Journal of Diabetes and Metabolism
ISSN: 2155-6156

Akerfeldt et al., J Diabetes Metab 2014, 5:12
DOI: 10.4172/2155-6156.1000465

Research Article Open Access

Serum Leptin is Decreased Thirty Days after Surgery

Torbjörn Akerfeldt*, Miklos Lipcsey, Lena Gunningberg, Christine Leo Swenne and Anders Larsson

Department of Surgical Sciences, Section of Anaesthesiology & Intensive Care, Uppsala University, Uppsala, Sweden

Abstract

Background: Leptin plays an important role for the regulation of food intake, energy expenditure and glucose control. The aim of this study was to study the effect of surgery on circulating levels of human leptin in a human elective surgery model.

Methods: A prospective observational study was conducted. Blood sampling was carried out prior to surgery and four and thirty days after elective surgery, respectively. Patients undergoing orthopedic surgery (n=29) and coronary bypass patients (n=21) were included in the study. Serum leptin levels were measured using sandwich ELISA. C-reactive protein (CRP) was analyzed by turbidimetry.

Results: Leptin values was significantly decreased thirty days after surgery in both orthopedic (p=0.002) and coronary bypass patients (p=0.003) in comparison with presurgical values.

Conclusion: Elective surgery is associated with decreased leptin levels in the late postsurgical phase.

Keywords: Serum; Leptin; Inflammation; Elective surgery; Cardiopulmonary bypass; Humans

Introduction

Surgery patients often have an inflammatory response and they are also in a catabolic state [1]. This catabolic state is an important clinical problem especially in patients that prior to surgery have a poor nutritional status (e.g. many elderly patients). At the same time, hyperglycemia is also frequently occurring in trauma patients treated in intensive care units and that hyperglycemia is associated with increased mortality [2,3]. A number of trials have compared outcomes in patients randomly assigned to lower or higher blood glucose levels [4,5]. Initial studies indicated that an intensive glucose control could reduce mortality but subsequent studies have not been able to confirm these observations [6-8]. Considering the role of leptin for the regulation of body weight and nutrition we wanted to explore the effects of elective surgery on circulating leptin levels. The surgical model is a suitable model for studying the effects of surgical trauma and inflammation on leptin concentrations as the injury is well standardized both in time and size. The associations between leptin and inflammation are bi-directional: proinflammatory cytokines stimulate the release of leptin, which in turn perpetuates the inflammatory response. The leptin production is mainly stimulated by the cytokines TNFα, IL6, and IL 1β [9] leading to a rapid increase in leptin concentrations. Increased leptin levels are reported in a number of acute inflammatory conditions such as infections and sepsis but also in more chronic disorders such as rheumatoid arthritis, diabetes and atherosclerosis [10-14].

The aim of the present study is to study the effect of a surgery on circulating leptin levels in humans. We chose orthopedic surgery and cardiopulmonary bypass surgery as they are both elective surgical procedures and the patients thus have low inflammatory activities prior to surgery. Both types of operations are known to induce a strong inflammatory response and thus suitable to study the effects of surgery and inflammatory response on circulating leptin levels.

Materials and Methods

Elective orthopedic surgery (n=29, 13 males and 16 females) and elective cardiopulmonary bypass surgery (n=21, 18 males and 3 females) patients, at the Uppsala University Hospital were included in the study. Patients with diagnosed diabetes mellitus were excluded from the study. The mean age was 67 years (range 45–80 years) for the orthopedic patients and 69 years (range 48–84 years) for the cardiopulmonary bypass patients. Fourteen of the orthopedic patients had knee surgery and fifteen of the patients had hip arthroplasty. The blood samples for leptin analysis were collected in the morning after an overnight fast. The majority of the blood samples aimed for routine analysis work were also collected in a morning fasting state. The samples were collected in Vacutainer tubes without additives, prior to surgery and four and thirty days after surgery, respectively. After clotting the samples were centrifugated at room temperature and the sera were collected and frozen at −70°C. The study was approved by the local ethical board at Uppsala University (2004:237) and all patients signed an informed consent prior to inclusion in the study.

