

Comparison of Ghrelin Level between On and Off-Pump Coronary Artery Bypass Grafting Patients

- 1- **Ali Asghar Moeinipour**, MD, Assistant Professor of Cardiac Surgery, Department of Cardiac Surgery, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: MoinipourA1@mums.ac.ir
 - 2- **Mohammad Abbasi Tashnizi** MD, Assistant Professor of Cardiac Surgery, Department of Cardiac Surgery, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: abbasitashnizim@mums.ac.ir
 - 3- **Hossein Ayatollahi** MD, Associate Professor of Pathology, Department of Hematopathology and blood bank, Imam Reza Hospital, Cancer molecular Pathology research centre, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: Ayatollahih@mums.ac.ir
 - 4- **Nahid Zirak**, MD, Assistant Professor of Anesthesiology, Department of Cardiac Surgery, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: zirakn@mums.ac.ir
 - 5- **Alireza Sepehri Shamloo**, Research Administrator, Student Research Committee, School of medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: sepehria871@mums.ac.ir
 - 6- **Farnaz Ahmadpour**, Medical Student, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: AhmadpourF891@mums.ac.ir
 - 7- **Farzaneh Akbari**, Medical Student, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: AkbariF891@mums.ac.ir
 - 8- **Mohammad Sadegh Basir**, Medical Student, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: BasirMS841@mums.ac.ir
 - 9- **Vahid Ghavami Ghanbar Abadi**, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +98511 8829262. E-mail: GhavamiGhV1@mums.ac.ir
 - 10- **Ahmad Amouzesi**, MD, Department of Cardiac Surgery, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: AmouzeshiA901@mums.ac.ir
 - 11- **Jamil Esfahanizadeh**, MD, Assistant Professor of Cardiac Surgery, Department of Cardiac Surgery, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: EsfahanizadehJ@mums.ac.ir
 - 12- **Mostafa Mirshapanah**, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: MirSHM861@mums.ac.ir
 - 13- **Seyed Hamid Reza HoseiniKhah Manshadi**, MD, Department of Cardiac Surgery, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985118525311. E-mail: HoseiniKhahHR881@mums.ac.ir
 - 14- **Mohsen Nematy***, MD, PGDip., PhD. Associate Professor, Department of Nutrition, Biochemistry and Nutrition, Endoscopic & Minimally Invasive Surgery, and Cancer Research Centers, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
- *Corresponding author: Mohsen Nematy

Abstract: Background: Malnutrition is a considerable problem after major surgeries in hospitalized patients. Moreover, increasing prevalence of cardiovascular diseases leads to an augmentation in number of cardiovascular surgeries. Ghrelin is an appetite-stimulating hormone that can prevent malnutrition. This study aimed to evaluate ghrelin levels in coronary artery bypass graft patients in two methods, on- and off-pump. **Method:** In this prospective cohort study, 40 patients who underwent off- and on-pump operation were designated during September 2011 through March 2012 at Imam Reza hospital, Mashhad, Iran. Written informed consents were obtained from patients before entering the study. Patients with HIV, HCV, HBS, malignancy, and weight loss of >50% in last three months were excluded. Nutritional status and ghrelin level were evaluated for three times: (0, 5th and 40th day after surgery). SPSS 11.5 software was used for data analysis by t-test and Mann-Whitney test. **Results:** Thirty-four patients were divided into two groups: off-pump (17 patients, mean age 64±1) and on-pump (17 patients, mean age 65±2). Mean value for ghrelin after 40 days was 62.00 (pmol/dl) and 44.00 (pmol/dl) in off and on-pump groups, respectively, with no significant difference (p>0.05). **Conclusions:** Ghrelin levels were not remarkably changed in off and on-pump methods after the surgery.

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Introduction

Malnutrition is a major and unrecognized problem in hospitalized patients (1) and it happens in all major surgeries (2). Nutritional status of patients after surgery plays a significant role (3) in morbidity and mortality of the patients and malnutrition causes higher rates of infection in sites such as sternum, sepsis, and wound infection and also increases respiratory problems (3). Ghrelin hormone is a newly discovered appetizer peptide (orexigenic) (4) which is produced by endocrine cells of gastric oxyntic glands and has a significant role in appetite stimulation (5-7).

