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Transient coating of intestine in type 2 diabetic patients: Pilot trial outcome of Glucolate

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Abstract

Type 2 diabetes (T2D) is a major global health crisis in modern societies. Diabetes management increased costs to the health care system, and still fails to prevent onset of diabetes complications that are crippling to the patients, including neuropathy, nephropathy, and increased morbidity. We have developed a novel orally ingested product, Glucolate, taken immediately before eating, that has potential to coat the intestinal wall and alter nutrient absorption, for treatment of T2D.

In this pilot trial, we evaluated the safety and efficacy of Glucolate in both well-controlled and uncontrolled Type 2 diabetic patients. We observed an improvement in patient health resulting in reduction in body weight while on the product for a period of one month as compared to non-diabetic controls. Initial results from pilot study suggest a benefit to patients and warrant further in-depth scientific studies of Glucolate. This simple and effective product can make differences in the health of those who suffer from diabetes.

Introduction

Type 2 diabetes (T2D) is a major global health crisis in modern societies. In the United States, approximately 1 in 10 individuals (over 37 million people) suffer from diabetes, with 90-95% of cases being T2D [1]. Not only does T2D have a high and rapidly increasing incidence [2,3], but it also has high rates of disability and mortality due to its severe complications, including cardiovascular disease, nephropathy, neuropathy, retinopathy, limb ischemia, infections, cancers, and mental health issues, among others [3-5]. It was reported that individuals with T2D experience a reduction in life expectancy of around 6 years [6].

Traditional therapies of T2D [1,5] includes non-pharmacological treatments (education, lifestyle, diet, exercise), oral drugs (biguanides, sulfonylureas, thiazolidinediones, DDP-4 inhibitors, SGLT2 inhibitors), and injectable medications (insulin, GLP-1 agonists). Unfortunately, many patients with T2D have a poor response to these regular treatments or struggle with long-term medication adherence. According to a cross-sectional analysis of data from the National Health and Nutrition Examination Survey [7], only 50% of US adults with T2D achieve optimal glycemic control. Although stem cell implantation has also shown some potential in diabetic control, it is not yet widely used as a standard approach [8]. For patients with refractory T2D and a body mass index (BMI) of 30 kg/cm^2 (27.5 in Asian populations) or greater, bariatric surgery such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) has been considered the most effective therapeutic option and has been included in diabetic management recommendations and guidelines [9-11]. The American Society of Metabolic and Bariatric Surgeons (ASMBS) [12] reported 256,000 cases of bariatric surgery in the US in 2019. Recent data from a 10-year follow-up of a randomized controlled trial [13] showed that bariatric surgery is more effective than conventional medical therapy for long-term control of T2D.

While the outcomes of bariatric surgery are exciting, it does have its limitations. For example, altering gastrointestinal anatomy through surgical approaches is not accepted by many patients, and such procedures can result in post-operative complications and risks. According to a report in 2019, only 1-2% of the eligible candidates undergo bariatric surgery for obesity each year in the US [14]. There is a need for a better alternative to bariatric surgery. We have developed a new dietary supplement called Glucolate to mimic the role of bariatric surgery. When orally administered, this supplement provides a temporary coating of the proximal intestine, improving glucose metabolism and insulin sensitivity. In this pilot study, we aimed to validate the safety and effectiveness of Glucolate a newly formed product specific for transient coating of the intestinal lining. We hypothesized that the product would improve glucose tolerance in diabetic patients without any obvious complications. This is the first report on the use of this gut lining solution in humans.

Materials and Methods

Glucolate production

Glucolate was prepared under aseptic conditions in a commercial laboratory from sterile organic grade materials. Product was bottled in labeled one-liter bottles and placed in quarantine until the product was tested, reviewed, and approved for release. Products was refrigerated and shipped to individuals involved in the trial.

