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Case Study

Effect of GlucoSEB™ Supplement on the Blood Glucose Level in Diabetic Patients: A Case Study

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ABSTRACT

Diabetes is becoming a globally prevalent disease that puts a burden on healthcare systems and poses challenges to risk management. Diabetes leads to microvascular and macrovascular complications. Therefore, maintaining normoglycemia is essential to improving the quality of life and preventing morbidity and mortality in people with diabetes (PwD). A current study was performed to check the effect of GlucoSEB™ supplement on the blood glucose level of Type 2 diabetes mellitus (T2DM) patients. Subjects in this study were blinded to the treatment; they received a placebo for the initial seven days, followed by GlucoSEB™ for the next seven days. Blood glucose was monitored with a continuous glucose monitoring (CGM) device. Administration of GlucoSEB™ caused a decrease in blood glucose level, glucose area under the curve (AUC), and an improvement in time in range (TIR). Also, GlucoSEB™ was well tolerated by all the patients, indicating the safety of the supplement. Thus, GlucoSEB™ supplementation positively influenced blood glucose parameters and helped curb blood glucose excursions.

Keywords
Diabetes; GlucoSEB™; Blood glucose level; Continuous glucose monitoring; Safety; Tolerance.

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia is associated with long-term damage and dysfunction. It can lead to various complications; microvascular complications include neuropathy, nephropathy, and retinopathy, while macrovascular complications include cardiovascular disease, stroke, and peripheral vascular disease.[1] Diabetes has now become a global health crisis and will affect about 10.5% of the World population by 2021.[2] Similarly, a national survey in India stated that the prevalence of diabetes and impaired glucose tolerance was about 11.4% and 15.3%, respectively. The survey reported that the urban population is at higher-risk (16.4%) as compared to rural areas (8.9%) in terms of developing diabetes, which is attributed to changing dietary habits and an inactive lifestyle.[3] There are two major types of diabetes: Type 1 and Type 2, of which Type 2 is more prevalent in 90-95% of all diagnosed diabetes cases.[4] Many efforts are being made to reduce the risk of diabetes or minimize the deleterious complications of diabetes through strict control of blood glucose. A wide range of drugs are available on the market for diabetes management; however, they have limitations with respect to efficacy, onset and duration of action, and side effects. On the other hand, some natural remedies also exist for blood glucose management, but most of them lack randomized clinical trials for safety and effectiveness. Traditional medicines are known for their anti-diabetic properties; currently, many plants are tested for their glucose-lowering effects via *in vitro* and *in vivo* studies. Schreck and Melzig[5] prepared aqueous and methanolic extracts of plants and tested their hypoglycemic action on $Caco_2$ cells. They found that methanolic extracts of *Aronia melanocarpa, Cornus officinalis*, *Crataegus pinnatifida*, *Lycium chinense*, and *Vaccinium myrtillus* fruits decreased glucose uptake by 40-80%; glucose uptake was inhibited by 50-70% by aqueous extracts of the bark of *Eucommia ulmoides* and the fruit skin of *Malus domestica*. Similarly, methanolic extracts of *Juglans regia* and *Peumus boldus* reduced fructose transport by 30-40%. Some other medicinal plants also possess anti-diabetic properties, such as *Allium sativum*, *Eugenia jambolana*, *Momordica charantia*, *Ocimum sanctum*, *Phyllanthus amarus*, *Pterocarpus marsupium*, *Tinospora cordifolia*, *Trigonella foenum graecum*, and *Withania somnifera,* etc.,[6] and

would be potential candidates in preparing herbal formulations for sugar management.

As a fact, diabetic patients have altered gut microbiota and tend to have leaky guts. They also suffer from issues related to oxidative stress. The enzyme supplementation would help assist metabolic processes that are otherwise compromised due to gut dysbiosis. Therefore, digestive enzyme supplementation plays an important role in restoring digestive health. Enzymes like amylase, protease, and lipase work on the food matrix and help in releasing nutrients that improve the glycemic status of diabetic patients. Additionally, some classes of carbohydrases, like glucosyltransferase (E.C. 2.4), can transfer glucose onto the saccharide or non-saccharide acceptor molecule to form bioactive components.[7] External supplementation of these enzymes can convert sugar into some other useful products, such as oligosaccharides, long-chain polymers, and glucocojugates, and reduce free glucose released in the digestive tract,[8] which decreases the absorption of glucose from the intestine, thereby controlling blood glucose levels. This study aims to understand the glucose-lowering effect of a formulation (GlucoSEB™) in which digestive enzymes and herbal extract are combined.

