Hirsch, I., . . . Beck, R. W. (2017). REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Well-Controlled Type 1 Diabetes. Diabetes Care, 40(4), 538-545. doi:10.2337/dc16-2482

[51] Hirsch, I. B., Sherr, J. L., & Hood, K. K. (2019). Connecting the Dots: Validation of Time in Range Metrics With Microvascular Outcomes. Diabetes Care, 42(3), 345-348. doi:10.2337/dci18-0040

degree of precision".[52] HbA1c tests measure the amount of glycosylated hemoglobin in the blood which is currently the metric of choice for assessing the efficacy of new diabetes products, guiding health care providers' choice of medications, and supporting regulatory approval and reimbursement policies.[53, 54]

"HbA1C, in the setting of a normal hematological profile and in the non-pregnant population, reflects mean glucose value over the previous 8-12 weeks". [55] There is variation among HbA1c and glucose concentrations and it is likely the result of the variability in the red blood cell life spans.[56] Hence, HbA1c levels can be affected by conditions that affect the life span of red blood cells. For instance, untreated iron deficiencies will yield falsely high HbA1c levels; hemolysis, splenomegaly, and some medications will result in falsely low HbA1c levels. These values are independent of true glycemia. HbA1c can also be affected by stressful events that temporarily lessen glycemic control, which is another concept to consider as this is not reflective of real diabetes control. It has also been recognized that many clinical situations could result in falsely low (and occasionally falsely high) HbA1c levels.[57] Given this knowledge, it

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[52] Beck, R. W., Bergenstal, R. M., Riddlesworth, T. D., Kollman, C., Li, Z., Brown, A. S., & Close, K. L. (2019). Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care, 42(3), 400-405. doi:10.2337/dc18-14

[53] Juvenile Diabetes Research Foundation. (2018). Type 1 diabetes management: is HbA1c an out-of-date measure? Retrieved from https://jdrf.org.uk/stories/type-1-diabetes-management-hba1c-date-measure/

[54] Runge, A. S., Kennedy, L., Brown, A. S., Dove, A., Levine, B. J., Koontz, S., . . . Wood, R. (2018). Does Time-in-Range Matter? Perspectives From People With Diabetes on the Success of Current Therapies and the Drivers of Improved Outcomes. Clinical Diabetes, 36(2), 112-119. doi:10.2337/cd17-0094

[55] Alarcon-Casas Wright, L., & Hirsch, I. B. (2017). Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapeutics, 19(Supplement 2), S16-S26. doi:10.1089/dia.2017.0029

[56] Malka, R., Nathan, D. M., & Higgins, J. M. (2016). Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. Science Translational Medicine, 8(359), 1-9. doi: 10.1126/scitranslmed.aaf9304

[57] Welsh, K. J., Kirkman, M. S., & Sacks, D. B. (2016). Role of Glycated Proteins in the Diagnosis and Management of Diabetes: Research Gaps and Future Directions. Diabetes Care, 39(8), 1299-1306. doi:10.2337/dc15-2727

can be presumed that HbA1c is not always a true reflection of glucose profiles because its accuracy can be compromised by many variables affecting the survival of red blood cells.

"As a measure of mean blood glucose over a two to three-month period, HbA1c does not capture short-term variations in blood glucose or exposure to hypoglycemia and hyperglycemia in individuals with type 1 diabetes; HbA1c also does not capture the impact of blood glucose variations on an individual's quality of life".[58] Because glycemia is a complex process, clinical interpretations of redundant mechanisms that rely on glucose as an energy source may be another limitation to HbA1c.[52] Connections have been made to the limitations of HbA1c testing and the lack in accuracy to reflect a patient's complete glycemic profile.[59,60,61]

Another limitation to using HbA1c as the metric determining metabolic control lies in the fact that there can be wide ranges of glucose concentrations for a given HbA1c value. Studies have shown a range of approximately 80 mg/dL in average glucose values for the same HbA1c value.[62] This means that an HbA1c of 8% could be associated with average glucose levels

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[58] Agiostratidou, G., Anhalt, H., Ball, D., Blonde, L., Gourgari, E., Harriman, K. N., . . . Weinzimer, S. A. (2017). Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endo. Diabetes Care, 40(12), 1622-1630. doi:10.2337/dc17-1624

[59] Hilliard, M. E., Wu, Y. P., Rausch, J., Dolan, L. M., & Hood, K. K. (2013). Predictors of Deteriorations in Diabetes Management and Control in Adolescents With Type 1 Diabetes. Journal of Adolescent Health, 52(1), 28-34. doi:10.1016/j.jadohealth.2012.05.009

[60] American Diabetes Association. (2017). Glycemic targets. Sec. 6. In Standards of Medical Care. Diabetes Care, 40(Supplement 1), S48-S56. doi:10.2337/dc17-S009

[61] Runge, A. S., Kennedy, L., Brown, A. S., Dove, A., Levine, B. J., Koontz, S., . . . Wood, R. (2018). Does Time-in-Range Matter? Perspectives From People With Diabetes on the Success of Current Therapies and the Drivers of Improved Outcomes. Clinical Diabetes, 36(2), 112-119. doi:10.2337/cd17-0094

[62] Bergenstal, R. M., Gal, R. L., Connor, C. G., Gubitosi-Klug, R., Kruger, D., Olson, B. A., . . . Beck, R. W. (2017). Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A1c Levels. Annals of Internal Medicine, 167, 95-102. doi:10.7326/M16-2596

between 128-249 mg/dL.[63] Metabolic control as indicated by average HbA1c levels can vary significantly among different treatment regimens, with differences also being observed in HbA1c relationships between individuals within ethnic groups.[64,65] This inter-individual variability that exists in the relationship between HbA1c and mean glucose concentrations indicates that HbA1c may not be a great indicator of control for every patient. These facts regarding the limitations with HbA1c testing are prime examples of why additional metrics should be considered when defining real glycemic control.

After investigations into standardizing clinically meaningful diabetes-related outcomes were concluded, researchers did not insist that other outcomes replace current HbA1c standards for glucose control, but rather suggested that other metrics be used to supplement the limitations of HbA1c and include outcomes that incorporate other glucose profiles that can provide a more comprehensive understanding of the full picture.[66] Studies have shown that patients with the same HbA1c value had different rates of microvascular complications, prompting the endocrinology community to research metrics, other than HbA1c, for assessing glycemic control to reduce both short and long-term diabetes-related complications.[67] Cryer's research further

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[63] Beck, R. W., Connor, C. G., Mullen, D. M., Wesley, D. M., & Bergenstal, R. M. (2017). The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care, 40(8), 994-999. doi:10.2337/dc17-0636

[64] Ziegler, R., Heidtmann, B., Hilgard, D., Hofer, S., Rosenbauer, J., & Holl, R. (2011). Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatric Diabetes, 12(1), 11-17. doi:10.1111/j.1399-5448.2010.00650.x

[65] Wilson, D. M., Xing, D., Cheng, J., Beck, R. W., Hirsch, I., Kollman, C., . . . Wolpert, H. (2011). Persistence of Individual Variations in Glycated Hemoglobin. Diabetes Care, 34(6), 1315-1317. doi:10.2337/dc10-1661

[66] Agiostratidou, G., Anhalt, H., Ball, D., Blonde, L., Gourgari, E., Harriman, K. N., . . . Weinzimer, S. A. (2017). Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endo. Diabetes Care, 40(12), 1622-1630. doi:10.2337/dc17-1624

[67] Alarcon-Casas Wright, L., & Hirsch, I. B. (2017). Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapeutics, 19(Supplement 2), S16-S26. doi:10.1089/dia.2017.0029

implied that HbA1c goals should be individualized and that higher HbA1c targets may be more fitting for some patients with T1D.[68] Because HbA1c cannot provide information related to glucose variations, there is need for additional measurable outcomes for T1D patients. These notions appear to echo the general consensus that HbA1c should not be the sole focus when defining successful T1D management and glycemic control because of the reality that HbA1c goals will vary between patients.

"With the advent of new technologies to assess glycemia, recent evidence linking hypoglycemia with adverse outcomes, and the increased knowledge on the limitation of HbA1c and SMBG, new metrics need to be incorporated to better understand the dynamic nature of glucose, how to help patients achieve optimal control, and ways to reduce complications".[64] Time in range (TIR) is one such metric. Authors indicated that there is interest in the diabetes community to define measures of glycemic control aside from HbA1c that may include TIR or revised classifications of hypoglycemia.[69] Time in range is the percentage of time that a person spends with their blood glucose levels in a target range. It can be calculated by using the following formula:

$$\text{Time in Range (\%)} = \frac{\text{number of blood glucose values within specific range}}{\text{total number of blood glucose values}} \times 100$$

[68] Cryer, P. E. (2017). Individualized Glycemic Goals and an Expanded Classification of Severe Hypoglycemia in Diabetes. Diabetes Care, 40(12), 1641-1643. doi:10.2337/dc16-1741

[69] Riddle, M. C., Gerstein, H. C., & Cefalu, W. T. (2017). Maturation of CGM and Glycemic Measurements Beyond HbA1c—A Turning Point in Research and Clinical Decisions. Diabetes Care, 40(12), 1611-1613. doi:10.2337/dci17-0049

The range will vary depending on the individual, but general guidelines suggest starting with a range of 70 to 180 mg/dL.[70] "Target range and time in range can be expressed either as "% of glucose reading" or "hours per day". The proposed target range of 70-180 mg/dL was considered acceptable for clinical practice, as it has been observed that if 50% of the SMBG readings are in such range, HbA1c would be around 7%".[71] The average person with type 1 diabetes has a time in range of roughly 50-60%.[66] Range definitions for TIR are kept wide to allow for variations across the T1D population.

