DRAFT PROTOCOL NUMBER: Pending

TITLE: FREE TO GO
STUDY PHASE: CLINICAL STUDY
STUDY GROUPS: WITH AND WITHOUT JEJUNAL NUTRIENT ADMINISTRATION
IND OR IDE #: Not Applicable

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SUBJECTS/LOCATONS: ROYBAL DIABETES MANAGEMENT CLINIC
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AMENDMENTS/REVISIONS: None

ABSTRACT

Background The overall objective of our work is to develop therapy for obesity and diabetes that is as effective as gastric bypass surgery but without the cost and safety concerns. Gastric bypass leads to rapid, sustained diabetes remission in the majority of patients who undergo this procedure and is also highly effective therapy for obesity. However currently <1% of medically-eligible patients undergo this or other bariatric operations due to cost and safety concerns. Our approach is based on data suggesting that the benefit of gastric bypass is largely due to anatomical rearrangement of the intestine which leads to accelerated delivery of nutrients to the jejunum. This rerouting of nutrients stimulates the release of multiple neural, hormonal and enterokine responses that are associated with appetite suppression and improved glucose control.

In this proof-of-concept pilot proposal we are asking the question: can repeated rapid delivery of a mixed meal directly to the jejunum promote weight loss and blood glucose control?

Hypothesis: Administration of intermittent mixed meal bolus daily via jejunal tube over a 2 week period leads to weight loss and improved glycemic control that is associated with reduced food intake and is sustained for 2 weeks of follow up.

Specific Aims: In obese, ambulatory, adult patients with type 2 diabetes receiving mixed meal (intervention) or electrolyte solution (control) boluses daily via jejunal tube for 14 days, with 14 days follow up and with other oral nutrition permitted throughout, to compare the following:

Primary aim: weight change immediately following the intervention period between the study groups

Secondary aims to compare the following within and between groups: From Day 0 to Day 14: caloric intake (as determined by consumption of provided food), From Day 0 to Day 14: weight change (within group),From Day 0 to Day 28: weight change From Day 0 to Day 14 and also from Day 0 to Day 28: waist and hip measurement, hormones and biochemical measures, physical activity , body composition , symptoms, medication use, average self-monitored blood glucose level

Study Design: Prospective, randomized 2 group pilot study: 14 days with tube, 14 days follow up. The feeding tube will be anchored intraorally so that it is not apparent to observers when not in use.

Major Inclusion Criteria: 18-70 years of age, BMI $\geq$30kg/m^2, type 2 diabetes on oral antidiabetic agents only, A1C<9%.

Major Exclusion Criteria: Use of incretin-based therapy, insulin, contraindication to tube (prior upper gastrointestinal bleed or history of easy bleeding, altered foregut anatomy due to obstruction or surgery), known cardiovascular disease other than controlled hypertension, pregnancy, no acceptable contraception, known prior abdominal problems that could prevent the spontaneous passage of a 10 French jejunal tube if it were to dislodge distally.

Withdrawal Criteria: any request by subject, specified clinically significant complications secondary to the intervention.

Study Site: Edward R. Roybal Comprehensive Health Center (CHC) and ambulatory.

Method: Approximately day -14: In preparation for placement of intra-orally anchored jejunal tube dental spacers will be placed by study orthodontist. Approximately day -7: Dental anchor placed by orthodontist.

Day 0: Subject presents fasting to the CHC. Blood pressure, heart rate, weight, height and waist circumference and body composition on InBody520 BioSpace will be recorded. FitBit® activity monitor placed. Subjects will have a jejunal feeding tube placed by the investigator using a CORPAK EAS™ and will then be randomized to the control or intervention group.

Day 0-Day 14: Subjects will take a mixed meal or electrolyte solution at a prescribed rate and interval and will be requested to eat ad lib only from provided meals of known caloric amount or from a list of low calorie items. Subjects will maintain a log of all food intake, temperature at least daily, tube position and symptoms and blood glucose 4 times a day.

Day 7: The subject will return to the CHC for review for continuation in the study, of their log and caloric intake and for adjustment of medication if necessary and activity monitor download.

Day14: Day 0 measures will be repeated at the CHC and the tube removed. All uneaten food will be returned for caloric intake determination, activity monitor download.

Day 15-Day 28: The subject will maintain a medication and blood glucose log for 14 days after the removal of the tube.

Day 28: Exit outcome measures similar to those at Day 0.

Safety: The subjects will be monitored for fever, sore throat, displacement of the tube, gastrointestinal upset, vital signs, biochemical measures and weight change, and if pre-specified criteria are met or in the clinical judgment of the PI it is not appropriate to continue, will be withdrawn from the study.

Outcome Measures: weight change, caloric intake, waist and hip measurement, hormones and biochemical measures, physical activity , body composition , select symptoms, medication use, average self-monitored blood glucose level

Reimbursement: Subjects will receive standardized meals of known caloric amount for 2 weeks and up to $300 cash.

Statistics This is a pilot study and sample size estimates are not appropriate. However based on studies of dietary restriction with a 1250 kcal diet for 1 week we anticipate identifying a significantly greater weight loss in the intervention arm with a sample size of 10 subjects/group. Fifteen subjects/group will be enrolled to allow for drop-outs.

Analysis: Primary analysis will be to compare change from baseline in outcome measures between the 2 groups using paired t-test. SC CTSI Biostatistics Department has aided in the study design.

Human Subjects: This is a moderate risk study using a variant of a standard ambulatory intervention. Potential benefit in identifying a safe, simple weight loss intervention justifies risks.

TABLE OF CONTENTS

SCHEMA, SYNOPSIS, OR STUDY SUMMARY

1.0

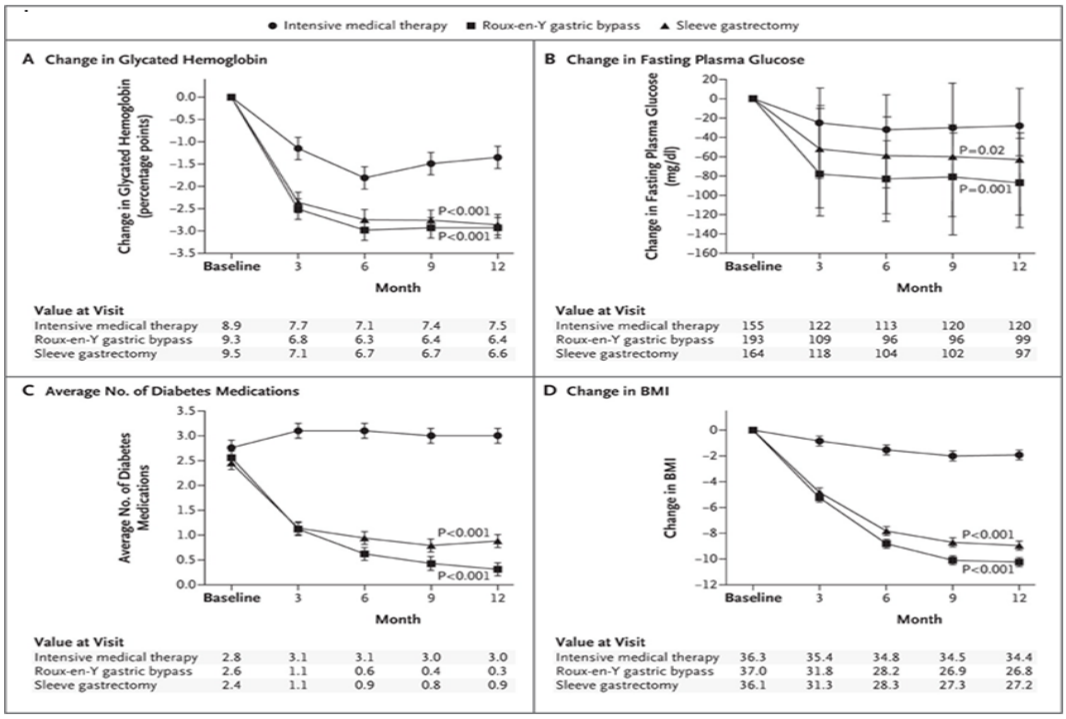
BACKGROUND AND HYPOTHESES

More than two-thirds (69%) of US adults are overweight, with more than 36% obese and more than 6% having morbid obesity. [1] Over 80% of type 2 diabetes is attributed to excess weight and obesity,[2] but safe, effective, low-cost treatment is not available. **Failure to control obesity underlies the increasing cost of diabetes care** in the US which rose by 41% from 2007 to $245 billion in 2012.[3] Most of the cost of care (62%) is provided by government insurance.[3] Pharmaceutical therapy has proven disappointing for management of obesity: it is relatively ineffective, associated with severe side-effects and expensive.

Various bariatric surgical procedures are highly effective at inducing weight loss and lead to drug-free remission in 40-90% of patients. [4, 5] (Fig 1). However a recent US study [6] of 29,820 Blue Shield plan members who underwent bariatric surgery (at a cost of over $28,000/procedure) and a comparison group of persons not undergoing surgery but with diagnoses closely associated with obesity found no reduction in overall health care costs with surgery during a 6-year follow-up period. This was due to high inpatient costs that were not offset by a reduction in office visits and prescription medications. Bariatric surgery is not available to the vast majority of the world's population who might benefit from it, including low income individuals, the young, the elderly and those with early or mild disease. Due to concerns about short and long term risk, surgery is generally limited to adults with complicated obesity and a BMI of ≥35kg/m2, or severe obesity with a BMI of ≥40kg/m^2.[7] Furthermore many individuals elect not to undergo bariatric surgery for a variety of reasons that include concerns about the risks, unwillingness to undergo an irreversible procedure and the belief that their obesity does not justify the intervention.

There is thus an unmet clinical need for a safe, low-cost alternative to bariatric surgery.