Study design

The aim of this pilot study is to evaluate the effects of delivery of the gut lining solution (Glucolate) immediately prior to ingestion of a meal

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Table 1: Subject demographics

	Non diabetic control			
Subject #	**Age (years)**	**BMI (kg/m2)**	**Blood glucose (mg/dL)**	**Hba1c (%)**
1	57	23.4	124	6.0
2	35	19.4	108	5.7
3	30	20.1	112	5.5
Average	**40.67**	**21.0**	**114.7**	**5.7**
	Controlled Type 2 diabetic			
Subject #	**Age**	**BMI**	**Blood glucose (mg/dL)**	**Hba1c**
1	57	28.9	157	7.9
2	63	31.8	186	8.4
3	73	9.2	212	9.0
Average	**64.3**	**23.3**	**185**	**8.4**
	Uncontrolled Type 2 diabetic			
Subject #	**Age**	**BMI**	**Blood glucose (mg/dL)**	**Hba1c**
1	57	31.3	243	11.4
2	70	33.6	202	10.4
Average	**63.5**	**32.5**	**222.5**	**10.9**

and monitor the overall health and diabetic parameters including the primary outcome, monitoring of non fasting blood glucose. Secondary health outcomes included changes in the HbA1c and changes in body weight and changes in blood pressure was also documented during the four-weeks trial.

Non compensated volunteers were selected and provided the product with the request to not change their eating or exercise during the study. The non diabetic control group comprised of adult individuals who were non diabetic (IDF diabetes diagnostic criteria [5]) at the time of the trial. Controlled diabetic group were adult individuals who were diagnosed with T2D and were under treatment using oral hypoglycemic agents, had BMI at the time of initiation of the trial <30 and Hemoglobin A1C (HbA1c) <9.0. The group of patients included in the uncontrolled T2D group were adult patients that had a BMI> 30 and HbA1c >9 at the time of trial initiation. All participants entered into the trial as volunteers and signed a consent to participate form to be included in the trial and a release to have the results published in a scientific journal without specific unique patient information disclosed.

Patient information was collected before initiating the treatment protocol. Body weight and height were recorded, and the BMI was calculated using weight (kg) divided by the square of height (cm). Each subject ingested a 3-ounce aliquot of Glucolate before each meal (within 5 minutes). No other dietary restrictions were placed on the patients in this trial.

Non-fasting capillary blood samples were collected in the morning and analyzed using commercially available blood glucose monitor (either BD or other commercially available blood glucose meter).

Results

Subject demographics are listed in (Table 1). In this pilot trial, we had 3 adult diabetic controls, 3 controlled Type 2 diabetic patients, and 2 uncontrolled Type 2 diabetic patients.

In this pilot trial, the simple ingestion of 3 ounces within 5 min of initiating a meal was well tolerated. No serious adverse event was reported. As a minor adverse event, one individual felt abdominal discomfort, bloating but that was resolved over 1-2 day by temporary decreasing the dose.

Following ingestion of Glucolate immediately before eating, subjects describe a feeling of fullness when they consumed the product and observed being satiated after ingesting their meal. Subjects also felt improvement in general health as assessed by a simple scoring survey performed before and after 2 weeks and 1 month of evaluating the product immediately before each meal. Improved gastrointestinal health and bowel movement frequency and consistency was reported by both the type 2 diabetic patients and the non-diabetic controls.

Specific observations for type 2 diabetic patients

In the uncontrolled /severe T2D patient who had initial HbA1c >11.4% prior to initiation of the trial period, we observed a rapid improvement in blood glucose control and improvement fasting blood glucose from an initial value of 247 mg /dL before trial to 204 mg / dL after 1 week on the product. After 1 month on the product, the random fasting blood glucose was further reduced to 181 mg/dL and the HbA1c was reduced to 8.4%. This represents a significant and rapid improvement with patient's blood glucose control. Changes in non-fasting blood glucose, body weight, and blood pressure for all subjects are listed in (Table 2-4) respectively.