"Time in range captures fluctuations in glucose levels continuously, whereas HbA1c testing is done at static points in time".[72] Since TIR can be measured anywhere at any time (via diabetes devices) there is a large advantage in having the capability to study the times of day or choices made by the patient that yielded better TIR percentages. This feature allows a patient to look in real time at what actions directly elevated and reduced blood glucose levels, and provides the opportunity to make changes to better control glycemic excursions. Time in range provides a more simplistic view of the "cause-and-effect" relationship of T1D and is presented in a manner that is easily understood by both patient and provider. Time in range gives T1D patients more control of their diabetes because of the convenience to access up-to-date information and make adjustments as necessary. "Some researchers believe that time in range serves as a better predictor of complications, since it is a direct measure of glucose in the blood vessels.

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[70] diaTribe Foundation. (2020). Time in Range. Retrieved from https://diatribe.org/time-range

[71] Alarcon-Casas Wright, L., & Hirsch, I. B. (2017). Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapeutics, 19(Supplement 2), S16-S26. doi:10.1089/dia.2017.0029

[72] Agiostratidou, G., Anhalt, H., Ball, D., Blonde, L., Gourgari, E., Harriman, K. N., . . . Weinzimer, S. A. (2017). Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endo. Diabetes Care, 40(12), 1622-1630. doi:10.2337/dc17-1624

Conversely, HbA1c is an indirect measure of blood glucose since it is dependent on the turnover of red blood cells".[66]

Time in range is also more specific and sensitive than current HbA1c testing. It more accurately presents profiles for individuals who have blood glucose levels rarely outside of their defined thresholds. Patients who are more in range are less likely to experience short-term or long-term health effects than those who have more frequent blood glucose excursions.[73] As a result, it is more representative of the patient's entire glycemic profile. TIR helps providers know what areas of the management plan need to be focused on more closely to better improve metabolic control. Hirsch and his team stated that patients and providers agreed that using TIR as a primary metric for disease control is more accurate and is easier for most people to understand and use the data to make necessary adjustments quickly.[74]

Another advantage to reviewing TIR is that "time in range percentages are more likely to be comparable across patients that HbA1c values, which often have patient-specific variations in significance".[75] The specificity of time in range can be best understood by comparing variations in glucose levels throughout a 24-hour period in T1D patients that all have the same HbA1c and average blood glucoses. Figure 1 is a visual representation of TIR that demonstrates how it can vary between patients with other identical glycemic metrics. As one can see, time in range has the ability to highlight differences in real glycemic control and the variances that HbA1c cannot capture.

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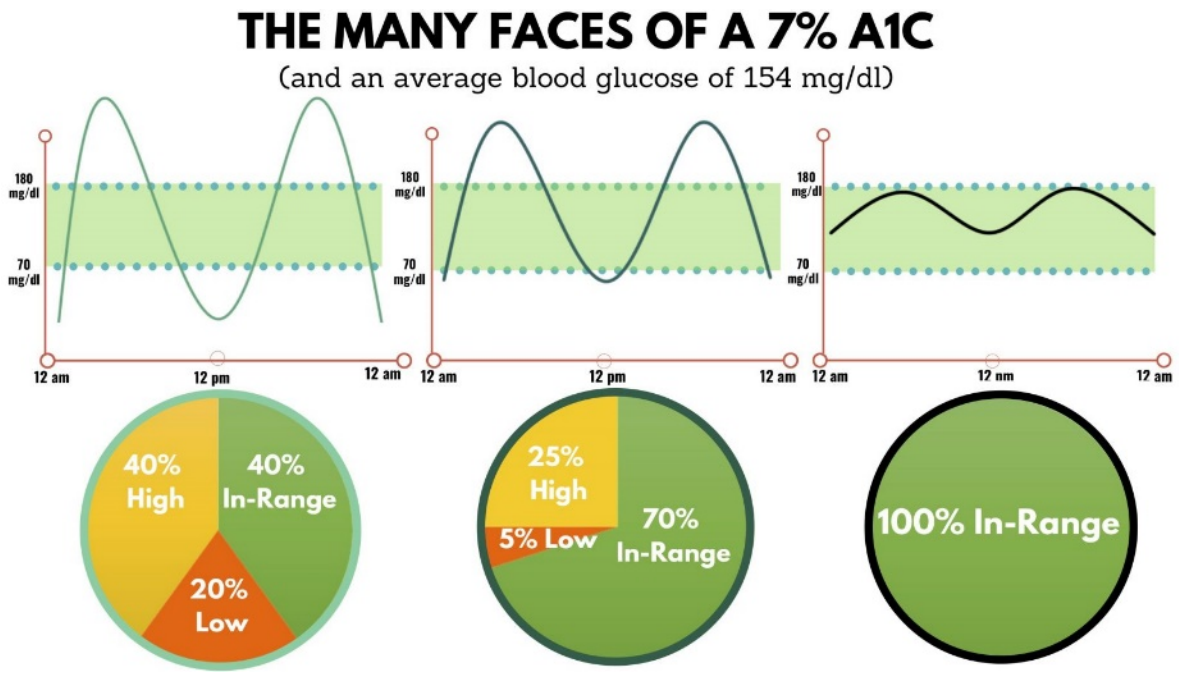
[73] Agiostratidou, G., Anhalt, H., Ball, D., Blonde, L., Gourgari, E., Harriman, K. N., . . . Weinzimer, S. A. (2017). Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endo. Diabetes Care, 40(12), 1622-1630. doi:10.2337/dc17-1624

[74] Hirsch, I. B., Sherr, J. L., & Hood, K. K. (2019). Connecting the Dots: Validation of Time in Range Metrics With Microvascular Outcomes. Diabetes Care, 42(3), 345-348. doi:10.2337/dci18-0040

[75] diaTribe Foundation. (2020). Time in Range. Retrieved from https://diatribe.org/time-range

Figure 1. Differences captured by time in range



Researchers have deemed TIR to be a solid metric of glycemic control that presents actionable data.[76] It provides applications on both a patient level by providing opportunities to make immediate adjustments to treatment and management behaviors, and on a provider level by presenting a clear picture of severe glucose excursions. A study conducted by Runge and collaborators showed that time in range was the highest ranking outcome believed to have the largest impact on daily life for patients with type 1 diabetes. Time in range emerged as the top outcome measure that both reflects patients' priorities and can be used to quantitatively evaluate treatment efficacy.[77] Patients with type 1 diabetes clearly recognize the value of TIR and the

[76]Battelino, T., Danne, T., Bergenstal, R. M., Amiel, S. A., Beck, R., Biester, T., . . . Phillip, M. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. doi:10.2337/dci19-0028

[77]Runge, A. S., Kennedy, L., Brown, A. S., Dove, A., Levine, B. J., Koontz, S., . . . Wood, R. (2018). Does Time-in-

impact that it has on their daily struggle with glycemic control. Time in range is a great complement to HbA1c and should be considered an integral aspect of daily decision making for patients with type 1 diabetes.[78]

Limitations for time in range are less biological than those noted for HbA1c. The most obvious limitation is the ability to access and use diabetes devices like CGM. If a patient is unable or unwilling to use a diabetes device to continually check blood glucose levels throughout the day, then a patient would need to manually perform glucose monitoring. Not only would patients without devices need to physically perform the blood glucose checks, but they would also have to record it, often in the form of a log book. The rates of noncompliance with self-monitoring blood glucose frequencies are already an obstacle, and research has shown various reasons how and why patients are noncompliant with accurately reporting blood glucose levels to providers.

A majority of the associations made among diabetes-related metrics and glycemic outcomes appeared to center around general adherence to treatment plans, performance of self-management habits like blood glucose monitoring frequency, use of diabetes devices such as CGMs or insulin pumps, and time in range. A general summary of the relationships is presented in Table 1. With regard to general treatment adherence, researchers found that a pediatric patient's adherence to treatment regimens resulted in better glycemic control thereby making glycemic control dependent on treatment adherence.[79] Throughout the literature, "blood glucose

Range Matter? Perspectives From People With Diabetes on the Success of Current Therapies and the Drivers of Improved Outcomes. Clinical Diabetes, 36(2), 112-119. doi:10.2337/cd17-0094

[78] Battelino, T., Danne, T., Bergenstal, R. M., Amiel, S. A., Beck, R., Biester, T., . . . Phillip, M. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. doi:10.2337/dci19-0028

[79] McNally, K., Rohan, J., Shroff Pendley, J., Delamater, A., & Drotar, D. (2010). Executive Functioning, Treatment Adherence, and Glycemic Control in Children With Type 1 Diabetes. Diabetes Care, 33(6), 1159-1162.

monitoring frequency (BGMF) was often chosen as an indicator of treatment adherence given its central role in diabetes management and its robust association with glycemic control in multiple studies".[80]

Data analyzed by Rausch and associates suggested that increased numbers of daily blood glucose checks did predict better glycemic control and could be used as a tool for self-management to achieve target goals.[81] "Although improvement of glycemic control can result in significant risk reduction for future diabetes-related complications, suboptimal glycemic control has major consequences on long-term health outcomes".[82] More frequent self-monitoring blood glucose (SMBG) is also associated with better metabolic control which can reduce occurrence of complications from poorly controlled diabetes.[80] This discovery is most important for pediatric patients because they will have diabetes longer than adults who are diagnosed later in life.
In a database inclusive of approximately 27,000 pediatric patients with T1D, increased daily frequency of self-monitoring blood glucose (SMBG) was associated with a 0.2% lower HbA1c value and a decreased presence of diabetes-related complications.[83] One such complication mentioned was diabetic ketoacidosis, or DKA, which was inversely related to SMBG

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doi:10.2337/dc09-2116

[80] Helgeson, V. S., Honcharuk, E., Becker, D., Escobar, O., & Siminerio, L. (2011). A focus on blood glucose monitoring: relation to glycemic control and determinants of frequency. Pediatric Diabetes, 12(1), 25-30. doi:10.1111/j.1399-5448.2010.00663.x

[81] Rausch, J. R., Hood, K. K., Delamater, A., Pendley, J. S., Rohan, J. M., Reeves, G., . . . Drotar, D. (2012). Changes in Treatment Adherence and Glycemic Control During the Transition to Adolescence in Type 1 Diabetes. Diabetes Care, 35, 1219-1224.