Fig 1 Medications vs. Bariatric Surgery in the Treatment of Diabetes and Obesity



N Engl J Med. 2012 Apr 26;366(17):1567-76

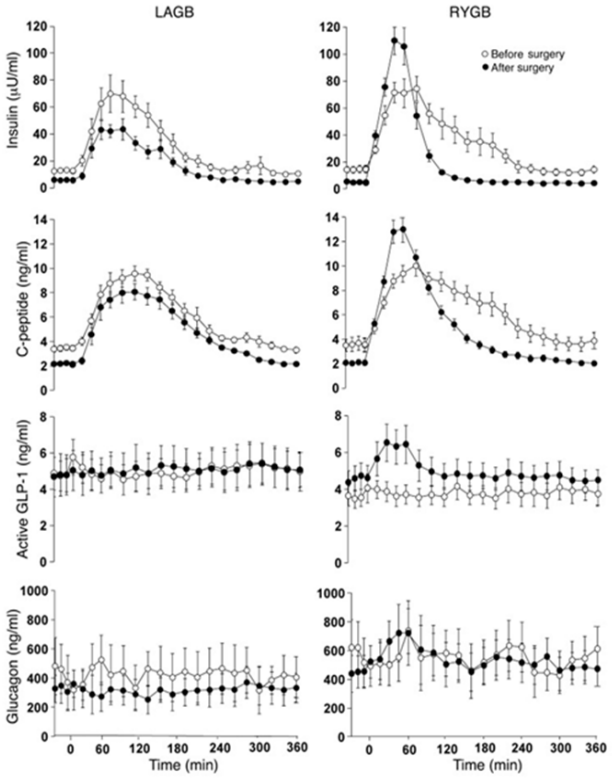
Background Physiology

Sustained weight loss is seen in the majority of patients undergoing gastric bypass surgery (GB). The amount and sustainability of the weight loss is far superior to that achieved by current pharmacological and lifestyle treatments.[8, 9] Contrary to earlier beliefs, mechanical restriction of food intake and malabsorption are now not considered to be major mediators of benefit. It is now widely accepted that following GB there is rapid increase in satiety that is likely mediated by

several different mechanisms, with neurohormonal signaling and enterokines playing a central role.[10] Over 100 enterokines (i.e. enteric hormones and other factors such as bile acids with systemic metabolic effects) help regulate energy balance. The enterokine GLP-1 is considered to be a major contributor to benefit. It is normally secreted by intestinal L-cells in response to nutrient ingestion, and has multiple appetite suppressing and glucose-lowering actions including promotion of insulin secretion, inhibition of glucagon, slowing of gastric emptying, portal-sensor/vagally mediated central actions, and in animals at least, promotion of pancreatic-beta cell regeneration. In post-operative GB patients, the GLP-1 response to oral glucose or a standard meal increases 4-6-fold.[11] A second hormone of particular interest is PYY which is co-secreted with GLP-1 also in response to nutrients, promotes satiety and is markedly increased following GB.[12] Changes occur rapidly: Dirksen et al reported that in a post-GB patient with type 2 diabetes glucose tolerance improved or worsened on successive days by feeding the patient by mouth or via a gastrostomy tube respectively[13] Falken et al showed significant changes in enterokines, glucose tolerance and satiety 3 days post GB.[14]

Studies in patients undergoing GB have identified a distinctive synergistic cascade of appetite-suppressing and glucose-lowering responses triggered by delivery of food directly to the jejunum. (Fig 2).[15] Rapid changes occur in numerous gut hormones (including a rise in intact and total GLP-1, PYY, CCK, C-peptide and insulin), gut-brain signaling via the vagus nerve and bile acid entero-hepatic circulation. These rapid changes mediate multiple short and medium term effects that suppress appetite and control glucose. Unlike other weight loss strategies (e.g. diet, exercise and gastric banding) GB is associated with a "fed" rather than a "non-fed" neurohormonal response that is considered to underlie the characteristic increase in satiety and activity seen post GB and the ability to sustain weight loss.[8-10, 16]

Fig 2 Comparison of Hormones on Meal Tolerance Test: Gastric Banding vs. Gastric Bypass



J Clin Invest. 2012 Dec 3;122(12):4667-74.

A simple nasojejunal feeding tube (NJT) is similar in many ways to gastric bypass as it also leads to nutrient bypass of the foregut and delivery directly to the jejunum. (Fig 3)

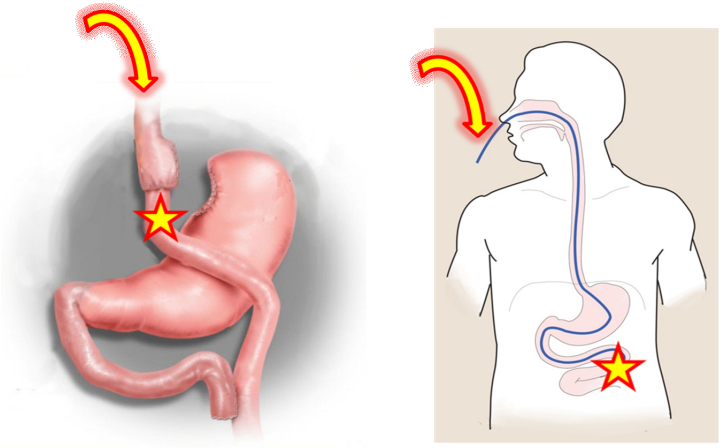


Fig 3 Comparison of Gastric Bypass and Nasojejunal Feeding. The star indicates where ingested nutrient first contacts the intestinal mucosa.

In this study we propose evaluating proof of concept that rapid delivery of nutrients directly to the jejunum promotes weight loss and glucose control that is superior to that seen when a non-nutrient liquid is delivered to the jejunum.

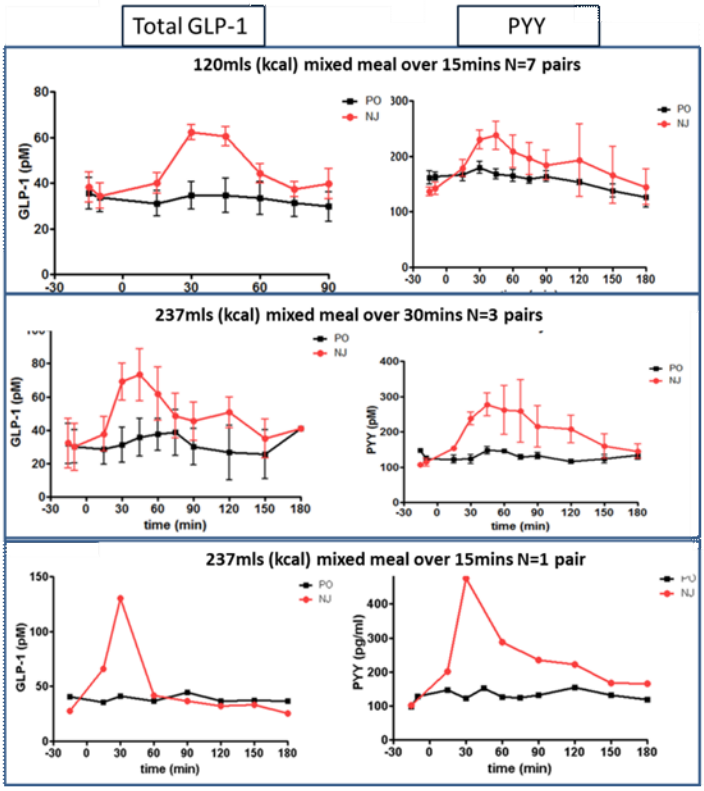
Proof of concept would justify the development of methods to allow direct delivery of bolus nutrient to the jejunum that could be an alternative, lower cost, reversible alternative to GB surgery.

Preliminary Data

In late 2012 we initiated pioneering human proof-of-concept studies of our hypothesis that delivery of nutrients directly to the jejunum with standard NJT simulates the actions of GB. To our knowledge we are the first investigators to use the newly approved CORTRAK 2 Enteral Access System (EAS™) to rapidly and safely place jejunal tubes using

electromagnetic guidance in non-sedated outpatient volunteers. Key preliminary findings support both our technical approach and hypothesis.

So far we have:
-Successfully placed 23 of 25 nasojejunal tubes attempted in an average time of about 15 minutes (one tube could not be passed through the nasopharynx, 1 through the pylorus).
-Conducted 23 paired 3 hour 11 sample meal tolerance tests in obese adult subjects with type 2 diabetes. Each subject underwent a nasojejunal (NJ) and a paired oral (PO) test. Some data is shown in Figure 4.



Beale, Lee et al, unpublished data 2013

We identified a significant increase in GLP-1, C-peptide, insulin and PYY and a trend towards a lower glucose in 7 paired tests with a dose of 120mls Ensure Nutrition Shake over 15mins (8kcal/min) and a much greater response in 3 individuals who underwent paired tests of 237mls Ensure Nutrition Shake over 30mins (also 8kcal/min). A single individual who underwent a paired test of 237mls over 15minutes (16kcal/min) had the greatest GLP-1 response but this dose was poorly tolerated and not repeated. All tubes were placed just distal to the ligament of Treitz at the entrance to the jejunum. (Unpublished: pending completion of assays).

Similar Work by Others

Recent work published in 2013 by Breitman et al, [17] Salinari et al, [18] and Marathe et al [19, 20] offer support of our concept. In these studies obese and non-obese and diabetic and non-diabetic subjects demonstrated significant increase in incretin hormone responses with jejunal feeding in studies of 2 and 3 days duration. Of note, Marathe et al [20] demonstrated a rate dependent effect of incretin stimulation with a greater effect observed at 4kcal/min vs. 2kcal/min. Corroborating data is also provided by Kaushik et al[21] who described release of satiating hormones with jejunal feeding during treatment for pancreatitis. Similarly Welch et al[22] reported a reduction in total caloric intake in normal volunteers offered an oral meal during a low calorie jejunal infusion of lipid but not saline. We consider these preliminary findings to strongly justify further objective evaluation and refinement of our approach.

Tube and Non-Nutrient Liquid May Alter Oral Food Intake

Rolls and Roe[23] reported in a study of 54 lean and obese women that the volume of liquid food infused intragastrically affected subsequent energy intake in both lean and obese women. There was a mean decrease in energy intake of a subsequent meal of 13% after a 400-ml preload compared with an iso-energetic 200-ml preload (P=.013). For this reason a controlled study should include a tube and non-nutrient liquid administration.