Researches have shown that while fasting, ghrelin levels have the highest level in the blood circulation, and during one hour after eating, its level decreases in the blood which may be involved in the desire to start eating (8-9). Just before each meal, this hormone is at its peak; after the meal, its level decreases in the blood, which demonstrates its effectiveness in starting to eat and continuing it (10). Other studies in which patients continued with a meal showed that the hormone decreases after the test meal (11). Some studies with subcutaneous prescription of the ghrelin hormone to healthy people indicated that the hormone can increase appetite and as a result, it causes an increase in food intake for 24 hours (8).

Ghrelin is an important and potential environmental-stimulator signal for the brain to start eating (12). Ghrelin stimulates growth hormone release from anterior pituitary gland (13-14) and stimulates the hypothalamus-pituitary-adrenal joint and increases movements of the stomach (11).

Ghrelin and one form of this hormone ([125I-His9]-ghrelin) are distributed extensively in the cardiovascular system (15-16). [125I-His9]-ghrelin is discovered to be increased in cardiovascular diseases such as atherosclerosis (15), although it is shown to inhibit adverse outcomes after atherosclerosis (17) and may improve heart function in patients with chronic heart failure (18). In addition, ghrelin has a positive inotropic effect on the heart and can cause cardiac vasodilatation (19-22). Plasma concentrations of ghrelin are inversely associated with body weight and when losing weight, ghrelin levels are elevated (8). This hormone is suppressed in obese patients (23) with feedback mechanism to reduce weight (24).

Effects of increased appetite and food intake by ghrelin made the clinicians to prescribe this hormone to patients with cachexia due to cancer and chronic renal failure (25-26). This hormone has a protective role against cancer by regulating some processes that occur in cancer such as cell proliferation, apoptosis, inflammation, and oxidative stress (27-28). The

hormone increases energy intake and appetite besides regulating energy expenditure (7, 12, 20, 29-30).

Studies of executive in hospitalized patients in the years 2003-2007 showed that long-term hospitalized patients in the ICU had decreased levels of ghrelin which changed to close to normal levels at the end of their hospital stay (31).

Measurement of hormone levels showed similar results in patients with femoral head fractures who were hospitalized for one month (32). In one study on patients with coronary artery surgery, suppression resonance of the hormone after surgery compared with before surgery and the control group showed its role in reducing appetite and food intake at hospitalized patients with acute illnesses (33).

Considering the recently discovered hormone ghrelin (4) which stimulates appetite and eating (5), few studies have been conducted worldwide about it (32, 34). It is noteworthy to mention that the modern practice of cardiac surgery was established by Gibbon (35) in 1953 using cardiopulmonary bypass, and coronary artery bypass without using cardiopulmonary pump by Kelessov in 1966 (36). Since then, numerous articles have been written about advantages and disadvantages of the two methods; but so far, none of them has been proved to be the best method for coronary artery bypass (37-39). In the pump method, careful anastomosis may be more difficult due to bleeding and high mobility due to heart beat.

Yet, to the best of our knowledge, no study has been done regarding the effects of on-pump CABG on the level of ghrelin hormone compared with off-pump CABG and other cardiac surgeries method worldwide (34) and our work is the first study in this field.

According to the increasing prevalence of cardiovascular diseases in recent years followed by an increase in cardiac surgeries and their diversity due to recent technological developments (40-41), the current study was designed to investigate nutritional status of patients who underwent CABG surgery regarding ghrelin hormone levels (stimulating appetite hormone) and find out how differently CABG affects this hormone level with or without cardiopulmonary pump.

Off-pump and on-pump CABG have their own advantages and disadvantages (42) and so far, there is no study investigating the pumping effects on the ghrelin hormone levels. Obviously, if each of the above methods leads to less suppression of the hormone after the surgery, it can be assumed as the preferred method in bypass surgery because of prevention from malnutrition after surgery. Moreover, the method that has less effect on ghrelin is introduced as the preferred method in the cardiovascular surgery due to beneficial effects of ghrelin on coronary artery

(34). This study deals with comparing levels of ghrelin hormone in patients who underwent CABG surgery using two methods, with or without cardiopulmonary pump.

Material and Methods

In this cohort prospective study, 35-85 year-old patients in cardiac clinic of Imam Reza Hospital, Mashhad, Iran, who underwent elective off-pump or on-pump CABG, were studied from September, 2011 to March, 2011.

