Comparative Study between Traditional Fasting versus Overnight Infusion of Lipid or Carbohydrate on Serum Insulin Level and Random Blood Sugar in Obese Patients Undergoing Elective On-Pump Coronary Artery Bypass Grafting

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Abstract

Introduction: Post-operative insulin resistance represents a metabolic disorder. We compared the effects of pre-operative fasting with pre-operative infusion of lipid emulsion or carbohydrate on insulin resistance, insulin level and random blood sugar.

Methodology: In this study, 63 patients subjected to coronary artery bypass grafting surgeries were randomized using closed envelope technique into three equal groups:

• Group (IG) (N=21): Patients will receive 500cc of glucose 10% that contains 50g of glucose and provides patients with 200Kcal with 556mosmoles/L.

• Group (IIS) (N=21): Patients will receive 100cc of SMOF-lipid FRESENIUS KABI (soybean 30%, medium chain triglycerides 30%, olive oil 25%, fish oil 15% and 20mg Vitamin E) that contains 20g lipid and provides patients with 200Kcal with osmolarity of 380mosmoles/L.

• Group (IIIC) (N=21): Patients will be fasting overnight from 11pm till 9am except for clear fluids that will be allowed till 5am.

The outcomes that were investigated are serum insulin level and random blood sugar.

Results: For obese patients who undergone coronary artery bypass grafting surgeries pre-operative infusion of lipid emulsion enriched with medium chain triglycerides and fish oil resulted in reduction in levels of serum insulin and random blood sugar, when compared with traditional fasting and pre-operative carbohydrate infusion.

Conclusion: Pre-operative infusion of lipid emulsion enriched with medium chain triglycerides and fish oil reduces the levels of TG and VLDL.

Key Words: Lipid emulsion – Fasting – Carbohydrate – Insulin level – Random blood sugar.

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Introduction

THE adverse metabolic effects of pre-operative fasting have been studied comprehensively. In brief, fasting depletes liver glycogen reserves, increases whole-body protein catabolism, elevates plasma fatty acids concentrations, and increases resting energy expenditure [1]. Although insulin level often increases, blood glucose also increases due to the development of insulin resistance. Conventional pre-operative fasting time may aggravate insulin resistance and cause hyperglycemia, especially if it lasts longer than the expected 6-8 hours as it may reach as long as 10-16 hours [2].

Metabolic response to surgery and trauma involves an increased metabolic rate and a state of hypermetabolism. Thus, substrate oxidation markedly increases, resulting in an accelerated catabolic situation characterized by a net breakdown of glycogen, fat and protein. The effect of insulin on its receptors is affected leading to decreased cellular glucose uptake with post-operative hyperglycemia. Insulin resistance occurs both in the liver and in extrahepatic tissues mainly muscles. Endogenous glucose production is increased and the uptake of glucose in the periphery is reduced [3].

In adipose tissue, insulin resistance increases lipolysis which increases free fatty acid flux with further aggravation of hepatic and extrahepatic insulin resistance through altering the insulin signaling pathway. The reduction of this accelerated lipolysis is a target for the treatment of insulin resistance. After all, the overnight high free fatty acids are subject to beta oxidation which is a powerful stimulus to hepatic gluconeogenesis that may again lead to insulin resistance [4].
Medium Chain Triglycerides (MCTs) are saturated fats with 8-10 carbon atoms. For oxidation in the mitochondria they do not need Carnitine Palmitoyltransferase 1 (CPT 1) enzyme to facilitate their entry. Therefore they can be of beneficial effect in patients with insulin resistance who have a defect in the carnitine shuttle system. While MCTs were found to reduce insulin resistance in humans, other studies on the contrary demonstrated no effect of MCTs on insulin concentration or blood glucose. Fish oil was found to prevent the decline in Glucose Transporter 4 (GLUT 4) which is the transporter of glucose to the skeletal muscles and the same study suggested that fish oil activates the AMP kinase with its consequences on blood glucose homeostasis.

The aim of this study is to compare the effects of overnight infusion of lipid or carbohydrate solution and the conventional overnight fasting on free fatty acids and insulin levels in obese patients undergoing elective first time on-pump CABG to detect the ideal macronutrient which could be given for these patients to change their state from the fasting to the fed state.

**Patients and Methods**

This prospective, double blinded randomized clinical trial, study was conducted in the Department of Anaesthesiology at Kasr Al-Aini Hospital in the period from September 2014 to July 2016. After approval of the Hospital Ethical Committee and after obtaining a written informed consents, 63 patients of both sexes in Kasr Al-Aini Hospital undergoing elective first time on-pump CABG using Cardiopulmonary Bypass (CPB) were enrolled.

Patients were randomized using closed envelope technique into three equal groups:

- **Group (G) (N=21)**: Patients received 500cc of glucose 10% containing 50g of glucose and providing patients with 200Kcal with osmolarity of 556 mosmoles/L. Flow rate of the infusion was 62.5cc per hour.