How jejunal feeding in this study differs from that used for standard jejunal feeding

Jejunal feeding is used in ambulatory and hospitalized patients to provide nutrition when this cannot be taken by the standard gastric route, or as a choice by the physician to minimize reflux associated with gastric feeding, usually in semiconscious or critically ill patients. In such cases it is well accepted standard care that the tube feeds should be started slowly and often given at a slow rate around the clock in order to achieve target caloric and nutritional intake.[24] It is frequently reported that jejunal feeds are “poorly tolerated”. Interpretation of the effect of jejunal feeds on weight is complicated by the underlying need for the jejunal feeds which includes conditions such as pancreatic cancer, pancreatitis and gastroparesis. A key difference in the approach proposed in this study is the administration of bolus feeds at a far higher rate than normally given during standard feeding protocol with the express intention of inducing a satiated state at low caloric intake.

How Jejunal Feeding differs from the ketogenic enteric nutrition or "Bride Diet "and other low calorie diets

Low and very low calorie diets, if sustained, lead to weight loss. This is often associated with a lack of hunger during the low calorie intake period that may be due to the induction of ketosis and ghrelin suppression.[25] In general weight loss following caloric restriction is not sustained and short-term metabolic gains dissipate.[16] This has been attributed to the body's attempt to regain its previous weight with resumption of a non-restricted intake. The superior sustained weight loss seen with GB may be due to neurohormonal signaling of an "overfed" state during the low calorie phase leading to defense of the lower weight once the intervention is withdrawn. We aim to simulate this "fed" response with jejunal feeding.

With respect to the ketogenic enteric nutrition diet, this 200-260kcal/day diet induces ketosis during a continuous administration of primarily protein into the stomach. This strategy is reported to minimize protein catabolism during the diet. The intragastric continuous infusion is distinct from the jejunal bolus approach we propose. The diet is of interest to us however as it demonstrates the safety and acceptability of ambulatory tube use for weight loss. A report by Cappello et al described its use in over 19,000 individuals in Italy.[26]

How much weight loss can be expected with a diet equivalent to gastric bypass diet for 14 days (see table 2)

Recent data from Lingvay et al[27] and Jackness et al [28] suggest that individuals taking a typical post GB very low calorie diet of 250-500kcal/day lose about 3% of body weight or 3-4kg in one week. An average deficit of 500 kcal/day should result in an initial weight loss of approximately 0.5 kg/week (1 lb/week).[29] Weight loss is greater in men and younger individuals and is influenced by genetic factors.[29] It is also greater post bariatric surgery in those with a higher pre-operative weight. However, after three to six months of weight loss, energy expenditure adaptations occur which slow the bodyweight response to a given change in energy intake, thereby diminishing ongoing weight loss.[30] [31]

Outcomes with Very Low Calorie Diet (VLCD).(see table 2) Currently thousands of individuals undergo prolonged very low calorie diets following gastric bypass surgery without problem and these are used alone too. Standard of care requires ensuring subjects take appropriate amounts of protein daily (equivalent to 1g/kg of lean body weight).

Table 2 Calorie Restricted Diets: weight loss, safety and tolerability

Ref	**Population**	**Intervention**	**Duration**	**Weight loss**	**Safety and Tolerability**
Bray[29]	In general	Calorie deficit of 500 kcal/ day	various	0.5 kg(1lb)/week	Tolerable but poorly sustained
Lingvay[27]	N=10 Age: 53.2 years (95% CI, 48.0–58.4); BMI: 51.2 kg/m^2 (46.1–56.4) Diabetes duration: 7.4 years (4.8–10.0) HbA1c: 8.52% (7.08–9.96%).	Typical peri-bariatric surgery diet 250kcal/day for 1 week With and without RYGB Inpatient stay Separated by≥6 weeks Patients were own controls.	7 days	Diet only: 5% -7.26 kg (6.41-8.11) (start: 141kg) Surgery + diet: 3% -3.95kg (1.7-6.2) (start: 131kg)	No report of any adverse events related to diet or surgery
Jackness[28]	RYGB with diabetes: N=11 Matched controls: N=14 BMI of 41.2 kg/m2. Diabetes duration: 5.7 +/-0.9 years (range, 0.5 - 15) HbA1c 8.4 +/-0.3%; (Range, 6.2 – 11.1%).	500 kcal/day macronutrients similar to Post RYGB.	21 days	Diet Controls:: -8.6kg (Start: Wt: 114.2+/-6.6kg; BMI: 39,2+/1 kg/m^2) Surgery Group: -9.1kg (Start Wt: 121.4+/-6.7kg BMI: 43.2 + 2.3 kg/m^2) Overall:ie 7.6 +/-0.4% over 3 weeks 2.5%/week ? higher in 1st week	No report of any adverse events
Cappello[26]	19,036 patients age 44.3 ± 13 M:F = 2:5) BMI 36.5 ± 7.1 22% diabetes	200 to 260kcal/d 50–65 g of proteins plus vitamins and electrolytes/d.	2.5 10-day cycles 25 days	10.2 ± 7.0 kg of body weight, 5.8 ± 5.5 kg fat mass and 2.2 ± 3.3 kg of lean body mass.	No significant adverse effects except asthenia and constipation - easily controlled

		Enteral nutrition through a fine nasogastric tube.		Est. 3kg/week	
Jazet[32]	Eighteen insulin-treated obese type 2 diabetic patients BMI 37.6 +/-1.1 Insulin Units/day: 137+/-22 Cessation of all glucose-lowering medication.	450 kCal/day VLCD(Modifast 50 g protein, 50–60 g carbohydrates and7 g lipids daily)	30days	-11.7 +/-0.7 kg -4.9+/-1.0kg/m^2	No significant adverse effects

HYPOTHESIS: Administration of intermittent mixed meal bolus daily via jejunal tube over a 2 week period leads to weight loss and improved glycemic control that is associated with reduced food intake and is sustained for 2 weeks of follow up.

2.0 OBJECTIVES AND PURPOSE

Specific Aims: In obese, ambulatory, adult patients with type 2 diabetes receiving mixed meal (intervention) or electrolyte solution (control) boluses daily via jejunal tube for 14 days, with 14 days follow up and with other oral nutrition permitted throughout, to compare the following:

Primary aim: weight change immediately following the intervention period between the study groups

Secondary aims: to compare the following within and between groups:

a. From Day 0 to Day 14: caloric intake (as determined by consumption of provided food)
b. From Day 0 to Day 14: weight change (within group)
c. From Day 0 to Day 28: weight change
d. From Day 0 to Day 14 and also from Day 0 to Day 28: waist and hip measurement, hormones and biochemical measures, physical activity , body composition , select symptoms, medication use, average self-monitored blood glucose level

3.0 STUDY DESIGN

Study Design: Prospective, randomized, 2 group, pilot study: 14 days with jejunal tube, 14 days follow up. Subjects will receive intermittent bolus feeding into the jejunum with either mixed meal or non-nutrient liquid. The study will otherwise be the same. In this study the jejunal tube will be secured intraorally on an orthodontic molar band to avoid uncomfortable and conspicuous nasopharyngeal placement.

Recruitment Information sessions and study materials will be provided to clinic physicians who may refer subjects from within the LA County Healthcare Network to explain the study protocol. IRB approved flyers will be placed in approved recruitment areas. In addition clinic providers will request permission from patients to forward their names and contact information to the study recruiter if they meet eligibility criteria. If the patient agrees to have their name forwarded to the study team then this will be documented in the permanent medical record. The study recruiter will contact potential subjects and describe details of the study using an IRB script. If the potential subject remains interested in participating the PI and CoI will follow-up with further discussion and review of the protocol with the potential subject. Participants will be provided with diabetic education describing the signs and symptoms of hyperglycemia and hypoglycemia and their management. This will be provided by the study doctor when the protocol is discussed with the potential subject and will be reviewed at each subsequent visit.

Approved illustrations of the proposed intervention as well as the informed consent will be provided to the potential subject and they will be allowed to review this in their own time. All questions will be addressed by the PI and CoI before consent is signed.

Study Site: Edward R. Roybal Comprehensive Health Center.

Method:

Approximately Day -14: After Informed consent has been taken and dentition has been assessed, the study orthodontist will place dental spacers (small rubber strips) around an upper molar.

Approximately Day -7: Approximately 1 week (minimum 2 days) later a stainless steel orthodontic molar band modified to anchor the jejunal tube will be cemented to the selected molar. This will also be done in the Dental Clinic at Edward R. Roybal CHC without sedation or anesthesia. Two visits may be required for this step: 1 to measure for the dental band and the second to place it.

There may be as little as 2 days or as long as several weeks from the time the spacers are placed to the time the tube is placed depending on subject and study team member availability and technical aspects of the band and tube placement (i.e. how long it takes for the spacers to separate the teeth adequately, whether the subject requires 1 or 2 visits to fit the molar band and whether the subject has the tube placed the same day as the molar band).

Day 0: The subject will be seen at the CHC in the fasted state. All women between 18 and 50 years of age who have not undergone hysterectomy or tubal ligation will undergo a urine pregnancy test. If the test is positive then they will not be eligible to participate. Baseline vital signs, weight, height and waist and hip circumference will be recorded and baseline labs drawn. Body composition will be measured by the Biospace InBody 520 device (Biospace, Cerritos CA 90703 http://www.biospaceamerica.com/). This device measures body composition non-invasively as the subject stands on a scale-like device while grasping two handles – one in each hand. The device works by sending a very low voltage electrical signal through the body to determine water content, body fat percentage, and lean mass. The machine will be kept in the basement of the CHC. The FitBit Monitor is placed on the subject's wrist or clothing and will record activity for up to 2 weeks at a time without need for any adjustment be the wearer.

Body weight will be measured in the morning on a calibrated scale with the subject wearing light clothing. Waist circumference will be measured by wrapping a flexible measuring tape around the narrowest point of the midsection. The tape will be kept parallel to the floor. Hip circumference will be measured by wrapping a flexible tape around the hips at the widest diameter of the buttocks. The tape will be kept parallel to the floor. The waist-to-hip ratio will be determined by taking the waist circumference and dividing by the hip circumference.

Subjects will have a 10 French 140cm tube placed using a CORPAK EAS™ by the PI or CoI following standard technique and will be randomized to the intervention or control group. (See Appendix A: Tube Placement Using EAS™). It usually takes about 20 minutes to place the tube but can take as little as 5 minutes or up to an hour. If the tube cannot be positioned in the intestine within 1 hour it may be allowed to move into position naturally overnight. In this case the participant would come back a day or 2 later to check that the tube has reached the correct position. In this case the tube feeds would only start when the tube is shown to be in the correct position.

Subjects will be provided with detailed instructions and logs for the following: (See Appendix B: Subject Packet).

