RESEARCH PROTOCOL

Study Title:	**Reversal of type 2 diabetes mellitus disease burden through a patented program using the non-pharmaceutical approach**
Short Title:	**Revert to non-clinical diabetes with Help Your Diabetes®**
Implementing Agency/ies:	Help Your Diabetes®
Protocol Date:	February 15, 2021
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ABBREVIATIONS AND DEFINITIONS OF TERMS

- **A1c** glycated hemoglobin $A1_C$
- **ADA** American Diabetes Association
- **BMI** body mass index
- **BP** blood pressure
- **BUN** blood urea nitrogen
- **CAD** coronary artery disease
- **CAE** clinical adverse event
- **CVD** cerebrovascular disease
- **CDC** Centers for Disease Control and Prevention
- **DCCT** Diabetes Control and Complications Trial
- **DCED** Donor Committee for Enterprise Development
- **DKA** diabetic ketoacidosis
- **DM** diabetes mellitus
- **eGFR** estimated glomerular filtration rate
- **ER** emergency room
- **FPG** fasting plasma glucose
- **GCP** Good Clinical Practice
- **GDM** gestational diabetes mellitus
- **GWAS** genome-wide association studies
- **HbA1c** glycated hemoglobin $A1_C$
- **HHS** hyperosmolar hyperglycemic state
- **HIPAA** Health Insurance Portability and Accountability Act
- **HYD®** Help Your Diabetes®
- **ICH** International Conference on Harmonization
- **LB** lower bound
- **low-carb** low-carbohydrate
- **MoCA** Montreal Cognitive Assessment Test for Dementia
- **n** sample size, number, statistical count
- **NCBI** National Center for Biotechnology Information
- **NCHS** National Center for Health Statistics
- **NDA** non-disclosure agreement
- **NGSP** National Glycohemoglobin Standardization Program
- **NHIS** National Health Interview Survey
- **NHLBI** National Heart, Lung, and Blood Insitute
- **NICE** National Institute of Health and Care Excellence
- **NIH** National Institutes of Health
- **OGTT** oral glucose tolerance test
- **PAD** peripheral arterial disease
- **redox** reduction-oxygenation reactions
- **ROS** reactive oxygen species
- **RPS** random plasma glucose

- **SD** standard deviation
- **SE** standard error
- **Sig.** statistical significance
- **SMS** short message service
- **T1DM** type 1 diabetes mellitus
- **T2DM** type 2 diabetes mellitus
- **UB** upper bound
- **UPE** ultraweak photon emission
- **US / USA** United States of America

ABSTRACT

Type 2 diabetes remains to affect American at an epidemic scale. It is a disease seen to affect people regardless of ethnic or economic background. At a prevalence of over 34.2 million in the year 2020, it can be said that nearly 1-in-10 Americans suffer from type 2 diabetes. The alarming statistic of type 2 diabetes, accompanied by its heavy burden of disease, suggests the urgent need for a more comprehensive approach to treating and managing diabetes. Help Your Diabetes® is one of a few proprietary programs that was developed with the hopes of alleviating the country of this growing disease burden by reversing the clinical state of type 2 diabetes in some patients. The Help Your Diabetes® reversal program provides supervised lifestyle and dietary plans and continuous monitoring by a network of diabetes care specialists—non-pharmacologic solutions to guide patients into a clinically healthier plasma glucose level (HbA1c ≤ 5.9%) and a state in which they are no longer dependent on anti-diabetes medications, including metformin. This study shall measure the effectivity of this program in clinically reversing a type 2 diabetes disease state through a descriptive analysis of a consecutive case series of 125 participants enrolled with Help Your Diabetes®.

PROTOCOL SYNOPSIS

Study Title	Reversal of type 2 diabetes mellitus disease burden in Americans through a patented program using the non-pharmaceutical approach
Study Rationale	Type 2 diabetes mellitus is a disease that has continuously reached world-wide epidemic levels. The physiological and financial burden takes an immense toll on the overall health and lifestyle of many Americans. This study aims to measure the effectivity of one proprietary program that targets a fully reversal of the clinical status of T2DM in its participants.
Study Objective(s)	**Primary Aims** ▪ Determine the effectivity of the HYD® T2DM reversal program **Secondary Aims** ▪ Determine HYD®'s effectivity on lowering plasma glucose ▪ Determine HYD®'s effectivity on decreasing patient drug dosages ▪ Determine HYD®'s effectivity to other clinical parameters
Study Design	This study is a sequence of consecutive case series, evaluating the effectiveness of the HYD® Program
Subject Population Criteria	**Inclusion Criteria** ▪ Americans, aged 18 years old or older ▪ Diagnosed with T2DM as defined by the ADA ▪ Complete baseline and post-program test results **Exclusion Criteria** ▪ Non-Americans or those less than 18 years of age ▪ Non-diabetic as defined by the ADA ▪ Diagnosed with T1DM ▪ Incomplete baseline and post-program test results
Number of Subjects	Across all potential sites, a total pool of 125 subjects
Study Duration	Data collection spanned 8 years since 2013. Each subject's participation shall last an ideal span of 2-to-6 months. Initial protocol drafting shall last 1-to-2 weeks. The entire study will last at least 8 years.
Study Phases	▪ Screening & Enrolment ▪ Observation ▪ Follow-up

Safety Evaluations	The study shall abide by and incorporate the necessary HYD® regulations and policies—as well as state and federal laws—necessary to ensure safe participation in its program. A vigilant monitoring and reporting system for clinically adverse effects, should they arise during the study, will be implemented.
Statistical and Analytic Plan	The study shall produce a case series of descriptive statistics representing clinically significant changes that have occurred throughout program participation. A correlational analysis of these changes will help determine if these changes are statistically significant in the sample population.
Data and Safety Monitoring Plan	Multiple measures to provide data safety, as well as the anonymization of identifiable information, will be taken. Written data will be encoded into electronic spreadsheets, saved in file formats that can be encrypted, protected, or transferred safely. A file back-up plan may also be considered to avoid permanent data loss.

BACKGROUND INFORMATION AND RATIONALE

1. Introduction

Type 2 diabetes mellitus (T2DM) is affecting Americans at a startling, increasing rate. The National Diabetes Statistics Report of the Centers for Disease Control and Prevention (CDC) published that an estimated 34.2 million Americans suffer from diabetes—a prevalence of 10.5% of the US population. In other words, about 1-in-10 Americans would have T2DM. This latest prevalence, reported in 2020, is nearly 4 million cases more than what was published by the CDC in their previous 2017 report (9.4%) (Centers for Disease Control and Prevention, 2020). Having first emerged at epidemic proportions in the 20th century, T2DM continues to seemingly remain "unchecked" well into the 21st century (Engelgau, et al., 2004).

Hyperglycemia—or the clinical finding of high blood sugar—is the core pathology of T2DM. Hyperglycemia is a known major risk factor for a myriad of medical complications and overall wellness impediments. Among the medical complications that develop in the setting of T2DM due to hyperglycemia are microvascular complications—i.e., diabetic retinopathy, diabetic neuropathy, diabetic nephropathy—and macrovascular complications—e.g., atherosclerosis leading to coronary artery disease (CAD), peripheral arterial disease (PAD), and cerebrovascular disease (CVD) (Fowler M. J., 2008). A persistent progression of diabetes burden, especially in the USA, highlights that T2DM is definitely more than just hyperglycemia and uncontrolled sugar metabolism. In fact, T2DM is a whole sequela of metabolic problems including but not limited to carbohydrate, lipid, and protein metabolism associated with insulin resistance and impaired insulin secretion (Florence & Yeager, 1999). Despite the fact that current T2DM pathology goes beyond hyperglycemia, the pharmacologic and dietetic control of dietary sugar and simple carbohydrates has often remained the primary (and sometimes only) thrust for most diabetes management plans.

The continuous upward trend of T2DM burden in the USA and worldwide suggests the growing urgency for more comprehensive approaches to prevent, delay, and manage the diabetes. This study protocol proposes a collection of multiple descriptive analyses in the form of consecutive case series designed to assess and evaluate the effectivity of the Help Your Diabetes® program, focusing on its patented non-pharmacologic approach to managing diabetes symptoms and morbidity—the Type 2 Diabetes Reversal System.

2. Review of Related Literature

2.1. Diabetes Classification

The term *diabetes* etymologically comes from the Latin and Greek words for siphon. This directly references to the excessive passage of urine or polyuria, one of the three classical symptoms noted in DM: polyuria, polydipsia (increased thirst), and polyphagia (increased

hunger). The term *mellitus* refers to the Latin word for honey-sweet, in reference to another common presentation in most DM patients—glycosuria or excessive sugar in the urine. Historically, before the wide utilization of laboratory diagnostic methods, the clinical picture of DM was described and classified based on these symptoms. Nowadays, these symptoms would only present in severe or uncontrolled cases, with pharmaceutical and non-pharmaceutical approaches reversing the effects of DM and alleviating its symptomatic presentation.

Diabetes has also been long classified into 3 major types, based on how diabetes disease onset was initially understood. The so-called 3 major types of diabetes are type 1 diabetes mellitus (T1DM) or juvenile-onset diabetes, type 2 diabetes mellitus (T2DM) or adult-onset diabetes, and gestational diabetes mellitus (GDM) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; Engelgau, et al., 2004).