Hierarchical random sampling was used in this study. Among patients who were undergoing on-pump or off-pump CABG surgery, two were randomly selected for each group until reaching the calculated sample size ($n = 20$ per group).

Since there is no study in this field, totally 40 people were selected with attention to inclusion and exclusion criteria.

In this study, variables such as age, sex, BMI, arm circumference, ghrelin levels, and type of surgery were compared.

Venipuncture was performed, and the blood was collected into tubes containing ethylenediamine-tetraacetic acid (EDTA). The samples were centrifuged and stored at -20°C until assay. The concentrations of human ghrelin were measured using enzyme-linked immunoassays (Millipore-USA).

The sensitivity of the assay was 100 pg/ml. The inter- and intra-assay coefficients of variation were 6.28% and 0.9%, respectively.

All surgeries were performed by one surgeon and all experiments were done by a clinical pathologist. At the end of every blood test, quality control test was performed for the normal range and higher than normal data. In the case of any disruption in the quality control results based on Westsgard laws, eliminating defects, the experiment was repeated.

Data collection form was used to record information in which demographic, anthropometric, and laboratory findings were recorded (to attend in the exclusion criteria or not). Moreover, accuracy of data collection form was approved by the experts. In this study, the people who underwent on-pump surgery were called encountered group and those who underwent off-pump were called non-encountered group. Nutritional status was followed up in both groups for 40 days at days 0 (just before the surgery), 5, and 40 and blood samples were used to measure ghrelin hormone using Eliza method.

During the study period, four patients were excluded from the study due to incomplete assessment, one patient due to death, and one patient due to lack of good physical condition.

In this study, patients aged 35 to 85 years who required elective coronary surgery and patients with heart failure and stroke were enrolled. People with

known HIV, HCV, and HBS, patients who were undergoing emergency surgery or involvement of the 3VD LAD, patients who underwent longer than standard average coronary bypass surgery, patients with malignancy anywhere in the body, patients with more than 50% weight loss in the last three months, and patients with peptic ulcer were also excluded.

Mashhad University of Medical Sciences Research Ethics Council approved the project and the consent was freely and knowingly filled by the subjects.

SPSS 11.5 software was used for data analysis and variables were described by indices, charts, and tables. In the analysis, normalization of quantitative variables was determined by the Kolmogorov-Smirnov test. T-test or equally non-parametric test was used for the interval scaled variables, and otherwise Mann-Whitney was used for comparison. For all test, p-value less than 0.05 was considered significant.

Results

Thirty-four patients who underwent CABG surgery completed the study (mean \pm SD Age: 65.03 ± 9.2 , mean \pm SD BMI: 26.07 ± 4.4). There were no significant differences in ghrelin levels between any of the 3-point study (Day 0, day 5, and day 40) between the off-pump and on-pump groups. However, after 40 days of surgery, increased ghrelin levels and BMI reduction occurred in both groups.

During tracking the 40-day period, in patients who underwent on-pump, a 0.38 percent and in patients who underwent off-pump a 2.5% reduction in BMI was observed. However, this difference was not significant at the 0.05 level. (P-value=0.096). On the other hand, in patients who underwent on-pump and off-pump, 22% and 28% increase in ghrelin hormone levels occurred, respectively. There were no meaningful relationship between ghrelin levels and BMI reduction (p-value = 0.293).

Discussion

In the current study, our main aim was to measure ghrelin levels in patients who underwent coronary artery bypass graft surgery (CABG) at day 0 (before surgery), day 5, and day 40 in order to introduce one of the off-pump and on-pump CABG as the preferred method. Our results showed that there was no significant difference between the off-pump and on-pump groups in the level of ghrelin hormone.

In addition, after 40 days of follow-up, there was an increase in the measured level of ghrelin and a reduction in body mass index (BMI) as mentioned in Table 1. Further studies revealed no significant relationship between ghrelin levels and BMI reduction (p-value=0.293).

