Postoperative Dynamic of Leptin and Fibroblast Growth Factor 21 in 123 Patients Recovering from Cardiac Surgery

**Background:** Cardiac surgery triggers acute changes in serum leptin and fibroblast growth factor 21 (FGF-21). Considering their pleiotropic role in inflammation and abnormal glucose metabolism, perseverance of their abnormal serum level can have a long-term impact on recovery and end-organ failures. Long-term dynamics after cardiac surgery are unknown.

**Material/Methods:** Serum was collected from 123 patients before cardiac surgery (t_{baseline}) and 24 h (t_{24h}), 7 days (t_{7d}), and 3 months (t_{3m}) later. Also, interleukin 6 (IL-6) and C-reactive protein (CRP) assessed nonspecific inflammatory responses. Neurodegeneration was gauged with serum amyloid β1-40 and β1-42. Demographic and clinical information, including disposition at 28 days and t_{3m} from admission, were collected.

**Results:** Serum leptin increased at t_{24h} (leptin_{baseline}=613±747.9 vs leptin_{24h}=768±718.1; P=0.0083) and decreased at t_{7d} (leptin_{7d}=499.5±540.2; P=0.043). FGF-21 levels increased at t_{24h} and t_{7d}. Cytokines normalized by t_{3m}. Presurgical leptin levels were higher in Asians and were the primary determinant of postoperative leptin changes. Leptin levels were most elevated in patients undergoing aortic valve and arch surgery; the perioperative increase was significant only in patients with mitral valve surgery. Leptin levels were most elevated in patients undergoing aortic valve and arch surgery; the perioperative increase was significant only in patients with mitral valve surgery. Leptin and FGF-21 did not correlate with markers of general inflammation (CRP, IL-6), which partially resolved after t_{3m}. Amyloid β1-42 at t_{3m} correlated with leptin peak at t_{24h}. Low prehospital FGF-21 level correlated with the incidence of perioperative stroke; postoperative FGF-21 correlated with discharge to facility vs home.

**Conclusions:** Leptin and FGF-21 evolve independently from the inflammatory response in the aftermath of cardiac surgery and correlate with cardiac remodeling and neurodegeneration markers.

**Keywords:** C-Reactive Protein • Critical Care Outcomes • Fibroblast Growth Factor 21 • Leptin • Survivors • Thoracic Surgery • Treatment Outcome

**Abbreviations:** APACHE – Acute Physiologic Assessment and Chronic Health Evaluation; CRP – C-reactive protein; FGF-21 – fibroblast growth factor 21; IL-6 – interleukin 6

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Background

Severe stress results in acute abnormalities of metabolic regulation of carbohydrates and lipids, which are detrimental to mortality and morbidity [1-3]. Patients undergoing coronary artery bypass grafting (CABG) seem particularly vulnerable. Prolonged abnormalities in carbohydrate metabolism can sustain ongoing sympathetic over-activation, inflammation, and changes in metabolome [1,2]. These conditions can accelerate arteriosclerosis and sustain sterile neuroinflammation, leading to premature neurodegeneration, denying patients the full long-term benefit of surgery [3,4].

Leptin is a critical hormone intersecting carbohydrate and lipid metabolism, with pleiotropic immunological activities [5]. Abnormal regulation of this hormone leads to the myocardium’s susceptibility to ischemia, inflammation persistence, and hyperglycemia [2,5-9]. Furthermore, leptin regulates satiety, which can be critical for maintaining an optimal body mass index (BMI) after surgery. Prior work demonstrated that leptin serum levels are diminished at 30 days after orthopedic surgery or cardiopulmonary bypass surgery [7]. Another study demonstrated an initial increase that was followed by diminishing levels, but the observation period was less than 24 h, and the study focused on the adult population [5]. The peri-surgical increase in leptin levels is limited to serum and adipose tissue [10]. Changes in leptin levels can impact response to shock and infection susceptibility [8,11,12]. Consequently, these data are well aligned with the observation that preoperative abnormal leptin levels are correlated with a compos-ite risk of the adverse cardiovascular level after cardiac surgery [13]. Fibroblast growth factor 21 (FGF-21) has a similar function, driving behavior aimed at increased carbohydrate intake. Combined, the abnormal regulation of these hormones can lead to hyperglycemia, persistent sterile inflammation in the kidney and brain, and susceptibility of the myocardium to ischemia, culminating in unfavorable long-term neurocognitive sequela [1,2]. All these effects mitigate the beneficial effects of heart surgery. It has been suggested that markers may be in-volved in unfavorable outcomes after cardiac surgery, including cognitive decline and unfavorable cardiac remodeling [14,15]. However, the longitudinal dynamics of the markers after major surgery are unknown. Although the hormones are released during acute stress, it is unclear if their stress-induced secretion outlasts the acute recovery from surgical stress, thereby contributing to long-term recovery from surgery.