T1DM, though its exact cause remains unknown, is considered to be an inborn autoimmune disease. It arises in when the body's own immune systems starts to develop defenses against the developing pancreas's own beta cells. Beta cells are the cells of the pancreas responsible for the synthesis of insulin, the body's main hormonal tool in metabolizing sugars. The eventual destruction of beta cells disables the body's function produce its own insulin, resulting in a build-up of glucose in the blood. The resulting disease profile is one that is totally dependent on an external source of insulin, hence the other name of T1DM—insulin-dependent DM. The causes behind T1DM remain to be discovered, but current research points to a strong, hereditary or genetic association. Current research also proposes a process of juvenile-onset molecular mimicry against pancreatic beta cells as a pathway that can cause T1DM. These studies suggest that certain viral infections lead the immune system into developing antibodies against viral proteins that just happen to share the same targets (epitopes) as pancreatic beta cells, leading to the chronic destruction of beta cells (Coppieters, Wiberg, & von Herrath, 2012). Type 1 diabetes accounts for nearly 10% of all diabetes in the USA. Without insulin, type 1 diabetics face death, so an accelerated trend behind the development of pharmacological insulin and insulin analogs has been a long driving force in both the innovative and economic side of public health in the country (Leichter, 2003).

T2DM is the more common clinical process of DM, affecting nearly 90% of all diagnosed DM cases in the USA. The pathological process involved in T2DM is more of an intolerance to glucose and an insensitivity or resistance to insulin than an actual lack of insulin production. In the setting of T2DM, the body's tissues fail to recognize and use insulin in the proper optimal way. More insulin must be produced by pancreatic beta cells to produce the minimal favorable outcome in metabolizing blood glucose throughout the body (glycemic control). The net effect of poor glycemic control is a chronic increase of blood glucose (hyperglycemia), the gradual destruction of tissues from the increased blood sugar, the gradual destruction of beta cells from "fatigue", and an eventual clinical pattern similar to T1DM wherein the body would depend on external insulin due to beta cell destruction. The general cause of T2DM is multifactorial, historically associated to poor diet and inactive lifestyles (as muscle activity and weight loss have strong associations to increasing insulin sensitivity)—hence the common name for T2DM, adult-onset DM or acquired DM (Engelgau, et al., 2004). However, the growing availability of genetic

studies, such as genome-wide association studies (GWAS) and other association studies on candidate genetic variations, have pointed to genetic and hereditary risk factors that significant improve one's susceptibility to "acquiring" T2DM (Cutiongco-dela Paz, et al., 2019). Genetic markers have also pointed to just how well a patient may respond to certain anti-diabetes medications such as metformin—the effectivity of such drugs and their required dosage seems to have a strong genetic basis (Paz-Pacheco, et al., Evaluation of candidate genetic variations as pharmacogenetic markers for metformin among Filipinos, 2019; Paz-Pacheco, et al., Evaluation of candidate genetic variations as pharmacogenetic markers for metformin among Filipinos, 2019). Even gene expression—responsible for disease outcome and symptomology—may have a strong genetic background (Nevado, et al., 2019). Though not as deadly as T1DM, since early and low-risk cases of T2DM can be primarily managed pharmacologically without insulin, T2DM has reached epidemic levels (Centers for Disease Control and Prevention, 2020). The clinical moniker of T2DM as "adult-onset" or "acquired" is also commonly growing outdated. The T2DM epidemic has produced a rise in T2DM in the young with incidence as early as 6-15 years old, increasing the overall public health burden (Alberti, et al., 2004); and new innovations behind genetic testing have been producing more and more genetic markers with promising potential as diagnostic markers in predicting the onset of T2DM (Cutiongco-dela Paz, et al., 2019; Centers for Disease Control and Prevention, 2020).

GDM refers to the processes of glucose intolerance and insulin sensitivity (including hyperglycemia and diabetes risk) observed during pregnancy. In such cases, a return to normal metabolic state is expected and often seen after delivery. The metabolic error here is credited to the increase of several hormones in the setting of pregnancy, including estrogen, human placental lactogen, and cortisol, that have the ability to block or counteract with the body's own insulin. GDM often begins about 20-24 weeks into the average pregnancy and is diagnosed in nearly 3%-8% of all pregnant women in the USA (Johns Hopkins Medicine, 2021; Engelgau, et al., 2004).

As a growing amount of studies reveal that the pathological picture of diabetes is an overlap between errors of metabolism rooted in acquired, hereditary, genetic, and dietary/lifestyle reasons, the rigid classification of diabetes into 3 major types is steadily becoming less and less useful for the overall management of diabetes. It is clear that effective diabetes management needs to cover approaches beyond glycemic control, including nutrition and diet, lifestyle changes, and pharmacologic/non-pharmacologic control of hormones, proteins and lipids, as well. The consideration of early detection of screening of diabetes risk through the use of established clinical and genetic markers is also crucial in hampering the T2DM epidemic.

2.2. Diabetes Prevalence

The National Health Interview Survey (NHIS) is a vital survey overseen by the National Center for Health Statistics (NCHS) of the CDC that started collecting disease prevalence data in the USA since 1957. It is considered to be the longest running health survey in the USA, and among the most startling findings published by the NHIS is a 4- to 8-fold increase of diabetes diagnoses in the past 50 years, from 1.6 million confirmed cases in 1958 (0.9% prevalence) to

12.1 million confirmed by 2000 (4.4% prevalence) (National Center for Health Statistics, 2020; Engelgau, et al., 2004). By 2017, the prevalence would be around 9.4%, and by 2020, a report of 10.5% prevalence would be published in the CDC's National Diabetes Statistics Report (Centers for Disease Control and Prevention, 2020; National Center for Health Statistics, 2020).

Globally, prevalence data on diabetes is well-documented, showcasing a steady rise in disease prevalence year after year. Varying prevalence rates have been reported in descriptive studies performed among particular regions and among specific ethnicities. New data in the USA suggests that African Americans, Native Americans (including the Native Pacific Islanders of Hawaii and Guam), Hispanic/Latino Americans, and Asian Americans have a particularly higher risk for T2DM, suggesting ethnic, cultural, and genetic predispositions. Prevalence among Native Americans has shown to be up to 5 times those of White Americans (HealthyPeople, 2020). Though specific ethnic and regionalized population-based data remains sparse on T2DM prevalence over the past half century, recent studies have reflected a general increase, nonetheless (National Center for Health Statistics, 2020; HealthyPeople, 2020).

The epidemic disproportion between advances in current diabetes management and the continuing growth in diabetes prevalence reflects to a certain gap or lack in ongoing method to screen, prevent, manage, and treat the illness. There is an urgency for practitioners to strengthen their efforts in bridging the gap between the established mechanisms and theories in research and observed risk factors that continue to worsen epidemiological environment and prevalence of diabetes.

2.3. Diabetes Risk and Burden

All forms of diabetes share the characteristic of chronic hyperglycemia—an uncontrolled increased level of glucose (sugar/carbohydrates) in the blood. This is perhaps why the target of diabetes management historically and modernly has primarily been the prevention and control of hyperglycemia via a wide array of pharmaceutical therapies (e.g.: metformin, anti-diabetes drugs, insulin analogs, etc.) and non-pharmacologic interventions (e.g.: lifestyle modification, physical exercise, dietetics, nutrition & supplementation, etc.).

The importance of preventing chronic hyperglycemia cannot be overstated, as complications arising from diabetes—directly or indirectly—are epidemiologically known to be among the leading causes of morbidity and mortality (Fowler M. J., 2008; Centers for Disease Control and Prevention, 2020). DM was the 7th leading cause of death back in 2014, and despite varying prevalence data across different regional study populations, DM seems to epidemically impact all corners of the world, despite social, economic, and ethnic background.

Besides death, DM is associated with many major complications that can affect the body systemically, therefore manifesting in various parts of the body. Severe cases of T2DM have been associated with stroke (secondary to cerebrovascular disease/CVD), acquired blindness (secondary to diabetic retinopathy), heart attack (secondary to coronary artery disease/CAD) renal failure (secondary to diabetic nephropathy), and lower-limb amputation (secondary to

peripheral arterial disease/PAD). The sequelae of insulin resistance and glucose intolerance that leads to hyperglycemia causes systemic physical and biochemical changes to the body's blood plasma that damages microvasculature and other small connective tissue necessary for normal tissue oxygenation and function. Lack of adequate tissue oxygenation leads to ischemic damage which, over time, will lead to late-stage organ damage, as is the case in diabetic retinopathy, diabetic nephropathy, or diabetic neuropathy—the clinically distinguished "microvascular" complications.

Other physical and biochemical processes in the setting of hyperglycemia have been proposed to further elucidate the etiology of long-term diabetes morbidity. The free radical theory suggests that a hyperglycemic state predisposes cells and tissue to damage from reactive oxygen species (ROS). Also known as free radicals, ROS are unpaired, "wild" electrons from molecules of byproducts of imbalances in the natural biochemical reactions that run the body called reduction-oxygenation (redox) reactions. Redox reactions are popularly considered by biologists, biochemists, and nutritionists to be the body's cellular process of packaging and transferring energy (electrons). Biophysical and chemical changes caused by the hyperglycemia (e.g.: increased glucose, pH changes, electrostatic and chemiosmostic changes, etc.) are said to favor free radical release, and ultimately insulin resistance, glucose intolerance, and possible cellular damage (including possible beta cell damage) (Garvan Institute of Medical Research, 2009).

