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Original Research Article

The Impact of SGLT2 Inhibitor Therapy on Postprandial Gut Hormone Response and Gut Microbiome Profile in Patients with Type 2 Diabetes: A 6-Month Prospective Pilot Study

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Abstract:

Background: The metabolic benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) extend beyond glycosuria. We hypothesized that these effects are mediated through modifications of the gut-pancreas axis.

Objective: To evaluate the effects of empagliflozin on postprandial glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) levels and on the gut microbiome in patients with type 2 diabetes mellitus (T2DM).

Methods: In this prospective, randomized, active-controlled, open-label pilot study, 62 patients with T2DM were assigned to receive either empagliflozin 25 mg (n=31) or glimepiride 4 mg (n=31) daily for 6 months. A standardized mixed-meal test was performed at baseline and study end. Fecal samples were collected for 16s rRNA sequencing.

Results: After 6 months, the empagliflozin group demonstrated a significantly greater increase in the incremental area under the curve (iAUC) for both postprandial GLP-1 (+35.2%, p=0.003) and PYY (+28.7%, p=0.011) compared to the glimepiride group. Empagliflozin therapy also led to a significant increase in microbial alpha-diversity (Shannon index, p=0.008) and a rise in the relative abundance of SCFA-producing bacteria, including Roseburia (p=0.002) and Faecalibacterium (p<0.001). Changes in Faecalibacterium abundance were inversely correlated with HbA1c (r = -0.47, p=0.009).

Conclusion: This pilot study suggests empagliflozin may enhance the secretion of satiety-inducing gut hormones and modulate the gut microbiome. These potential gastro-centric mechanisms warrant further investigation in larger, controlled trials.

Keywords: SGLT2 Inhibitors, Gut Microbiome, GLP-1, PYY, Type 2 Diabetes, Empagliflozin.

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Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have established themselves as a cornerstone in the management of type 2 diabetes mellitus (T2DM), with proven benefits on glycemic control, body weight, cardiovascular outcomes, and renal protection [1]. Their primary mechanism of action is the inhibition of glucose reabsorption in the proximal tubule, leading to glycosuria [2].

However, the caloric loss via urine accounts for only about 50% of the observed weight loss, suggesting the involvement of additional, extra-renal mechanisms [3].

The gastrointestinal tract plays a pivotal role in glucose metabolism and energy homeostasis. Enteroendocrine L-cells, located predominantly in the distal ileum and colon, secrete hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) in response to nutrient ingestion [4]. These hormones promote satiety, slow gastric emptying, and enhance insulin secretion, making them critical regulators of postprandial metabolism.

Furthermore, the gut microbiome, now recognized as a virtual endocrine organ, is intricately involved in host metabolism. Dysbiosis, characterized by a loss of microbial diversity and a shift in composition, is a hallmark of T2DM[5]. Specifically, a reduction in beneficial, short-chain fatty acid (SCFA)-producing bacteria like Faecalibacterium prausnitzii and Roseburia is commonly observed and is associated with increased inflammation and impaired glucose tolerance [6].

We hypothesized that by altering the nutrient load delivered to the distal intestine, SGLT2i therapy modulates the gut environment, thereby stimulating L-cell hormone secretion and inducing a favorable

restructuring of the gut microbiota. This study aimed to investigate these novel gastroenterological mechanisms of empagliflozin over a 6-month period.

Methods

Study Design, Duration and Participants: This was a single-center, prospective, randomized, and active-controlled, open-label pilot study conducted at a tertiary care endocrine unit. Study duration was six months from April 2024 to September 2024. The study protocol was approved by the Institutional Ethics Committee. All participants provided written informed consent.

We enrolled 62 adults aged 40-70 years with T2DM inadequately controlled (HbA1c 7.5-9.5%) on a stable dose of metformin (≥1500 mg/day) for at least three months. Key exclusion criteria included: use of other glucose-lowering agents, history of diabetic ketoacidosis, severe renal impairment (eGFR <60 mL/min/1.73 m²), chronic gastrointestinal diseases, antibiotic or probiotic use within 3 months of enrollment, and significant hepatic disease. Participants were instructed to maintain their habitual diet throughout the study period, and 3-day food diaries were collected at baseline and 6 months to qualitatively assess dietary stability.

Participants were randomly assigned (1:1) using a computer-generated sequence to receive either:

- Empagliflozin group: Empagliflozin 25 mg once daily.
- Active Control group: Glimepiride 4 mg once daily.
- Both groups continued their pre-existing metformin therapy.