1. Bolus nutrient administration and flushing of tube
2. Eating: to eat ad lib from provided meals of known caloric amount
3. Daily self-monitoring and tube care
4. 24 hour contact information
5. Need to monitor blood glucose prior to tube bolus
6. Use of FitBit activity monitor and daily activity

Prior to leaving, the subject will self-administer the first tube bolus and demonstrate by verbal response understanding of requirements for the study.

- Day 0-Day 14: (see Table 3)
- Intervention subjects will take mixed meal via jejunal tube at 10mls/min to satiety or to a maximum volume of 200mls 4 times a day. They will also take 200mls electrolyte solution 4 times daily orally.
- Control subjects will take electrolyte solution via jejunal tube at 10mls/min to satiety or to a maximum volume of 200mls 4 times a day. They will also take 200mls mixed meal solution 4 times daily orally.
- If for any reason the tube feed cannot be administered the remainder should be taken orally to ensure recommended daily intake of major nutrients and fluid is achieved.
- In addition all subjects will take the following daily: 2 10meq potassium chloride tablets, 2 600mg calcium tablets and 1 multivitamin tablet daily and 1/2tsp salt.
- In addition all subjects will be requested to eat ad lib from provided meals of known caloric amount.
- All subjects may also eat ad lib from very low or calorie "free" foods and drinks throughout the study from a provided list.
- Subjects will maintain a log of all food intake will check their daily temperature, tube position and symptoms and will contact the study team for specified symptoms or if they have any concerns they would like addressed.
- As subjects adhering to very low-calorie diets usually have a fall in blood pressure, especially during the first week antihypertensive drugs will be discontinued unless moderate to severe hypertension is present.[33]

- Subjects will be requested to be as physically active as they like. Thus they are at liberty to increase, decrease or maintain their usual activity level.
- Similarly as most diabetic patients eating very low-calorie diets have marked improvement in hyperglycemia with blood glucose concentrations falling within the first one to two weeks oral hypoglycemic drugs will be discontinued for the first week of therapy. [33] An increase in activity level may also cause a fall in blood glucose levels. To aid in maintaining safe blood glucose levels subjects will be required to report to the study team if their blood glucose is over 250mg/dl on more than 2 consecutive measures or any value over 300mg/dl or less than 70mg/dl on any occasion. Symptoms of hypoglycemia (sweating, weakness, palpitations, confusion) will be reviewed with the participant at each visit. They will be advised to check their blood glucose if possible if such symptoms occur and to take one 15g glucose tablet (to be carried at all times) and repeat this every 15minutes until self-monitored blood glucose is over 80mg/dL or symptoms resolve.

Table 3 Summary of Nutrient Administration Days 0-Day 14

Item:	**Intervention Group:**	**Control Group:**
Ensure High Protein Shake (400kcal/800mls/100% protein RDA/day)	Via tube*	By mouth
Unflavored Pedialyte Electrolyte Solution (80kcal/800mls/~50% electrolytes/day)	By mouth**	Via tube*
Additional vitamins and electrolytes	By mouth	By mouth
Ad Lib food from that provided	By mouth	By mouth
Ad Lib "calorie-free" foods from provided list	By mouth	By mouth

*If unable to administer by tube the remainder to be taken by mouth

**Optional artificial flavoring (provided) may be added by subject if they wish to the orally ingested Pedialyte to increase palatability. This will be documented in the daily log.

Day 7: Subjects will return to the clinic for review of log and caloric intake. Medications will be triturated at the study clinician's discretion in an attempt to attain euglycemia. The position of the tube tip will be assessed per FDA approved procedure by reinsertion of the subject's own transmitting stylet and the tube will be repositioned if not located beyond the Ligament of Treitz.

Day14: Baseline measures will be repeated. The position of the tube tip will be assessed per FDA approved procedure by reinsertion of the subject's own transmitting stylet and then removed. All uneaten food will be returned for caloric intake determination, activity monitor download.

Day 15-Day 28: The subject will maintain a symptom and blood glucose log for 14 days after the removal of the tube.

Day 21: Subjects will return to the clinic for review of log and activity monitor. Medications will be titrated at the study clinician's discretion in an attempt to attain euglycemia.

Day 28: Exit outcome measures similar to those at Baseline and Day 14.

Possible Additional Study Visits: Subjects will be seen at additional visits by the study team if they so request or if deemed appropriate by the study clinicians. Subjects will be encouraged to contact the study team if they do not feel well or if certain criteria are met. These specific criteria are:

a. Self monitored blood glucose values over 200mg/dL on 3 scheduled checks
b. Failure to ingest prescribed amounts of fluid
c. Failure to administer tube feed on 2 successive occasions
d. A morning oral temperature reading >37.2ºC (98.9ºF) or an afternoon temperature of >37.7ºC (99.9ºF)
e. Pain that does not resolve spontaneously over 3 or 4 hours or with use of acetaminophen

Additional visits may be scheduled to determine position of the tube or to reposition the tip if it was not successfully placed in the jejunum at the initial visit or if the tube is blocked in which case attempts will be made to unblock it or it may be replaced.

4.0 DRUG/DEVICE INFORMATION

4.1 DRUGS

The only drug to be use is optional generic acetaminophen in recommended dose.

4.1.1 Standardized amounts of non-prescription nutrients and electrolyte solution will be administered both orally and via NJ tube.

4.1.1.1 High Protein Shake ® Abbott Park, Illinois, U.S.A. All subjects will take 800mls divided equally and administered 4 times a day. This will provide the following each day: 100% of RDA high quality protein, 400kcal, 800mls water, 20% of potassium requirements and 16% of sodium requirements (Per 14 fl oz. bottle: 210 calories, protein 25g, carbohydrate 23g, fat 2.5g, sodium 240mg, potassium 290mg)

4.1.1.2 Unflavored Pedialyte ® Abbott Park, Illinois, U.S.A. All subjects will take 800mls of Pedialyte /day divided equally and administered 4 times a day. This will provide the following each day: 80kcal, 800mls water, approx. 40% of potassium requirements and 40% of sodium requirements. **(**Osmolality, mOsm/kg H2O: 250; per liter: Sodium, mEq: 45; Potassium, mEq: 20; Chloride, mEq: 35; Zinc, mg: 7.8; Dextrose, g: 25; Calories: 100). No artificial sweeteners or flavors.

4.1.1.3 The only difference is that the intervention group will receive the High Protein Shake via the tube and take the Pedialyte orally whereas the control group will take the Pedialyte via tube and the High Protein Shake by mouth.

4.1.1.4 Klor-Con 1 tablets 10meq/tab. All subjects will take 2 tablets/day which will provide remaining potassium requirements (approximately 30-50% of RDA).

4.1.1.5 Table salt (generic): All subjects will take 3grams/day (half a teaspoon) to provide remaining sodium requirements (approximately 30-50% of RDA).

4.1.2 Kirkland Signature Daily Multi Vitamins & Minerals 1/day will provide 50-100% of RDA

4.1.3 Kirkland Signature Calcium 600 Mg + D3 500 Tablets 2/day will provide 80-100% of RDA

4.1.4 Liquid acetaminophen (generic) 500mg/15mls: if desired for throat pain. Maximum 60mls/day.

4.2 Glucose tablets (generic) 15g: to be carried at all times for use in the event of hypoglycemia.

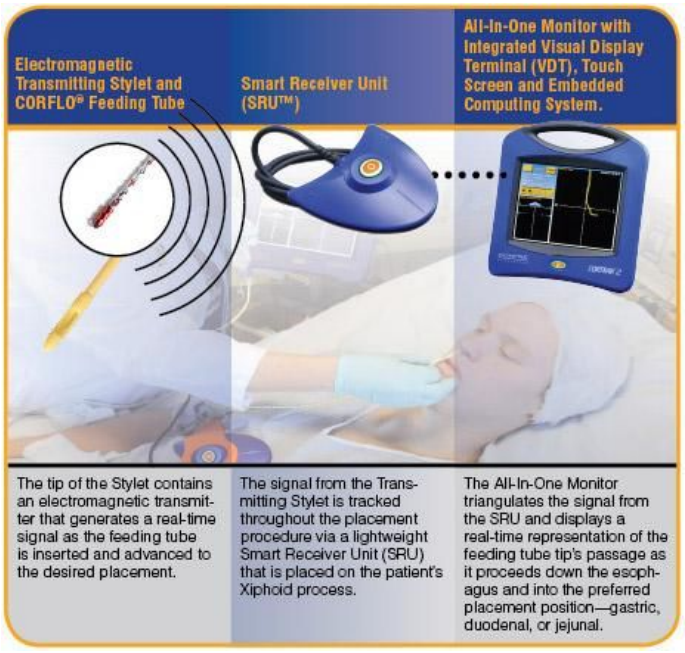
4.3 For anesthesia of the pharynx if requested by the study participant and no contraindication: viscous lidocaine 2% (generic): 5 mL gargled for 3 minutes and may be swallowed. One dose only 5minutes prior to the procedure. The maximum dose for this agent is no more frequently than every 3 hours with a maximum of 8 doses per 24-hour period.[34] Contraindication: Hypersensitivity to lidocaine or any component of the formulation; hypersensitivity to another local anesthetic of the amide type.

4.4 DEVICE

CORTRAK® 2 ENTERAL ACCESS SYSTEM (EAS™) [35-41]

This system is FDA cleared for placement of enteral feeding tubes without x-ray confirmation. A transmitting stylet is used to place the enteral tube. The tip of the stylet contains an electromagnetic transmitter that generates a real-time signal as the feeding tube is inserted and advanced to the desired placement. The signal from the transmitting stylet is tracked throughout the placement procedure via a lightweight receiver unit (Smart Receiver Unit: SRU) that is placed on the patient's xiphoid process. A monitor triangulates the signal from the SRU and displays a real-time representation of the feeding tube tip's passage as it proceeds down the esophagus and into the preferred placement position — gastric, duodenal, or jejunal. (See Fig 6)

Fig 6



Advantages of **CORTRAK® 2 ENTERAL ACCESS SYSTEM (EAS™)**

Safe

a. Eliminates or significantly reduces patient exposure to X-ray
b. Confirms accurate placement quickly
c. Clinicians are able to identify misplaced tubes immediately to significantly reduce adverse events

Accurate

a. In a multi-center study 99.5% of placements correlated with abdominal X-ray
b. 89% -100% success rates reported with gastric, jejunal, and duodenal placement
c. Additional depth cross-sectional view may more accurately predict location compared with X-ray

Fast

a. Real-time visualization of the relative tube tip position eliminates waiting time for X-ray confirmation

Support

a. CORPAK's Clinical Educators assist with implementation planning, on-site education training programs and customized protocol development with hospital education teams
b. CORTRAK 2 Learning Center at www.cortraksystem.com provides high-quality, on-demand training and training checklist, link to Mosby's Nursing Skills)

Flexibility

a. Choice of operating mode for easy upload of data for training, review, or research
b. 2D and 3D views provide more information than X-ray for confident placement without X-ray

Evidence

a. Growing clinical research base demonstrating system's safety and efficacy
b. Used by more than 200 healthcare systems worldwide

Of note the PI and CoI have been trained and certified in use of the EAS and have been using it in preliminary studies in outpatients. To date they have placed approximately 25 jejunal tubes with this system without incidence.