Biophysicists and dieticians subscribing to the newly emerging fields of bioenergetics, photobiology, photochemistry, and thermal medicine also suggest that an imbalance in the upkeep and transfer cellular energy (in the form of photons) made favorable in the setting of chronic diseases like diabetes leads to cellular and tissue destruction and death. This has been reportedly measured by the increased levels of photons (in the form of UPEs or ultraweak photon emissions) released by the body in a diseased state, coupled with low-photon intake due to the ingestion of "energy-empty" products found in processed foods (Tsuchida, Iwasa, & Kobayashi, 2019; LaCour, 2021).

A further state of debilitating macrovascular complications can further arise in long-term diabetes. Atherosclerotic changes can occur in larger organ vessels caused by plaque build-up and arterial stiffening due to chronic ischemic damage (microvascular damage) and the sequela of poor lipid, hormone, and protein metabolism. Macrovascular atherosclerosis leads to devastating disease outcomes, such as heart attacks, stroke, and amputation; and in the setting hyperglycemic crisis due to poor glycemic control, DM can manifest as one of two medical emergencies, namely hyperomolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA) (Fowler M. , 2009).

In the year 2016, DM alone was responsible for over 16 million emergency room consults and 7.8 million hospitalizations in the USA—1.7 million of which for major vascular diseases: 313 thousand of which for stroke, 438 thousand of which for heart attack, 130 thousand of which for lower-extremity amputation. 209 thousand cases of DM in 2016 have also been reported discharged for hyperglycemic crisis. By 2017, the year-end cost of managing diagnosed diabetes

in the USA estimated at about $327 billion--$237 billion in direct costs and $90 in indirect costs (a significant rise from $188 billion in direct costs and $73 billion in indirect costs in 2012). By 2017, it was estimated that each patient with a confirmed diagnosis of diabetes would add about $9,601 in excess annual medical costs (form a previous average of $8,417 in excess costs back in 2012).

The overall effect of a chronic disease like DM has also been well-established to lead to numerous indirect burdens, such as patient discouragement or frustration, caregiver burnout, clinical depression, immune suppression, and a heavy economic/financial toll (Polonsky, 1999). Research studies have replicated the association between depression and diabetes numerous times, strengthening the fact that both conditions share multiple underlying pathological processes and mechanisms psychologically and biologically. Unfortunately, cases of depression and other mental symptoms such as anxiety and frustration are often missed in the diagnosis and management of diabetes (Holt, de Groot, & Golden, 2014). This may be due to the lack of a psychiatric or psychological edge in commonly used diabetes screening tools, as well as a cultural stigma behind the appropriate use and prescription of psychiatric and psychological interventions, including counseling.

DM is also a well-associated condition to other challenging medical comorbidities, such as hypertension, dyslipidemia, and obesity. If seen together with these comorbidities, they produce an even graver clinical picture distinguished as metabolic syndrome. In addition to the traditionally acknowledged issues in DM, new evidence has emerged that T1DM, T2DM, and even GDM could have strong associations with additional comorbidities such as cognitive impairment (“brain fog”), incontinence, fracture risk, infection risk, and cancer risk (HealthyPeople, 2020; Nathan, 2015). Needless to say, the human and economic costs introduced by an epidemic like diabetes is more than enough to bring diabetes research into light and translate data into applicable interventions to prevent and manage the disease more effectively.

2.4. Trends in T2DM Management and the Four Transition Points of DM Intervention

T2DM is a continuous disease—there is no complete or permanent cure. Historically, the prognosis of being diagnosed with T2DM once meant the patient would forever be dependent on medications and lifestyle limitations. But given a larger understanding of the T2DM as a multifactorial metabolic condition through progressive and expansive research, this is no longer the case. T2DM may never be completely cured in the body (the exact molecular causes behind insulin resistance and glucose intolerance still remain an unknown in current medical research), but there are various interventions and lifestyle changes that can be performed—if properly—to bring even the most debilitating complications caused by DM into remission (WebMD LLC, 2021; Nathan, 2015). The HYD® program considers diabetes as reversed if the right dietary and lifestyle changes are enough to bring a patient’s HbA1c down to 5.9% or lower and remove all dependencies on anti-diabetic medications including metformin (Help Your Diabetes, 2018).

Currently, the medical and health care community recognizes four main “transition points” in the natural progression of disease in diabetes that offers care providers a chance to

reduce the health and economic burden of DM. It is at these four points (i.e.: prevention, testing, care access, and care quality) that proactive interventions can be introduced to expect favorable outcome (HealthyPeople, 2020).

A growing number of dietary plans and supervised diet programs have been prescribed by health care providers to provide intervention at the level of prevention (WebMD LLC, 2021). The control of simple carbohydrate intake—the most common form of dietary intervention against diabetes—tackles the concern of high blood glucose levels in the process of diabetes etiology; but it is far from the only dietary measure required to completely prevent diabetes onset. Lipid metabolism is also a major player in the established pathophysiology of diabetes. Hyperlipidemia and dyslipidemia, or an increase and imbalance of lipid (cholesterol) in the blood stream is known to further microvascular and macrovascular damage. Increased body weight is also associated to dyslipidemia is well associated to insulin insensitivity and poor glucose control. Dietary measures effective at preventing DM onset have to be comprehensively nutritious and cannot simply be “low-carb”. Likewise, cigarette smoking and excessive alcohol intake have been reported in numerous replicable studies to have a direct association to insulin resistance. Proactive DM prevention thus requires a balanced diet, an avoidance of non-nutritious carbohydrates and lipids, an active lifestyle, smoking cessation, and alcohol intake moderation (Harvard TH Chan School of Public Health, 2021).

The second possible of intervention hits at the level of diagnostics and testing. A main contributor to the growing burden of DM is the growing number of undiagnosed diabetics in the population. Undiagnosed diabetics are most often diabetes cases without the predominant presenting symptoms or clinical signs. These include patients that are asymptomatic or won’t probably present with a clinical concern until too advanced in disease stage. Other cases include patients that are sub-clinical, or “borderline”, that don’t necessarily reach threshold levels in which most physicians would confidently call a diagnoses. Left on their own and without proper education or preventive measures, sub-clinical diabetics can rapidly progress to the DM disease state before ever knowing. Where health care availability and accessibility is problematic due to various concerns such as economic and geographic, undiagnosed cases include symptomatic and problematic DM patients that are unable to receive proper diagnostics and therapy for their illness. In the USA, nearly one-fourth (23.8%) of the American diabetic population is undiagnosed (Centers for Disease Control and Prevention, 2020). Universally reviewed diagnostic cut-offs of glucose in blood guide the current diabetes diagnosis guidelines (with a few nuances and exemptions found in Asian, Japanese, Asian American, and Japanese American laboratory cut-offs, guided by recent population and genetic studies) (Nathan, 2015).

According to the American Diabetes Association (ADA), a diagnosis of diabetes can be made with a fasting plasma glucose (FPG) level of 126 mg/dL or more (with fasting defined as no caloric intake for at least 8 hours); an HbA1c level of 6.5% or more (via laboratory methods only NGSP-certified and standardized to the DCCT assay); a random plasma glucose of 200 mg/dL or more in the setting of classic hyperglycemia symptoms or hyperglycemic crisis; or a plasma glucose of 200 mg/dL or more during a 2-hour OGTT with a glucose load of 75 g anhydrous glucose dissolved in water (American Diabetes Association Professional Practice Committee,

2021). Many uncontrolled cases of diabetes in America stem from a growing number of undiagnosed cases. Randomized trials backing the US Preventive Services Task Force shows that screening for T2DM may not have a significant impact in improving outcomes after 10 years, but screening and proper diagnosis does promise benefits in preventing end-organ damage among high-risk cases after 23-30 years. The US Preventive Services Task Force thus recommends routine blood glucose screening in high-risk persons, namely those aged 40-70 years, the overweight or obese, those presenting with a strong family history of DM, and those presenting with other chronic metabolic comorbidities (hypertension, dyslipidemia, etc.) (Pippitt, Li, & Gurgle, 2016).

The third level implements proactive interventions at the level of care access. The current out-of-pocket and self-insured health system dominant in the US has led to a growing number of people without good health care coverage. As it is across other diseases, public health studies have shown that a lack of health care coverage is directly associated to poor glycemic control. In a study performed in 2012, persons unable to make a health care visit in one year were 5.5 times more likely to have an HbA1c readings greater than 9% against those who managed to at least get four or more health care visits. Uninsured persons were 2.4 times more likely to get HbA1c levels higher than 9% versus those with active insurance (Zhang, et al., 2012). Most strategies targeted at this transition point appeal to public health measures, governance, and policy maker to improve health care accessibility for those in need of health care.

The fourth transition point of intervention taps at the appropriateness and overall quality of health care given to diabetes patients. At this level, most management plans aim only to control plasma glucose levels with the use of pharmaceuticals with little-to-no adjunctive therapies involving the non-pharmacological approaches. The disregard for a holistic, biopsychosocial model for health and the end-result in a pharmaceutical-only approach to T2DM—or any disease for this matter—is an often incomplete, inappropriate management plan that falls short in meeting the health goals of the patient and care provider. Successful diabetes care has shown to encompass systematic approaches that build and support behavioral change (lifestyle, activity, diet, and stress management), adequate self-monitoring, appropriate pharmaceutical dosing, and educational awareness of how to prevent debilitating complications (wound care, hygiene, proper supplementation, infection protection, immunizations, etc.) (American Diabetes Association Professional Practice Committee, 2021).