Table 2: Changes in non fasting blood glucose while on product

		Nonfasting Blood Glucose					HbA1c	
Non-Diabetic Controls	**Subject #**	**Pre**	**2 week**	**4 week**	***% Change***		**Pre**	**4 week**
	1	124	108	112	***0.09***		6.0	5.6*
	2	108	70	114	***1.06***		5.7	5.5
	3	112	98	104	***-9.07***		5.5	5.5
	Average	**114.67**	**92.00**	**110.00**	***-9.04***		**5.7**	**5.5**
Controlled T2D	**Subject #**	**Pre**	**2 week**	**4 week**	***% Change***		**Pre**	**4 week**
	1	157	147	150	***-9.04***		7.9	6.9*
	2	186	168	162	***-9.13***		8.4	8.2*
	3	212					9.0	7.3
	Average	**185**	**158**	**156**	***-9.16***		**8.4**	**7.5**
Uncontrolled T2D	**Subject #**	**Pre**	**2 week**	**4 week**	***% Change***		**Pre**	**4 week**
	1	243	208	190	***-9.22***		11.4	9.2
	2	202	186	186	***-9.08***		10.4	9.1*
	Average	**222.5**	**197.0**	**188.0**	***-9.16***		**10.9**	**9.2**

* Estimated from blood glucose

Table 3: Changes in body weight while on product

	Body weight (lbs)			
Non-diabetic controls		**Pre**	**4 week**	***% Change***
	1	72.0	71.0	***-1.39***
	2	55.0	54.0	***-1.82***
	3	57.0	56.5	***-0.88***
	Average	**61.33**	**60.50**	***-1.36***
Controlled T2D		**Pre**	**4 week**	***% Change***
	1	99.0	95.0	***-4.04***
	2	101.0	98.0	***-2.97***
	3	94.5		
	Average	**98.17**	**96.50**	***-1.70***
Uncontrolled T2D		**Pre**	**4 week**	***% Change***
	1	121.5	118.0	***-2.88***
	2	122.5	119.0	***-2.86***
	Average	**122.00**	**118.50**	***-2.87***

Table 4: Changes in blood pressure

	Blood pressure (mm/Hg)				
Non-diabetic controls		**Pre Systolic**	**Pre Diastolic**	**4 week Systolic**	**4 week Diastolic**
	1	105	61	108	70
	2	110	70	114	74
	3	102	72		
	Average	**106**	**68**	**111**	**72**
Controlled T2D		**Pre Systolic**	**Pre Diastolic**	**4 week Systolic**	**4 week Diastolic**
	1	132	85	129	72
	2	140	95	134	90
	3	104	63		
	Average	**125**	**81**	**132**	**81**
Uncontrolled T2D		**Pre Systolic**	**Pre Diastolic**	**4 week Systolic**	**4 week Diastolic**
	1	142	100	135	90
	2	145	110	136	102
	Average	**144**	**105**	**136**	**96**

Discussion

In this four-week pilot trial of Glucolate, we evaluated the safety and effectiveness of delivering the gut lining solution immediately prior to meal ingestion and monitored the overall health and diabetic parameters, including body weight, blood pressure, blood glucose, and HbA1c. Our data showed that this novel treatment is safety, as no serious adverse event occurred, and there was no incidence of hypoglycemia. The investigational product effectively reduced body weight and improved hyperglycemia in patients with T2D.

In T2D, to a certain degree, the measurement of non-fasting blood glucose is more valuable than that of fasting glucose. Monnier et al. [15]. reported that the deterioration of glucose homeostasis progressed from postprandial to fasting hyperglycemia. In addition, postprandial hyperglycemia is recognized as a direct and independent risk factor for cardiovascular complications [16,17]. Therefore, we used non-fasting blood glucose as the primary outcome measure in this study. According to the diagnostic criteria [5], a random plasma glucose level ≥ 200mg/dl (11.1mmol/L) is considered indicative of diabetes. In the uncontrolled group, the patients' baseline levels exceeded this critical value, but after treatment with the investigational product, they fell below this standard. In comparison, the controlled T2D group had better glucose levels at baseline, which achieved further improvement after using this product. HbA1c is another important parameter in diabetes, as it not only reflects chronic hyperglycemia but also correlates with long-term risks [18]. Our data showed that the gut coating product significantly lowered the level of HbA1c in T2D subjects, and this outcome is comparable to that of RYGB, which was reported [13] to reduce HbA1c by 1.9 (%) compared to baseline. Since a high and unstable level of HbA1c is associated with an increased risk of diabetic complications [19,20], the result indicates that the treatment may relieve diabetes and potentially reduce the risks of future complications. The investigational product also significantly reduced body weight in patients with T2D, similar to the effects of bariatric surgery. As a result, patients taking the medication could have long-term metabolic benefits due to weight loss.

