Ghrelin levels in patients who are obese andfail to have sustained weight loss after gastric bypass surgery

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A. Study Purpose and. Rationale

Obesity is a significant health problem in the United States, contributing to many serious diseases, including heart disease, diabetes and high blood pressure. The percentage of Americans with obesity continues to rise, but successful long term treatments for obesity are limited.

One treatment for obesity that has been quite successful is gastri& bypass surgery. In gastric bypass surgery the stomach and the beginning of the small intestine are disconnected from the be top of the stomach and reattached to a later part of the small intestine but out of the path of food. This results in a smaller stomach for food, isolation of the majority of the stomach tissue from. food nutrients and a change in normal digestion. It has been thought that this promoted weight loss by leaving patients with a smaller stomach which would make them feel full earlier and by disrupting the normal digestion of high calorie foods, leading to abdominal discomfort if large amounts of these foods are eaten. Recent research suggests that bypass surgery may also contribute to weight loss by lowering levels of a "hunger stimulating" hormone made by the stomach called ghrelin (1).

Ghrelin is a newly characterized hormone that is made primarily in the stomach and sensed by the brain. It is normally made in higher arnounts when the stomach is deprived of nutrients, such as the time before a meal. It is sensed by cells in the brain which respond by making other hormones that stimulate the sensation of appetite and the search for food (2). After eating, the level of ghrelin in the blood typically goes down to levels lower than before the meal. It has been shown in animals and humaris to be important in both meal time hunger and long term weight regulation.

Researchers examined super obese (i.e. BMI >50, in their study, mean BMI was 67) patients who had lost weight after gastric bypass surgery and found that the levels of ghrelin in their blood were much lower than in people who were of normal weight and people who had lost weight by diet and exercise (1). One explanation for this is that by surgically isolating most of the stomach and the beginning of the small intestine from the path of food for a long period of time the stomach cells no longer make ghrelin in the same amounts and therefore causing the levels to be much lower than would usually be expected.

These observations suggest a possible explanation as to why some patients who have bypass surgery do not have the sustained weight loss that most do. Is it possible that in some patients who have bypass surgery that the surgery does not cause changes that decrease ghrelin levels and therefore the "hunger stimulating" hormone levels continue to be high, making weight loss more difficult?

In this study we will examine the blood levels of ghrelin obese patients before and after gastric bypass surgery and compare the levels in patients who have a successful weight loss with those who do not to determine if failure to have a sustained weight loss is associated with a higher blood ghrelin level compared with patients who do lose weight with bypass (3). As we expect the population of patients in this study will not be super obese (mean of approximately 47), we will also be able to address if the ghrelin patterns observed in patients of more representative successful patients also show as dramatic of decreases in their ghrelin levels. Knowing this information may help to improve the surgical procedure, may point scientists to medications that can help to cause or maintain weight loss or help to eventually identify other important signals for weight control.

B. Study Hypothesis

Is failure to have a sustained weight loss after gastric bypass surgery associated with higher pre and post surgery ghrelin levels?

C. Study Design

The study design is a prospective, observational, case-control study. We will enroll 110 patients referred for the study by health -care professionals at the Obesity Center after they have been accepted for gastric bypass surgery. Based on an average failure rates of 15%, but allowing for as low as 5%, (4) and allowing for a combined loss to follow-up and technical failure of procedure of tO%, this number will enable us to study 5-15 patients who will by I year have failed to initiate and/or maintain a loss of 50% of their excess body weight (5).

Prior to surgery they will be admitted to the General Clinical Research Center for an overnight fast and then starting at 6 am blood will be sampled for ghrelin, insulin and leptin levels, They will receive breakfast, lunch and dinner. During the day, blood will be collected every 30 minutes and overnight every 60 minutes. Additionally, a single hemoglobin A I C level will be drawn.

At 12 months after surgery, we will determine which patients have failed to initiate and/or maintain a successful weight loss and this subset of patients will be matched by initial BMI, age and sex to patients who have had a successful weight loss. We anticipate that there will be sufficient patients to allow a I to 3 match of patients who failed gastric bypass to patients who succeeded. Patients will again be admitted to the GCRC for the same measurements of ghrelin, insulin and leptin.

D. Statistics Sample size:

Based on mean 24 hour ghrelin levels for gastric bypass patients and obese patients of 3058 pg-days per milliliter (sd=1605) and 9365 pg-days per milliliter (sd=4063), respectively, we would need 100 patients in total to expect to have enough who eventually failed to lose weight, based on a power of 80% to detect a difference of similar magnitude at an alpha level of 0.05.

The 24 hour ghrelin levels for all subjects will be used to calculate a mean area under the curve for the two groups before and after surgery. These will be compared using t-test.

E. Study subjects

Inclusion criteria
Patients with obesity who have qualified for gastric bypass surgery.
Exclusion criteria
Patients less than 18 years old, greater than 50 years old.

F. Recruitment of subjects

Subjects will be recruited from patients who are followed at the Obesity Center and are planned for gastric bypass. Health care providers at the Center who feel a patient would be appropriate for the study can inform patients of the study. If the patient is interested, the study investigator would review the study, risks, benefits and compensation with the patient and obtain informed consent.

G. Confidentiality

The patients will be identified by a code number which will not be the social security number, date of birth or medical record number of the patient. The study data will be kept in a secure location with access granted only to appropriate study investigators.

H. Potential risks

Only the minimal risks associated with routine phlebotomy and peripheral intravenous catheter.

I. Potential benefits

At this time, there is not likely to be a direct benefit to any of the participants.

J. Compensation

Patients will be compensated for local travel expenses.

K. Cost to subjects

None.

L. Alternative therapies

Not applicable.

M. Minors/ at risk patients as research subjects

Not applicable

N. Radiation or radioactive substances

Not applicable

O. References

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