This study aimed to investigate the longitudinal dynamics of leptin and FGF-21 in patients recovering from cardiac surgery. We hypothesized that leptin and FGF-21 abnormalities would be limited to the acute inflammatory response and follow serum interleukin 6 (IL-6) and C-reactive protein (CRP). To assess the clinical impact, we assessed serum levels of amyloids β1-40 and amyloids β1-42. In addition, considering hormone function, we investigated the effects of leptin in patients with diabetes or a higher BMI.

Material and Methods

Patient Enrollment

Our study protocol was approved by the Institutional Review Board (IRB) of the University of Pennsylvania and was performed according to the guidelines of the 2003 Helsinki Declaration (#815686; approved March 02, 2020).

All patients scheduled for elective heart surgery were approached for consent. We excluded patients with pre-existing immunological aberrancies who were on immunosuppressant medications in the last 6 months (oral or intravenous predni-sone more than 5mg daily; eTNFa, cIL-6, cIL-3, and cCD20 an-tibody therapy; immunoglobulin, plasmapheresis, methotrex-ate, and chemotherapy). The study did not include patients with inherited and known dyslipidemias and those who had undergone transplantation.

The demographic characteristics of patients is presented in Table 1.

Sample Processing

Upon patient consent, serum was isolated and stored at -80°C. Blood was collected at 4 times as follows: The baseline sample \( t_{\text{baseline}} \) was collected before or shortly after arterial or central line placement. The second sample was collected 24 h after the first sample \( t_{\text{24h}} \), during the patient’s stay in the Intensive Care Unit (ICU). The third sample was obtained at the patient’s discharge from the hospital or 7 days after the \( t_{\text{baseline}} \) sample \( t_{\text{7d}} \). The last sample was collected no sooner than 3 months after surgery \( t_{\text{3m}} \) but no later than 4 months after. The 4 samples represents baseline, acute stress response, convalescence, and medium-term recovery, respectively.

Clinical Data

The electronic medical records were used to collect the demo-graphic and clinical data for all enrolled patients. The patients self-determined their race and ethnicity. Several variables regard-ing the duration of surgery and anesthesia were collect-ed from the medical records retrospectively. Preoperative hemoglobin A1c (HbA1c) and lipid profiles were collected from routine preoperative laboratory tests, when available. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated within 1 h and \( t_{\text{sh}} \) after admission to the ICU. The burden of chronic disease was calculated using
| Table 1. Demographics and clinical characteristics of the study sample. |
|---------------------------------------------------------------|
| **Patient characteristics (N=123)**                          |
| Age, mean±SD [years]                                         | 64.22±12.27 |
| Sex – Male no. (% of total)                                  | 93 (75.6%) |
| BMI mean±SD [kg/m²]                                          | 28.4±5.99 |
| Race (% Caucasian, % Black, % Asian, % Other)                | 83.7%, 6.5%, 4.1%, 5.7% |
| **Anesthesia & surgery data**                                |
| Duration of anesthesia; mean±SD [min]                        | 394.17±117.9 |
| Duration of surgery; mean±SD [min]                          | 277.75±100.92 |
| Coronary artery bypass surgery*; no.                        | 64 |
| Mitral valvuloplasty & replacement*; no.                     | 16 |
| Aortic valvuloplasty & replacement*; no.                     | 36 |
| Others*; no.                                                 | 6 |
| **Perioperative management**                                 |
| Estimated blood loss [ml]                                    | 197.13±260.4 |
| Total crystalloid during surgery [ml]                        | 1254.91±606.24 |
| Corticosteroid administration (% of all cases)               | 15.4% |
| Ketorolac administration (% of all cases)                    | 7.4% |
| Acetaminophen administration (% of all cases)                | 71.3% |
| ASA administration (% of all cases)                          | 66.4% |
| **ICU stay**                                                 |
| APACHE score at 1 h, mean±SD                                 | 17.08±6 |
| APACHE score at 24 h, mean±SD                                | 9.95±15.17 |
| APACHE score at 48 h, mean±SD                                | 9.33±4.99 |
| **Comorbidities**                                           |
| CCI median (95% CI)                                          | 4 (3.7-4.53) |
| Acute Coronary Syndrome                                     | 15.4% |
| Chronic heart failure                                       | 22% |
| Connective tissue disease (non-active)                       | 15.4% |
| Cerebrovascular disease                                     | 9.8% |
| Type 2 diabetes                                              | 28.5% |
| COPD                                                         | 6.5% |
| **Outcomes**                                                 |
| Mortality                                                   | 1.6% |
| CVA                                                        | 9.8% |
| PE                                                        | 5.7% |
| DVT                                 | 8.9% |
| AKI                                               | 22.1% |