There is scant information regarding the effect of ghrelin on malnutrition following major surgeries (43). However, there were some researches attempting

to find a role for this recently discovered hormone on nutritional status (8, 27-28, 43-44). For example, measuring the amount of ghrelin was the main purpose of some studies after gastric bypass. This surgery limits the secretion of ghrelin by preventing nutrients to contact with cells which produce this hormone (8). It also leads to weight loss by inhibiting ghrelin levels to increase before meals (44). These findings are not consistent with our results which indicated that there is no significant relationship between ghrelin levels and BMI. Although, another study performed on patients with cancer-related cachexia, demonstrated that plasma ghrelin level is in a negative relationship with BMI (27). So far, there is not any definite association between ghrelin levels and BMI.

In this cohort prospective study, the process of collecting data was accurately performed. At each stage, the measurements were compared with the standard tests and confirmed by specialists. Measuring ghrelin hormone with Eliza method was time-consuming and costly, so the selected sample size was restricted. However, a larger sample size would result in more reliable and consistent data.

This research was conducted to investigate the effect of total plasma ghrelin but not the acylated form. There is a linear relationship between these two forms, however measuring the acylated form of ghrelin might have changed our results. The role of peptide YY (PYY) on the outcomes was not considered in the present study and this was one of the limitations of this work. PYY is a gastrointestinal peptide which decreases appetite and food intake (45-47) and has impacts on the cardiovascular system (48).

In summary, we have not found any role for ghrelin in improving patients' nutritional status after off-pump and on-pump CABG. Because of some experimental limitations and also lack of

understanding the whole effect of this hormone, we suggest measuring the impact of acylated ghrelin and PYY on CABG surgery in order to obtain more reliable results in future works. Considering ghrelin hormone in other major surgeries could be beneficial as well. On the other hand, taking into account other hormones in favor of achieving more accurate outcomes might be a useful way.

Conclusions

According to the results of this study, the effects of the two methods, off-pump and on-pump, is not significantly different in the rate of ghrelin hormone level after the CABG surgery, and considering ghrelin hormone as a stimulant appetite, there is no preference for one of the two methods in giving nutritional advices to people at risk of malnutrition.

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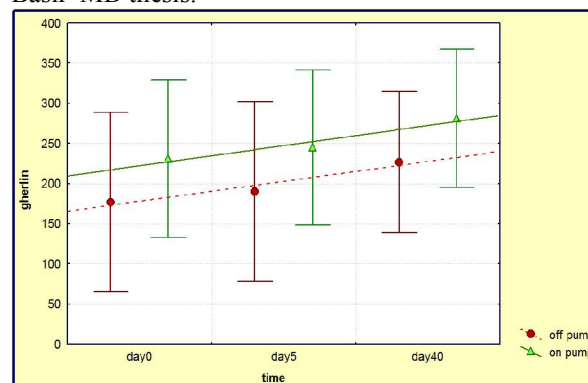


Figure 1: Comparison of ghrelin level between on-pump and off-pump CABG patients at days 0, 5, and 40.

Table 1: Comparison of on-pump and off-pump CABG patients' characteristics.

	Off-pump group (n=17)	On-pump group (n=17)	p-value
Age (year)	64.41±4.4	65.69±2.8	NS
Gender (male/female)	(10/7)	(10/7)	NS
Ghrelin level (pmol/dl)			NS
(day 0)	176.94	230.94	NS
(day 5)	190.06	244.71	NS
(day 40)	226.65	281.18	NS
BMI (kg/m ²)			NS
(day 0)	26.0±4.3	24.6±3.2	NS
(day 5)	26.0±4.4	25.0±3.2	NS
(day 40)	25.4±4.1	24.5±2.9	NS
Ghrelin level changes (pmol/dl)			NS
(day 0-5)	13.1 (1.4)	13.7 (2.1)	NS
(day 0-40)	49.7 (14.7)	50.2 (10.9)	NS

Mailing address of corresponding author:

Mohsen Nematy
 Department of Nutrition, School of Medicine,
 Biochemistry and Nutrition, Endoscopic & Minimally
 Invasive Surgery, and Cancer Research Centers,
 Mashhad University of Medical Sciences (MUMS),
 Paradise Daneshgah, Azadi Square, Post code 91779-
 48564, Po BOX: 91775 – 379, Mashhad, Iran
 E-mail: NematyM@mums.ac.ir. Tel: +98 (511)
 8002103 (direct), 8002107 & 8827033 (secretary)
 Fax: +98 (511) 8002421 & 8002422

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