Findings in this proposed study hope to strengthen the claims behind a system that provides intervention at the final transition point, unique to Help Your Diabetes®. The system at HYD® hopes to move diabetic participants from a state of symptomatic, clinical diabetes and inadequate or incomplete diabetic care and into a state of non-symptomatic, sub-clinical diabetes with adequate, comprehensive adjunct non-pharmaceutical care. Founded on the hopes of bringing non-pharmacologic solutions to treat diabetes, HYD®'s patented program goes beyond the typical supervised diet program by providing a comprehensive approach that incorporates regular consults, lifestyle modifications, dosage monitoring, supplementation, physical exercises, community support, and diabetes education all in conjunction to patients'

current prescribed medications and the concurrent management plans from their primary physicians (Help Your Diabetes, 2018).

3. Compliance Statement

This study shall be conducted in full accordance with all applicable Help Your Diabetes® policies and procedures, as well as all federal and state law regulations including the Good Clinical Practice (GCP): Consolidated Guideline approved by the International Conference on Harmonization (ICH). All episodes of non-compliance will be documented.

There will be restricted access to raw databases, and only the study's investigators, research associates, and reviewers will be authorized to handle raw data. Measures are undertaken for the safekeeping and integrity of data. Raw data will be encoded into electronic data tables of access limited only to the study's investigators, associates, and reviewers. Once clinical data is encoded, no revisions will be made without the expressed unanimous agreement of the investigators. The dissemination of electronic data will be regulated and controlled by the Help Your Diabetes® and its investigators. All investigators, associates, and reviewers will enter a non-disclosure agreement (NDA) to preempt the unwarranted extension of intellectual property.

New knowledge obtained from the study will be attributed to the investigators, associates, and reviewers as the authors and discoverers. Citations and reproduction of concepts relevant to any new findings from this study should be made after informing and securing consent from the study authors and sponsors. Citations should acknowledge the study authors appropriately.

Publication of this study will at least include the lead investigators as the principal authors with co-investigators, associates, and reviewers as co-authors. Written documents will be discussed thoroughly upon completion, upon medical/technical review, and prior to submission.

The investigators will perform the study in accordance with protocol, will obtain consent or assent, and will report unanticipated problems involving risks to subjects or others in accordance with Help Your Diabetes® policies and procedures and all state and federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research participants during and after the study.

STUDY OBJECTIVES

1. Primary Objective

- To determine the effectivity of the Help Your Diabetes® nutritional and non-pharmacological reversal program for type 2 diabetes mellitus

2. Secondary Objectives

- To determine the effectivity of the HYD® program to patient plasma glucose levels
- To determine the effectivity of the HYD® program to patient anti-diabetes drug adjustments
- To determine the effectivity of the HYD® program to other clinical parameters

INVESTIGATIONAL PLAN

1. General Schema of Study Design

This study will conduct multiple retrospective descriptive studies in the form of consecutive case series projecting the efficiency of the HYD® program to type 2 diabetes mellitus and other clinical parameters.

2. Study Duration and Number of Sites

2.1. Duration of Study Participation

The study will retrospectively review participant charts going back 8 years ago, from the period 2013 to 2021. Each participant's duration in the study will vary on the personalized plan HYD® prescribed to them. The duration of a complete program has ranged from as short as 3 month to as long as 7 months, with an average of 5 months per program participant.

2.2. Total Number of Study Sites & Total Number of Subjects Projected

The study will be conducted at least 4 physical clinical sites in the United States where the HYD® program is offered. The physical sites include the HYD® Corporate Diabetes Treatment Center at Grapevine (Texas) and at three licensee clinics hosted by physicians offering the HYD® in El Dorado Hills (California), Huntington (New York), and Indiana (Pennsylvania). Remote staff employed by the Corporate Diabetes Treatment Center will also offer the program via virtual consult, servicing the areas of the following metropolitans and cities: Honolulu (Hawaii), Seattle (Washington), Salt Lake City (Utah), Denver (Colorado), Los Angeles (California), San Diego (California), Las Vegas (Nevada), Phoenix (Arizona), Houston (Texas), San Antonio (Texas), Oklahoma City (Oklahoma), Wichita (Kansas), Kansas City (Missouri), St. Louis (Missouri), Indianapolis (Indiana), Cincinnati (Ohio), Nashville (Tennessee), Minneapolis (Minnesota), Chicago (Illinois), Lancaster (Pennsylvania), Philadelphia (Pennsylvania), Boston (Massachusetts), Charlotte (North Carolina), Charleston (South Carolina), Atlanta (Georgia), Orlando (Florida), Tampa (Florida), and Miami (Florida).

The study assumes to provide data on at least 100 to 125 participant cases. Sample size calculations and projected number of participants will be guided accordingly by the annual average inflow of clients/patients with HYD®. Statistical treatment and estimation of the appropriate sample sizes shall be computed using methods adapted by the Donor Committee for Enterprise Development (DCED) in their Practice Guidelines or Conducting Research (Fairbairn, Kessler, & Tanburn, 2015).

3. Study Population

The target population for study participants shall consist of all Americans, aged 18 years old or older, diagnosed with type 2 diabetes mellitus as defined by the ADA (American Diabetes Association Professional Practice Committee, 2021), and having purchased and duly consented into the HYD® program for T2DM reversal.

3.1. Inclusion Criteria

All the following will be required from a HYD® program participant to be an eligible participant in this study:

- Diabetes mellitus diagnosis, as defined by the ADA (American Diabetes Association Professional Practice Committee, 2021) by at least one of the following criteria at the time of program participation:
  - Fasting plasma glucose (FPG) of at least 126 mg/dL (7.0 mmol/L)
  - Glycated hemoglobin $A1_C$ (HbA1c) of at least 6.5%
  - Plasma glucose post-2-hour 75 g oral anhydrous glucose tolerance test (OGTT) of at least 200 mg/dL (11.1 mmol/L)
  - Random plasma glucose (RPG) if at least 200 mg/dL (11.1 mmol/L) with classic signs and symptoms of hyperglycemia or hyperglycemic crisis

- Complete baseline and post-program clinical parameters, such as anthropometrics, laboratory results, and medication dosages

3.2. Exclusion Criteria

Any of the following will warrant a HYD® program participant ineligible for participation in this particular study:

- Non-diabetic, as defined by the presence of all of following ADA (American Diabetes Association Professional Practice Committee, 2021) criteria at the time of program participation:
  - FPG less than 100 mg/dL (5.6 mmol/L)
  - Plasma glucose less 140 mg/dL (7.8 mmol/L) post-2-hour 75 g OGTT
  - HbA1c less than 6.5%

- Diagnosis of type 1 diabetes mellitus at the time of program participation

- Incomplete baseline and post-program clinical parameters, such as anthropometrics, laboratory results, and medication dosages

STUDY PROCEDURES

1. Screening & Enrolment

Americans aged 18 years or older diagnosed with type 2 diabetes mellitus are invited to participate in the HYD® proprietary T2DM reversal program online via the website https://helpyourdiabetes.com/ or through phone at 1-800-321-9054, where they can book a schedule for a Wellness Consultation. During the Wellness Consultation, a Wellness Coordinator from HYD® will determine a candidate's eligibility to participate in the HYD® program. Consent, payment, and financing agreements are collected upon completion of enrolment, and patient is given a New Patient Kit informing the participant of important contacts, phone numbers, and details regarding their plan.

Program participants who meet all the applicable inclusion criteria and are without any exclusion criteria are considered further eligible to participate in this study.

2. Observation

2.1. Baseline Visit

Upon acceptance into the HYD® program, a Plan of Action will be drafted to determine the participant's prescribed program length. The Plan of Action is determined by a rubric of points called the Diabetes Score, a proprietary scoring system based on baseline HbA1c levels (taken by a DCA Vantage® Analyzer), the running number of oral medications prescribed daily, the number of units insulin prescribed daily, the overall total of medications prescribed daily, weight, and age.

The most recent anthropometrics, lab results, and list of medications are taken and recorded by the Wellness Coordinator and the HYD® Support Doctor during the first visit.

2.2. Monitoring

An unlimited number of support sessions are made available throughout the plan period through 1-on-1 phone calls, video calls, and emails. Entertaining and monitoring of such sessions vary according to the availability of the Wellness Coordinator and/or the Support Doctor, but access to these is made available 7 days a week. Monitoring of program progress and compliance can be performed through these support sessions with the Support Doctor recording blood sugar readings and recommending updates to current medications in coordination with the participant's primary physician.

Weekly group phone calls and video conferences are also held throughout the program period, where participants can listen in on various pre-determined health topics recommended

for diabetes management. Here, participants can also join in on Q&A sessions and dynamic forum discussions.

The program also provides several activities and products for the participant included in the plan. Among these activities and products are proprietary meal plans, access to over 240 diabetic-appropriate home kitchen recipes, a quick reference guide to food (Enjoy/Avoid List), shopping lists, weekly training videos, monthly newsletters, monthly HYD® nutritional supplements, and a 30-day HYD® Gentle Cleanse.

3. Follow-up

Upon completion of plan, the participant submits a set of lab results to be received and recorded by the Wellness Coordinator or the Support Doctor. A final Wellness Consultation is performed to determine if the participant has successfully achieved the goals of the program.