* Some patients had more than one procedure.
the Charlson Comorbidity Index [16,17]. The severity of illness during the ICU stay was determined using the Marshalls Organ Dysfunction Score [18]. Survival was determined at 28 days and $t_{3m}$ from admission.

**Assessment of Biomarkers**

Leptin and FGF-21 were anlayzed using enzyme-linked immuno-sorbent assay, according to the manufacturer instructions (BioLegend, San Diego, CA, USA). In addition, inflammatory markers (IL-6, CRP) and neurodegeneration markers (amyloid β1-40, amyloid β1-42) were analyzed using multiplex technology (ThermoFisher, Waltham, MA, USA) on a MagPix machine (Luminex, Austin, TX, USA) [19].

**Statistical Analysis**

The normality of distribution of studied variables was determined using the Kolmogorov test and descriptive variables. Data were are presented as mean±standard deviation or median and interquartile ranges. The data were compared using the t test ($t[n]$) or Mann-Whitney U test ($U[n]$). Analysis of variance ($F[df;n]$) or the Kruskal-Wallis test ($H[df;n]$) was used for variables with multiple subgroups. Longitudinal and pairwise analysis was done in most of the statistical contrasts. Correlations were calculated with the Pearson correlation coefficient (r). Regression analysis was done using the stepwise method. A P value less than 0.05 was considered statistically significant for all tests. SPSS version 26 (IBM Corp, Armonk, NY, USA) was used for analysis.

**Results**

**Patient Characteristics and Baseline Levels of Leptin and FGF-21**

Sex or age over 60 years old did not affect serum leptin and FGF-21 levels at baseline. Asian patients had a significantly higher level of leptin ($H[3;102]=9.23; P=0.029$) at baseline, but only 5 patients of this race were enrolled in the study (Figure 1).

Patients with pre-existing diabetes had elevated serum leptin at $t_{baselines}$. The increase in leptin and FGF-21 at $t_{24h}$ was significant for all tests. SPSS version 26 (IBM Corp, Armonk, NY, USA) [19].

**Changes in Leptin and FGF-21 After Cardiac Surgery**

Sex, age, race, BMI, and collected history of pre-existing illnesses did not affect the leptin level at $t_{3m}$, $t_{7d}$, and $t_{3m}$. Multiple regression analysis (including age, BMI, Charlson Comorbidity Index, procedure type, stay in ICU, and hospital duration of anesthesia and surgery, as well as APACHE at 1 and $t_{24h}$, after admission and baseline leptin demonstrated that the preoperative level of leptin accounted for 31% variation in the postoperative level of leptin at 24h ($F[12;74]=5.44; P<0.0001$), 25% at $t_{7d}$ ($F[12;63]=7.61; P<0.0001$), and 11% at $t_{3m}$ ($F[12;44]=1.96; P<0.05$).

We found that leptin levels increased significantly at $t_{3m}$, then declined below baseline $t_{7d}$ after surgery, to normalize at $t_{3m}$ ($U[60;3]=7.81; P=0.049$) (Figure 2A). FGF-21 remained elevated at $t_{24h}$ and $t_{7d}$ ($U[45;3]=21.38; P=0.0009$) (Figure 2B). Patients undergoing mitral valve-related surgeries only had a transient increase in the acute postoperative period ($P=0.033$) (Figure 2C). Interestingly, patients with CABG had a somewhat steady level of leptin throughout all observation periods. Leptin and FGF-21 did not correlate significantly at $t_{24h}$, $t_{7d}$, and $t_{3m}$.