CASE STUDY PROTOCOL

Six Type 2 diabetic (T2D) patients were recruited for the study (age above 30 years, HbA1C≤10.0%, BMI 25 to 40 kg/m^2) at Hormone India Diabetes and Endocrine Center, Bhopal, India. Subjects with less physical activity, a carbohydrate-rich diet, and who were ready to sign a consent form and willing to adhere to protocol were included in the study. The exclusion criteria were defined as pregnant or lactating females; BMI>40 kg/m^2; Type 1 diabetic (T1D) patients; and T2D patients who were under treatment with short-acting secretologue, glucosidase inhibitor, or insulin-based treatment. Patients with major chronic complications (including but not limited to autoimmune disease, inflammation, etc.); chronic smoking and alcohol intake; organic insufficiency (cardiac, hepatic, renal, respiratory); use of food supplements specifically containing fibers or polysaccharides; currently taking or having in the past 30-days used gastrointestinal (GI)-related probiotics or prebiotics or any enzymes (prescription or over the counter (OTC)) history of any surgery in the past 3-months.

The study was carried out for 14-days. Patients were given two placebo capsules (maltodextrin) per meal (lunch and dinner) for the initial 7-days, followed by supplementation with two GlucoSEB™ capsules per meal (lunch and dinner) for the next 7-days. Capsules were consumed approximately 30-minutes before meals. GlucoSEB™ was provided by Specialty Enzymes and Probiotics, USA. The formulation is a blend of digestive enzymes, i.e., amylase, protease, lipase, glycosyltransferase, and herbal extract. The change in blood glucose level was monitored by a continuous glucose monitoring (CGM) system, FreeStyle Libre Pro® (glucose sensor and reader), procured from Abbott, IL USA. The sensor was installed on Day 1, and patients were blinded to treatment. They consumed their regular diet, except for one meal on Day 7 and Day 13, on which they had a fixed meal of similar macronutrient composition (serving approx. 600-700 calories). Day 1 (CGM installation day) and Day 14 (CGM removal day) were excluded from data analysis as they did not cover the glucose response of the entire day. Patients took their regular medication throughout the study period. The patients were instructed to maintain a diary to record food logs, exercise/activity logs, and capsule consumption times for data analysis.

RESULTS

All six patients completed the study without any adverse events, indicating the supplement was well tolerated and safe for consumption. Blood glucose was monitored using CGM. From the raw data, various parameters were derived, *viz*., mean blood glucose, mean amplitude of glycemic excursion (MAGE), high blood glucose index (HBGI), time in range, etc. Every patient had a different response to GlucoSEB™ treatment, as discussed below:

Patient 1

A 54-year-old male was recruited in the study (body mass index (BMI)=25.4 kg/m^2) with T2D (HbA1c=6.8%) and concomitant medication of Glimepiride (2 mg), Sitagliptin (100 mg), and Pioglitazone (15 mg) (once a day) for controlling blood glucose level. The patient had uncontrolled diabetes, but after administration of the supplement (Day 8 to Day 13), many parameters improved (Table 1), such as mean blood glucose (decreased by 35.50 mg/dL, p-value=0.021), MAGE (decreased by 26.40 mg/dL), and time in range (increased by 23.16%, p-value=0.029). The patient received a fixed meal on days 7 (Placebo capsule) and 13 (GlucoSEB™ capsule). The glucose area under curve (AUC) was derived from raw data until 4 hours after food consumption to determine the effect of the supplement on blood glucose. The glucose concentration (AUC) decreased by 24.17% (p-value=0.00002). Thus, GlucoSEB™ positively influenced blood glucose parameters and helped curb blood glucose excursions without increasing the risk of hypoglycemia.

Patient 2

A 50-year-old female patient was enrolled in the study who had T2D, a BMI of 30 kg/m^2, and an HbA1c of 8.3%. She was on Glimepiride (2 mg), Metformin (500 mg), Pioglitazone (15 mg) (once a day), Sitagliptin 100 mg (once a day), and Atovastatin 10 mg (once a day, at night only). She had fair glycemic control with these medications. Blood parameters like mean blood glucose (BG), MAGE, and HBGI did not change (Table 1). However, the time in range was increased by 10.17% (p-value=0.016). The results suggested that administration of supplements led to improved time in range (TIR) by probably decreasing the risk of hypoglycemia, though the time below range (TBR) difference is statistically nervous system (NS) (9.83 to 1.50%, p-value=0.35).