Study Procedures and Measurements

Clinical and Biochemical Assessments: Visits were scheduled at baseline, 3 months, and 6 months. Weight, BMI, and blood pressure were recorded. Fasting blood samples were drawn for HbA1c, lipid profile, and fasting plasma glucose. Adverse events were monitored and recorded at each visit.

Mixed-Meal Tolerance Test (MMTT): A standardized MMTT (Ensure® 300 mL, 450 kcal) was performed after an overnight fast at baseline and 6 months. Blood samples for plasma active GLP-1 and total PYY were collected at -10, 0, 15, 30, 60, 90, and 120 minutes. The incremental area under the curve (iAUC) was calculated.

Microbiome Analysis: Fresh fecal samples were collected at home by participants using a DNA stabilization kit (OMNIgene•GUT, DNA Genotek) at baseline and 6 months and stored at -80°C. Microbial DNA was extracted, and the V4 region of the 16S rRNA gene was amplified and sequenced on an Illumina MiSeq platform. Bioinformatic analysis was performed using QIIME2 and DADA2 for amplicon sequence variant (ASV) calling. Alpha-diversity was assessed using the Shannon index. Beta-diversity was visualized using Principal Coordinates Analysis (PCoA) of Bray-Curtis dissimilarity. Given the exploratory nature of the microbiome analysis and the high dimensionality of the data, false discovery rate (FDR) correction was applied to p-values for taxonomic comparisons using the Benjamini-Hochberg procedure (q-value < 0.10 considered significant).

Statistical Analysis: Statistical analysis was performed using SPSS (v.27.0) and R (v.4.2.1). The primary outcome was the between-group difference in the change of GLP-1 iAUC from baseline to 6 months. Data are presented as mean ± standard deviation or median [interquartile range]. Between-group comparisons were made using an independent samples t-test or Mann-Whitney U test.

Within-group changes were analyzed using a paired t-test or Wilcoxon signed-rank test. Categorical variables were compared using the chi-square test. Correlations were assessed using Pearson's or Spearman's coefficient.

A p-value < 0.05 was considered statistically significant for primary and secondary clinical outcomes. For the microbiome analysis, FDR correction was applied as noted above.

Results

Patient Characteristics and Metabolic Outcomes: All 62 randomized patients completed the study. The two groups were well-matched at baseline (Table 1). After 6 months, both groups achieved significant and comparable reductions in HbA1c (Empagliflozin: -1.2%, Glimepiride: -1.1%, p=0.67 for between-group difference). However, the empagliflozin group exhibited a significant reduction in body weight (-3.2 kg) and systolic blood pressure (-5.1 mmHg), while the glimepiride group had a slight weight gain (+0.8 kg) and no significant change in BP.

Table 1: Baseline Characteristics and Metabolic Outcomes

Characteristic	Empagliflozin (n=31)	Glimepiride (n=31)	P-value
Age (years)	58.4 ± 7.8	57.1 ± 8.3	0.521
Male, n (%)	17 (54.8%)	16 (51.6%)	0.802
BMI (kg/m²)	31.5 ± 4.1	30.9 ± 3.8	0.551
HbA1c (%)	8.4 ± 0.6	8.3 ± 0.5	0.482
Diabetes duration (yrs)	9.2 ± 5.1	8.7 ± 4.8	0.689
--- After 6 Months ---	**Change from baseline**	**Change from baseline**	**P-value (Δ)**
Δ HbA1c (%)	-1.2 ± 0.4	-1.1 ± 0.5	0.387
Δ Body Weight (kg)	-3.2 ± 1.5	+0.8 ± 1.1	**<0.001**
Δ SBP (mmHg)	-5.1 ± 6.3	-0.3 ± 5.8	**0.003**

Gut Hormone Responses: At baseline, there were no differences in fasting or postprandial GLP-1 and PYY levels between groups. After 6 months, the empagliflozin group showed a significantly enhanced postprandial response for both hormones compared to the glimepiride group (Figure 1A-B). The iAUC for GLP-1 increased by 35.2% in the empagliflozin group versus 4.1% in the glimepiride group (p=0.003). Similarly, the iAUC for PYY increased by 28.7% with empagliflozin compared to a 2.3% decrease with glimepiride (p=0.011).