**Perioperative Course and Dynamics of Leptin and FGF-21**

The increase in leptin and FGF-21 at $t_{3m}$ and $t_{7d}$ did not correlate with the duration of anesthesia, surgery, or time of the by-pass. Estimated blood loss was weakly correlated with leptin level at $t_{24h}$ ($r=0.2; P=0.047$), $t_{7d}$ ($r=0.399; P=0.0001$), and $t_{3m}$ ($r=0.395; P=0.001$), but not with volume of crystalloids given

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Figure 1. Asian race was related to an elevated level of leptin at the baseline. Figures were generated using Prism by Graph Pad Dotmatics version 9. * Two-tailed significance less than 0.05.
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Figure 2. During the observation period, the dynamics of leptin and fibroblast growth factor 21 (FGF-21) as compared with inflammation markers, interleukin 6 (IL-6), C-reactive protein (CRP). (A) Leptin increased acutely at t_{24h} (P<0.0001) to decline at t_{7d} (P=0.043) while normalizing at t_{3m}. (B) FGF-21 was elevated at both t_{24h} (P<0.0001) and t_{7d} (P<0.0001) and normalized at t_{3m}. (C) Markers of acute inflammation, including IL-6 (D) were elevated at t_{24h} (P<0.0001), while (E) CRP remained elevated across all of the time points (P<0.0001) as compared to baseline. Leptin levels slightly varied by surgery type at the baseline level and dynamics after surgery. Figures were generated using Prism by Graph Pad Dotmatics version 9. * Two-tailed significance less than 0.05 when data compared to baseline.
during the procedure. Intake of aspirin, ketorolac, and acetaminophen showed no effect on leptin or FGF-21 at any time point. No patients were given steroids in our cohort. FGF-21 at t
24h
(r=0.59; P<0.0001) correlated strongly with the intake of benzodiazepines but not with that of opiates.

Leptin and FGF-21 and Short- and Long-Term Outcome

Leptin levels at t
24h
 correlated weakly yet significantly with amyloid β1-42 but not with amyloid β1-40 at t
3m
 (Figure 3). Central nervous system failure resulted in aberrations in FGF-21 at t
24h
 (U[85;7]=2.42; P=0.01). Patients experiencing a stroke during surgery had lower baseline levels of FGF-21 (U[91;7]=2.24; P=0.023).

Leptin and FGF-21 serum levels did not correlate with APACHE scores at admission, t
24h
, and 48 h. Length of stay in the hospital or ICU did not correlate with leptin or FGF-21 levels at any time. Disposition at the discharge from the hospital indicated that FGF-21 at t
24h
 (U[76;15]=1.97; P=0.049) and t
7d
 (U[71;8]=2.06; P=0.038) was lower if the patient was transferred to the long-term facility versus to home discharge (Figure 4). Only 1 patient died in that group, rendering statistical analysis not feasible.

Discussion

This study encompassed a longitudinal sampling of patients who underwent heart surgery, with a follow-up at t
3m
. Our primary goal was to establish the relationship between serum leptin and FGF-21 longitudinal dynamics and postsurgical inflammatory and stress response, considering the function of these cytokines [9, 20-22]. We were particularly interested in the relationship of leptin and FGF-21 to presurgery BMI and pre-existing diabetes because of the role of leptin in long-term carbohydrate metabolism [2,4,5,9,21,23,24]. Pre-existing data suggested a link of leptin levels to susceptibility to pneumonia and sepsis as well as to long-term cognitive decline and cancer propagation [8,11,25-28]. FGF-21 modulates and augments several leptin functions, but no longitudinal studies of the serum hormone levels after cardiac surgery have been conducted to date [21,22].

Our study demonstrated that leptin levels peaked after around t
7d
 and recovered to pre-baseline levels after t
3m
. This observation was similar to that of a prior study which detected normalization of the level by day 30 in patients undergoing cardiopulmonary bypass [5,7,13]. Our results showed that at t
7d
, leptin levels were lower, in contrast to another study that...
showed normalization of levels by day 4 [5,7,13]. Normalization by day 4 is likely part of a downward trend. We demonstrated that the type of surgery is one of the critical factors in determining the postsurgical dynamics of leptin. Patients undergoing arch repair had the highest baseline level but also had the steepest decrease in leptin levels after surgery. Patients undergoing valve surgery exhibited a much more modest trend, while patients undergoing CABG had minimal leptin dynamics. The reason for these differences is unclear, but they have been related to different etiologies leading to a particular surgery. The most common indication for arch surgery is aneurysmal changes, and leptin can accelerate the progression of this disease in animal models [29,30]. What is particularly interesting is that surgery of the arch dramatically reduces the level of leptin, suggesting removal of the source. This somewhat puzzling finding warrants further study to establish the causative effect. We expected that CABG would have the most pronounced level of leptin changes because of the role of leptin in sugar metabolism and progression of atherosclerosis via smoldering inflammation [5,8,9]. However, in the present study, CRP and IL-6 did not correlate with leptin levels, suggesting that leptin was an independent factor in postoperative inflammation. Also, the level of surgical insult measured via several perioperative factors demonstrated low correlations with leptin dynamics, suggesting that heart surgery by itself is a strong enough trigger for leptin release. This nonspecific role of leptin in modulating postsurgical response was noted in a study describing the pericardial fat release of leptin [10]. Interestingly, YKL-40 and leptin levels correlated, suggesting that ongoing tissue repair and leptin release may be interconnected, and that the serum leptin level may be potentially driven by epicardial fat [31,32]. Also, the pre-existing leptin levels were the most crucial variable in determining the postsurgical leptin response. A similar observation was made by Gu et al, in which preoperative leptin level was a risk factor for adverse effects after cardiac surgery [13]. That study was done in older Asian adults, suggesting that race may be a determining factor as it was described before [13]. This may suggest that there is a more complex interaction between long-term outcomes of surgery and race via leptin-driven mechanisms.