<u>Intraoral Anchor (see Fig 7)</u>

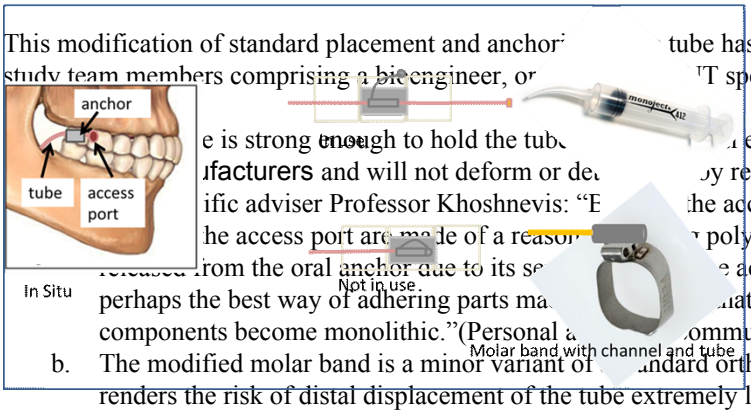
For the purposes of this study we will secure the tube intraorally rather than through the nasopharynx to the skin. The rationale for this is:

a. To minimize discomfort to the subject due to placement of the tube through the sensitive nasopharynx
b. To eliminate the risk of complications in the nasopharynx such as nose bleed, sinusitis and malposition
c. To improve social acceptability of the study by rendering the tube inapparent to the casual observer.
d. To simplify tube maintenance by avoiding the need for taping or other means of securing the tube externally.

To achieve this we will:

a. Modify a standard orthodontic molar band on an upper molar with the addition of a metal channel to anchor the tube in the mouth. The channel is welded to the buccal surface of the band.
b. Place standard orthodontic spacers following standard orthodontic procedure on either side of the selected molar
c. Approximately 1 week later place the modified molar band
d. Modify a standard CORPAK enteral feeding tube by cutting off the access port and leaving only an approximately 4mm flange
e. Pass the tube through the channel in the alert subject so that the tube passes through the lateral oropharynx and then, by standard placement technique, to the jejunum
f. Fashion an integrated tube cap to close the tube when not in use
g. Provide a syringe with a blunt tapered tip to administer fluids per protocol.

Fig 7



This modification of standard placement and anchor tube has been reviewed and evaluated by multidisciplinary study team members comprising a bioengineer, or T specialist and upper GI surgeon and endoscopist who

e is strong enough to hold the tub end of the channel as it is solvent bonded/glued per ufacturers and will not deform or de y rendering the risk of distal displacement extremely low. ific adviser Professor Khoshnevis: "E he access port is solvent bonded to the tube and both the he access port are made of a reaso polymer material, the chance of the tube ever being rom the oral anchor due to its se e access port segment is nearly zero. Using solvent is perhaps the best way of adhering parts ma at can be dissolved by the solvent agent as the adhered components become monolithic."(Personal a ommunication).

b. The modified molar band is a minor variant of andard orthodontic molar band and is very secure and similarly renders the risk of distal displacement of the tube extremely low.
c. The tube position in the oropharynx is lateral to sites triggering the gag reflex and allows for virtually normal speech, swallowing and eating with minimal or no gagging and is virtually undetectable by others.
d. Some discomfort and mild pain (maximum ~4 out of 10) can be expected mostly in the first 4-5days of use. This can be eased with several maneuvers including change of body position and acetaminophen in standard dose.
e. The discomfort and pain can be expected to be minimal after the first 5 days such that the subject is barely aware of the tube's presence.
f. There is minimal risk of throat or gastrointestinal complications with a 10 French jejunal tube placed in the described manner and for duration of 2 weeks.

5.0 SELECTION AND WITHDRAWAL OF RESEARCH SUBJECTS

5.1 Inclusion Criteria:

- 18-70 years of age
- Type 2 diabetes on oral antidiabetic medication
- BMI $\geq$30kg/m^2
- A1C <9%

5.2 Exclusion Criteria:

- Use of any of the following medications: dipeptide-peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin), GLP-1 analogs (e.g., exenatide) or medication that could alter glucose tolerance (e.g. steroids)
- Contraindication to tube (e.g. Prior upper gastrointestinal bleed, or history of easy bleeding, altered foregut anatomy due to obstruction or surgery)
- Known cardiovascular disease other than controlled hypertension.
- Pregnancy or unwilling to take contraception
- Active esophagitis
- Known hiatal hernia
- Active gastric ulcer and/or duodenal ulcers,
- Previous restrictive surgery of the gastrointestinal tract
- Crohn's disease
- Active cancer
- History of gastrointestinal hemorrhage

- Known upper gastrointestinal lesions with potential to bleed
- Use of NSAIDs or anticoagulants
- Psychiatric disorders other than mild depression
- Likely inability to adhere to study protocol including alcohol or drug dependent patients
- Type I diabetes,
- Liver, kidney or multi-organ dysfunction.
- Known eating disorders
- Inability to attend scheduled or unanticipated study visits
- Known prior abdominal problems or operations that could lead to adhesions or strictures and that could prevent the spontaneous passage of a 10 French jejunal tube if it were to dislodge distally.

5.3 Withdrawal Criteria

- Non-adherence to study instructions by subject for more than 2 days.
- Any request by subject
- Fever over 100.4 F, more than 1 episode of vomiting, gastrointestinal upset not relieved by reduction in tube feed, dislodged anchor or tube, average daily glucose over 200mg/dL on 2 or more days, weight change of >7% in first week of tube use.
- Clinical judgment of the PI (reason to be specified)

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

The site of enteral feeding tube placement will be randomized. Subjects will be not be stratified.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

NA

8.0 ASSESSMENT OF EFFICACY AND SAFETY

Safety of this study plan has been reviewed with the multidisciplinary team and by review of relevant literature.
Steps taken to minimize potential risks are summarized in table 4.

The following study team members, who are all USC faculty members have evaluated aspects of this protocol related to their area of expertise and have concluded that this is a low risk study, with potential benefit outweighing possible harm.

Specifically:

a. Stability and safety of oral anchor: Orthodontists: Dr Hongsheng Tong DDS and Dr John Pham DDS (resident)
b. Stability of orojejunal tube in anchor: Bioengineer Professor Behrokh Khoshnevis PhD
c. Safety of orojejunal tube in oropharynx: ENT: Dr Uttam Sinha MD
d. Safety of orojejunal tube in gastrointestinal tract and low calorie diet similar to that post gastric bypass surgery: Foregut and Bariatric Surgeon and Endoscopist: Dr Peter Crookes MD
e. Safety of nutritional intervention and diabetes management: Endocrinologists Dr Elizabeth Beale MD, WeiAn Lee DO

Oropharyngeal Care with Anchor and Tube In-Situ

Standard care as used following placement of orthodontic braces will be recommended. Subjects will be advised to brush and floss their teeth after every meal. Complications are not anticipated even in subjects with type 2 diabetes. Acetaminophen liquid may be taken in standard doses if needed to decrease tube discomfort.

The anchors will be manufactured in-house by Dr Tong using medical-grade orthodontic materials. The anchor will be bonded to the molar using fluoride containing cement to minimize the unlikely possibility of dental decay. The anchors will be placed and removed by the study team orthodontists.

It is considered highly unlikely that infection will develop due to use of the tube anywhere along its path. If fever develops for any reason however, whether considered due to the intervention per se or to intercurrent illness, the subject will be removed from the study.

Very Low Calorie and Low Calorie Tube Feeds

Cappello et al [26] reported on the use of a very low calorie nasogastric tube feed diet (200-260 kcal/d) for 10 day periods with no

serious complications in a group of over 19,000 people. The problems encountered were damage to the external part of the tube (e.g. shaving) 2%, "gastric hypersecretion" (nos) 2%, nausea and vomiting 1%, and intolerance to the nasal tube 0.03%. The following were not observed: ulceration or bleeding due to the tube, breakage of the tube in esophagus or in the stomach, perforation or bleeding of the stomach. Sukkar et al [42] in another similar smaller study reported on 22 patients who received 10 days of very low calorie nasogastric tube feeds (200-260 kcal/d). Subjects were monitored for the following side effects relating to enteral nutrition (abdominal distension and pain, diarrhea, vomiting, reflux, naso-gastric, tube obstruction, de-positioning or accidental removal of the naso-gastric tube, others) and those related to the very low calorie/high protein diet (cardiac arrhythmia, ketosis, hypoglycemia, others). Out of 26 patients enrolled, 3 patients (9 %) were withdrawn due to poor compliance and 1 (3 %) for allergy to milk protein. Of the remaining 22 subjects there were no reported major complications or side effects resulting from the enteral nutrition in any patient. In particular, no cardiac arrhythmias were reported, nor diarrhea or cramps. The following were reported: constipation (3/22; 13.6 %), dizziness or headache during the first 2 days [20/22; 90.9 % (only two needed medication)], general weakness (3/22; 13.6 %), halitosis (5/22; 22.7 %) controlled by sugarless mint chewing-gum. The naso-gastric tube was blocked in 3 patients and required repositioning.