Gut Microbiome Changes

Alpha-diversity: The empagliflozin group demonstrated a significant increase in microbial richness and evenness, as measured by the Shannon index (Baseline: 3.51 ± 0.41; 6 months: 3.82 ± 0.38; p=0.008). No significant change was observed in the glimepiride group (p=0.421).

Beta-diversity: PCoA revealed a significant separation of microbial community structures between the two groups at 6 months (PERMANOVA, p=0.012), indicating a distinct shift in the empagliflozin group.

Taxonomic Changes: Empagliflozin treatment led to significant alterations in specific bacterial taxa (Table 2). Most notably, we observed a significant increase in the relative abundance of SCFA-producing genera, including Faecalibacterium and Roseburia. Conversely, the proportion of the pro-inflammatory genus Ruminococcus gnavus decreased.

Table 2: Changes in Key Bacterial Genera from Baseline to 6 Months

Bacterial Taxon	Empagliflozin Group (n=31)	Glimepiride Group (n=31)	P-value (Δ between groups)
	Δ Relative Abundance (%)	**Δ Relative Abundance (%)**	
Faecalibacterium	+1.52 ± 0.45	-0.11 ± 0.21	**<0.001**
Roseburia	+0.83 ± 0.31	+0.05 ± 0.18	**0.002**
Bifidobacterium	+0.41 ± 0.28	+0.12 ± 0.24	0.134
Ruminococcus gnavus	-0.65 ± 0.22	+0.08 ± 0.17	**0.018**
Bacteroides	-0.31 ± 0.41	-0.10 ± 0.35	0.289

A significant inverse correlation was found between the increase in Faecalibacterium abundance and the reduction in HbA1c (r = -0.47, p=0.009) in the empagliflozin group.

Discussion

This pilot study provides preliminary evidence that the metabolic benefits of SGLT2 inhibition with empagliflozin may be mediated, in part, through modifications of the gut-pancreas axis. Our key findings are threefold: (a) Empagliflozin was associated with enhanced postprandial secretion of GLP-1 and PYY; (b) It was associated with a shift in gut microbiome composition, including increased overall diversity and relative enrichment of SCFA-producing bacteria; and (c) These changes were associated with clinical improvements in body weight.

The observed enhancement of GLP-1 and PYY secretion offers a potential explanation for the weight loss effects of SGLT2i. We propose a mechanism whereby glycosuria increases the delivery of carbohydrates to the distal intestine, potentially stimulating L-cells [8], akin to the effect of non-absorbable sugars [9]. Furthermore, our results suggest that empagliflozin may promote a shift in the gut microbial ecosystem. The increased abundance of Faecalibacterium, a major producer of the anti-inflammatory SCFA butyrate, is of interest, as butyrate can improve insulin sensitivity and has been shown in vitro to stimulate GLP-1 secretion [10,11]. The observed correlation between the rise in Faecalibacterium and improved glycemia, while intriguing, is only associative and does not imply causality.

Limitations: Our study has several important limitations that must be acknowledged. First, the open-label design introduces potential for performance and detection bias, particularly for subjective endpoints; however, the primary

outcomes (laboratory measures, sequencing data) are objective.

Second, the sample size, while sufficient to detect significant changes in our primary endpoint, is modest for microbiome research and may limit the generalizability of these findings. Third, and critically, while we collected food diaries to qualitatively monitor diet, the lack of strict dietary control is a significant limitation, as diet is a primary driver of microbiome composition. The observed changes, while statistically significant, are modest in magnitude, and their clinical relevance remains to be determined. Fourth, we relied on 16S rRNA sequencing, which provides taxonomic but not functional data. The lack of direct SCFA measurement or other functional metabolic readouts (e.g., inflammatory markers) means our proposed mechanisms remain speculative. Fifth, despite FDR correction, the exploratory nature of the microbiome analysis and the multiple comparisons performed increase the risk of false-positive findings. Finally, the 6-month duration may be insufficient to observe stable, long-term microbiome adaptations, and seasonal variations over the study period (April-September) could be an unmeasured confounder.

Conclusion

This pilot study suggests that SGLT2 inhibitor therapy with empagliflozin may enhance the secretion of satiety-inducing gut hormones and be associated with changes in gut microbiome composition. These findings generate the hypothesis that gastro-centric mechanisms could contribute to the pleiotropic benefits of this drug class. The results are preliminary and must be interpreted with caution due to the study's limitations. Larger, double-blind, placebo-controlled trials with longer follow-up, strict dietary control, and functional metabolic analyses are required to confirm these observations and establish causality.

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