4. Unscheduled Appointments

Appointments for baseline and follow-up Wellness Consultations are pre-scheduled over the phone. Some HYD® clinics may also send text reminders via SMS or email prior to appointment dates and dates to report labs and medications (which can also be performed over phone or email). Unscheduled appointments, especially through the current pandemic period, are not entertained.

5. Subject Completion/Withdrawal

5.1. Study Graduation

A participant is considered graduated from the study after the follow-up Wellness Consultation is completed and once the Support Doctor determines if participation in the program rendered the diabetes reversed or simply controlled (not reversed). A participant is considered an early graduate if they meet study completion requirements (full diabetes reversal) before their prescribed plan duration.

5.2. Withdrawal & Termination

Withdrawal or termination from the study is permitted by the study participants due to whatever reasons (e.g.: withdrawal of consent, failure to comply with program, failure to complete study requirements, adverse event, death, etc.).

A participant unwilling to participate in the study may continue to participate and complete their involvement with the program. Participants withdrawing from the program entirely will have their records deleted. Information regarding participant termination will remain

confidential, but their terminated participant records will not be used for the study's descriptive and analytical purposes.

STUDY EVALUATION & MEASUREMENTS

1. Screening & Monitoring Evaluation

Several qualitative and quantitative outcome measures will help investigators determine the efficiency of the HYD® program in T2DM reversal.

1.1. Medical Record Review

The Wellness Consultation will conduct a medical record review and interview with the participant, collecting data regarding their personal information (i.e.: marital status, age, residence, occupation, and length of employment), diabetes history (i.e.: length of diagnosis, symptomatology, and personal goals or understanding towards diabetes reversal), plasma glucose history, medical history, surgical history, social history, insurance information (if applicable), and pertinent medications list (with complete dosages).

1.2. Physical Examination

The Wellness Consultation will record pertinent anthropometrics mainly through contactless phone consultations, namely height and weight. Height and weight can also be used to calculate a participant's body mass index (BMI), a measure used to further evaluate health risk in terms of body fat (e.g.: obesity, etc.). There are numerous contemporary recommendations in computing for BMI based on ethnic background, but the BMI to be used in this study will be adapted from the standardized BMI calculation as recommended by the National Institutes of Health (NIH)-National Health, Lung, and Blood Institute (NHLBI) (National Institutes of Health, 2021).

Blood pressure will be recorded during the Wellness Consultation and reported at least weekly until the end of the participant's plan. The normal systolic blood pressure is no more than 120 mmHg, and the normal diastolic is no more than 80 mmHg—also notated as 120/80. Normal rises and falls in blood pressure are expected throughout the day due to one's daily activity, emotional, and stress levels; but abnormal increases and decreases in blood pressure are considered possible clinical signs of underlying disease (Centers for Disease Control and Prevention, 2021).

1.3. Laboratory Evaluations

The primary laboratory results recorded during the Wellness Consultations are HbA1c and FPG. Participants are encouraged to submit other lab results acquired throughout their plan period. Other pertinent laboratory evaluations that this study can look into includes estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN) levels, creatinine levels, and total cholesterol levels.

1.4. Other Evaluations & Measures

The study will also utilize the proprietary Diabetes Score system of HYD®. The Diabetes Score assigns a certain number of points for a participant in each of 5 criteria: (1) HbA1c, (2) number of anti-DM medications prescribed, or amount of insulin units required per day, (3) total number of maintenance medications prescribed daily, (4) weight, and (5) age group. The Diabetes Score recruits the participant into 1 of 3 HYD® proprietary plans: (1) a 2-month plan for those garnering 5-9 points, (2) a 4-month plan for those garnering 10-18 points, and (3) a 6-month plan for those garnering 19-25 points.

2. Risk of Bias Evaluation

2.1. Confounders

All research studies are not without confounders—variables unaccounted for in the analysis of data. This study shall disclose confounders such as age, gender, ethnicity, and family history—all of which have direct or indirect associations to diabetes disease and treatment outcomes.

Differences in energy balance and glucose metabolism found in different age and gender groups influence predisposition to T2DM and prognosis. Age-matched studies have shown that women often present with better insulin sensitivity than contemporary men (Tramunt, et al., 2020). Glycemia, or glucose levels in blood plasma, is also known to increase with age, and there have been multiple suggesting that the pathophysiology of diabetes in older adults is different than that of younger individuals (Selvin & Parrinello, 2014). Behavioral and psychological differences between varying gender and age group may also confound the study results.

Among different ethnic groups, global and regional data remains limited. However, in the US, age-adjusted prevalence studies have elucidated significant disparities in DM predisposition among the major ethnic groups. In 2013, Native Americans have been recorded to have the highest prevalence (33%). Hispanic Americans and Non-Hispanic Black Americans have 12.6% and 11.8% prevalence, respectively, and Asian Americans have 8.4%. Non-Hispanic White Americans and Native Alaskan Americans have the lowest prevalence rates at 7.1% and 5.5%, respectively (Spanakis & Golden, 2014).

T1DM, though historically considered to be the “acquired” form of DM, actually has stronger links to heredity and lineage than T1DM (which was historically considered the diabetes of newborn-onset). The recent boom of genetic, whole genome, and twin studies have identified and validated variations in DNA that are shared in family groups strong in association to T2DM risk (American Diabetes Association, 2021).

2.2. Bias Due to Missing Data

Participants in this study are required to submit laboratory results before and after the start of their HYD® program plan. Though all participants are requested to the same laboratory evaluations outside the usual plasma glucose tests for the study, not all participants are able to do so. Variations in data available on each patient brings about a bias of “missing” data in others. Data cleaning and patient chart review can be performed to minimize missing data. Due screening and elimination of incomplete data entries with the use of statistical software can also be performed.

3. Safety Evaluation

The study will use approaches only deemed safe by the HYD® proprietary program. The study methods and program have been guaranteed safe by HYD® and their Support Doctors. Participants have also agreed to apply recommendations from the HYD® program that warrant a significant change to their medications list and diabetic care plans only if agreed upon by their own primary physicians. Any proprietary products and services rendered by HYD® (such as supplements, cleanses, exercises, and meal plans) have all been evaluated as safe and suitable by HYD® and abide by the necessary federal and state regulations and policies where they apply.

STATISTICAL CONSIDERATIONS

1. Primary Endpoint

HbA1c and medication dosages are the statistical considerations of this study, as the HYD® program defines a decrease of HbA1c to 5.9% and the removal of anti-DM medications as a successful reversal of T2DM.

The primary HbA1c outcome will be an end-result of a 5.9% HbA1c level or lower after a successfully completed their prescribed plan. The primary outcome measurement for anti-DM medications is an end-result dose of 0 in previously prescribed anti-DM medications, including metformin and insulin analogs.

2. Secondary Endpoints

Secondary outcomes for reporting include percent-decreases in plasma glucose levels expressed in HbA1c or FPG after a fully completed HYD® plan as clinically significant in managing the control of diabetes (but not its reversal). The study will also describe percent-decreases in anti-DM medications after HYD® plan completion as clinically significant in DM control. Based on the guidelines reported by the NCBI of USA and research recommendations by the NICE of UK, as reduction of 0.5% in HbA1c can be considered clinically significant, but among patients with a baseline HbA1c of < 8.5%, a reduction of 0.4% can already be considered significant (Adler, et al., 2019; Hameed, Manzar, Raza, Shareek, & Hussain, 2021).

Other outcomes to be described will be post-HYD® program percent-changes in other pertinent drug dosages, other pertinent clinical findings (i.e.: BP) and other pertinent lab results (i.e.: total cholesterol, BUN, creatinine, eGFR, etc.). A clinically significant decrease in BP at least 5 mmHg in systolic blood pressure (Guthrie, et al., 2019).

3. Statistical Control of Bias and Confounding

The study will produce a series of descriptive statistics that will best describe the overall effect of the HYD® program to T2DM. To produce favorable statistical power and confidence intervals within subgroups similar to the study's general population it represents (e.g.: confounders, by age group, gender, etc.) the amount of variability and deviation in these results will also be expressed through descriptive statistics with their respective standard deviations and standard errors.

4. Statistical Methods

4.1. Baseline Data

Baseline data—anthropometrics, laboratory results, medication dosages, etc.—shall be represented in descriptive statistics. Descriptive statistics shall present the overall sample in respect to the study population of American adult diabetics the study hopes to represent. Wherever applicable or necessary, matching of analysis subgroups by variables such as age, sex/gender, or age group can be performed to further control for confounders and other potential biases. Mean percentages, percent-change, and standard deviations will be calculated and presented to elucidate a thorough description of the study sample and the outcome measures before the intervention (HYD® program) and after the intervention.

4.2. Analyses of Primary Outcomes of Interest

The primary outcomes of interest shall determine if the HYD® program, as an intervention and a novel non-pharmacological approach to T2DM reversal, is as effective as it claims to be. A proposed correlational analysis shall be performed on the collected descriptive statistics to produce correlation coefficients to better elucidate the efficiency of the program.

Standard deviation, standard error, and correlation coefficients can best express how effective the program was in achieving clinically significant changes among participants. Cut-off values and ranges used to determine clinically significant changes will be based on the proprietary definition of "T2DM reversal" and other significance levels determined by nationally or internationally recognized clinical practice guidelines.