[82] Rausch, J. R., Hood, K. K., Delamater, A., Pendley, J. S., Rohan, J. M., Reeves, G., . . . Drotar, D. (2012). Changes in Treatment Adherence and Glycemic Control During the Transition to Adolescence in Type 1 Diabetes. Diabetes Care, 35, 1219-1224.

[83] American Diabetes Association. (2017). Glycemic targets. Sec. 6. In Standards of Medical Care. Diabetes Care, 40(Supplement 1), S48-S56. doi:10.2337/dc17-S009

frequency.[84]

Strong relationships were also identified between an increase in blood glucose monitoring frequency and HbA1c levels. Self-measurement of blood glucose (SMBG) was associated with up to 0.5% improvement in HbA1c values with each additional check, up to a maximum of 5-6 checks per day.[85] SMBG frequency was associated with better metabolic control with a decrease of 0.2% in HbA1c levels for each additional check per day. Interestingly enough, increasing SMGB checks above 5 per day did not result in further HbA1c improvement.[81]

A recent quality improvement project conducted by University of Michigan QI Initiative demonstrated that in addition to SMBG, adherence to other self-management habits were associated with improved glycemic outcomes as measured by HbA1c. The study evaluated the relationship between six specific self-management habits and HbA1c. Habits concentrated on the use of CGM or SMBG frequency, administration of at least three insulin doses throughout the day or use of an insulin pump, the timing of which insulin was given (either before or after a meal), completing reviews of blood glucose data for patterns and making adjustments to the insulin regimen at least once since the previous diabetes clinic visit. The findings suggested that performance of these behavioral habits were associated with decreased HbA1c levels with the largest decrease in HbA1c values being observed in patients that performed multiple behaviors.[86]

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[84] Ziegler, R., Heidtmann, B., Hilgard, D., Hofer, S., Rosenbauer, J., & Holl, R. (2011). Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatric Diabetes, 12(1), 11-17. doi:10.1111/j.1399-5448.2010.00650.x

[85] Blackwell, M., & Wheeler, B. J. (2017). Clinical review: the misreporting of logbook, download, and verbal self-measured blood glucose in adults and children with type I diabetes. Acta Diabetol, 54(1), 1-8. doi:10.1007/s00592-016-0907-4

[86] Lee, J. M., Garrity, A., Hirschfeld, E., Wichorek, M., Inas, T., & Rioles, N. (2019, June 21). Six Habits for Type 1 Diabetes and the Association with HbA1c. Retrieved from UM Pediatric Diabetes Clinic Newsletter: https://www.umpedsdiabetes.com/lower-a1c-habits?utm_source=Newsletter27&utm_medium=Newsletter&utm_campaign=Newsletter27

For patients who used diabetes devices such as continuous glucose monitors (CGM) or insulin pumps, reported HbA1c levels were lower than those of patients who did not use devices as a part of their daily management plan.[87] Data also showed that time in range is increased when insulin dosing decisions are made using information obtained from a CGM versus values reported from conducting SMBG checks.[88]

Lastly, there have been several links made between time in range and HbA1c. In fact, "there is a good correlation between HbA1c and time in range percentages that may permit the transition to TIR as the preferred metric for determining the outcome of clinical studies, predicting the risk of diabetes complications, and assessing of an individual patient's glycemic control".[89] These metrics are inversely related and for every 10% change in TIR there is a 0.5%-0.8% change in HbA1c.[90] With respect to the relationship between time and range and HbA1c, TIR remained comparable with HbA1c across a broad range of patients with diabetes of varying demographics and technologies used for management.

Connections between time in range and associated complications of type 1 diabetes have also been identified. In particular, time in range is strongly associated with risk of microvascular

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[87] Miller, K. M., Foster, N. C., Beck, R. W., Bergenstal, R. M., DuBose, S. N., DiMeglio, L. A., . . . Tamborlane, W. V. (2015). Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry. Diabetes Care, 38(6), 971-978. doi:10.2337/dc15-0078

[88] Aleppo, G., Ruedy, K. J., Riddlesworth, T. D., Kruger, D. F., Peters, A. L., Hirsch, I., . . . Beck, R. W. (2017). REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Well-Controlled Type 1 Diabetes. Diabetes Care, 40(4), 538-545. doi:10.2337/dc16-2482

[89] Vigersky, R. A., & McMahon, C. (2019). The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technology & Therapeutics, 21(2), 81-85. doi:10.1089/dia.2018.0310

[90] Battelino, T., Danne, T., Bergenstal, R. M., Amiel, S. A., Beck, R., Biester, T., . . . Phillip, M. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. doi:10.2337/dci19-0028

complications; TIR is lower in those who develop microvascular complications than those who do not. Time in range has been found to have an association specifically with the risk of development or progression of retinopathy and development of microalbuminuria (MA); the presence of MA indicates endothelial dysfunction which can result in other cardiovascular events or death. [91] "Research shows that with each 10% drop in TIR, there is an increase in risk of retinopathy by 64% and of microalbuminuria by 40%".[92] In general, as time in range increases, diabetes complications decreases.

Table 1. Diabetes management and metrics relationships

Variables	Correlation	Relationship Trends
BGMF + Metabolic Control	Positive	↑ ↑
BGMF + T1D Complications	Negative	↑ ↓
BGMF + HbA1c	Negative	↑ ↓
Adherence + Metabolic Control	Positive	↑ ↑
Device Use + HbA1c	Negative	↑ ↓
Device Use + TIR	Positive	↑ ↑
TIR + Complications	Negative	↑ ↓
TIR + HbA1c	Negative	↑ ↓

[91] Beck, R. W., Bergenstal, R. M., Riddlesworth, T. D., Kollman, C., Li, Z., Brown, A. S., & Close, K. L. (2019). Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care, 42(3), 400-405. doi:10.2337/dc18-1444

[92] Hirsch, I. B., Sherr, J. L., & Hood, K. K. (2019). Connecting the Dots: Validation of Time in Range Metrics With Microvascular Outcomes. Diabetes Care, 42(3), 345-348. doi:10.2337/dci18-0040

It is important to note that "glycemic control is not a valid proxy for treatment adherence. This means that clinicians that obtain above-target HbA1c values for a particular patient and assume poor treatment adherence are likely to miss other relevant contributors to glycemic control such as dosing, timing of insulin administration, and variability of blood glucose monitoring".[93] This idea only stresses the importance of reviewing metrics other than HbA1c when gauging diabetes success.

When assessing glycemic targets, the ADA states that HbA1c goals should be less than 7.5% across all age groups.[94] "While there have been significant improvements in insulin analogs and insulin delivery systems, such as continuous subcutaneous insulin infusions with insulin pumps, continuous glucose monitoring, and closed loop systems, normal glucose control, particularly in children, is rarely achieved".[95] In fact, Wood and colleagues found that the age-specific ADA HbA1c target was actually only met by approximately 32% of patients.[96] When reviewing success for meeting time in range targets, it is helpful to know that for patients younger than 25 years of age, an HbA1c goal of less than 7.5% translates to a time in range target around 60%.[97] Unlike HbA1c goals, TIR targets can be flexible depending on the patient's

[93] Rausch, J. R., Hood, K. K., Delamater, A., Pendley, J. S., Rohan, J. M., Reeves, G., . . . Drotar, D. (2012). Changes in Treatment Adherence and Glycemic Control During the Transition to Adolescence in Type 1 Diabetes. Diabetes Care, 35, 1219-1224.

[94] American Diabetes Association. (2017). Glycemic targets. Sec. 6. In Standards of Medical Care. Diabetes Care, 40(Supplement 1), S48-S56. doi:10.2337/dc17-S009

[95] Miller, K. M., Foster, N. C., Beck, R. W., Bergenstal, R. M., DuBose, S. N., DiMeglio, L. A., . . . Tamborlane, W. V. (2015). Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry. Diabetes Care, 38(6), 971-978. doi:10.2337/dc15-0078

[96] Wood, J. R., Miller, K. M., Maahs, D. M., Beck, R. W., DiMeglio, L. A., Libman, I. M., . . . Woerner, S. E. (2013). Most Youth With Type 1 Diabetes in the T1D Exchange Clinic Registry Do Not Meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes Clinical Guidelines. Diabetes Care, 36(7), 2035-2037. doi:10.2337/dc12-1959

[97] Battelino, T., Danne, T., Bergenstal, R. M., Amiel, S. A., Beck, R., Biester, T., . . . Phillip, M. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International

individual relationship to type 1 diabetes. For instance, pregnant women will have different needs and ideal glucose ranges than a patient who has had controlled diabetes for several years.[91]

"Improved insulin pumps and blood glucose meters, continuous glucose monitoring devices, and integrated sensor-augmented insulin pump systems with automatic threshold suspend capabilities have provided clinicians and patients with new tools to achieve target HbA1c levels more readily and safely".[98] A therapeutic intervention is considered effective if the improvement of HbA1c is greater than 0.4%, or the corresponding increase in TIR is approximately 5%.[99] "Many adolescents with type 1 diabetes meet treatment goals; however, nearly two-thirds engage in suboptimal diabetes management and have an out-of-range glycemic control".[100] This may be suggestive that HbA1c targets should not be the sole predictor of glycemic control or a patient's level of success with managing their diabetes. "In selecting glycemic goals, the ADA recommends that the long-term health benefits of achieving a lower HbA1c should be balanced against the risks of hypoglycemia and the developmental burdens of intensive regimens in children and youth".[101] This statement is a nice segue to the proposition to consider other non-HbA1c metrics to determine metabolic control. Patients and providers should utilize the technology as well as all of the information available to them to determine the optimal