To date, the present study is the first long-term observation of the FGF-21 dynamic after cardiac surgery, except for one abstract that was published 10 years ago [33]. In our study, FGF-21 levels increased at t_ab and fell below the pre-baseline levels at t_spr. This profile was similar to that of IL-6 and CRP dynamics. Elevated FGF-21 levels correlated with central nervous system failure and the intake of benzodiazepines. Although central nervous system failure was defined alongside the clinical score, this observation was correlated with another study that showed an interaction between FGF-21 and the emergence of delirium or neurodegeneration [15,18,34]. The correlation between FGF-21 levels and the use of benzodiazepines may contribute to the difference in observed central nervous system failure. However, long-term decline was a predictor of unfavorable discharge, a finding well aligned with the critical role of FGF-21 in the metabolome, tissue healing, and neurodegeneration [34-37].

This study had several strengths. It had a large patient population, and we were able to study the presurgical state. Our sample was large and allowed us to make comparisons between baseline and later values. Because of the significant variability in baseline levels, the use of a longitudinal design was one of the most important advantages, specifically because hyperleptinemia is linked to persistent inflammation [22]. Also, we studied diverse adult patients in regards to sex, age, pre-existing medical conditions, and surgery type. We collected clinical data on the severity of surgery, perioperative management, and serum levels of inflammation markers (CRP, IL-6). Several pre-existing conditions important for leptin and FGF-21 levels were included in the data collection and analysis [15,22,24]. Finally, the methodology (enzyme-linked immunosorbent assay, multiplex) used to assess the serum level of the markers is very well established and robust, especially for measurements of IL-6, CRP, and FGF-21.

This was an exploratory study. Consequently, we could not conduct power analysis for FGF-21, in particular. In addition, our patient cohort was biased toward Whites and men; however, leptin levels are elevated in patients of Asian descent [13]. The significant limitation of the techniques used is relatively low sensitivity; however, only amyloid serum levels were close to the detection limits, potentially biasing the results. Furthermore, leptin levels are affected by glucocorticosteroids, circadian rhythm, and level of inflammation [9,38,39]. Our study did not account for these variables in an optimal way. Finally, FGF-21 levels may be affected by genetic variance [40].

Leptin and FGF are highly regulated by muscle and the liver [24]. Changes in muscle mass were not accounted for in this study. Liver function remained essentially nominal judging from liver injury markers; however, they can be a poor predictor of impaired synthetic function. There is a considerable amount of data linking leptin to immune-compromised immunity; however, in our sample, no patient experienced septic shock, and postoperative infectious complications were low [5,8,9]. Also, leptin biological activity is modulated by smoking and alcohol consumption, and we did not control for these factors. The correlations between leptin and FGF-21 and neuro-injury (amyloid) need to be quantified in more detail; however, FGF-21 seems to be generally protective in neuroinjury [19,34,35]. The abnormalities in FGF-21 and leptin may be a part of broader hyperglycemia and inflammation instead of being directly involved in the postsurgical inflammation process. Next, studies should analyze the changes in leptin in conjunction with glucocorticosteroid
metabolism, as leptin is dependent on steroids released during stress, in particular [9,24]. This is particularly important as exogenous steroids are used during some cardiac cases. There is a growing need to establish the role of leptin as the independent risk factor for postoperative complications in the context of pre-existing levels, race, and diabetes. Our pilot data demonstrated specific clinical correlates with neurodegeneration and cardiac remodeling markers; however, these findings must be validated with appropriate functional testing.

Conclusions

Leptin and FGF-21 evolve independently from the inflammatory response in the aftermath of cardiac surgery and correlate with cardiac remodeling and markers of neurodegeneration. Functional correlates of these correlations need to be established in the next study.

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Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board at the University of Pennsylvania (#815686).

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Declaration of figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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