**TITLE: Acute effect of biliopancreatic diversion with duodenal switch (BPD-DS) and Sleeve Gastrectomy (SG) on postprandial plasmatic acylcarnitines profile and fatty acid kinetics**

The design and general direction of the grant have not been changed. The original aims of our application are in good progress and still planned to be completed by 2017.

**Laboratory Methods**

We worked on validation and development of a new method of semi-quantitative acylcarnitines dosage using LC-MS/MS. Before this grant, our lab was able to measure 6 species of acylcarnitines (C2, C3, C5, C16, C18:1, C18:2), using quantitative methodology. However, semi-quantitative measurements of medium-chains and other short and long chain acylcarnitines were not developed in our laboratory until now. We encountered technical problems, that extended the period of method development we planned in the beginning. We acquired new internal standards that solved these technical problems. We used internal standards of C0, C2, C3, C4, C5, C8, C14 and C16 (Cambridge Isotope Laboratory, Inc.) and were able to measure C0, C2, C3, C4, C5, C5-DC, C8, C8:1, C3-DC, C10, C10:1, C14, C14-OH, C14:1, C12, C12:1, C16, C18:2, C18:1 and C18 plasmatic acylcarnitines, as well as quantitative C2, C3,C5,C16,C18:1 and C18:2 with the same assay.

1) **Acute effect of biliopancreatic diversion with duodenal switch (BPD-DS) and Sleeve Gastrectomy (SG) on postprandial plasmatic acylcarnitines (AC) profile and fatty acid kinetics**

We began enrollment for the proposed protocol since July 2015 and we presently recruited 11 subjects (8 Sleeve Gastrectomy and 3 BPD-DS). Due to changes in clinical practices in our center for bariatric surgery, with now more than 70% of bariatric surgeries being sleeve gastrectomy, we chose to include a group of patient undergoing sleeve gastrectomy to the present research proposal. This group of patients was already planned in the funded protocol from Canadian Diabetes Association, but we decided to include AC measurements funded from this grant also in patients undergoing sleeve gastrectomy.

We completed metabolic studies, using PET/CT imaging, glucose and fatty acid kinetics and indirect calorimetry described in the proposed proposal in preoperative period and early postoperative period (12 days after surgery) for 3 subjects (2 SG group and 1 BPD-DS group). Preliminary results from 2 subjects before and after SG and 1 subject before and after BPD-DS suggest a decrease in myocardium dietary FA partitioning and an important increase in visceral adipose tissue partitioning after bariatric surgery. These results will need to be confirmed. We plan that 4 of our recruited subjects will have surgery in the next month and will complete both preoperative and early postoperative metabolic protocol. AC, as well as measurements of fatty acid kinetics will be completed in the next 12 months (07/2017) as it was planned in the original protocol.

2) **Effect of BPD-DS and SG on fasting and postprandial acylcarnitines profile**

In other cohorts of subjects that we studied prospectively before and 3 days after BPD-DS and SG, we obtained retrospectively plasmatic AC fasting and postprandial measurements.
A) Effect of BPD-DS
9 diabetic and 9 non-diabetic subjects undergoing BPD-DS for severe obesity had quantitative measurements of AC (C2, C3, C5, C16, C18:2, C18:1) by LC/MS/MS at fasting and postprandially before surgery and 3 days after surgery. Before surgery and 3 days after surgery, fasting C3, C5, and C16 correlated significantly with HOMA-IR (r=0.42 to 0.64, P<0.03), but did not correlate with disposition index (DI). Fasting C16 and C18:1 tended to be higher in T2D vs. non-diabetic subjects (P<0.07) but were not different according to HOMA-IR status (high or low level of resistance). Postprandial C3 and C5 were higher in the insulin-resistant compared to the insulin-sensitive group, while not different according to diabetes status. Fasting and post-prandial C3 and C5 were significantly lower after surgery (P ≤ 0.002). We concluded that short chain AC correlate more with HOMA-IR, which reflects hepatic insulin-resistance, than T2D status per se, and are significantly reduced 3 days after BPD-DS along with HOMA-IR. Fasting long chain acylcarnitines tend to be higher in T2D and to increase after BS, which may be a reflect of increase fatty acid substrate to mitochondria in post-operative period.

We presented these results in a national meeting (Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism) and the abstract was published in Canadian Journal of Diabetes. This abstract has been provided to your organisation while it was accepted. The analyses of targeted short, medium and long-chain AC measurements were limited by the methodological problems and we plan to pursue further analyses of medium-chain AC profile with the new technique we developed.

B) Effect of SG
We obtained semi-quantitative measurements of short, medium and long chain plasmatic AC in 9 diabetics subjects before and 3 days after SG. We found that fasting and postprandial short chain AC: C3, C4 and C5 were significantly decreased after SG as well as medium-chain C8 and C8:1 in diabetic subjects. On the opposite, long chain fatty acids were not significantly different after SG but tended to be increased. This may reflect an improvement of mitochondrial long chain fatty acid b-oxidation despite a similar or increased long chain fatty acid substrate.

We plan to publish these results in a manuscript that will compare the effect of BPD-DS and SG on fasting and post-prandial AC.

Future directions
Studies that will answer to secondary aims planned in the research proposal will continue to be conducted until 07/2017.

1- To determine the association between plasma AC and endogenous production of NEFA (NEFA appearance rates (RaNEFA)) and NEFA appearance rate from dietary fatty acids (spillover NEFA) in order to understand the contribution of different sources of NEFA to the plasma AC pool.
2- To determine the association between plasma AC and dietary fatty acid partitioning in the heart, liver, muscle, subcutaneous and visceral adipose tissues
3- To determine if changes in insulin sensitivity, insulin secretion and intestinal hormones levels correlate with changes in levels of plasma AC.
4- To determine if caloric restriction alone explains changes in AC profile occurring after BPD-DS.
List of published abstracts:


List of presentation in national meetings:


Anne-Marie Carreau, Thomas Grenier-Larouche, Laurent Biertho, André Tchernof, André C. Carpentier, Effect of biliopancreatic diversion on fasting and postprandial acylcarnitine profiles, Montreal Diabetes Research Center Annual Retreat, 2016/02, Montréal, Canada.