Enteral Feeding Tube Placement

Although enteral tube placement is a common clinical practice and is performed by lay individuals in the home environment when necessary, it has been associated with serious complications including malposition into the airway, perforation of the trachea and esophagus and pneumothorax. These complications occur almost exclusively during blind intubation in sedated, unconscious or otherwise poorly responsive patients and neonates and when the tube is placed through the nasopharynx. In this study we will use the EAS^{TM} system and CORTRAK tubes which have demonstrated greater safety than standard blind placement due to real time visualization during placements. Tubes will be placed following manufacturer's recommended procedure to minimize risk. Furthermore all subjects will be fully alert throughout the procedure and able to interact with the trained investigator who is placing the tube; tubes will be placed by the oral route with a "swallow down" placement technique rather than a "push" technique. These precautions can be expected to minimize the already very low rate of complications that can arise during tube placement, making a serious problem extremely unlikely. Aspiration of stomach contents may occur if the subject has not fasted prior to tube placement. If on enquiry the subject has not fasted then the test will be cancelled. Blind intubation requires x-ray confirmation prior to tube use to minimize complications related to tube misplacement however the EAS^{TM} system is FDA approved to not require x-ray confirmation of placement thereby avoiding risks associated with radiation. [35-41]

Ambulatory Use of Jejunal Tube for 14 Days Nasal and oral feeding tube for feeds are standard accepted clinical practice for subjects requiring nutritional support up to 30 days. The American Gastroenterological Society recommends that consideration be given to replacing a naso or oro enteral feeding tube with a percutaneous tube after 30days. [43] Although not currently widely accepted as medical therapy, the ketogenic enteric diet has been extensively used in Europe and is now available through franchises internationally. Although the underlying physiological approach that we are hypothesizing is markedly different to this diet, it does demonstrate that use of enteral tubes for 10 days is feasible and acceptable to many individuals having been used in over 24,000 subjects in one center. [26] This study involves a variant of standard enteral tube feeding, the main differences being the indication for the intervention and the rate of the tube feed administration. Subjects in this study will be far more closely monitored than in standard clinical practice. Some discomfort can be expected to occur in the throat due to the tube and may be relieved by slight relocation of the tube to relieve pressure or overall body repositioning of the e.g. lying down after prolonged sitting at a desk. Discomfort tends to decrease after 4-5 days of use. Acetaminophen will be offered to subjects for use if desired. If fever develops suggestive of local infection then the subject will be withdrawn from the study and referred to their usual care provider for further management. This problems has not however been reported in thousands of patients undergoing the ketogenc enteric diet.[26, 42]

Inadvertent Dislodgement of the Tube

Enteral feeding tubes not infrequently become accidentally dislodged in general use. This is considered highly unlikely to cause problems in this study as the tube will be anchored entirely intraorally. Most displacement is due to inadvertent pulling on the extracorporeal part of the tube by a sedated or otherwise confused patient, or failure of tape to maintain position of the tube. If the tube were to slip through the anchor it is anticipated that it would pass directly through the gastrointestinal tract. Per co-investigator Dr. Peter Crookes a tube that becomes dislodged and is swallowed will almost certainly pass spontaneously through the intestinal tract as long as there are no abnormalities in the intestine such as adhesions or strictures and the chance of the tube being retained and requiring endoscopic or surgical removal is so low that it does not need to be mentioned as a risk to subjects. We will exclude all subjects with a history of abdominal infections or surgeries or other illnesses that could lead to strictures or adhesions.

Evidence that the molar band is very secure is supported by several references:

- Banks, P. and T.V. Macfarlane, *Bonded versus banded first molar attachments: a randomized controlled clinical trial.* J Orthod, 2007. **34**(2): p. 128-36; discussion 111-2.[44]
- Millett, D.T., et al., *Adhesives for bonded molar tubes during fixed brace treatment.* Cochrane Database Syst Rev, 2011(6): p. CD008236[45]
- Nazir, M., et al., *Banding versus bonding of first permanent molars: a multi-centre randomized controlled trial.* J Orthod, 2011. **38**(2): p. 81-9.[46]

The following table and figure from Nazir et al [46] summarizes this information and provides data that the molar band is a very secure system especially in the short term as used in this study.

Table 2 Cluster adjusted chi-square test to compare first time failures between molar bands and bonds

Failure at tooth level			
	Failures *n* (%)	No failures *n* (%)	Total *n* (%)
Bands	4 (2.6)	148 (97.4)	152 (100)
Bonds	28 (18.4)	124 (81.6)	152 (100)

Inter-cluster correlation=0.0860.
ICC 95% confidence intervals=[0.000, 0.0192].
Pooled adjustment chi-square statistic=14.295 and P=0.0002.
Group adjustment chi-square statistic=14.295 and P=0.0002.

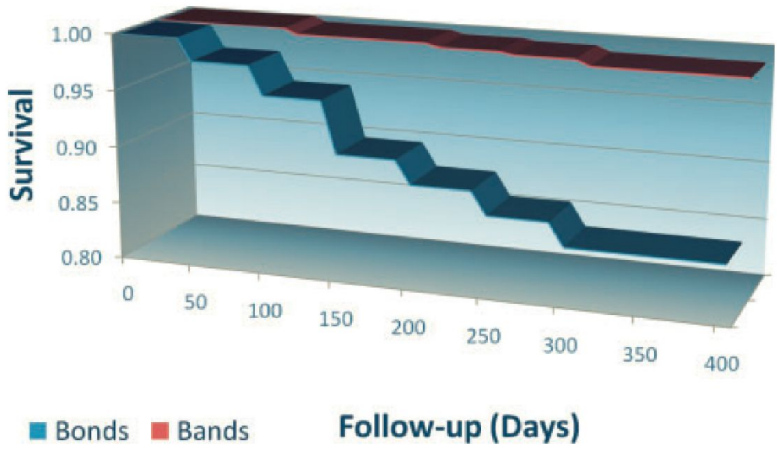


Figure 3 Survival functions for molar bands and bonds (Cox proportional hazards regression)

Ensuring participants won't chew through the tube if they have bruxism

The tube anchor is located on the upper posterior buccal molar. The 140cm tube immediately passes backwards from the anchor to the lateral oropharynx where it descends straight down into the gastrointestinal tract. It is maintained in this position by gravity and peristalsis. The tube is thus unable to move medially across the occlusal surface of the teeth and hence bruxism does not pose a risk.

Mouth guards

Participants are not required to wear a mouth guard either while awake or asleep as the tube is positioned well lateral and posterior occlusal surfaces of the teeth.

Precautions to be taken to prevent the tube being accidentally swallowed

The following precautions will be taken to decrease the chance that the tube will be accidentally swallowed:

Participants will be asked to monitor for any loosening of the molar band daily and also to monitor for any evidence of abrasion or wear on the intraoral portion of the tube. They will do this by checking that the band is secure manually and by looking for wear on the tube when it is brought slightly forward to be attached to the syringe for each tube feeding. They will be requested to report any concerns in this regard to the study team as soon as it is detected. They will also be told how to remove the band or tube if it should become so loose or worn that it could dislodge spontaneously. Furthermore to decrease risk of the band becoming dislodged the band will be kept in place for as short a period as possible.

Procedure if the tube is accidentally swallowed and how it will be retrieved.

The risk of accidental swallowing of the tube is considered to be extremely remote due to the precautions taken in the design of the anchor and tube as described above. If the tube is accidentally swallowed the participant will contact the study team and co-investigator Dr. Peter Crookes who is a foregut surgeon and endoscopist. He will arrange appropriate follow-up for the participant. Clinical back-up in this area will be provided by co-investigator Dr. James Buxbaum (gastroenterologist and endoscopist). References for the following data can be found in the recent systematic review of the topic of ingested foreign bodies in adults. [47] As most ingested foreign bodies pass through the gastrointestinal tract without any difficulty conservative treatment by means of close observation will likely be the approach used. This is the treatment of choice as the tube is blunt and narrow (<2.5 cm diameter) and the tip will already be past the pylorus. Spontaneous passage can be expected within 4–6 days. Rare cases have been reported where it has taken up to 4 weeks to pass a foreign object. Until the tube has passed, the participant will be asked to monitor their stools continuously. No change in eating behavior will be required during this period. If the tube is not passed after about 1 week then weekly outpatient x-ray examination will likely be recommended in order to document, the foreign body's passage. As the tube is radiopaque its passage can be documented. (See product insert uploaded at iSTAR #18.2).

If the tube does not pass spontaneously then it may be retrieved by Dr. Crookes or Dr. Buxbaum using upper or lower endoscopy. It is unlikely that emergency esophagogastroduodenoscopy (EGD) will be required as this is recommended when the esophagus is completely occluded (because of the risk of aspiration and/or pressure necrosis), when the ingested object has a sharp point or edge (because of the risk of perforation, with ensuing mediastinitis or peritonitis), and when a battery has been ingested (because of the risk of necrosis and fistula formation)-none of which can reasonably be expected to occur in this study. Similarly even an urgent but non-emergency EGD (within 12 to 24) hours is unlikely to be required as this is recommended for non-occluding esophageal foreign bodies such as magnets. Recovery of a foreign body by means of colonoscopy is not common practice according to the available data as after the ileocecal valve has been passed the foreign body is usually excreted without any complications.

There is a remote possibility that surgery (including the option of minimally invasive laparoscopic surgery) could be required to remove the tube. This has become progressively more unusual as endoscopic retrieval rates improve. The only absolute indication for surgery is reported to be perforation which is highly unlikely to occur with the blunt soft tube. Relative indications for surgery after ingestion of foreign bodies exist in the case of complications that cannot be resolved endoscopically or after unsuccessful attempts at endoscopic recovery.

Data to support claims that the tube will almost certainly pass spontaneously through the intestinal tract without any intestinal abnormalities

A recent review by Ambe et al [47]summarizes findings from numerous articles on the topic of ingested foreign bodies in adult. It has been widely reported that the majority of foreign bodies in the gastrointestinal tract will pass spontaneously but that about 10-20% will require non-operative intervention and less than 1% will require surgery. In the current study, in the very unlikely event that the tube were to be accidentally ingested, the rate of spontaneous passage can be expected to be far higher than 80%. The reasons for this are as follows:

a. Impaction most often occurs at areas of acute angulation or physiologic narrowing. The esophagus is the most frequent site of blockage (50–75%) because of physiological narrowing at the cricopharyngeal sphincter, the aortic arch and the diaphragmatic hiatus. Other relatively narrow and angled areas are the duodenum and the entrance to the jejunum at the Ligament of Treitz. In this study the tube will be placed by the study team through the esophagus, the duodenum

and beyond the ligament of Treitz so obstruction at these levels would be extremely unlikely. Once through the esophagus, the majority of ingested foreign bodies pass through the alimentary tract uneventfully.

b. Patients with prior gastrointestinal tract surgery or congenital gut malformations account for a large number of obstructions. We will reduce the risk of obstruction by the exclusion criteria of a history of abdominal infections or surgeries or other illnesses that could lead to strictures or adhesions.

c. The participant will be excluded from the trial if the tube cannot be passed through the esophagus, stomach, duodenum and jejunum initially, the commonest sites for impaction.