5. Sample Size and Power

Assuming a potential population size of more than 20,000 diabetic cases at a confidence interval of at least 95% (and margin of error of 5.00), the minimum population sample size needed is 96. This sample size is feasible, given the potential pool of participants that can be gathered and recruited by the HYD® clinical and online platforms.

The study aims to provide data on at least 100 to 125 cases, minimizing the margin of error at 4.89 to as low as 4.37. Sample size calculations and participant projects have been computed using the methods adopted by the Donor Committee for Enterprise Development (DCED) in their Practice Guidelines or Conducting Research (Fairbairn, Kessler, & Tanburn, 2015).

SAFETY MANAGEMENT

1. Clinical Adverse Events

A clinical adverse event (CAE), for purposes of this study, is any untoward, unintended, or harmful event experienced by the study participant associate with any actions or changes taken from the HYD® proprietary T2DM reversal program. CAEs may or may not be directly related to the participants' current underlying clinical conditions, such as T2DM and other comorbidities.

For CAEs directly related to T2DM, the study shall adapt the description and definition of T2DM-associated and DM therapy-associated adverse effects as implemented in the Diabetes Control and Complications Trial (DCCT), a randomize controlled clinical trial conducted in multiple venues in the US and Canada (American Diabetes Association, 1995). Though the necessary safety precautions and evaluations have been performed in accordance to HYD® proprietary regulations and federal and state laws and policies, the study investigators shall remain vigilant for CAEs that may occur throughout a patient's participation. In addition to this, no change or new recommendation prescribed by the study or the HYD® program shall be mandated upon a participant without the agreement of the participant's own primary physician.

The CAEs anticipated in poorly controlled diabetes cases includes hyperglycemia (due to treatment inadequacy) and hypoglycemia (due to imbalance in treatment and/or dosages). The typical clinical picture for hyperglycemia contains various combinations of the symptoms of polyuria, polydipsia, and polyphagia. Sometimes glucosuria, numbness, and neuropathies are experienced in more chronic or severe cases. Hypoglycemia symptoms includes sweating, cold sweating, shakiness, dizziness, hunger, irritability, and the inability to concentrate. More severe cases of hypoglycemia can present with tachypnea, tachycardia, confusion, and loss of consciousness. First response and aid for clinical diabetic hypoglycemia includes intake of sugar/glucose. The primary physician is duly notified in the case of hypoglycemia, as it can be fatal or debilitating.

Some anti-DM drugs can cause CAEs as side effects to their intake. Most side effects are felt upon primary intake after the introduction of a new drug or a new drug dose. Side effects are often manageable, but in the case of a severe side effect, such as allergic reactions or anaphylaxis, drugs are stopped and a different drug or drug class is assigned. In the case of anaphylaxis or anaphylactic shock, the appropriate first aid in the form of epinephrine injections and appropriate ER consult to prevent life-threatening progression of the severe allergic reaction. More common drug reactions and side effects to oral anti-DM drugs includes upset stomach, gas, and diarrhea, which can be managed with dietary changes and adjunct nutritional supplementation. More severe forms of gastrointestinal side effects from anti-DM drugs may warrant the need to adjust drug dose or change drug class, with the approval or recognition of the participant's primary physician.

CAEs that may be expected from the program include reactions or injury from the program's proprietary supplements, exercise regimen, recipes/meal plans, and cleanses. The HYD® program, its Wellness Coordinators, and the assigned Support Doctors will duly instruct the participants in the appropriate manner to monitor and avoid possible CAEs from the program's inclusive products and activities. Plans are personalized and supervised as to ensure that the participants receive what they need in order to achieve effective and safe clinical T2DM reversal.

Another CAE to be closely monitored is weight loss, a side effect in most anti-DM drugs and therapies. Overall, weight loss can be turned to a beneficial side effect that can further help participants reverse the symptomatology of their T2DM. Events of weight loss are recorded and monitored to help participants reach and maintain a certain weight loss goal necessary to reach a healthy BMI, decrease the risk of comorbidities such as hypertension, dyslipidemia, and obesity, and optimize the overall health and wellness outcome and goal upon reversing T2DM.

2. Adverse Event Reporting

Minor adverse events, grievances, and other concerns can be reported by the participant to HYD® anytime—via phone call would be the fastest method. Participants are advised to seek urgent or emergent medical care if any CAE is severe, or in the case of a medical emergency. All CAEs will be noted in the study records and on any participant or case report forms, including full descriptions of the CAE's nature, onset, intensity (mild, moderate, severe), duration, proposed causality, and outcome.

CAEs are recorded by Support Doctors. Major CAEs can subject the participant to disqualification from the study, but the participation in the HYD® may continue. If necessary, CAEs are further reported to the participant's primary physician for continuation of appropriate care. Throughout the study period, repetitive or emergent CAEs may be reported to HYD® administration and the study's lead investigators if any protocol amendments or changes are necessary to avoid CAE occurrence.

STUDY ADMINISTRATION

1. Data Collection and Management

Data collection shall be administered by HYD® employees and staff, including HYD® licensee physicians, Support Doctors, and Wellness Coordinators. Data management will solely be the responsibility of the investigators along with research consultants, reviewers, and writers in their employ, contracted or retained, bound by a detailed NDA.

1.1. Data Sources (Existing Records)

Primary and baseline identifying data will be sourced from the participants themselves, queried by HYD® employees on demographic information, program goals, and history (diabetic, medical, surgical, social, etc.). Data will be recorded—in freehand or typed—on New Client Application forms. The New Client Application form shall be attached to other printed/submitted material (laboratory results, physician's notes, etc.) to form the Client's Chart.

Data for statistical analysis will be tabulated on appropriate spreadsheet processing software, such as Microsoft Excel. All data tabulated shall be extracted from the Patient's Chart.

Information on related literature, related studies, and related methodologies used to help build the study protocol and its significance will be sourced from the following: (1) prominent journals on biosciences, medicine, health, and wellness journals; (2) online proprietary platforms of renowned local or international academic institutions; and (3) online proprietary platforms of HYD®.

1.2. Data Security & Confidentiality

Data security and confidentiality in this study is ensured in various methods. Raw data tabulated in a spreadsheet shall be kept in separate data forms (paper and electronic) from data tables to be used for statistical analyses and data presentation. Data used in analysis and presentation shall not use direct identifiers (such as participant names) and shall use participant ID numbers instead. Those handling both raw and anonymized data shall be bound by an NDA.

Data files shall be kept in formats that may allow password protection or transfers into password-protected devices. Data files can also be kept in formats that can be encrypted, if necessary. The social exchange or transfer of data files shall be limited to encrypted or secured channels—such as protected email instead of public website messenger widgets or unprotected messaging applications.

A data backup plan can also be adopted by the team of investigators and authors to safekeep important information from total deletion.

2. Confidentiality

All data and records generated in this program and in this study shall be kept strictly confidential in accordance with HYD®'s institutional policies, federal/state laws, and the Health Insurance Portability and Accountability Act of 1996, regardless of the involved study site or study personnel. Such data and records shall be used for no other purpose other than the conduction and implementation of this study.

No identifiable data shall be used for further studies without the prior approval of the HYD® lead investigators of this study, the IRB involved (if applicable), or any active determination that the study is IRB-exempt. In the case that further studies are permitted or proposed, the lead investigators of this study shall determine the necessary data-use agreement between the other provider or investigator and any other recipient researchers before permitting anonymized or limited data sets.

3. Regulatory and Ethical Considerations

3.1. Risk Assessment

The risks involved in this study shall be declared as minimal. T2DM is considered a global epidemic that affects populations regardless of ethnicity, region, or economic status; the movement for new and improved treatment therapies for such as disease is a widely accepted direction in the practice of medicine and the field of research. A study that can present a new approach to effectively reversing T2DM at the clinical level is a protocol that shall be met with the least amount of possible physical, psychological, economic, or societal harm or opposition. Nonetheless, the study shall vigilantly monitor for any clinical adverse effects (CAEs) that may arise from any therapeutic or treatment recommendations and changes from the HYD® program.

3.2. Potential Benefits of Study Participation

Study participants may benefit from the successful reversal of their T2DM. This entails a complete weaning off their current anti-DM maintenance medications and reaching a target HbA1c of 5.9% or lower. Their participation in the study and HYD® program will help them in developing a DM management plan tailor fit to their needs, goals, and limitations.

Lifestyle and dietary changes beneficial to participants' DM status as well as their overall health outcomes will be implemented throughout their stay in the study and the program. Subsequent outcomes such as manageable weight loss, effective smoking cessation, financial savings from having to purchase less medications, and immunity boosts have all been reported in participants that have successfully benefited from the program.

3.4. Risk-Benefit Assessment

For a fixed financed price based on program length and recommendations personalized for each participant, the participant can enjoy the program regimen and all its inclusive perks. The long-term possibility of participants getting to spend less on maintenance medications and other costs from diabetes complications and comorbidities proves to be the main justification for proceeding with this study.

4. Recruitment Strategy

Participants are recruited mainly through the proprietary advertisements, featured in the HYD® website and other social media platforms such as Facebook. Online and television featurettes of the HYD® program, including news features, instructional videos, interviews, and testimonials also provide additional avenues of participant recruitment.

Participants are also sourced from affiliated clinics and practitioners designated as HYD® Licensee Physicians, who may refer viable T2DM patients as participants to the program. Blog and website owners, as well as professionals and practitioners with online platforms may also apply as online affiliates to HYD®, hosting promotional leads and links through which additional participants can be sourced.

