

ONE YEAR RESULTS OF AN ENDOSCOPIC, DUODENAL-JEJUNAL EXCLUSION DEVICE FOR WEIGHT LOSS AND CONTROL OF TYPE 2 DIABETES

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Background: The duodenal-jejunal bypass liner (DJBL, GI Dynamics, Inc., Lexington, MA) is an endoscopic implant that mimics the intestinal bypass component of the Roux-en-Y gastric bypass. Previously reported studies have shown promising improvements in type 2 diabetes (T2D) and weight loss for up to 6 months. This report describes improvements in T2D and metabolic changes in subjects with T2D who were implanted with the DJBL for one year. **Methods:** This is a prospective, non-randomized, open label study with 22 patients enrolled. **Inclusion criteria:** Age higher 18 years and less 65 years, BMI higher 35 kg/m²; and type 2 diabetes with or without other co-morbidities, unsuccessful history with nonsurgical weight reduction methods, candidates to bariatric surgery. There were 9 early endoscopic removals due to device movement (3), nausea/vomiting (1), abdominal pain (1), GI hemorrhage (1), non-device related abdominal neoplasm (1) and Principal Investigator request (2). **Results:** At one year (n=13 patients), observed absolute weight loss of 20.4 kg (p less 0.0001), excess weight percentage loss of 35.3% (p less 0.0001), body mass index of 7.4 kg/m² (p less 0.0001) and waist circumference of 10.1cm (p=0.0001) was observed. Likewise, glucose levels decreased from 175.6 to 126.7 mg/dL (p less 0.0001) and glycosylated hemoglobin from 8.8 to 6.4% (p less 0.0001). The use of diabetic medications, except metformin was reduced and 19.2% of patients no longer required any anti-diabetic drugs. Insulin (p=0.02) and C-peptide (p=0.015), cholesterol (p=0.001), LDL (p=0.01), and triglycerides (p=0.006) levels were normalized at 1 year. **Conclusions:** The endoscopic DJBL has a durable effect on glucose control, weight loss and metabolic function for one year, suggesting this new device is a suitable option for the treatment of T2D and obesity.

Enteropeptidase: a gene associated to a starvation human phenotype as a novel target for the treatment of obesity and type II diabetes

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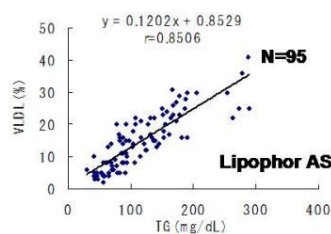
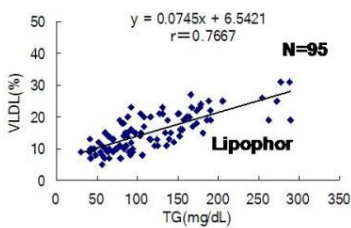
- Many obesity related genes have been proposed as targets for the treatment of obesity. However, these obesity genes did not provide efficient drug therapy for obesity treatment. This is mainly due to the redundancy of the biochemical pathway involved in obesity and the lack of specificity of the gene targets. It is therefore a challenge to identify crucial gene(s) targets involved in energy metabolism associated with lean or starvation phenotype. Congenital Enteropeptidase deficiency is an extremely rare pathology which answers to all these criteria. Enteropeptidase catalyzes the conversion of inactive trypsinogen into active trypsin via the cleavage of the acidic propeptide from trypsinogen. We have generated knock out transgenic mice for enteropeptidase which shows the same phenotype like in human. These data and in vivo preclinical data using per os small molecule for long term treatment (9 weeks) will be presented.

Newly developed profiling of lipoproteins by PAGE to determine the heterogeneity of low-density lipoproteins (LDLs)

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Aim: To explore the potential of newly developed polyacrylamide-gel disc electrophoresis (PAGE) for lipoprotein profiling in clinical practice. **Design and Methods:** Blood samples were collected from 95 patients with metabolic syndrome. Lipid parameters were assayed by commercial (Lipophor) and newly developed PAGE (Lipophor AS), including small, dense low-density lipoprotein (LDL) (n = 41), and triglyceride-rich lipoprotein remnant cholesterol (n = 37). We also used a commercial kit to measure small, dense LDL (n = 41). **Results:** By PAGE, we obtained the percentage of the area under the curve (AUC %) of each peaks and calculated respective AUC% x total cholesterol (AUC%xTC) values. The calculated values of LDL-AUC%xTC, small LDL-AUC%xTC, and HDL-AUC%xTC values were correlated well with values from homogeneous assay for LDL-cholesterol, small, dense LDL-cholesterol, and HDL-cholesterol assays (r = 0.94, 0.81, and 0.89, respectively). Lipophor AS is better correlation between TG and VLDL than Lipophor (r = 0.77, and 0.85, respectively). **Conclusions:** PAGE combined with measurement of total cholesterol and triglycerides provides a rapid evaluation of anti- or pro-atherogenic lipoproteins and a simple profiling system for both the "quantity" and "quality" of lipoproteins, allowing a better assessment of the risk of coronary artery diseases.



