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ForePass endoscopic bypass device for obesity and insulin resistance—metabolic treatment in a swine model

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MESSAGE

Metabolic surgery (MS) causes long-lasting type 2 diabetes (T2D) remission through mechanisms that are beyond the mere weight loss being linked to the bypass of the upper gut. The ForePass device combines a channelled gastric balloon with an intestinal sleeve and aims at reducing simultaneously food intake and nutrients' absorption. In an experiment in four pigs, ForePass significantly lowered blood glucose and powerfully increased insulin-mediated glucose uptake, insulin clearance and reduced endogenous glucose production (EGP) over an observation period of 4 weeks without relevant complications. The weight gain was 79% lower than that observed in 4 sham-operated pigs. ForePass modified the composition of faecal microbiota raising the proportions of bacteria associated with metabolic health. Clinical studies are warranted.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

⇒ Metabolic surgery (MS) is a highly effective treatment for obesity and type 2 diabetes, leading to sustained weight loss over time. Notably, MS can reverse several obesity-related comorbidities such as chronic inflammation, hypertension and non-alcoholic fatty liver diseases, including nonalcoholic steatohepatitis (NASH).

WHAT ARE THE NEW FINDINGS

⇒ We showed that ForePass influences glucose kinetics, enhancing insulin-mediated whole-body glucose uptake, hepatic insulin sensitivity and insulin clearance. Moreover, ForePass modifies plasma metabolites and the variety and structure of faecal microbiota, increasing bacteria that beneficially impact glucose metabolism.

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FORESEEABLE FUTURE

⇒ As a highly effective procedure, ForePass can be considered an incisionless alternative to traditional surgical procedures. ForePass can also be used for high-risk patients who are ineligible for MS, reject a surgical approach, prefer a bridge to MS, or as a complement or substitute to new anti-obesity and anti-diabetes medications. The use of ForePass may provide a much-needed alternative to MS.

IN MORE DETAIL

A dramatic increase in T2D rates has been observed over the past 40 years.[1] T2D is closely associated with obesity, with over 80% of individuals with T2D having also obesity.[1]

Standard treatments for T2D and obesity include lifestyle interventions, medical therapy and MS. Nevertheless, lifestyle interventions and anti-obesity medications are only partially effective in determining long-term weight loss.[2] In contrast, MS has the potential to achieve long-lasting remission of T2D and reversal of several obesity complications.[3]

The ForePass device is an endoscopic alternative to MS that links the stomach to the jejunum via a gastric funnel connected to an intestinal sleeve. The balloon, which reduces the gastric volume by approximately 2/3, is traversed by a central channel that connects to the sleeve, which extends through the duodenum and proximal jejunum (figure 1A–C). Hence, ingested foods bypass the duodenum and proximal jejunum arriving directly into the mid-jejunum.

We hypothesised that the ForePass, which limits food intake and bypasses the upper gut, significantly improves glucose disposal and reduces weight gain in pigs relative to controls.

To this end, we assessed glucose disposal, weight gain, metabolomics and faecal microbiota in eight pigs that were assigned to either Sham-operation (controls) or Forepass. Experimental procedures are shown in detail in the online supplemental appendix.

After 4 weeks, we observed a large reduction (79%) in the overall weight gain in part due to reduced food intake (22%) and in part to incomplete food digestion with increased faecal nutrient loss in the group with ForePass as compared with sham operation (table 1). We did not observed