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Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. doi:10.2337/dci19-0028

[98] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. (2010). Effectiveness of Continuous Glucose Monitoring in a Clinical Care Environment. Diabetes Care, 33(1), 17-22. doi:10.2337/dc09-1502

[99] Vigersky, R. A., & McMahon, C. (2019). The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technology & Therapeutics, 21(2), 81-85. doi:10.1089/dia.2018.0310

[100] Hilliard, M. E., Wu, Y. P., Rausch, J., Dolan, L. M., & Hood, K. K. (2013). Predictors of Deteriorations in Diabetes Management and Control in Adolescents With Type 1 Diabetes. Journal of Adolescent Health, 52(1), 28-34. doi:10.1016/j.jadohealth.2012.05.009

[101] American Diabetes Association. (2018). Children and Adolescents. Sec. 12. In Standards of Medical Care in Diabetes. Diabetes Care, 41(Supplement 1), S126-S136. doi:10.2337/dc18-S012

approach for diabetes management, as the approach will vary by each patient and their specific needs and abilities.[102] In order to set realistic goals, patients and providers must openly communicate expectations and the likelihood of a patient's ability to achieve said targets.

[102] Beck, R. W., Connor, C. G., Mullen, D. M., Wesley, D. M., & Bergenstal, R. M. (2017). The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care, 40(8), 994-999. doi:10.2337/dc17-0636

Chapter 3. Needs Assessment

3.1 Assessment of Need

It is evident that one of the larger challenges facing patients with type 1 diabetes is achieving glycemic targets. Sadly, only about 17% of children and adolescents with type 1 diabetes are meeting the American Diabetes Association's HbA1c goal.[103] Similarly, the data collected for the UM QI Initiative shows that in the UM pediatric endocrinology clinic population only 25.6% of patients are meeting the ADA HbA1c goal. There is a slight increase attaining the national HbA1c goal in patients who use CGM (see Table 2). This inability to meet glycemic targets can have severe implications for a patient's incidence of diabetes-related complications, and overall quality of life. In hopes of addressing these disparities in attaining glycemic goals, the current project considered whether metabolic success is being accurately evaluated, or if there was a need to shift focus on glycemic metrics and outcomes for T1D patients. If more focus becomes placed on time in range as a metric defining true glycemic control, then patients could be better informed to make adjustments to treatment, thereby improving metabolic control. As a result, we would expect a greater percentage of patients meeting glycemic targets.

[103] Foster, N. C., Beck, R. W., Miller, K. M., Clements, M. A., Rickels, M. R., DiMeglio, L. A., . . . Garg, S. K. (2019). State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016–2018. Diabetes Technol Ther, 21(2), 66-72. doi:10.1089/dia.2018.0384

Table 2. Glycemic targets for UM pediatric T1D patients		
	All T1D Patients	CGM Users
Condition	**n=1212**	**n=720**
HbA1c ≤ 7.5% (n)	310	246
% Meeting HbA1c Target	25.6*	34.2*
Time in range ≥ 60% (n)	-	124
% Meeting TIR Target	-	17.2

3.2 Metrics

The metrics applied to this thesis project were derived primarily from the study conducted by the UM QI Initiative in 2019 which revealed that HbA1c levels improved as UM patients with T1D adhered to six specific self-management habits. Similar to the QI study, the measures used for this project evaluated whether the patient uses CGM or checks blood glucose four times per day, gives three of more insulin injections per day, uses an insulin pump, gives insulin before eating, reviews blood glucose data at least once between diabetes clinic visits, and makes adjustments to insulin doses at least once between diabetes clinic visits. Additional feedback from UM faculty advisors also indicated interest in conducting research to see if a similar relationship between those same six habits and time in range existed. Insight from UM and JHU faculty advisors and results from an extensive literature review appeared to align with the need for this thesis investigation.

3.3 Sources

UM QI Data Repository provided the initial data collected from the UM pediatric endocrinology clinic. HbA1c values were collected from 1,212 unique patients receiving care in the clinic during the entire year of 2019. Flowsheets added to the electronic medical record were

used to collect information regarding performance of the six specific self-management habits. Time in range data was extracted directly from device download reports.

Chapter 4. Project Description

The University of Michigan Pediatric Diabetes clinic is part of the T1D Exchange Quality Improvement Collaborative (T1DX QIC), a quality improvement (QI) initiative of multiple diabetes care centers that was formed to improve outcomes for people with T1D, particularly glycemic outcomes. This thesis project proposed to conduct a secondary analysis of data collected under the UM QI initiative. Preliminary QI data shows that HbA1c levels are significantly lower in patients who perform six specific self-management habits on a regular basis. This thesis project focused on a sub-analysis of those six behavioral habits and their relationship to time in range (rather than HbA1c) for pediatric patients who are on continuous glucose monitors (CGM).

Chapter 5. Methodology

5.1 Study Design

A series of flowsheet elements were previously added to the electronic health record by the UM QI team. Certified diabetes educators (CDE) and pediatric endocrinologists used these flowsheets to record information related to management habits at every diabetes clinic visit. This information was reported by the patient or downloaded from the diabetes device by clinical staff. Pediatric patients with T1D often return to the clinic every three months for follow-up appointments. Given the frequency of these routine visits, the data set for the thesis focus included information from 1,212 patients.

Retrospective chart reviews were conducted to obtain clinical data related to biomedical parameters (HbA1c values and time in range percentages), and behavioral determinants (frequency of blood sugar testing, number of insulin bolus doses, patient usage of diabetes devices such as insulin pump or CGMs, etc.). Data from the most recent clinic visit in which there was complete flowsheet data and available TIR values was included. The six T1D habits that were reviewed in this project were as follows: patient uses CGM or checks blood glucose four times/day; patient gives three or more insulin injections per day; patient uses an insulin pump; patient gives insulin before eating; blood glucose data has been reviewed for patterns at least once since the previous clinic visit; insulin doses have been changed (either by family or clinic) at least once since the previous clinic visit. Individual scores were assigned to each self-management habit. One point was given for each habit that was performed. A total score was then calculated for each patient representing the overall self-management habits performance level. Total scores ranged from 0-6 points, reflecting the presence or absence of a behavior (refer to Table 3). A higher habit score indicated that a patient was participating in more of the

habits; a lower score indicated less adherence to the chosen self-management behaviors. Time in range values were extracted from the device download report (located either in the medical record or the patient's online device account using shared log-in codes) and were reported as a percentage.

Table 3. Scoring matrix for the six habits

Self-Management Habit		**Response Options**	**Definition of "Performs habit"**
1	Blood Glucose Testing Frequency on download	0 to 10 or more times	Checks blood glucose 4 times/day OR uses Continuous Glucose Monitor
	Uses CGM	Yes, No	
2	Average number of bolus insulin doses per day on download (for pump) & patient report (for Multiple Daily Injections)	0 to 10 or more times	Gives 3 or more insulin injections per day
3	Type of Intensive Therapy	Multiple Daily Injections, Insulin Pump Therapy	Uses insulin pump
4	Timing of Insulin with meals	"At least several minutes before the meal", "Immediately before the meal", "during or after the meal"	Response of "At least several minutes before the meal" or "Immediately before the meal"
5	Number of times blood glucose or insulin data was downloaded and reviewed for blood glucose patterns since the last diabetes clinic visit:	0 to 10 or more times	Reviewed blood glucose data for patterns at least once since the last clinic visit
6	Number of times insulin was adjusted by family or by diabetes team since the last diabetes clinic visit:	0 to 10 or more times	Changed insulin doses at least once since the last clinic visit (by family or clinic)

5.1.1 Sample

The cohort used for analysis was a subpopulation of the UM pediatric endocrinology clinic. Only patients with type 1 diabetes who use a CGM were included in the project data set. The total number of patients followed in the UM pediatric diabetes clinics during 2019 was 1,212. From this list, patients were excluded if they were non-CGM users which resulted in 720 patients. Of those remaining individuals, further exclusions were made if there was incomplete data for time in range in the download reports or medical records. The final number included for review was 654 patients. As shown in Table 4 below, the sample was nearly equally proportioned with both male (48.8%) and female (51.2%) patients, with an average age of 14.6 years. The predominate race for this cohort was white (88.4%). Average time in range was 40.4% with a standard deviation of approximately 20%; average total score for the six self-management habits was 4.1 points out of a possible 6 points total.

Table 4. Cohort characteristics	
Characteristic	Total **n=654**
Age (years), n(%)	
0-12	222 (33.9)
13-17	265 (40.5)
18+	167 (25.5)
Sex, n(%)	
Male	319 (48.8)
Female	335 (51.2)
Race, n(%)	
White	578 (88.4)
Black	20 (3.1)
Other	56 (8.6)
Insurance	
Private	577 (88.2)
Medicaid	77 (11.8)
Time in Range (%)	40.4 ± 20.0
HbA1c (%)	8.2 ± 1.4
Habits Score_Total	4.1 ± 1.1
CGM Type	
Dexcom	559 (85.5)
Medtronic	60 (9.2)
Libre	33 (5.0)
Average Sensor Glucose	203.1 ± 45.5
Average days in DL report:	14
Avg. days of DL from HbA1c:	95.8

5.1.2 Measurements

Demographic information was requested and included in the original data set. Traits such as sex, race/ethnicity, type of insurance, and level of formal parental education were provided by the data repository.