CRP and cystatin C assays

Serum CRP (reagent: 6K2601) and cystatin C (reagent: 1014, Gentian, Moss, Norway) were analyzed by turbidimetry with an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA). The equation used for calculating estimated GFR (eGFR) in mL/min/1.73 m^2 from the cystatin C results in mg/mL was $y = 79.901x^{-1.4389}$ [15].

Leptin ELISA

Serum leptin was analyzed with a commercial sandwich ELISA (DY398, R&D Systems, Minneapolis, MN, USA), according to the recommendations of the manufacturer. The total coefficient of variation (CV) for the assay was approximately 6%.

***Corresponding author:** Torbjörn Akerfeldt, Department of Surgical Sciences, Section of Anaesthesiology & Intensive Care, Uppsala University, Uppsala, Sweden, Tel: 46-18-6110000; E-mail: torbjorn.akerfeldt@akademiska.se

Received September 23, 2014; **Accepted** November 12, 2014; **Published** November 16, 2014

Citation: Akerfeldt T, Lipcsey M, Gunningberg L, Swenne CL, Larsson A (2014) Serum Leptin is Decreased Thirty Days after Surgery. J Diabetes Metab 5: 465 doi:10.4172/2155-6156.1000465

Statistical calculations

Statistical analysis was performed with Statistica 7.1 (StatSoft, Tulsa, OK, USA). Comparisons between presurgical samples from orthopedic and cardiopulmonary bypass surgery patients were performed with Mann-Whitney U test and comparisons between presurgical and postsurgical samples were performed with Wilcoxon matched pair test. An association between leptin and CRP was tested with Spearman rank correlation. Descriptive statistics were reported as median and IQR (interquartile range) unless otherwise stated. We regarded $p<0.05$ as statistically significant throughout the text.

Results

Patient characteristics, cystatin C and CRP values

Median cystatin C values prior to orthopedic surgery was 0.97 (interquartile range (IQR) 0.86–1.23) mg/L) corresponding to a median estimated GFR (eGFR) of 84 (IQR 59–99) mL/min/1.73 m^2 while median cystatin C values prior to cardiopulmonary surgery was 1.08 (IQR 0.95–1.30) mg/L) corresponding to a median eGFR of 71 (51–83) mL/min/1.73 m^2.

In the orthopedic group, median CRP value prior to surgery was 1.9 mg/L (IQR 1.2-8.7). Four days after surgery the median value was 137.3 mg/L (IQR 104.1-178.2) and thirty days after surgery the median value was 5.1 mg/L (IQR 2.0-10.8).

In the cardiopulmonary surgery group, median CRP value prior to surgery was 3.3 mg/L (IQR 1.0–7.6). Four days after surgery the median value was 167.0 mg/L (103.7-222.7) and thirty days after surgery the median value was 3.4 mg/L (2.0–5.6).

Leptin values

The median leptin value prior to surgery was 17706 pg/mL (IQR 9480-37139) in the orthopedic group. Four days after surgery the median value had decreased (p=0.13) to 13202 pg/mL (IQR 7925-24935) and thirty days after surgery the median value had decreased further (p=0.002 vs. presurgical values) to 10629 pg/mL (IQR 7640-20847). Likewise, the median value in the cardiopulmonary surgery group was 14039 pg/mL (IQR 7925-28300). Four days after surgery the median values was 13515 pg/mL (IQR 6364-32542; p=0.84) and thirty days after surgery the median value was 5824 pg/mL (IQR 4677-9752; p=0.0031 vs. presurgical values and p=0.0030 vs. day 4).