Patient 3

A 35-year-old female patient with a BMI of 25.6 kg/m^2 and T2D (Hba1c=7.6%). She was taking Gliclazide (60 mg), Pioglitazone (15 mg), and Metformin (500 mg) once a day. The supplement could not show any major effect on the blood glucose level of this patient, but numerically, TBR decreased with GlucoSEB™,

Table 1. *Change in Blood Glucose Parameters after Treatment with GlucoSEB™ in Patients Under Study*

Patient	Blood Glucose Parameter	Mean of Placebo	Mean of Treatment	Change after Treatment	*p*-value
1	BG (mg/dL)	243.90	208.40	-35.50	0.021
	MAGE (mg/dL)	246.10	219.70	-26.40	0.095
	HBGI	4.24	3.00	-1.23	0.079
	Time in range (%)	9.17	32.33	23.16	0.029
	Time below range (%)	0	0	0	-
	Fixed meal AUC	3371.00	2556.00	-815.00	0.00002
2	BG (mg/dL)	122.20	123.10	0.90	0.899
	MAGE (mg/dL)	120.00	127.00	7.00	0.429
	HBGI	2.42	2.38	-0.03	0.510
	Time in range (%)	84.33	94.50	10.17	0.016
	Time below range (%)	9.83	1.50	-8.33	0.35
	Fixed meal AUC	1890.00	2245.00	355.00	0.028
3	BG (mg/dL)	103.50	114.70	11.20	0.108
	MAGE (mg/dL)	128.90	126.40	-2.50	0.830
	HBGI	2.58	2.47	-0.11	0.073
	Time in range (%)	76.67	84.17	7.50	0.438
	Time below range (%)	20.00	8.67	-11.33	0.214
	Fixed meal AUC	2329.00	2384.00	55.00	0.844
4	BG (mg/dL)	221.70	207.30	-14.40	0.060
	MAGE (mg/dL)	230.20	199.00	-31.20	0.143
	HBGI	3.46	3.07	-0.39	0.063
	Time in range (%)	37.33	40.50	3.17	0.312
	Time below range (%)	0	0	0	-
	Fixed meal AUC	3002.00	2676.00	-326.00	0.126
5	BG (mg/dL)	125.20	101.30	-23.90	0.001
	MAGE (mg/dL)	130.20	110.00	-20.20	0.010
	HBGI	2.37	2.52	0.16	0.0004
	Time in range (%)	97.50	98.17	0.67	0.673
	Time below range (%)	0.83	1.67	0.83	0.453
	Fixed meal AUC	1891.00	1400.00	-491.00	<0.000001
6	BG (mg/dL)	115.30	103.90	-11.40	0.015
	MAGE (mg/dL)	155.20	137.40	-17.80	0.236
	HBGI	2.46	2.56	0.105	0.013
	Time in range (%)	88.33	80.83	-7.50	0.179
	Time below range (%)	2.83	14.00	11.167	0.014
	Fixed meal AUC	1804.00	1337.00	-467.00	0.025

i.e., time below range decreased from 20 to 8.67% (p-value=0.214, NS) (Table 1).

Patient 4

A 36-year-old patient with a BMI of 26.3 kg/m^2 and HbA1c of 7.6% was included in the study. His prescribed medicine was Dapagliflozin (10 mg) and Metformin (1000 mg) (twice a day). This patient had frequent BG readings above the recommended range. Various blood parameters improved with GlucoSEB™ capsules along with regular medicine (Table 1). Mean blood glucose decreased by 14.40 mg/dL, MAGE decreased by 31.20 mg/dL, time in range increased by 3.17%, and concentration of glucose decreased by 10.85% on a fixed meal day with respect to placebo treatment. These results demonstrated the efficacy of GlucoSEB™ in the management of high blood glucose levels.

Patient 5

A 49-year-old male patient registered in the study had a BMI of 26.8 kg/m^2 with T2D (Hba1c=7.9%). The regular medication included Metformin (500 mg), Vildagliptin (50 mg) (once a day), and Telmisartan (40 mg) (once a day); the blood glucose level was within the acceptable range. The blood parameters improved significantly after taking GlucoSEB™ capsules (Table 1). Mean blood glucose decreased by 23.90 mg/dL (p-value=0.001), MAGE decreased by 20.20 mg/dL (p-value=0.010), and glucose concentration on a fixed meal day was lowered by 26.95% (p-value≤0.000001). While HBGI and time in range remained affected.

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Patient 6

A 41-year-old male patient with a BMI of 26.8 kg/m^2 and a HbA1c of 7.1% registered in the study. His regular medicines included metformin (500 mg) and Vildagliptin (50 mg) (once a day). After administration of GlucoSEB™ significant decrease in mean blood glucose was observed (Table 1). Mean blood glucose decreased by 11.40 mg/dL (p-value=0.015), MAGE decreased by 17.80 mg/dL, and fixed meal glucose concentration decreased by 25.88% (p-value=0.025).