Using the encounter date with a corresponding HbA1c value as a guide, data downloaded from a patient's CGM on or near the encounter date was extracted from the medical record or directly from the user's diabetes device account using shared log-in information. A window of ±

90 days was applied when collecting data from the device downloads in cases where a download report was not available on the day of the clinic visit. Time in range was reported as a percentage. Average sensor glucose values, with standard deviations, were also collected from the same time point.

Diabetes management was quantified using the data for performances of the six self-management habits which was pulled directly from the clinic flowsheets in the electronic medical record (see Appendix 5). One point was given for each habit performed (see Table 3). A total score was calculated by summing the point values assigned to each habit, with a total of 6 points being possible if a patient was adherent to all six self-management habits.

5.2 Data Organization

Using a tabulated workbook in Microsoft Excel, data was imported from the repository. Protected Health Information (PHI) was removed as much as possible to reduce risk of a breach in confidentiality. Appointment dates were the only remaining pieces of PHI, permitting the data set to be shared in a limited format. Basic tables were created using the Descriptive Statistics feature of Excel's data analysis package, or were developed manually. A table was created using key demographic traits to quickly identify the cohort's characteristics (see Table 4). All versions of the data set were securely stored per the UM Data Use Agreement.

The data analysis plan was to use regression models to identify a relationship between the six self-management habits performed by pediatric patients with type 1 diabetes (T1D) and the association with optimal glycemic outcomes as measured by time in range. The proposed relationship was that the self-management habits would predict TIR; higher scores from 6 habits would equate to higher TIR values.

5.2.1 Control/Validity

Measures were taken throughout the project to ensure data integrity. The diagnosis of type 1 diabetes was based on clinician-defined diabetes, which is also a flowsheet item (see Appendix 4) that providers completed in the medical record. This was used as a way to reduce error from misclassification based on diagnostic codes. Regular meetings with Johns Hopkins University and University of Michigan faculty advisors were conducted to review data set results, evaluate the relevance of identifiable trends, address issues with interpreting downloaded data from the medical record, and to make adjustments if needed to the current practice.

5.2.2 Limitations

Data related to the duration these patients have had type 1 diabetes was not readily available for the entire population which may have prevented use of some knowledge regarding the potential experience level this cohort had with managing diabetes. Lack of previous research in this area was also a limitation to this project. Much research is available for assessing relationships between self-management habits and glycemic outcomes using HbA1c values, but limited work has been done with time in range as the desired predicted outcome.

5.3 Regulatory Compliance

Per the Johns Hopkins Medical Institution Institutional Review Board (JHMI IRB), no application was required for submission to any Johns Hopkins regulatory committee since the data set originated locally at the University of Michigan. Thus, an application was submitted to the University of Michigan's medical research review board. The Institutional Review Boards of the University of Michigan Medical School (IRBMED) oversee human subjects research

conducted at the Medical School and Michigan Medicine. The University of Michigan served as the IRB of record for this project. IRBMED granted a Letter of Exemption (Appendix 2) stating that the project was exempt from ongoing regulatory reviews.

Chapter 6. Project Results and Discussion

6.1 Overview

In general, there was a correlation detected between time and range and the six self-management habits. Patients who performed a self-management habit had higher time in range values than those who did not perform the habit. Furthermore, time in range increased as more self-management habits were performed. Although the impact that adherence of the behavioral habits had on time in range values was minor in a clinical sense, it was still quite statistically present.

6.2 Data Analysis

The primary objective was to test for a relationship between the self-management habits and the association with optimal glycemic outcomes as measured by time in range. The variables were segmented into two groups: predictive factors (HbA1c, average sensor glucose, scoring for self-management habits) and a criterion (time in range). To assess the associations of each independent variable with time in range, a multivariate regression analysis was constructed first. To more clearly assess the effects of adherence to the six self-management habits on time in range, a regression analysis adjusted for only those two variables was conducted as it was the focus of the multivariate model.

6.3 Results

Average time in range was 40.36% (±19.97) which was quite comparable to the mean TIR (41 ± 16%) Beck and colleagues found during their study to validate time in range as an

outcome measure for clinical trials.[104] The target value for time in range was set to 60%, as this corresponds to a HbA1c target of 7.5%. Total scores for the six habits averaged 4 points, and the average patient age was 14 years (refer to Fig.2).

Figure 2. Descriptive statistics

Time in Range (%)	
Mean	40.36
Standard Error	0.78
Median	40
Mode	39
Standard Deviation	19.97
Sample Variance	398.62
Kurtosis	-0.50
Skewness	0.16
Range	98
Minimum	0
Maximum	98
Sum	26396
Count	654

Habits Total (0-6pts)	
Mean	4.13
Standard Error	0.04
Median	4
Mode	4
Standard Deviation	1.13
Sample Variance	1.28
Kurtosis	-0.58
Skewness	0.03
Range	5
Minimum	1
Maximum	6
Sum	2701
Count	654

Age (years)	
Mean	14.62
Standard Error	0.18
Median	15.07
Mode	13.49
Standard Deviation	4.59
Sample Variance	21.06
Kurtosis	-0.46
Skewness	-0.36
Range	22.87
Minimum	1.94
Maximum	24.81
Sum	9562.37
Count	654

Metabolic control was noted to be affected by the performance of self-management habits and was slightly higher in patients 18 years of age and older versus any other pediatric age group sampled (Table 5). This may be attributed to the increased independence with disease management that often accompanies the transition into adulthood. Interestingly enough, even

[104]Beck, R. W., Bergenstal, R. M., Riddlesworth, T. D., Kollman, C., Li, Z., Brown, A. S., & Close, K. L. (2019). Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care, 42(3), 400-405. doi:10.2337/dc18-1444

though only 59.4% of the UM pediatric endocrinology population uses CGM, 18.8% of that cohort met the current time in range targets compared to the 32.9% of the total UM T1D population that currently meets the national standard for HbA1c levels. The data did suggest that patients who performed a particular habit spent more time in glycemic target ranges than patients who did not perform the same self-management habit. As shown in Figure 4, time in range percentages were consistently higher when a habit was performed compared to when a habit was not performed. As the level of adherence increased reflected by a higher total habit score, time in range also increased (Fig. 3). This gave rise to better metabolic control in the groups that were adherent to self-management behaviors as demonstrated by higher time in range values.

Children 18 years of age and older appeared to be better controlled as indicated by some of the highest TIR values amongst the cohort across all habits. Male and females were shown to have comparable mean TIRs when a habit was performed. Females, however, did tend to have slightly higher TIR values than males when a habit was not performed by both sexes.

Table 5. Properties and prevalence by habit

		Sex		*Age Group*		
	Total	Male	Female	0-12 years	13-17 years	18+ years
Overall						
n (%)	654	319 (48.8)	335 (51.2)	222 (33.9)	265 (40.5)	167 (25.5)
Mean TIR (%)	40.4	39.7	41.0	41.5	38.5	42.4
TIR > 60, n (%)	123 (18.8)	54 (16.9)	69 (20.6)	40 (18.0)	32 (12.1)	44 (26.3)
Habit #1						
Performs, n (%)	654 (100)	319 (100)	335 (100)	222 (100)	209 (78.9)	167 (100)
Performs, Mean TIR	40.4	39.7	41.0	41.5	38.5	44.8
Does not perform, Mean TIR	-	-	-	-	-	-
Habit #2						
Performs, n (%)	599 (91.6)	293 (91.8)	306 (91.3)	211 (95.0)	191 (72.1)	151 (90.4)
Performs, Mean TIR	40.7	40.2	41.1	41.8	38.6	43.0
Does not perform, Mean TIR	36.8	33.3	39.9	36.5	37.6	36.7
Habit #3						
Performs, n (%)	465 (71.1)	217 (68.0)	248 (74.0)	158 (71.2)	151 (57.0)	117 (70.1)
Performs, Mean TIR	41.4	41.5	41.3	43.2	37.8	44.8
Does not perform, Mean TIR	37.8	35.8	40.1	37.4	40.2	36.8
Habit #4						
Performs, n (%)	505 (77.2)	252 (79.0)	253 (75.5)	187 (84.2)	163 (61.5)	118 (70.7)
Performs, Mean TIR	41.9	41.5	42.2	42.2	40.3	44.9
Does not perform, Mean TIR	35.2	32.7	37.2	38.0	32.3	36.3
Habit #5						
Performs, n (%)	175 (26.8)	87 (27.3)	88 (26.3)	86 (38.7)	51 (19.2)	35 (21.0)
Performs, Mean TIR	42.0	42.0	42.0	41.4	39.2	47.6
Does not perform, Mean TIR	39.8	38.8	40.7	41.6	38.3	41.0
Habit #6						
Performs, n (%)	303 (46.3)	151 (47.3)	152 (45.4)	132 (59.5)	108 (38.9)	62 (37.1)
Performs, Mean TIR	42.5	42.6	42.4	41.8	43.2	46.3
Does not perform, Mean TIR	38.5	37.1	39.8	41.2	35.1	40.1