5. Informed Consent/Assent

Consent from the participant shall be collected before screening and before any procedure or activity in the program during the study proper. Consent is officiated and collected in the form of a signed and duly comprehended Consent Form.

The lead investigators may provide the Consent Form is appropriately interpreted formats translated in other languages, if consent must be collected from a non-English speaking participant. Informed assent may be collected from legal guardians or first-degree relatives of participants unable to complete a Consent Form (i.e.: in the setting of visual impairment, physical disability, or dementia). If the case arises, dementia may be assessed on the basis of medical history, a clinical evaluation, or through a MoCA Test.

PUBLICATION

All plans for publication are to be discussed among the investigators and authors. Only data without individually identifiable information and data previously with identifiable information now anonymized will be published.

PRELIMINARY RESULTS

1. Descriptive Data

A pool of 137 diabetic participants were recorded in this study with 7 participants (5.69%) having been newly diagnosed within the same year as their recruitment into the program. This sample of participants was predominantly male (72.26%, n = 99) at an average age of 65.50 years. The following preliminary descriptive data expresses the clinical and anthropometric features of the study sample. The presented data was derived from the study's dataset currently undergoing full analyses.

The mean body mass index of the participants is at 31.46, collectively putting the average at the level of obesity when benchmarking the healthy body mass index at 18.5 to 24.9. Also noteworthy is that 88 participants (64.23%) entered the program with complaint of diabetic symptoms (e.g.: polyuria, polydipsia, polyphagia, nocturia, neuropathy, decreased libido, blurring of vision, acute pain, etc.), but 119 participants (86.86%) have had clinical levels of uncontrolled hyperglycemia, depicted as a laboratory result of HbA1c greater than or equal to 5.9%.

Table 1: Descriptive clinical features

Clinical Features	**Participants (N=137)**
Age (mean years ± SD)	65.50 ± 9.64
Sex (% male)	72.26 (n = 99)
Anthropometrics	
Height (mean inches ± SD)	68.2 ± 4.4
Weight (mean pounds ± SD)	208.8 ± 46.4
BMI (mean ± SD)	31.46 ± 5.79
Medical History	
T2DM diagnosis duration (mean years ± SD)	11.89 ± 10.76
Newly diagnosed T2DM (%)	5.69 (n = 7)
Uncontrolled hyperglycemia (%)	86.86 (n = 119)
Symptomatic (%)	64.23 (n = 88)
Hypertension (%)	62.20 (n = 79)
Dyslipidemia (%)	50.39 (n = 64)
Pharmaceutical History	
Insulin (%)	29.20 (n = 40)
Metformin (%)	70.80 (n = 97)
Other oral antiglycemic drugs (%)	54.01 (n = 74)
Antihypertensive drugs (%)	55.47 (n = 76)
Anticholesteremic drugs (%)	37.96 (n = 52)
Other Pertinent History	
Family history of T2DM (%)	23.20 (n = 29)
Tobacco smoking (%)	2.36 (n = 3)
Alcohol drinking (%)	38.10 (n = 48)
Caffeine drinking (%)	70.08 (n = 89)

Participants in this study were allocated into different programs based on HYD®'s proprietary screening tool and processes. 49.64% of participants (68) were allocated into the 4-month plan.

Table 2: Other descriptive parameters

Intervention Measures	
Program Subscribed	
2-month Plan (%)	19.71 (n = 27)
3-month Plan (%)	16.06 (n = 22)
4-month Plan (%)	49.64 (n = 68)
6-month Plan (%)	6.57 (n = 9)
Unknown/unreported	8.03 (n = 11)
Program Subscribed	
Fully Completed (%)	80.29 (n = 110)
Early Withdrawal (%)	15.33 (n = 21)
Incomplete (%)	4.38 (n = 6)
Participant Stay Length	
Days (mean ± SD)	136 ± 78
Months (mean ± SD)	5 ± 3

2. Baseline Data & Clinical Effectivity

Baseline clinical data has showed that HYD®'s proprietary prevention has decreased participant HbA1c levels by an average of 1.62% (a percent-change of 18.57% decrease of A1c levels) and an average decrease in FPG by 41.32 mg/dL (a percent-change of 20.09% in decrease of plasma glucose).

The prevention has also shown to benefit participants in terms of weight loss. Participants have lost an average of 20.4 lbs (or a decrease of about 3.1 kg/m^2 in BMI) throughout their stay in the program (a percent-change of 9.4% in weight loss and improvement in BMI).

Table 3: Baseline clinical data and observed changes

Clinical Parameter	**Pre-Intervention**	**Post-Intervention**	**Mean Change**	**% Change**
Glycemic Parameters				
HbA1c (% ± SD)	7.65 ± 1.57	6.04 ± 0.68	-1.62 ± 1.63	-18.57
FPG (mg/dL ± SD)	154.44 ± 53.60	113.19 ± 18.94	-41.32 ± 55.02	-20.09
Pertinent Anthropometrics				
Weight (lbs ± SD)	208.8 ± 46.4	191.3 ± 41.9	-20.4 ± 12.4	-9.4
BMI (kg/m^2 ± SD)	31.46 ± 5.79	28.75 ± 5.36	-3.1 ± 1.9	-9.4
Other Evaluations				
Systolic BP	135.42 ± 24.75	124.74 ± 13.89	-11.34 ± 21.74	-6.80
Diastolic BP	78.49 ± 13.89	75.95 ± 9.29	-5.68 ± 13.73	-5.45
eGFR	72.65 ± 18.71	71.94 ± 22.70	-0.98 ± 11.08	-0.93
Serum BUN	19.33 ± 6.03	21.75 ± 7.19	2.66 ± 6.32	17.59
Serum Creatinine	88.32 ± 29.42	91.24 ± 32.51	1.25 ± 15.97	1.64
Serum Total Cholesterol	159.91 ± 36.59	151.21 ± 36.85	-12.26 ± 31.74	-5.88

The program has also proven beneficial in lowering the medication doses of participants, implying a positive control of symptoms and possible effective control of diabetes. Among the 97 participants taking metformin, a decrease in 47.42% of their baseline dose was recorded. In the 40 participants taking insulin, an 85.00% decrease in baseline dose was recorded.

For brief subgroup analysis, the baseline doses of other antiglyemic drugs as well as other pertinent medications (i.e.: antihypertensives, anticholesteremics, etc.) were recorded. A 76.89% decrease in baseline dose was recorded among the 67 participants taking other antiglycemics. The 76 participants on antihypertensive medications presented with a 30.71% decrease, and the 52 participants with anticholesteremics (mostly statins) presented with a 22.58% decrease in dose upon completion of the program.

Table 4: Baseline medication doses and changes

Pharmaceutical Parameter	Pre-Intervention	Post-Intervention	% Change
Diabetic Medications			
Metformin (mg ± SD, *n = 97*)	1452.20 ± 575.75	726.63 ± 770.59	-52.12
Insulin (IU ± SD, *n = 40*)	35.38 ± 20.39	6.38 ± 12.48	-85.00
Other Antiglycemic Agents (*n = 74*)	NA	NA	-76.89
Other Pertinent Medications			
Antihypertensives (*n = 76*)	NA	NA	-30.71
Anticholesteremics (*n = 52*)	NA	NA	-22.58

3. Clinical Significance

Baseline data presented the clinical effectivity of the proprietary program in lowering participant glycemic parameters, anthropometrics, and maintenance medication dose. To evaluate for clinical significance, however, only participants obtaining an HbA1c level of 5.9% or lower and completely taken off their antiglycemic medications (including metformin) by the end of their program stay will be considered as a successfully reversed case of T2DM.

A total of 61 participants had successfully decreased their HbA1c levels to 5.9% or lower after their program stay. The program therefore granted beneficial T2DM control to 44.53% of its participants. However, out of the 61 participants who graduated from the program with T2DM control, 36 of them (26.28%) had their T2DM clinically reversed. The 25 remaining participants (18.25%) reached target HbA1c levels but could not be completely weaned off their maintenance anti-glycemic medications and were categorized as clinically controlled.

In participants who didn't achieve clinical reversal, 99% of them didn't follow the guidelines of checking in once a week, sending in a daily food log once a week and following the program as directed.