Correlation between leptin and CRP values

There was no significant correlation between presurgical leptin and CRP values in the orthopedic patient group (Spearman rank=0.19, p=0.34) while there was a significant correlation in the cardiopulmonary surgery group (Spearman rank=0.57, p=0.008). There was also a significant correlation in the cardiopulmonary surgery group four days after surgery (Spearman rank=0.48, p=0.03).

Discussion

Increased levels of leptin reduces food intake and increases energy expenditure [16,17] while transgenic leptin-deficient animal models exhibit an increased food intake, and development of obesity. Leptin exert its effect via leptin receptor. In humans, these receptors are widely distributed in the body including adipose tissue, brain, heart, kidney, liver and pancreas. Leptin could thus affect many different organs. Low leptin levels are associated with hyperglycemia while leptin treatment has been shown to reduce the widely used hyperglycemia marker glycosylated hemoglobin in patients with lipodystrophia [18].

The surgical injury similar to other types of injury disrupts the normal homeostasis of the body. An effect of the trauma is that a hypermetabolic response occurs that results in hypercatabolism, hyperglycemia and vascular endothelial damage all of which may have systemic effects [19]. Hyperglycemia in trauma patients has been a topic of great debate during the last decade. The role of trauma-induced hyperglycemia as a protective response mechanism were first questioned by Van den Berghe and coworkers who showed that morbidity could be reduced by intensive insulin control (IIT) in ICU patients [20,21]. In contrast to this finding the NICE-SUGAR trial showed that an intense glucose control led to hypoglycemia which was associated with an increased mortality [6].

In this study the blood samples were collected 4 and 30 days after surgery to cover both the early and late phase after surgical trauma. We found decreased levels of leptin in the postsurgical phase and especially in the late phase. At day 30, most trauma patients are discharged from the hospital, but the study results indicate that these patients still have an altered metabolism measured as decreased leptin levels. C-reactive protein is one of the acute phase proteins that rises rapidly and quickly returns to within the normal range if treatment is employed. Day 4 is close to the peak for CRP while there are a number of acute phase proteins that react more slowly to an inflammatory challenge such as fibrinogen, haptoglobin, alpha-1-acid glycoprotein, and the erythrocyte sedimentation rate (ESR) and albumin. Similar to leptin in this study these markers will show a larger deviation at day 30 than at day 4.

Usually, trauma-induced hyperglycemia is thought to be secondary to elevated levels of epinephrine, glucagon, and cortisol [22,23]. Increased levels of leptin should in theory lead to increased food intake and increased glucose levels.

Leptin, having a molecular weight of 16 kDa, is likely to be rapidly filtered in the glomeruli. A reduced kidney function could thus influence the serum levels of leptin. The patients included in this study had only slightly decreased eGFR values with median values of 84 and 71 mL/min/1.73 m^2, respectively.

Leptin has a number of functions that could be of importance during the postoperative phase. It has been reported that leptin may be an angiogenic factor and involved in wound healing [24,25]. Leptin also have other functions that could be of important during the postoperative period. Leptin has been implicated in respiratory control and ob/ob mice have 50% less total lung capacity and lung compliance than their wild-type counterparts [26]. In humans, leptin has also been shown to be a predictor of lung function and lung volume [27]. In contrast to our study serum leptin concentrations are often reported to be increased in inflammatory and infectious conditions [28,29].

Clinical implication of the study is that it shows the importance of sampling time for leptin in relation to surgical procedures. The study also indicates that leptin could influence postoperative hyperglycemia.

Limitation of this study is that only elderly Caucasian Swedish subjects were included and thus generalizability to other ethnic groups is unclear. Further, it should be noted that this is a post-hoc study and thus there was no power calculation done on leptin when designing this trial.

Conclusions

The reduced leptin levels in the postsurgical phase in this study indicates that leptin also could be another player in the complex cytokine response in trauma patients that leads to hyperglycemia. Considering

the importance of hyperglycemia in trauma patients further studies are warranted on the role of leptin in trauma patients. Also, it would be interesting to evaluate the effects of leptin treatment in these patients.

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