Figure 3. Time in range by habit performance

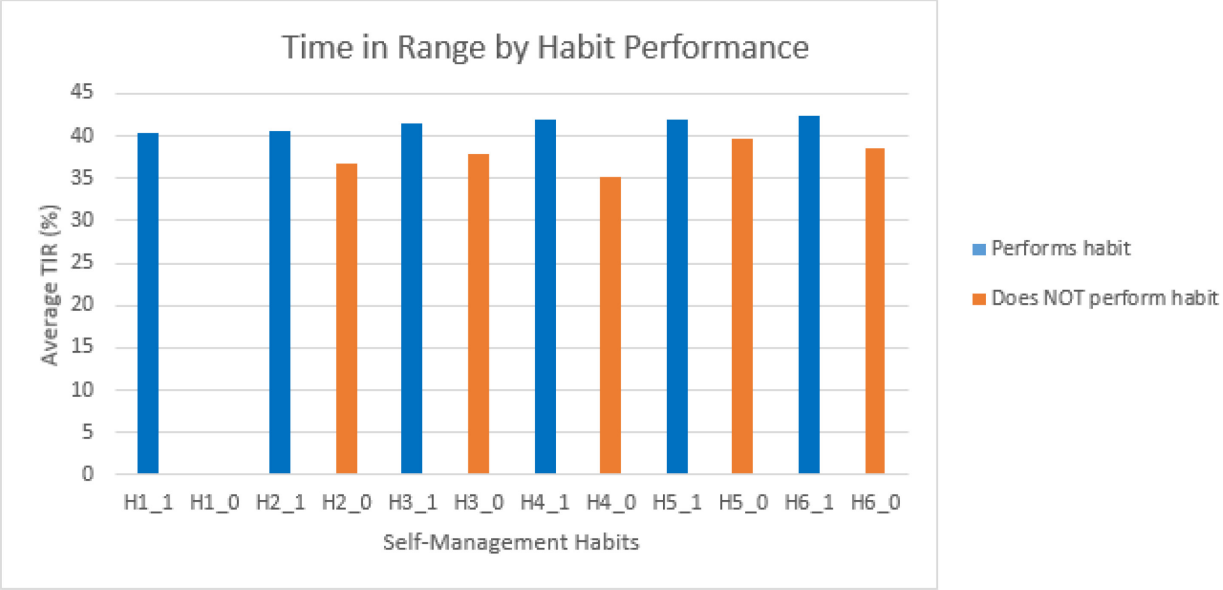
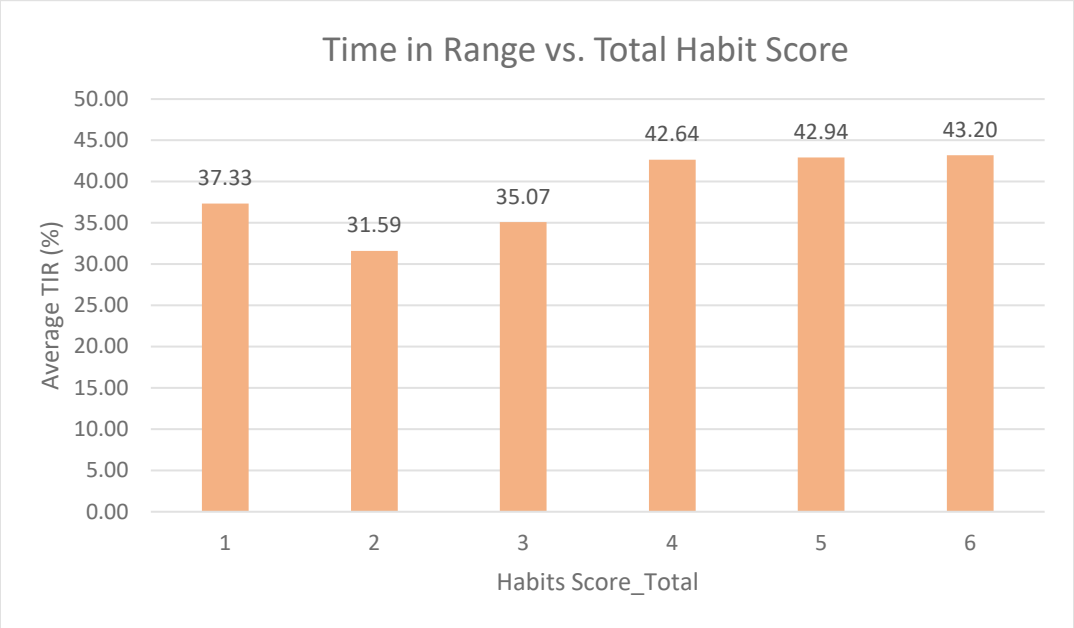


Figure 4. Time in range vs. total habit score



Although time in range was affected by the performance of a self-management habit, the observed difference between the sample means (41.5-31.4) by way of a t-Test was not convincing enough to say that the average time in ranges between patients that perform self-management habits differs significantly from patients who do not perform the same habits suggesting that the practical value was small. For this reason, the primary test for statistical significance was done using the regression analysis.

Results from the multivariate regression analysis were not statistically significant (refer to Appendix 6). It is expected that the nature of the variables was too inter-connected to be successful in differentiating individual relationships. Consequently, variables with high P-values were removed and a single linear regression analysis was performed (Fig. 5). The Significance F value and associated P-value was less than 0.005, suggesting that these results were in fact statistically significant and that a predicting relationship was identified between the self-management habits and time in range. Conversely, the low R^2 value (0.03) reflected a poor relationship between the two variables, despite the statistical significance. Again, this may be attributed to the close nature of the dependent and independent variables. A second linear regression analysis was conducted to evaluate the relationship between sex and time in range (Appendix 6.1). Unfortunately, there was no statistical significance to the findings.

Figure 5. Results of linear regression model

Regression Statistics	
Multiple R	0.161636927
R Square	0.026126496
Adjusted R Square	0.024632825
Standard Error	19.71795737
Observations	654

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	6800.644298	6800.644298	17.4914661	3.28086E-05
Residual	652	253496.1936	388.797843		
Total	653	260296.8379			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	28.58124281	2.920182032	9.787486702	3.3735E-21	22.84714684	34.31533878	22.84714684	34.31533878
Habits Total (0-6pts)	2.852227769	0.68197915	4.182280014	3.2809E-05	1.513087313	4.191368224	1.513087313	4.191368224

A correlation analysis (see Appendix 6.2) was also done in attempt to distinguish how strongly the relationship was between the six habits and time in range. Again, the correlation coefficient (0.16) was too low to determine a meaningful degree of predictive ability that the six habits had on time in range values therefore the results were deemed irrelevant with regard to a clinical application.

6.4 Descriptive Analysis

It was expected that the more adherent a patient with type 1 diabetes was to the self-management habits, the more glucose levels would be within target ranges. Therefore, the higher the total score for performing self-management habits would result in a higher percentage of time in range. In general, this is what was observed in the full analysis.

6.5 Limitations

Several of the dependent variables were highly intercorrelated thereby making it difficult to identify individual relationships that may have been more significant. Because of the closeness

of the predictor variables to the criterion, it was difficult to ascertain which aspect of the behavioral traits were more note-worthy.

6.6 Tests of hypotheses

The null hypothesis (H_0) that there was no correlation between self-managed behavioral habits and time in range was rejected as there was a relationship noted between the predictor variables (behavioral traits) and the criterion (time in range) by a p-value of less than 0.005 and a positive correlation factor.

The alternative hypothesis (H_1) which proposed that in pediatric patients with type 1 diabetes who use a continuous glucose monitor, there is a positive correlation between adherence to six self-management behaviors and attaining time in range targets was retained.

6.7 Alternatives Perspectives

Different statistical approaches with advanced software may have highlighted additional relationships among variables that were undetected by this sub-analysis of the UM CGM population. There may have also been too many individual data points involved in the sub-analysis to clearly distinguish key correlations.

Chapter 7. Recommendations and Discussion

7.1 Overview

In order to ensure that the information discovered as a result of thesis project is utilized in a manner that promotes better metabolic control with increased rates of glycemic goal ascertainment in patients with type 1 diabetes, there are several elements that should first be taken into consideration. Among these are the feasibility to implement the addition of time in range metric evaluations during clinical reviews with patients, the availability of appropriate device usage to accurately record time in range data in a standardized manner, and the willingness of patients to comply with adherence to self-management behaviors, regardless of diabetes device accessibility.

7.2 Applicability

If more focus can be placed on considering time in range as a glycemic metric when determining a patient's level of metabolic success, patients would have more useful resources to enhance their diabetes education related to decision making in order to make immediate adjustments to their treatment regimens, thereby improving overall metabolic control. As a result, we would expect a greater percentage of T1D patients meeting glycemic targets.

7.3 Discussion of analysis

The data from this project reveals that there is a positive relationship between adherence to self-management habits and time in range as an outcome. It is not being suggested that time in range be further studied as a replacement for HbA1c testing, but rather to be used more as a complementary metric since it has capabilities of capturing glycemic excursions that HbA1c is

unable to identify or predict. It is evident that the current methods to assess metabolic control are not inclusive of characteristics that clearly reflect more of the glycemic profile. As technology continues to evolve, clinicians and patients must be cognizant that adapting to newer methods of diabetes management must occur in order to continually improve metabolic control. Increasing access to diabetes devices, in conjunction with incorporating more reflective metrics into the evaluation of glycemic success is imperative.

7.3.1 Post-hoc Analysis

Information collected from patient records indicating the length of time since diagnosis of type 1 diabetes might have provided insight to the level of experience and duration with managing diabetes that was present in this particular population. It may have also been interesting to collect data regarding the level of independent diabetes management. It is common for parents to solely manage their child's diabetes until they reach a certain age of maturity and are thought to have a sufficient level of knowledge necessary to transition to a more independent role with diabetes management.

Chapter 8. Conclusion

8.1 Thesis Summary

The aim of this project was to see if the performance of six self-management habits had a perceived effect on time in range values. While the clinical relationship between time in range and the six habits was not as profoundly exhibited as had been hoped, the presence of a positive relationship did still exist. There were distinct differences observed between patients that performed a habit and patients that were noncompliant to the self-management behaviors with their respective time in range percentages. Overall, a relationship was identified between the two factors.