Table 5: Clinically significant T2DM control and reversal

Parameters for T2DM Reversal	%	% Clinically Revered [all parameters met]
HbA1c Parameters (*n = 137*)		
Decreased HbA1c	82.48% (n=113)	
Reached target HbA1c ≤ 5.9	**44.53 (n = 61)**	
Lowered HbA1c but not to target	37.96 (n = 52)	
No change to HbA1c	2.92 (n = 4)	
Increased HbA1c	2.92 (n = 4)	
Unknown/unrecorded	11.68 (n = 16)	
Metformin Parameters (*n = 97*)		
Decreased metformin dose	58.76 (n = 57)	
Eliminated metformin	**38.14 (n = 37)**	
Lowered metformin dose only	20.62 (n = 20)	
No change to metformin dose	34.02 (n = 33)	
Increased metformin dose	1.03 (n = 1)	**26.28 (n = 36)** (clinically reversed)
Unknown/unrecorded	6.19 (n = 6)	
Insulin Parameters (*n = 40*)		
Decreased insulin dose	92.50 (n = 37)	**18.25 (n = 25)** (clinically controlled)
Eliminated insulin	**60.00 (n = 24)**	
Lowered insulin dose only	32.50 (n = 13)	
No change to insulin dose	5.00 (n = 2)	
Increased insulin dose	0.00 (n = 0)	
Unknown/unrecorded	2.50 (n = 1)	
Other Antiglycemic Drug Parameters (*n = 74*)		
Decreased dose of other antiglycemics	74.32 (n = 55)	
Eliminated other antiglycemics	**64.86 (n = 48)**	
Lowered antiglycemic dose only	9.46 (n = 7)	
No change to antiglyemic dose	13.51 (n = 10)	
Increased antiglycemic dose	1.35 (n = 1)	
Unknown/unrecorded	10.81 (n = 8)	
Antihypertensive Drug Parameters (*n = 76*)		
Decreased antihypertensive dose	23.68 (n = 18)	
Eliminated antihypertensives	**15.79 (n = 12)**	
Lowered antihypertensives only	7.89 (n = 6)	
No change to antihypertensive dose	40.79 (n = 31)	
Increased antihypertensive dose	0.00 (n = 0)	
Unknown/unrecorded	35.53 (n = 27)	
Anticholesteremic Drug Parameters (*n = 52*)		
Decreased anticholesteremic dose	7.69 (n = 4)	
Eliminated anticholesteremics	**0.00 (n = 0)**	
Lowered anticholesteremic dose only	7.69 (n = 4)	
No change to anticholesteremic dose	51.92 (n = 27)	
Increased anticholesteremic dose	19.23 (n = 10)	
Unknown/unrecorded	21.15 (n = 11)	

4. Analysis for Statistical Significance

To further elucidate the effectivity of the program, the statistical significance of pertinent changes to quantitative clinical and laboratory parameters were measured by testing the standard error of the percent-changes observed. The percent-change of a parameter was determined as significant if both its upper and lower bounds remained the same sign (negative or positive). The decreases in the following quantitative parameters were deemed significant statistically as well as clinically.

Table 6: Statistical significance at 95% confidence interval

Clinical Parameter	Δ	% Δ	SD	SE	% Δ UB	% Δ LB	Sig.
Glycemic Parameters							
HbA1c	-1.62	-18.57	14.48	1.27	-16.09	-21.06	Significant
FPG	-41.32	-20.09	23.69	2.02	-39.30	-43.34	Significant
Pertinent Anthropometrics							
Weight	-20.4	-9.4	5.1	0.43	-8.50	-10.20	Significant
BMI	-31.46	-9.38	5.25	0.45	-8.50	-10.26	Significant
Medications							
Metformin	-660.47	-52.12	47.32	4.04	-44.20	-60.05	Significant
Insulin	-29.13	-85.00	26.07	2.23	-80.63	-89.37	Significant

5. Preliminary Conclusion

The proprietary intervention offered by HYD® aims to reverse the clinical status of type 2 diabetes mellitus—completely weaning off diabetics from their maintenance anti-glycemic drugs, including metformin and insulin analog, and decreasing their HbA1c levels to 5.9% or lower. The HYD® T2DM reversal program has long garnered positive reviews in the form of participant testimonials and critical appraisals.

The results of this study have shown, objectively, that the program offers clinically and statistically significant improvements to measurable parameters and diagnostic laboratories monitored in the setting of diabetes. The study results have also described clinically significant decreases in antiglycemic, anticholesteremic, and antihypertensive drug doses among 137 participants of the program, while successfully reversing the T2DM status in 36 of them.

The study also calls for further investigation—such as randomized clinical trials, cost-benefit analyses, market research, and cohort studies—into the efficacy of the program and the permanency of its benefits. The findings of this study can also be used to elucidate possible areas for improvement in the program. The statistics can possibly pave the way to further optimize the utility of the proprietary Diabetes Score system to allocate/recruit future participants for intervention and even possibly screen pre-diabetic clients for prevention. Help Your Diabetes®, providing the option to reverse type 2 diabetes through non-pharmaceutical means, positively contributes to the global effort of alleviating the epidemically proportioned burden of T2DM.

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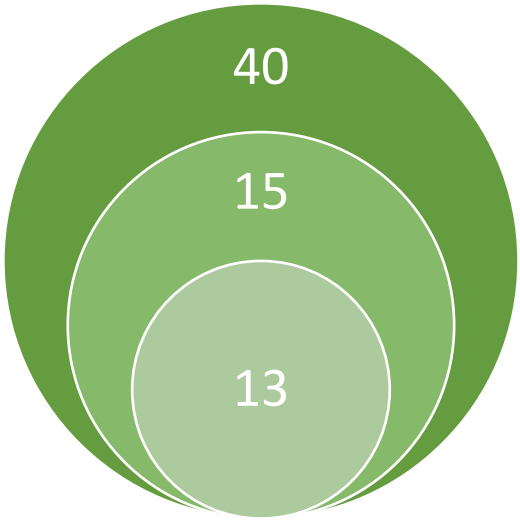
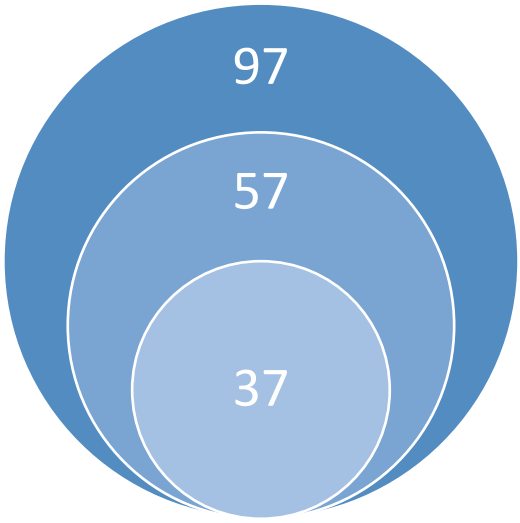
APPENDICES

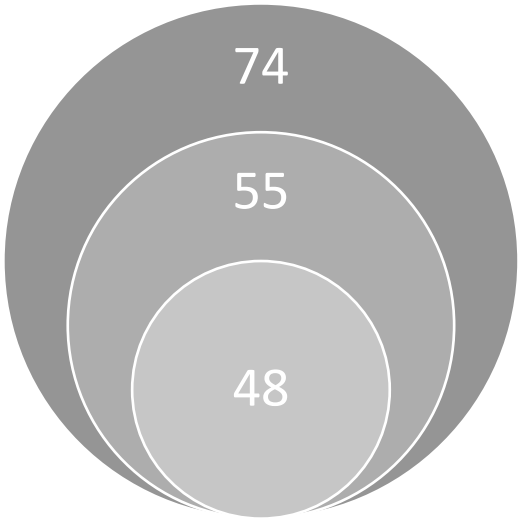
1. Appendix A: Data Presentation Figures



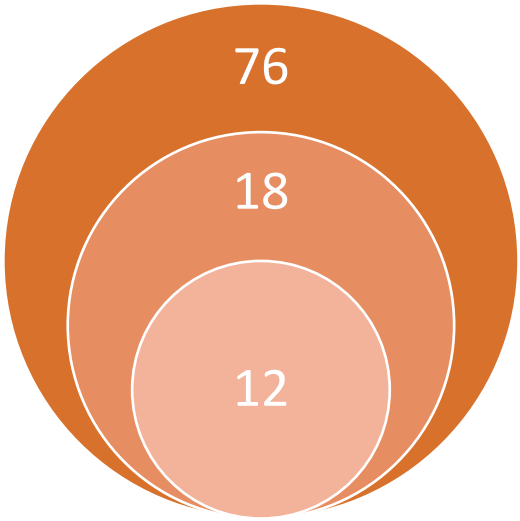
Total Participants Taking Insulin	40
Reduced Insulin	**37** (92.50%)
Eliminated Insulin	**24** (60.00%)



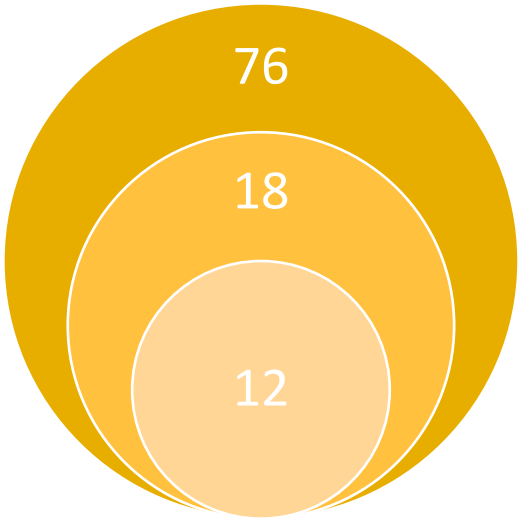
Total Participants Taking Metformin	97
Reduced Metformin	**57** (58.76%)
Eliminated Metformin	**37** (38.14%)



Total Participants Taking Other Antiglycemic Drugs	74
Reduced Antiglycemic Dose	**55** (74.32%)
Eliminated Antiglycemics	**48** (64.86%)



Total Participants Taking Antihypertensive Drugs	76
Reduced Antihypertensive Dose	**18** (23.68%)
Eliminated Antihypertensives	**12** (15.79%)



Total Participants Taking Anticholesteremic Drugs	52
Reduced Anticholesteremic Dose	**4** (7.69%)
Eliminated Anticholesteremics	**0**