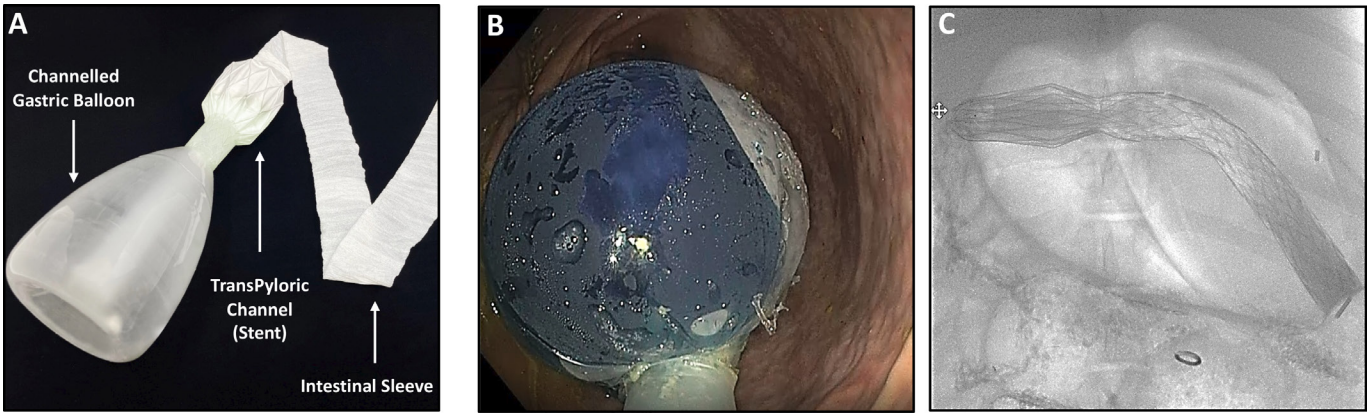

Figure 1 Characteristics of the Forepass device. (A) The overall structure of the ForePass device, which is composed of a silicone gastric balloon and an expanded polytetrafluoroethylene (EPTFE) intestinal sleeve. A nitinol stent-like funnel, which traverses the balloon, connects to the sleeve. The transplyloric stent, coated by EPTFE, helps to improve device stability. (B) An endoscopic image of the proximal end of the ForePass device, including the inflated gastric balloon. The balloon's colour is due to methylene blue added to the saline solution used to inflate the device. (C) An X-ray fluoroscopy image of the ForePass device positioned in the stomach and proximal gut. The balloon component of the device is placed in the stomach, while the transpyloric stent and intestinal sleeve are located further down, past the pylorus.

macroscopical or microscopical lesions of the stomach and duodenal mucosa and submucosa.

We observed a significant decrease in plasma glucose, insulin and C-peptide levels in response to an intragastric glucose load (figure 2A–C) in ForePass. Accordingly, insulin sensitivity was significantly higher in the ForePass than in the sham group (table 1).

Intragastric glucose administration combined with U-^{13}C-glucose and 6,6-deuterated glucose infusion resulted in a significantly lower glucose rate of appearance and disappearance in the ForePass than in the sham-operated group (figure 2D and E). Moreover, EGP was markedly suppressed with the ForePass (figure 2F) indicating a better hepatic insulin sensitivity.

Table 1 Upper part: weight gain and food intake

Weight gain and food intake			
	Sham-Op	ForePass	P value
Basal weight (kg)	46.88±1.95	46.50±1.51	NS
Final weight (kg)	56.38±1.77	48.5±1.67	0.029
Food intake (kg/day)	2.00±0.01	1.77±0.04	0.028
Glucose minimal model			
	Sham-Op	ForePass	P value
$S_G \cdot 10^2$ (per min)	1.28±0.15	1.57±0.06	NS
$p \cdot 10^2$ (per min)	0.37±0.13	0.17±0.03	NS
$S_I \cdot 10^4$ (pm/min)	0.41±0.031	0.65±0.032	0.029
Stable isotope glucose kinetic			
	Sham-Op	ForePass	P value
EGP AUC ·insulin AUC (µmol*pmol*min)	10.91±0.59	4.24±0.45	0.029
Insulin clearance (l/min)	2.61±0.009	2.96±0.06	0.029
R_d AUC/insulin AUC (µmol/pmol*min)	0.024±0.003	0.039±0.004	0.029

Upper part: weight gain and food intake. art: basal, final weight and food intake. Middle part: minimal model analysis of glucose, insulin and C-peptide time courses following glucose administration via gastric gavage after Sham-Operation or ForePass. Lower part: stable isotope glucose kinetics. Data are expressed as mean±SEM.
S_G, glucose effectiveness; p, minimal model parameter; S_I, insulin sensitivity; AUC, area under the curve; EGP, endogenous glucose production; R_d, rate of glucose disappearance.

Accordingly, we observed a higher hepatic insulin-sensitivity and insulin clearance as well as higher whole-body insulin-mediated glucose uptake in the ForePass versus the sham group (table 1).

To gain further insight into the mechanisms responsible for the improvement of insulin sensitivity following the ForePass implant, we performed polar metabolite analysis using GC/MS/MS. Figure 2G shows that the first two components of the principal component analysis explain 85.8% of the variance in plasma metabolites that significantly differ between sham-operation and Forepass. As observed in other studies testing markedly reduced energy intake,[4 5] we found increased circulating levels of amino acids and their metabolites in pigs with ForePass as compared with sham-operated animals (figure 2H, online supplemental table 1, online supplemental figure 1). Among amino acids, we found a surge of branched chain amino acids, valine, isoleucine and leucine, which are essential amino acids provided only with food. In agreement with the reduction of EGP, we observed a decrease in gluconeogenesis precursors with ForePass. Specifically, alanine, glutamine and glycine, but also lactate, which contributes from 7%[6] to 18%[7] to plasma glucose levels after an overnight fast.