8.2 Conclusions

Pediatric patients suffering from type 1 diabetes must make many decisions on a daily basis regarding the self-management habits that they will execute in order to control glycemic levels. Research has shown that adhering to treatment plans and routinely participating in self-management habits such as frequent self-monitoring of blood glucose, using continuous glucose monitors and/or insulin pumps, frequent bolusing and bolusing before meals, and reviewing diabetes data are associated with improved glycemic outcomes.[105] This thesis project's secondary analysis evaluated the prevalence of six habits in the pediatric T1D population at the University of Michigan and the relationship with glycemic outcomes as measured by time in range. Results suggested that time in range has the potential to serve as an outcome metric for glycemic control in the future.

[105]McNally, K., Rohan, J., Shroff Pendley, J., Delamater, A., & Drotar, D. (2010). Executive Functioning, Treatment Adherence, and Glycemic Control in Children With Type 1 Diabetes. Diabetes Care, 33(6), 1159-1162. doi:10.2337/dc09-2116

8.3 Implications

Since the positive association between time in range and the six habits has been identified, it is possible to make stronger claims that this glucose metric is clinically relevant and should be incorporated into evaluations of a patient's success with diabetes control. This information could be shared with clinicians, patients, researchers, and industry partners to educate and advance the technology behind diabetes management devices and to improve the quality of life for those diagnosed with diabetes.

8.4 Recommendations for Future Research

The results of this study highlighted the need to consider the full spectrum of a patient's daily glycemic profile instead of only focusing on the three-month average, as currently measured by HbA1c levels. "To fundamentally change clinical care with use of the new metrics, it would be important to demonstrate that the metrics relate to and predict clinical outcomes. In this regard, longer-term studies relating to time spent within specific CGM glycemic ranges, diabetes complications, and other outcomes are required".[106]

Recommendations:

1. A comparative project exploring time in range in groups without CGM and those with CGM would be valuable. Depending on the results, healthcare policies could be amended to push for the need for coverage of CGM devices since usage has already been proven to reduce complications, and costs associated with T1D management. Research has shown that requesting patients without CGM

[106] Battelino, T., Danne, T., Bergenstal, R. M., Amiel, S. A., Beck, R., Biester, T., . . . Phillip, M. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. doi:10.2337/dci19-0028

devices check as frequently as necessary to obtain an accurate (real-time) value for TIR is not cost effective, nor likely to be complied with by patients due to the cost of testing supplies, the time required to check every few minutes, and the inconvenience associated with more frequent self-monitoring.

2. A longitudinal study concentrating on self-management habits and glycemic outcomes measured by time in range might be helpful in shedding light on improvements in glycemic control and the factors that drive it over time. Several time points could be used to assess the effect an increase in habit performance has on time in range.

Appendices

Appendix 1. Facilities and Resources

Resources from the University of Michigan Pediatric and Adult Endocrinology Quality Improvement (QI) Initiative and the MDiabetes Data Repository were used for this project, primarily in the form of a limited data set. This thesis project was supervised by a faculty advisor from Johns Hopkins University and two pediatric endocrinologists that are also members of the QI team at the University of Michigan.

JHU Faculty Advisor: Jeffery Kantor, PhD

Dr. Kantor received his Doctorate from Baylor University in Experimental Psychology and has over 40 years' experience conducting, directing and evaluating research programs of all sizes. He has been an Adjunct at the Graduate level for over 10 years teaching at various types of academic institutions.

UM Faculty Advisors: Joyce M. Lee, MD, MPH and Inas H. Thomas, MD

Joyce is a *Robert P. Kelch, MD, Research Professor of Pediatrics and Communicable Diseases, Associate Professor of Pediatrics and Communicable Diseases, Medical School and Associate Professor of Nutritional Sciences, School of Public Health.* Her areas of practice center on pediatric diabetes, pediatric obesity, and epidemiology.

Inas is a *Clinical Associate Professor of Pediatrics and Communicable Diseases, Pediatric Diabetes Program Director and a member of the Pediatric Diabetes Transition Clinic.* Her research interests are dedicated to the study, prevention, and early treatment of type 1 diabetes.

Appendix 2. Regulatory Approvals

Medical School Institutional Review Board (IRBMED) • 2800 Plymouth Road, Building 520, Suite 3214, Ann Arbor, MI 48109-2800 • phone (734) 763 4768 • fax (734) 763 9603 • irbmed@umich.edu

To: Andrea Haddad

From:

Michael	Geisser
Alan	Sugar
Robertson	Davenport

Cc:

Andrea	Haddad
Inas	Thomas
Joyce	Lee

Subject: Notice of Exemption for [HUM00176732]

SUBMISSION INFORMATION:
Title: T1D Management Metrics_Protocol - 1/31/2020 5:23:04 PM
Full Study Title (if applicable): DEFINING SUCCESS: REEVALUATING DISEASE MANAGEMENT METRICS IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES
Study eResearch ID: HUM00176732
Date of this Notification from IRB: 2/28/2020
Date of IRB Exempt Determination: 2/27/2020
UM Federalwide Assurance: FWA00004969 (For the current FWA expiration date, please visit the UM HRPP Webpage)
OHRP IRB Registration Number(s):

IRB EXEMPTION STATUS:
The IRBMED has reviewed the study referenced above and determined that, as currently described, it is exempt from ongoing IRB review, per the following federal exemption category:

> **EXEMPTION 4(iii) at 45 CFR 46.104(d):**
>
> **Secondary research for which consent is not required**: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
>
> **(iii)The research involves only** information collection and analysis involving the investigator's use of **identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E**, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b)

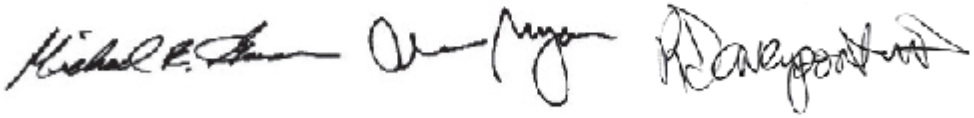
Note that the study is considered exempt as long as any changes to the use of human subjects (including their data) remain within the scope of the exemption category above. Any proposed changes that may exceed the

scope of this category, or the approval conditions of any other non-IRB reviewing committees, must be submitted as an amendment through eResearch.

Although an exemption determination eliminates the need for ongoing IRB review and approval, you still have an obligation to understand and abide by generally accepted principles of responsible and ethical conduct of research. Examples of these principles can be found in the Belmont Report as well as in guidance from professional societies and scientific organizations.

SUBMITTING AMENDMENTS VIA eRESEARCH:
You can access the online forms for amendments in the eResearch workspace for this exempt study, referenced above.

ACCESSING EXEMPT STUDIES IN eRESEARCH:
Click the "Exempt and Not Regulated" tab in your eResearch home workspace to access this exempt study.



Michael Geisser
Co-chair, IRBMED

Alan Sugar
Co-chair, IRBMED

Robertson Davenport
Co-chair, IRBMED

Appendix 3. Data Use Agreement

UNIVERSITY OF MICHIGAN

U-M Pediatrics and MDiabetes Data Repository

Responsible Use of Patient Data Disclosure Attestation

The use of Michigan Medicine's Protected Health Information (PHI) and identifiable biorepository resources for research or quality improvement purposes is a privilege, not a right. With this privilege comes the responsibility to protect the privacy of individuals who are the subjects of the data and/or biospecimens, to not use, disclose, or transfer data or biospecimens other than as permitted and to appropriately secure the data and/or biospecimens just like Michigan Medicine must do by federal and state law.

Data containing PHI will not be released to you until you demonstrate that the data will be secured through appropriate administrative, physical, and technical control throughout the life of the project. Even if all sensitive identifiers are removed from a dataset, the researcher must maintain highly ethical and secure handling practices with the patient data. Michigan Medicine reserves the right to terminate your access and use of its PHI should it find that you are in violation of any of the terms and conditions defined herein or as required by law.

PROJECT SPECIFIC INFORMAITON

Please Complete the following:

Project title: Defining Success: Re-evaluating Disease Management Metrics in Pediatric Patients with T1D

HUM #: 00176732 **Approval Status/Date:** 02/27/2020

PI Name: Andrea Haddad **Department:** Pediatric Endocrinology

Requestor's Name ***(if different than PI)*****:** _____

Data Type: PHI (Limited data set) **(Full PHI, Limited Data Set, de-identified)**

Project Synopsis/Description (please indicate if project includes pediatrics only, adult only, or combined patient data):

This is a retrospective chart review project using data from pediatric patients. The objective is to evaluate the relationship between six T1D self-management habits and a patient's time in range for glycemic outcomes.