Ileal interposition improves Glucose Tolerance and Insulin Resistance in Otsuka Long-Evans Tokushima Fatty rats.

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Backgrounds: Ileal interposition (IT) is an operative procedure in which the distal ileum is transposed isoperistaltically into the proximal jejunum and considered as a procedure for metabolic or anti-diabetic surgery. Our aim was to study the effects of IT on glycemic control, fat metabolism, and hormonal changes in obese rats with spontaneous diabetes (OLETF rats). **Methods:** Animals were divided into either an IT or a sham (SH) group. They underwent oral glucose tolerance test (OGTT) before, 4, and 8 weeks after the operation. All animals were killed 10 weeks after operation for analyses of tissue weight (liver, pancreas, epididymal fat, brown fat) and fasting plasma levels of glucose, insulin, glucagon-like peptide (GLP)-1, peptide YY (PYY), glucose-dependent insulintropic polypeptide (GIP), and leptin. **Results:** After operation, body weight increased in both groups compared to their preoperative weight, but it did not differ between IT and SH. At 8 weeks postoperatively, integrated blood glucose levels during the OGTT were decreased in IT compared to SH ($p < 0.05$). Ten weeks after operation, fasting plasma levels of insulin, GLP-1, and GIP did not differ between the two groups, but PYY levels were greater in the IT group ($P < 0.01$). Weight of epididymal and brown adipose tissues, homeostasis model assessment insulin resistance, and fasting plasma leptin levels were decreased in the IT group ($p < 0.05$). **Conclusions:** These results suggest that IT improves glucose and lipid metabolism by decreasing blood glucose, insulin resistance, and epididymal fat, increases in plasma PYY might be one of the mechanisms of these changes.

The effects of duodeno-jejunal bypass on glucose metabolism in obese type2 diabetic rat model.

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BACKGROUNDS: Bariatric surgery, especially gastric bypass or duodenal switch, has been shown to improve type 2 diabetes. However, its detail mechanisms are not well comprehended yet. There are two hypotheses that are advocated to explain effects of bariatric surgery on glucose metabolism: the foregut hypothesis and the hindgut hypothesis. The former theory is considered to depend on exclusion of duodenum and proximal jejunum from the nutrients transit, possibly enhancing secretion of anti-incretin factors, while the latter one is thought to be results from more rapid delivery of nutrients to the ileum, thereby enhancing the release of hormones such as glucagon-like peptide-1 (GLP-1). Duodeno-jejunal bypass (DJB) might include both theories, but it is still controversial which theory is dominant. **METHODS:** Male 20-week-old OLETF rats were divided into 3 groups and they underwent sham operation or two types of DJB, which are defined as DJB-J and DJB-I. These are differentiated by the length of alimentary limb (AL). In DJB-J, the biliopancreatic limb (BPL) was anastomosed to the side of distal limb to make 2.5cm AL and it can be considered as pure foregut model. In DJB-I, the BPL was anastomosed to the distal limb 25cm proximal to the ileum-end, and it can be thought as foregut plus hindgut model. All rats underwent OGTT at baseline, 4 and 8 weeks after surgery. **RESULTS:** There was some weight controlling effect in DJB-I group, but not in other groups. Regarding OGTT, DJB-I group demonstrated lower plasma glucose curve at 4 and 8 weeks after surgery comparing to other groups, but there were no significant difference between DJB-J and sham group. **CONCLUSION:** The improvement of glucose metabolism in DJB mainly depends on an inflow of bile and pancreatic juice to the ileum, and the exclusion of the duodenum may not contribute to the anti-diabetic effect.

Differential increase in HDL-c post bariatric surgery for Singaporean Patients according to Glucose Status.

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Background: HDL-c is negatively correlated with cardiovascular risk. Patients with diabetes and pre-diabetes or abnormal glucose tolerance (AGT) have low HDL-c. Few studies have compared the change of HDL-c post bariatric surgery between patients with normal glucose tolerance (NGT) and AGT. Aims of Study: To compare the change of HDL-c post bariatric surgery between patients with NGT and AGT. Methods: HDL-c levels at 0, 3 and 6 months were transformed using the multivariate repeated measures model, with glucose tolerance being the between-subject factor. Results: 46 patients (61% females) underwent laparoscopic bariatric surgery from September 2008 to November 2010. 78% had sleeve gastrectomy, 20% gastric bypass, and 2% bilio-pancreatic diversion. The mean age was 39 years (+/-10.6) with a mean BMI of 43.6kg/m² (+/-9.8). 54% had NGT versus 46% with AGT. Only 1 patient (4%) in the NGT group was on a fibrate pre-op but none in the AGT group. Average weight loss at 6 months was 25.5kg and 22.2kg for NGT and AGT respectively. HDL-c rose significantly in both groups (mean HDL-c for NGT were 1.06, 1.49 and 1.68 mmol/L at 0, 3 and 6 months; mean HDL-c for AGT were 0.89, 0.92 and 1.08 mmol/L; within-subject p=0.006). Thus HDL-c increased 58% in the NGT but only 21% in the AGT. HDL-c in the NGT was significantly higher than in the AGT group throughout the 6 months (between-subject p=0.009).