DISCUSSION

Type 2 diabetes is a highly prevalent disease of the 21st century that increases morbidity and mortality and reduces quality of life. Therefore, it is necessary to have good glycemic control. Various medicines are available on the market that act through different mechanisms, counteracting various pathophysiological bases of diabetes. In addition to pharmaceutical drugs, herbal extracts are also popular for diabetes treatment. A study by Majeed et al[9] showed that herbal formulations containing extracts of *Cinnamomum cassia*, *Momordica charantia*, *Pterocarpus marsupium*, *Gymnema sylvestre*, *Salacia reticulata*, *Eugenia jambolana*, and *Piper nigrum* were able to reduce HbA1C, fasting, and postprandial sugar levels after four months of treatment. This performance was comparable to that of Metformin. The herbal formulation was also able to improve the lipid profile, which can be beneficial in treating hyperlipidemia.[9] Another study involved the administration of mulberry leaf extract to determine its effect on postprandial glucose. The mulberry polyphenol 1-Deoxynojirimycin (DNJ) is known for its hypoglycemic effect, owing to which the postprandial glucose (iAUC) decreased by 26% as compared to control.[10] The hypoglycemic action of herbal extracts is attributed to the presence of polyphenols; these phenolic compounds suppress gluconeogenesis, inhibit dipeptidyl peptidase 4 (DPP-4), decrease insulin resistance, exhibit antagonist effects against α-amylase and α-glucosidase, and improve insulin secretion.[11] This bioactivity of polyphenols makes them promising agents for treating hyperglycemia. The GlucoSEB™ formulation is comprised of herbal extracts that contain polyphenols, which are potential glucosidase inhibitors; their physiological impact has been observed as improvements in various blood glucose parameters.

Other than polyphenols, a group of enzymes called glucosyltransferase (present in GlucoSEB™) can uptake glucose and transform it into a long-chain fiber. Glucosyl transferase forms α-1,2; α-1,3; α-1,4; or α-1,6 glycosidic bonds, depending on their mode of action. Glucosyltransferases like cyclodextrin glucanotransferase and dextransucrase can synthesize oligosaccharides *via* the transfer of glucosyl residues from starch and sucrose, respectively, to different types of acceptors molecules.[12] Wei et al[13] reported the formation of slow-digestion dextrins (SDD) in the presence of α-glucosidase and cyclodextrin glucosyltransferase. The action of glucosyltransferase resulted in a 45.7% increase in dietary fibers, which have a prebiotic effect and assist the growth of gut microflora, *viz*. *Bifidobacterium*, *Veillonella*, *Dialister*, and *Blautia*. Another study showed modification of isomaltooligosaccharides (IMOs) by using glucosyltransferase with sucrose as a donor molecule; the dietary fiber content increased by 35% and can be used in functional foods.[14] On the other hand, alternansucrase (a type of glucosyltransferase) uses sucrose as a substrate and constructs long-chain fibers that have to alter α-1,3 and α-1,6 bonds; these fibers also possess prebiotic properties.[15] Similarly, the presence of the α-1,6 bond increased after treatment with glucosyltransferase; four types of starches were modified with this mechanism. The treatment resulted in slowly digestible starch (SDS) and resistant starch (RS) formation; the change in starch structure caused a decrease in *in vitro* digestibility.[16] Thus, glucose absorption in the bloodstream would be reduced, which would help treat hyperglycemia. This hypothesis is proved by the improvement in the blood glucose parameters of the patients involved in this study. It was also observed that the action of GlucoSEB™ is irrespective of age, sex, or HbA1C. The enzyme formulation exhibited its glucose-lowering action even in the presence of concomitant medication, although it is unclear whether some minor negative results are associated with the consumption of regular medicines. In some patients, the duration of hypoglycemia (i.e., time below range) also improved. The results obtained show that the GlucoSEB™ was aiding in the maintenance of blood glucose levels in the normal range in diabetic patients. However, a comprehensive clinical study is required to prove the efficacy of GlucoSEB™ in lowering blood glucose levels. Overall, the data suggested a beneficial impact of GlucoSEB™ on blood glucose levels in T2D patients without increasing the risk of hypoglycemia and without any gastrointestinal disorder or any other major side effect.

The study performed with the supplementation of GlucoSEB™ in the management of hyperglycemia in T2D patients had some limitations. The current investigation was performed with a relatively small number of patients for a short period. Further studies with a large population would be beneficial to provide clear insights and shed more light on the details.

CONCLUSION

The GlucoSEB™ formulation is comprised of digestive enzymes like amylase, protease, and lipase, along with special enzyme glucosyltransferases and herbal extracts rich in polyphenols. The combination of these ingredients showed a glucose-lowering effect in the current case study. Administration of GlucoSEB™ to T2D patients significantly improved multiple blood parameters, like a decrease in mean blood glucose, MAGE, HBGI, and increased TIR while lowering TBR. Additionally, GlucoSEB™ is well tolerated in all patients. These results demonstrate the efficacy and safety of GlucoSEB™ in the management of hyperglycemia in T2D patients.

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CONSENT TO PARTICIPATE

All individuals provided written informed consent.

DATA AVAILABILITY STATEMENT

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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