To understand how caloric restriction and upper gut bypass could affect gut microbiota composition, we profiled the V4 region of the 16S rRNA gene in faecal samples. Faecal microbiota beta diversity, estimated both as weighted UniFrac (online supplemental figure 2A, p=0.026, R^2=0.42) and unweighed UniFrac (online supplemental figure 2B, p=0.023, R^2=0.32), was strongly affected by the ForePass device, indicating an effect on dominant faecal taxa (online supplemental figure 2C). The abundance of the genera *Treponema* and *Prevotella* decreased, while *Akkermansia*, *Christensenellaceae* R-7 group, *Bifidobacterium* and the Archaea *Methanobrevibacter* significantly increased (online supplemental figure 3A-F). The taxa increased with ForePass correlated significantly with the reduction of the area under the curve of EGP and insulin and with fasting C-peptide (online supplemental figure 4).

COMMENTS

Our study shows that the ForePass device reduces body weight gain by 79% in rapidly growing pigs due to reduced food intake and increased faecal energy loss. Glucose absorption was also

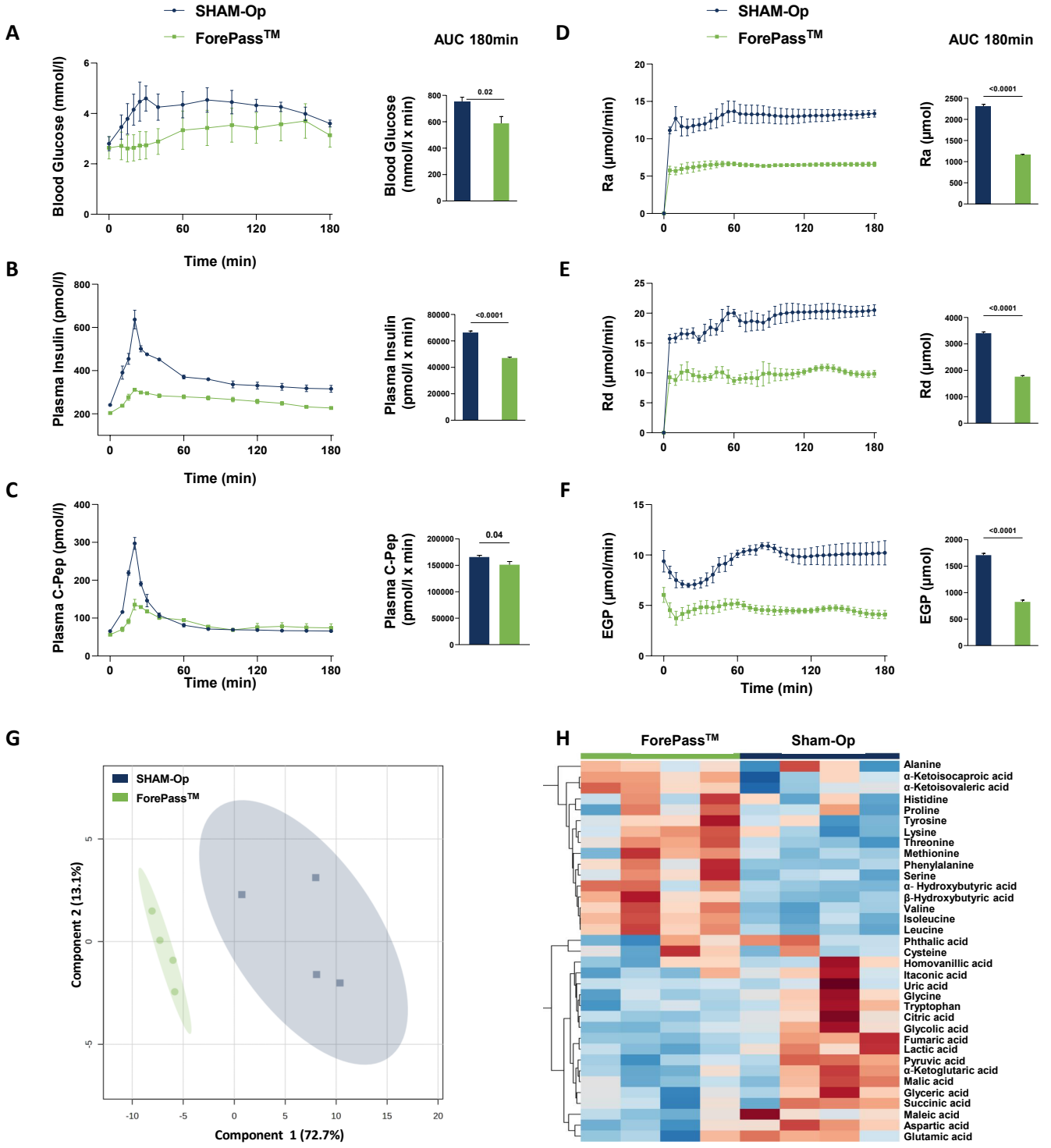

Figure 2 Metabolic shifts after ForePass. (A–C) Time courses and areas under the curve (AUCs) of blood glucose (A), plasma insulin (B), and plasma C-peptide (C) during an intragastric glucose administration (75g) using a combination of ingested and infused stable isotopically labelled glucose tracers in both ForePassTM and sham-operated pigs (Sham-Op). (D–F) Time courses and AUCs of the rate of appearance of exogenous glucose (Ra) (D), glucose rate of disappearance (Rd) (E), and endogenous glucose production. (G) Principal component analysis explains 85.8% of the variance of metabolites that significantly differ between ForePass and Sham-operation. (H) Heat map of polar metabolites 4 weeks after the interventions. Data are presented as mean values±SEM (n=4 pigs per group). Statistical significance values were calculated by Mann-Whitney U test and repeated measure analysis of variance were appropriate.

reduced by 67%. Whole-body and hepatic insulin sensitivity were significantly increased with consequent reduction of insulin secretion and improvement of insulin clearance.

Other endoscopic procedures, such as duodenal-jejunal bypass liner (DJBL) and duodenal mucosal resurfacing (DMR) have attempted to mimic the effects of MS on T2D and insulin

resistance. DJBL improves glycaemic control in people with T2D, with an average HbA1c reduction of 0.9% and a weight loss of 11.3 kg at 1-year follow-up as compared with controls.[8] However, in people with insulin resistance and T2D, DJBL does not suppress EGP.[9] DMR improves glycaemic control in T2D[10] likely via a weight-independent mechanism, since weight loss was not significant at 6-month follow-up.[10] In women with insulin resistance, obesity and polycystic ovary syndrome, DMR did not improve significantly hepatic insulin sensitivity as shown by the lack of EGP suppression at 6 months after the procedure.