Daily Activities with Tube In-Situ

The intra-oral tube placement renders it inapparent to the casual observer. This allows the subject to avoid embarrassment or unwanted explanations due to tube use and to continue with routine activities. The subject may experience discomfort or some anxiety due to tube placement and if rapid weight loss occurs, may experience increased fatigue. As this is a voluntary study the subject will have made an informed decision to have a tube in-situ for 2 weeks. Where possible, the tube will be placed during a 2 week period when the subject will be able to adhere to the study routine and rest appropriately. Ease of mind will likely be increased for the subject by knowing that at any time they desire they can remove the tube themselves, withdraw from the study and/or contact the study team.

Symptoms due to Jejunal Nutrient Administration

Subjects may experience dumping symptoms of nausea, palpitations, sweating and abdominal pain during or for about 1 hour after jejunal nutrient infusion. The dose of the nutrient administered will be selected by the subject to achieve comfortable satiety. They will stop administering nutrient if they experience unpleasant symptoms. Symptoms, if they occur are usually mild and are transient and self-limited. We will exclude potential subjects from the study if they have any known cardiovascular disease (other than controlled hypertension) to minimize potential risks to the subject associated with possible palpitations in association with dumping syndrome.

Venipuncture

This study involves venipuncture of a peripheral vein. This is associated with a small risk of minor bleeding and infection at the puncture site. To minimize this risk, aseptic precautions will be used.

Risk of Hypoglycemia or Hyperglycemia

Alteration in diet and physical activity could lead to alterations in blood glucose: both hyperglycemia and hypoglycemia. To minimize the risk of these complications the following precautions will be made:

a. All participants will have the symptoms and signs of hyperglycemia and hypoglycemia reviewed with them as well as recommended management at each visit starting with the recruitment visit when the protocol is reviewed.
b. As most diabetic patients eating very low-calorie diets have marked improvement in hyperglycemia with blood glucose concentrations falling within the first one to two weeks oral hypoglycemic drugs will be discontinued for the first week of therapy. [33] An increase in activity level may also cause a fall in blood glucose levels. To aid in maintaining safe blood glucose levels subjects will be required to report to the study team if their blood glucose is over 250mg/dl on more than 2 consecutive measures or any value is over 300mg/dl or less than 70mg/dl on any occasion.
c. Information on managing hypoglycemia is provided in the FREE TO GO Study Instructions given to the participant.

Table 4 Summary of Steps Taken to Minimize Risk of Intervention

Concern	**Precaution**
Modified anchoring of orojejunal tube	Development by senior bioengineering and orthodontic specialists
Safety of orojejunal tube for 2 weeks	Potential risks reviewed with senior ENT and bariatric surgeon and deemed highly unlikely to occur Subjects will monitor their temperature and the tube position daily and report to the study team if any concerns

Physical and psychosocial discomfort due to ambulatory use of orojejunal tube for 2 weeks	Intraoral anchoring makes tube inapparent to observers. They will be encouraged to take acetaminophen and take other steps to decrease discomfort of tube particularly in first few days of use. They will be shown how to remove the tube themselves at any time if they so desire
Back-up in event of distal tube displacement	Senior bariatric surgeon on study team
Safety of very low calorie diet for 2 weeks in subjects with type 2 diabetes	Close monitoring by specialist endocrinologist with adjustment of medication if needed. All subjects can take food and liquid ad lib. Mandatory minimum 480 kcal/d; 1.6litres fluid/day; 100% RDA high quality protein; 100% RDA electrolytes, minerals and vitamins.
Hyper- and Hypo-glycemia	Oral hypoglycemic drugs will be discontinued for the first week of therapy and participants will contact the study team if their glucose levels are less than 70mg/dL or over 250mg/dL. Participants will be educated on the symptoms of hypo- and hyper- glycemia and provided wth instruction and glucose tablets for the management of hypoglycemia.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Table 5

		Preparation		**With Tube**		**Follow Up**	
	Approximately Day-14	**Approximately Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21am**	**Day 28**
Location ALL at EDWARD R. ROYBAL CHC							
Clinical Evaluation	By orthodontist for suitability for molar band	By orthodontist for placement of molar band (may require 2 visits)	By MD Vital Signs Symptoms Physical Exam Weight Waist Hip	By MD Vital Signs Symptoms Physical Exam Weight Waist Hip	By MD Vital Signs Symptoms Physical Exam Weight Waist Hip	By MD Vital Signs Symptoms Physical Exam Weight Waist Hip	By MD Vital Signs Symptoms Physical Exam Weight Waist Hip
Labs (total 20 cc/visit)	none	none	BMP[a] Fasting: Adiponectin[b] Leptin[b] FGF-19[b] Insulin[b] Glucose[b] C-peptide[b] GLP-1[c] Ghrelin[c] PYY[c] CCK[c] Bile Acids[c] FT3[c]		BMP[a] Fasting: Adiponectin[b] Leptin[b] FGF-19[b] Insulin[b] Glucose[b] C-peptide[b] GLP-1[c] Ghrelin[c] PYY[c] CCK[c] Bile Acids[c] FT3[c]		BMP[a] Fasting: Adiponectin[b] Leptin[b] FGF-19[b] Insulin[b] Glucose[b] C-peptide[b] GLP-1[c] Ghrelin[c] PYY[c] CCK[c] Bile Acids[c] FT3[c]
Procedure	Place spacers	Place band	Place tube Place FitBit Body Composition Provide 1 week food	Return all uneaten food Provide 1 week food	Return all uneaten food Remove tube and band Body Composition		Remove FitBit Body Composition
Other Activities	none	Start Daily Flow Sheet	Review daily flowsheet including self-monitored blood glucose	Review daily flow sheet including self-monitored blood glucose Download FitBit/recharge	Review daily flow sheet including self-monitored blood glucose Download FitBit/recharge	Review daily flow sheet including self-monitored blood glucose Download FitBit/recharge	Review daily flow sheet including self-monitored blood glucose Remove and download FitBit
Food Intake	Ad lib		Day 0-Day 14 Tube Bolus and Provided Diet Ad lib free foods Supplements		Day 14-Day 28 Ad lib		

[a]at USC DORI [b]at Cedars-Sinai [c]at Cedars Sinai when funds available

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Primary aim: weight change immediately following the intervention period between the study groups
Secondary aims: to compare the following within and between groups:

a. From Day 0 to Day 14: caloric intake (as determined by consumption of provided food)
b. From Day 0 to Day 14: weight change (within group)
c. From Day 0 to Day 28: weight change
d. From Day 0 to Day 14 and also from Day 0 to Day 28: waist and hip measurement, hormones and biochemical measures, physical activity , body composition , select symptoms, medication use, average self-monitored blood glucose level

11.0 SPECIAL INSTRUCTIONS:

Samples will be collected by the PI or IRB approved research assistant from peripheral venipuncture.
The investigator will draw 20cc fasting blood at Day 0, 14 and 28 visits into a prepared tube containing aprotinin. This will be kept on ice and centrifuged, separated and aliquoted within 30mins of blood draw. Samples will then be stored at -20 degrees centigrade until transferred on ice to collaborator for assay.

Study Costs: All costs for this study will be paid from study funds. There will be no patient care costs incurred for payment from non-study funds. Costs covered by the study include study visits, supplies, equipment, blood draws, biochemical analysis and subject reimbursement.

12.0 DATA COLLECTION AND MONITORING

Confidentiality of Discussions: The privacy of the research subject will be protected by having discussions regarding the study and confidential health matters in a private room in the Roybal CHC or by telephone from a private office.
Initial and follow-up Case Report Forms (CRF): All data will be entered on IRB approved clinical medical record forms. All data will be kept in a locked cabinet in Dr Beale's office when not in use.
Data Security and Confidentiality Data will only be accessible by the primary investigator and co-investigators and research assistants for the purposes of the study. Data will be transcribed from the CRF to a non-network computer, password protected, accessible only by the investigators for the purposes of the study. Each enrolled patient will be assigned a study number and all data will be stored under this study number with no linkage to patient identifiers. Data will also be stored by Dr. Ionut in her computer protected computer database using a study specific identifier developed specifically for the study. The computer is password protected and is in a room accessible only to the laboratory personnel. All personnel have been HIPAA trained.
When the study is completed the data or data set will be maintained in a de-identified form on the PI's computer. Identifiers will be destroyed at the earliest opportunity consistent with the conduct of the research and/or clinical needs and will be maintained no longer than 2 years after completion of the study.

Source Documentation and Timeliness of CRF Completion. The CRF will be completed by the research staff daily. Data will be stored on REDCap.

Retention of Study Record: Study data will be retained for 5 years after publication. At this time or in case non-publication, the data will be destroyed.
Data Management: Data will be recorded on clinic record forms and will be entered into a database system for subsequent statistical analysis. Potential data errors will be detected by plotting frequency tables or histograms on outcome and exposure variables and data ranges will be checked to identify potential outliers. The frequency of missing values will be counted for each variable at each of the follow-up time points. Cross-tables will be used to verify the logical validity of related variables.

13.0 STATISTICAL CONSIDERATIONS

SC CTSI statisticians have provided assistance with study design. This is a pilot study. As such power studies are not appropriate. Effect sizes and parameter estimates derived from this study will be used in the design and power calculations

for future studies The primary aim is to compare weight change from Day 1 to Day 14 (the intervention period) between the 2 study groups.
The secondary aims are to compare the following between study groups:

a. From Day 1 to Day 14: caloric intake
b. From Day 1 to Day 28 (the intervention and follow-up period): Weight change
c. From Day 1 to Day 14 and also from Day 1 to Day 28:
    i. waist and hip measurement,
    ii. hormones and biochemical measures,
    iii. physical activity
    iv. body composition
    v. symptoms
    vi. medication
    vii. self-monitored blood glucose

Due to the exploratory nature of this study, it is possible that clinically relevant effects will be observed that do not reach statistical significance. Nevertheless, based on the work of Lingvay et al[27] we could consider a 30% difference between sites in weight loss between the groups to be clinically relevant.