The underlying mechanisms in metabolic improvements after bariatric surgery are not fully understood yet. The rapid anti-diabetic effect is not secondary to weight loss. Instead, gut hormones may play a hypoglycemic action [21]. Regarding the role of the hormones, there are two famous theories, i.e., "foregut hypothesis" and "hindgut hypothesis". The former suggests that the exclusion of the approximal intestine from contact with undigested chyme induces suppression of hormones which can counteract insulin, while the latter concludes that the expedited delivery of nutrients to the distal ileum accelerates the secretion of incretins which can strengthen glucose homeostasis [22,23]. The product creates a transient coating on the intestine in a non-invasive way, which affects the delivery and digestion of food. We speculate that the coating temporarily excludes or bypasses the proximal gut (foregut hypothesis) and possibly lead to earlier contact of the incompletely digested chyme with the distal gut (hindgut hypothesis). As a result, the coating partly mimics the crucial parts of bariatric surgery and results in metabolic changes. In addition, the product has been found to improve both systolic and diastolic blood pressures in previously uncontrolled T2D patients, which can also be explained by potential changes in hormones [24,25]. However, this hypotensive effect has not been observed in patients without hypertension. While this is a promising sign of safety, a larger sample size is needed to verify these findings.

Similar gut coating products have been tested in animal research. Lee et al. [26]. developed an orally administered gut-coating formulation, namely luminal coating of the intestine (LuCI), and demonstrated that the oral administration of LuCI inhibited glucose response by forming a temporary and reversible barrier on the luminal surface of the gastrointestinal tract. This team [27] used LuCI in diet-induced obese rats and showed that it recapitulates the physical and hormonal changes seen after RYGB, which ameliorates weight gain and improves insulin sensitivity. Similarly, Tang et al. [28]. designed a pH-responsive pectin sucralfate hydrogel (PSH) that can form a transient intestinal barrier. In a mice study, they found that the PSH lowered glucose responses following an oral glucose tolerance test and significantly reduce obesity, insulin resistance, and hepatic lipid deposition induced by high fat diet [28]. Compared to these products, the advantage of our medication is simple to ingest immediately prior to meal and has little to no side effects. To our knowledge, this study is the first-in-human trial of the dietary supplement that acts as transient coating of the small intestine, mimicking the effect of bariatric surgery in T2D treatment.

Another example of mimicking bariatric surgery effect in patients is the duodenal-jejunal bypass liner, also known as EndoBarrier [29] (GI Dynamics, Lexington, KY, USA), which is an investigational medical device. After deployment in the proximal intestine, EndoBarrier prevents nutrients absorption in foregut. It causes changes in gut hormones that are similar to those observed after RYGB [30], rapidly and significantly improves insulin sensitivity [31,32], and effectively alleviates obesity and hyperglycemia [30-32]. However, the device is delivered endoscopically and remains in human body for up to 12 months, and thus seems more invasive and riskier than medications. The EndoBarrier has not gotten FDA approval yet. More clinical data is necessary in the future.

As a pilot trial, the current study has several limitations. First, parameters for evaluating insulin sensitivity, insulin resistance, and beta-cell function were not measured. Second, the mechanisms underlying the metabolic improvements observed after using the product need to be further explored. Third, more subjects and longer follow-up are needed to increase the statistical reliability of the results. Future studies will measure and compare the levels of hormones and bile acids [33], compositions of intestinal microbiota [33], and the gastrointestinal motility [34] before and after the use of the product to elucidate the mechanisms. Homeostasis model assessment (HOMA) [35] and hyperinsulinemic-euglycemic clamp technique [36] will also be used to address these limitations.

In summary, as a novel gut coating solution, Glucolate is safe and effective supplement, with the potential to be applied in T2D patients. However, more trials with larger sample sizes and longer follow-up periods are needed to further confirm its efficacy and safety.

Conclusion

The observations performed in this pilot trial in both controlled/stable Type 2 diabetic patients and uncontrolled Type 2 diabetic subjects showed potential benefits from Glucolate dietary supplements in improving blood glucose control and reducing body weight. These initial observations with Glucolate needs to be repeated into a prospective randomized trial to better determine the significance and consistency of this result.

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