List the researchers with access to the data (include dept. name):

Name	Department
Andrea Haddad	Peds. Endo
Thas Thomas	Peds. Endo
Joyce Lee	Peds. Endo

Storage location for patient data: M-Box, secured shared drive

1

Michigan Medicine, including the U-M Pediatrics and MDiabetes Data Repository will grant access to patient data with the explicit expectation that all responsible data use and disclosure provisions outlined below are adhered to (*please initial each item*):

a) AH I confirm that my request for Patient Data Set meets the minimum necessary standard, i.e., I will access only the minimum necessary information to satisfy my particular purpose or function.

b) AH I may use and disclose the Patient Data Set only as permitted by my approved IRB application.

c) AH I am responsible for protecting the privacy of the individuals' information contained in the Patient Data Set entrusted to me throughout the life of my project.

d) AH I am responsible for creating and maintaining a secure data environment throughout the life of my project and must provide, upon request, my written data management plan describing the technical, physical, and administrative controls that I have in place to secure the Patient Data Set from unapproved uses and disclosures.

e) AH I may not make any attempt to identify or contact individuals whose protected health information is contained in the Patient Data Set entrusted to me; unless the personally identifying information was provided for recruitment purposes as approved by the IRB.

f) AH I am responsible for all misuses and inappropriate disclosures made by me or by my study team.

g) AH I must report all unapproved uses, disclosures or inadvertent re-identifications of Protected Health Information to Michigan Medicine Privacy office immediately upon discovery. Send notice to compliance-group@med.umich.edu.

h) AH I must take action to mitigate any harmful effects caused by all unapproved uses or disclosures of the Patient Data Set.

i) AH I must promptly notify Michigan Medicine's Privacy Office if I receive a subpoena, court or administrative order or other discovery request or mandate asking me to release any part of the Patient Data Set upon receipt of such a request. Send notice to compliance-group@med.umich.edu.

j) AH I cannot disclose, transmit or share the Patient Data Set outside the University of Michigan without appropriate approvals and without having the appropriate agreements in place with the non-UM entity. Contact Inyre Lee, Director, U-M Pediatrics and MDiabetes Data Repository at joyclee@med.umich.edu.

k) AH I will not remove the Patient Data Set from the designated storage location described above.

l) AH After completion of any IRB-approved use of identifiable information for cohort development purposes, and prior to distribution of resources, the U-M Pediatrics and MDiabetes Data Repository will provide coded datasets for final analysis. Any datasets in the PI's possession that include identifying information that is unnecessary for data analysis are to be destroyed upon receipt of the coded datasets. U-M Pediatrics and MDiabetes Data Repository will retain keys to the code and will be able to obtain more information about individual subjects later, if necessary and appropriate.

m) AH U-M Pediatrics and MDiabetes Data Repository (and if applicable, CBR, Data Office, and Precision Health Initiative) Directors will work with cooperatively with the PI to resolve any perceived compliance issues regarding this project, and either the Unit Directors or the PI may bring disputes to other responsible institutional individuals and entities for assistance with resolution.

By signing this document, I attest that I read each term and condition and understand my role and responsibility in relation to data privacy and security.

Andrea Haddad

Name of Principal Investigator (Print)

Andrea Haddad 03/02/2020

Signature of Principal Investigator **Date of Signature**

Definition

HIPAA – the Health Information Portability Accountability Act of 1996, Public Law 104-191 (as amended).

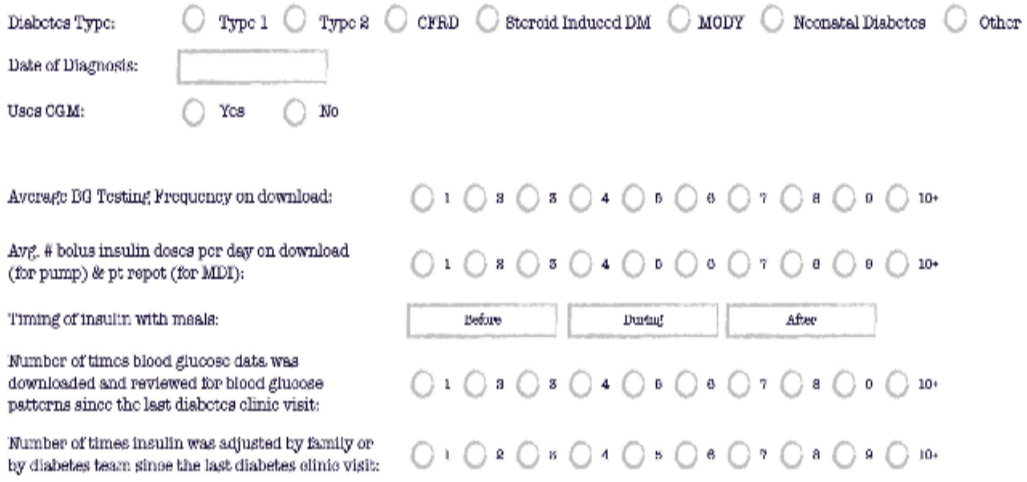
Covered Entity (CE) – any entity required to comply with HIPAA privacy and security rules. The University of Michigan Hospital System (UMHS) is considered a covered entity because it provides health care services. 45 CFR 160.103.

Protected Health Information (PHI) – information including, demographic data, that is created or received by a covered entity relating to the past, present, or future provision of healthcare or payment for the provision of health care to an individual that either directly identifies an individual or may be used to identify an individual. 45 CFR 160.103.

Limited Data Set (LDS) – are data sets stripped of certain direct identifiers specified in the privacy rule. LDS is not de-identified information under the HIPPA privacy rule. 45 CFR 160.103.

Minimum Necessary Standard – limits how much protected health information may be used, disclosed, and requested for research or other health care operational functions. The use and disclosure of protected health is limited to only what is necessary to satisfy a particular purpose or carry out a specific function. Minimum necessary standard is a key HIPPA privacy rule protection. 45 CFR 164.502(b).

Appendix 4. Flowsheets



Appendix 5. Process Measures

	Process Measures (T1D Habits)
1	Uses Continuous Glucose Monitor or checks blood glucose 4 times/day
2	Gives 3 or more insulin injections per day
3	Uses insulin pump
4	Gives insulin before eating
5	Reviewed blood glucose data for patterns at least once since the last clinic visit
6	Changed insulin doses at least once since the last clinic visit (by family or clinic)

Appendix 6. Multivariate Regression Analysis

Regression Statistics	
Multiple R	0.770978522
R Square	0.594407881
Adjusted R Square	0.592535918
Standard Error	12.74449178
Observations	654

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	3	154722.492	51574.16	317.5317479	6.6909E-127
Residual	650	105574.3459	162.4221		
Total	653	260296.8379			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	112.6811189	3.900258574	28.89068	1.0885E-118	105.0224919	120.3397459	105.0224919	120.3397459
HbA1c (%)	-0.456307402	0.534423708	-0.85383	0.393513314	-1.505712655	0.593097852	-1.505712655	0.593097852
Habits Total (0-6pts)	-0.263763295	0.455549551	-0.579	0.562789602	-1.158289651	0.630763061	-1.158289651	0.630763061
Avg. Sensor Glucose (m	-0.331917492	0.016866144	-19.6795	5.47444E-68	-0.365036194	-0.298798789	-0.365036194	-0.298798789

Appendix 6.1. Single Regression Analysis with Sex and Time in Range

Regression Statistics	
Multiple R	0.033597358
R Square	0.001128782
Adjusted R Square	-0.00040323
Standard Error	19.96941755
Observations	654

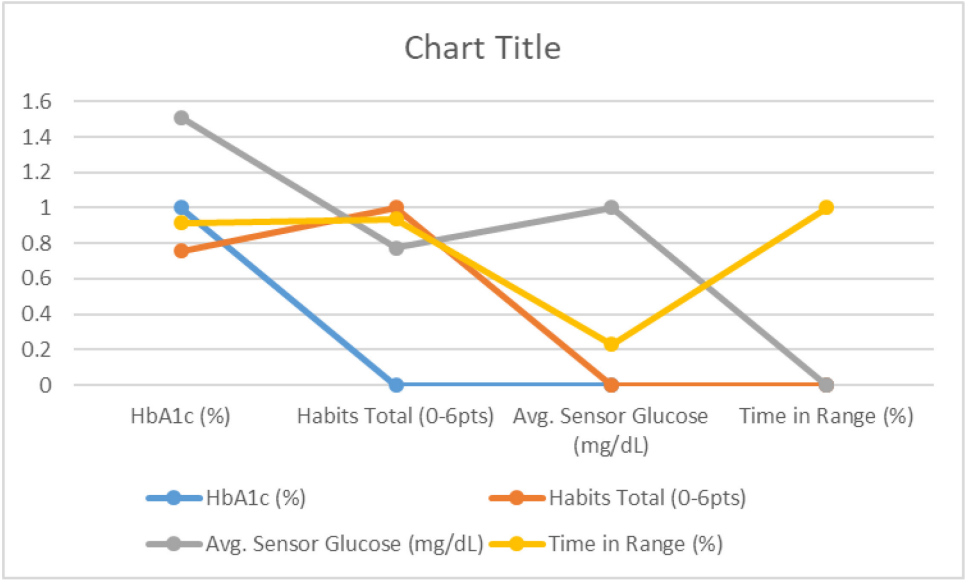
ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	293.8185035	293.8185035	0.736797844	0.391004015
Residual	652	260003.0194	398.7776371		
Total	653	260296.8379			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	39.67398119	1.118072733	35.48425788	2.1322E-154	37.47852341	41.869439	37.47852341	41.86943897
Sex Code	1.340944182	1.562199617	0.858369294	0.391004015	-1.72660518	4.40849354	-1.72660518	4.408493544

Appendix 6.2. Multivariable Correlation Results

	HbA1c (%)	*Habits Total (0-6pts)*	*Avg. Sensor Glucose (mg/dL)*	*Time in Range (%)*
HbA1c (%)	1			
Habits Total (0-6pts)	-0.244873872	1		
Avg. Sensor Glucose (mg/dL)	0.753574537	-0.224979134	1	
Time in Range (%)	-0.593689026	0.16163693	-0.770589423	1



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Curriculum Vitae

Andrea Haddad, CCRP is currently the Clinical Research Project Manager for the department of Pediatric Endocrinology at the University of Michigan. She earned her Bachelor's degree in Biological Sciences from the University of Michigan in 2010 and is currently earing her Master of Science in Research Administration from Johns Hopkins University. She has over 15 years of research experience. During that time, she has completed work in breast cancer, ophthalmology, various cancers of the head and neck, human immunodeficiency virus (HIV), and type 1 diabetes.

Andrea is a member of the National Council of University Research Administrators and the Society of Clinical Research Associates. She is also an active volunteer for the Juvenile Diabetes Research Foundation and the American Diabetes Association. She frequently serves as a presenter on a variety of topics at speaking engagements across the county to educate communities about the current research environment while promoting opportunities for participation in trials.