Data will be presented as mean +/- S.E.M. Differences between groups will be analyzed by one-way ANOVA followed by a Student's t-test for independent samples. A non-parametric test (Wilcoxon Rank) will be performed when appropriate. Change over time will be assessed with ANOVA for repeated measurements. In case of a significant result a post hoc analysis will be performed with the Student's ttest. All analyses will be performed using SPSS for Windows Version 12.0 (SPSS Inc., Chicago, USA).

14.0 REGISTRATION GUIDELINE

14.1 Specify phone number to register the patients: 626 232 3548.
Subjects will be randomized to caloric or non-caloric jejunal feeding.
Forms and records needed for registration:

14.2.1 Informed Consent
14.2.2 Daily self-monitoring sheet
14.2.3 Visit work sheet

At the time of registration, two copies of a signed and dated patient Informed Consent form with Bill of Rights will be available (an original for patient's medical chart; one copy for the patient; and the other for the PI's file).

15.0 BIOHAZARD COMTAINMENT

Blood sampling and IV line placement will follow standard biohazard safety precautions.
Sharps will be disposed of in clinic sharps containers.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

APPENDIX A: FREE TO GO NUTRITION

Note: If the listed items are not available the PI may authorize similar substitutes

TABLE A: Provided Study Nutrients: Must be Taken Every Day	
Item	**Amount and Route**
Ensure High Protein Shake	800mls/day by tube or mouth as advised
Pedialyte Solution	800mls/day by tube or mouth as advised
Klor-Con10m potassium tablets	2 tablets/day
Table salt	Half a teaspoon/day
Kirkland Signature Daily Multi Vitamins & Minerals:	1 tablet/day
Kirkland Signature Calcium 600 Mg + D3 500 tablets:	2 tablets/day

TABLE B: Provided Food: To be eaten as desired			
Item Provided	**Brand**	**#Servings provided**	**Cals/serving**
Oatmeal	Quaker Instant Variety	10	130
Eggs	California Ranch Fresh	10	90
Milk	Real Fresh	12	150
Soft tortilla	Guerrerro Flour	48	130
Sliced brown bread	Nature's Own Whole Grain Wheat	22	60
Sliced white bread	Nature's Own Whole Grain White	22	75
Soup	Progresso	10	130
Frozen entrée	Lean Cuisine	10	280
Non-frozen meal	Nissin Bowl	10	280
Canned meal	Campbells Chunky	10	140
Pudding	Snackpack	8	110
Cookies	Quaker Chewy Variety	8	100
Ice cream	Dreyers No Sugar	16	90
Canned fruit	Delmonte Light Variety	8	70
Apples	5 apples (fresh)	5	95
Bananas	5 bananas (fresh)	5	105
Orange juice	Minute Maid	12	140
Frozen Vegetables	Essential	10	40
Water Flavor Enhancer	Dasani Drops (Mixed Berry flavor)	96	0

TABLE C: Optional Items: Not provided. Can be added to other intake if desired		
Vegetables (1 cup raw)	Collard greens	Okra
Asparagus	Cucumbers	Peppers (green or red)
Bean sprouts	Egg plant	Radishes
Beet greens	Endive	Spinach
Broccoli	Escarole	Squash, summer
Brussels sprouts	Green beans	Tomatoes
Cabbage, (all kinds)	Green onion	Turnip greens
Chard	Kale	Watercress
Cauliflower	Lettuce (all kinds)	Wax beans
Celery	Mushrooms	Zucchini
Chicory	Mustard greens	
Drinks	**Sugar Substitutes**	**Desserts & Fruits:**
Bouillon, clear broth; (no fat)	(ALL sugar free)	Cranberries
Diet or Sugar free soda	Hard candy and gum	Lemons
Diet or Club soda	Gelatin	**Condiments**
Coffee/tea	Jam/Jelly	1 tablespoon ketchup or mustard
Sugar free drink mixes	1-2 tablespoon pancake syrup	Unsweetened pickles

Lemon juice Tomato juice Vegetable juice	Sweet 'n Low or Equal 2 tablespoon whipped topping	2 tablespoon low calorie salad dressing 3 tablespoon taco sauce

TABLE D: Provided. To be taken for hypoglycemia Low blood glucose) or if concerned that sugar is low.		
Glucose tablets (generic)	15g	Qty 30

TABLE E: Study Supplies	
Item	Quantity
Blood glucose strips	150
Thermometer	1
Fitbit Activity Monitor	1
Glucose meter	As needed
Glucose meter battery	As needed
Study log	4
Syringe to administer tube feed	15
Tylenol liquid (500mg/15mls)	As needed Maximum 60mls/day
Syringe to administer tube feed	15

APPENDIX B: FREE TO GO STUDY INSTRUCTIONS

24 HOUR CONTACT INFORMATION

Dr. Beale (626) 232-3548 or pager (213) 287-0123 Dr. Lee (626) 367-7860 or pager (323) 203-0362

Thank you for your participation in the FREE TO GO STUDY

You are requested to follow the following instructions for the 2 weeks you have the tube in place.

1. 4 times a day (before your usual meals and before sleeping)
    - Check and record your blood glucose level with your meter
    - Record your throat discomfort or pain level
    - Record if you have taken any pain medication since your last log
    - Check to make sure the molar band is secure and the tube undamaged
    - Record if you have any gastrointestinal upset
    - Give yourself the tube feed
    - Record the amount of tube feed you gave
    - Record the time taken to give the tube feed
    - Record how much of the tube feed (if any) was taken by mouth
    - Flush the tube with 10mls of water
    - Take the required oral feed
2. Every day:
    - Check and record your temperature at least once a day
    - Take the mineral and vitamin supplements you have been given
    - Write down the name and dose of any medication you take
    - Write down the type and amount of all food you eat and drink you take and keep ALL the leftovers
    - Wear your activity monitor at all times except when it might get submerged in water.
    - Be alert for symptoms of low blood glucose (hypoglycemia). These can include sweating, weakness, palpitations and confusion. If any of these symptoms occur you should check your blood glucose if possible and take one 15g glucose tablet (to be carried at all times) and repeat this every 15minutes until your blood glucose is over 80mg/dL or the symptoms have gone.
3. Record any other comments you would like to make in the comments section
4. Contact the Study Team at any time you have concerns or questions
5. You should contact the study team as soon as possible if any of the following occur:
    - You develop a fever of over 100.4 F (38.0 C)
    - You have a vomiting episode
    - You have 2 episodes of diarrhea
    - You are unable to give the tube feeds as requested for whatever reason twice in a row
    - You do not take the recommended oral feeds and supplements twice in a row
    - Either the anchor or tube is not in the correct position or are loose or damaged.
    - You do not want to continue with the study and want to remove the tube
    - You have 2 or more blood glucose levels over 250mg/dL twice in a row
    - You have any blood glucose level less than 70mg/day or over 300mg/dL
6. If you are concerned about your health and for whatever reason you are unable to reach the study team you should seek professional medical advice.for example by contacting your primary care doctor.

Helpful Hints

1. You should be able to carry on with your usual daily acitivties while the tube is in place. However you may feel more tired than usual and have some pain or discomfort so you should try to get adequate rest.
2. Some discomfort or pain can be expected when the tube is in place and this does not mean that you have a serious problem or an infection. It will likely occur mostly in the first few days and after that you will likely hardly be aware that the tube is in place. The discomfort or pain will often go away by itself or if you change your position or move the tube a few centimeters. You can take Tylenol liquid to help with this.too. You may find things that relieve or worsen the discomfort. If you do, please document this in your log.
3. Sometimes the tube gets kinked and you may not be able to give the tube feed. You can try to undo the kink by pulling back on the tube up to about the length of your hand (about 6inches or 15cms) and trying again.
4. Sometimes the tube gets blocked with tube feed. This can be prevented by flushing the tube after every feed. If you think the tube maybe blocked with feed you can try to unblock it by injecting water. You should not use any other liquid to unblock the tube
5. If you really do not want to have the tube in any more you can pull it out yourself. The tube is 140cm long. All you have to do is gently and smoothly pull the tube out of the mouth.

APPENDIX C: FREE TO GO DAILY LOG (TUBE PERIOD)

DATE:_____ STUDY DAY_____ STUDY ID #_____ Page 1/2

GENERAL	SID#:			
	Morning	Midday	Afternoon	Evening
Time:				
Blood glucose value:				
Throat discomfort or pain 0 (none)-10 (really bad):				
Tylenol taken since last log	Y N	Y N	Y N	Y N
Temperature (at least once a day):				
Is molar band secure?	Y N	Y N	Y N	Y N
Is the tube smooth and undamaged?	Y N	Y N	Y N	Y N
GI upset 0 (none)-10 (really bad):				
Tube feed given	Y N	Y N	Y N	Y N
Amount tube feed taken by mouth (if any) mls:				
Required oral feed taken	Y N	Y N	Y N	Y N
Time taken to give tube feed (minutes)				
Tube flushed	Y N	Y N	Y N	Y N
Multivitamin taken? Y/N	Y N	---	---	---
Klor-Con taken Y/N	---	Y N	---	Y N
Calcium and Vit D taken? Y/N	Y N	---	Y N	---
Additional salt taken? Y/N	---	---	---	Y N
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				

FOOD AND DRINK*				
	Morning	Midday	Afternoon	Evening
Item and amount				
Item and amount				
Item and amount				
Item and amount				
Item and amount				

Item and amount				
Item and amount				
Item and amount				
Item and amount				
Item and amount				

*Please use additional sheets if necessary

DATE: _____ STUDY DAY_____ STUDY ID #_____ Page 2/2

COMMENTS

*Please use additional sheets if necessary

FREE TO GO DAILY LOG (BEFORE AND AFTER TUBE PERIOD)

DATE: _____ STUDY DAY_____ STUDY ID #_____ Page 1/1

GENERAL	SID#:			
	Morning	Midday	Afternoon	Evening
Time:				
Blood glucose value:				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				
Med Taken (name/ dose):				

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