[11] With due precaution when comparing human and swine data, ForePass significantly reduces EGP showing its beneficial effect in improving hepatic insulin resistance and potential in the treatment of both T2D and non-alcoholic fatty liver disease, where EGP is a key element.[12] Moreover, ForePass reduces major gluconeogenic substrates and, consequently, gluconeogenesis.

ForePass had an effect not only on glucose homeostasis but also on the composition of gut microbiota. The literature provides evidence that the gut microbiota has a substantial impact on metabolism and can modulate various aspects of the metabolic syndrome beyond obesity, including insulin resistance and glycaemic control.[13 14] In this study, we found that the ForePass device promotes the formation of a microbiota pattern that is known to be associated with a better metabolic outcome.

In conclusion, the ForePass device reduces glucose absorption and EGP, enhances whole-body insulin-mediated glucose uptake and hepatic insulin sensitivity with increased insulin clearance, reduces gluconeogenic substrates and improves the abundance and composition of faecal microbiota promoting a configuration that positively affects glucose metabolism. ForePass is an endoscopic procedure that, contrary to MS, is completely reversible. It could be used for those hesitant to undergo MS, high-risk patients who are ineligible for MS, as a bridge to bariatric surgery or MS, as well as a complement or substitute to new anti-obesity and anti-diabetic medications for these lifelong diseases.

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Correction notice This article has been corrected since it published Online First. The first affiliation has been corrected.

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Contributors GM and GA designed the study. MGN, IB, VB and AG performed the surgical procedures. GA, SR and LP carried out the study. LO, HA and VT performed gut microbiota analyses. AG and SS measured stable isotopes. EP did the statistics. GA, AG, GM, MEC, and VT wrote the first draft. All authors actively contributed to the definitive version. AG and GM are jointly supervised this work.

Competing interests GA reports consulting fees from Metadeq and GHP Scientific. IB reports consulting fees from Apollo, Endosurgery, AndoTools, Nitinotes, Erbe Elektromedizin, Boston Scientific, Cook Medical and Pentax Medical. MGN reports consulting fees from Apollo EndoSurgery, USGI and Keyron. He is also a Scientific Advisor of Keyron and Morphic Medical. VB reports consulting fees from Apollo EndoSurgery. GM reports consulting fees from Novo Nordisk, Fractyl, Recor. She is also Scientific Advisor of Keyron, Metadeq, GHP Scientific, and Jemyll. All other authors declare no competing interests.

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