- **Group (L) (N=21)**: Patients received 100cc of SMOFlipid FRESENIUS KABI (soybean 30%, medium chain triglycerides 30%, olive oil 25%, fish oil 15% and 20mg Vitamine E) containing 20g lipid and provides patients with 200Kcal with osmolarity of 380 mosmoles/L. Flow rate of infusion of 12.5cc per hour. Study drugs in both groups were infused over a period of 8 hours (12:00-8:00AM) and all surgeries started at 9:00 AM.

- **Group (C) (N=21)**: Patients were fasting overnight from 1am till 9am. Clear fluids (plain water, apple juice or tea without milk) were allowed till 5am according to Practice Guidelines for Pre-operative fasting: An up-dated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters.

**Inclusion criteria:**

All patients were ASA II-III with BMI 30-40 and we selected obese patients with class I through II because they are potentially subjected to the complications of post-operative insulin resistance that may represent the main pathophysiology of obesity. All patients were with functional capacities of class I or II according to the New York Heart Association (NYHA), with normal kidney and hepatic functions and undergoing elective first time Coronary Artery Bypass Grafting (CABG) using Cardiopulmonary Bypass (CPB). All patients were type IIa WHO/Fredrickson classification of primary hyperlipidaemias.

**Exclusion criteria:**

Patients with diabetes mellitus, patients on fibrates and patients type I, IIb, III, IV and V WHO/Fredrickson classification of primary hyperlipidaemias were excluded from the study. Patients with history of allergic reactions to fish, egg yolk containing foods, peanut or soy products and patients with carbohydrate or fat intolerance were also excluded.

Infusion bottles and lines were sealed with dull silver foil papers by the pharmacist who was blinded to group allocation and were given by nursing staff who were blinded to the contents of the bottles. After all, the investigator who collected the samples were blinded to the content of the bottles and group allocation.

All infusion bottles for Group (G) and (L) were prepared by a pharmacist of the intensive care of cardiothoracic Surgery Unit and were given via peripheral line.

**Nutritional plan for all patients the day before surgery:**

The day before surgery all patients received nutritional regimen that provided them with 1300Kcal for females of Group G and L and 1500 Kcal for males of the same groups, whereas patients of Group C received 1500Kcal for females and 1700Kcal for males. The nutritional regimen consisted of 50% carbohydrate (50% simple and 50% complex of low glycemic index nature) and 30% fat with 20% intake from saturated fat and unsaturated fat.
80% from unsaturated fat and the rest of the caloric intake which is 20% was in the form of animal proteins.

All patients were premedicated with 0.1mg/kg morphine sulphate IM one hour before operation. Anesthesia was induced by IV fentanyl (7-10 μg/kg), propofol (0.5-1mg/kg), pancuronium (0.1 mg/kg) was given for muscle relaxation and anesthesia was maintained with expired isoflurane 0.5%-1.5% in oxygen, mechanical ventilation was controlled to maintain PaCO$_2$ 30-35mmHg.

All patients recieved 300U/kg heparin (Heparin®; Leo Pharma, Zaventem, Belgium) before the start of CPB. Activated coagulation time (using kaolin as an activator) was kept above 450 seconds throughout the CPB period.

Cardiopulmonary bypass was instituted with a single, two-stage right atrial cannula, an ascending aortic perfusion cannula, and an ascending aortic cardioplegia cannula-vent line. Standard cardiopulmonary bypass management included membrane oxygenators, arterial line filters, nonpulsatile flows of 2.4L/min/m$^2$, mean arterial pressure >50mmHg and moderate hemodilution (he-matocrit 20% to 25%). Systemic temperature was not allowed to drift less than 35ºC.

Blood cardioplegia was prepared by mixing oxygenated blood with a crystalloid additive by use of commercially available delivery systems and was administered at 37ºC.

After the surgical procedure, heart was reperfused and the patients were separated from CPB. After removal of the aortic cannula, heparin activity was neutralized with protamine sulfate (Protamine®; Leo Pharma) at a ratio of 1-1.3mg protamine for 100U heparin. Protamine administration was further guided by activated clotting time measurements aiming at a value less than 120 seconds.

At weaning from the cardiopulmonary bypass, Inotropes, vasopressor, and volume boluses were titrated to achieve mean blood pressure of not less than 60mmHg. The central venous pressure was kept at 10-15cm water and if hypotension persisted despite volume replacement, adrenaline infusion was initiated at a rate of 0.05 μg/kg/min and adjusted to a maximum of 0.1 μg/kg/min, thereafter if hypotension persisted, noradrenaline was initiated at a rate of 0.02 μg/kg/min and adjusted according to the mean blood pressure to be not less than 60mmHg. After surgery all patients were admitted to the Intensive Care Unit.

In the ICU, if blood glucose exceeded 180mg/dl an insulin infusion of 1IU/hr was initiated and titrated till blood glucose achieved the accepted range of 80-180mg/dl. Post-operative fluid therapy consisted of lactated ringer solution and colloids as needed. Oral fluids of low caloric nature were allowed with audible intestinal sounds and three meals of low glycemic index nature were allowed in the first 48 hours.

Statistical analysis:

Categorical variables were assessed using Chi-square or Fischer's Exact Test when appropriate. The normally distributed data was presented as mean (SD) and analyzed using two-way analyses of variance with repeated measures and post hoc Dunnett test as appropriate. Conversely, data not normally distributed (tested by Kolmogorov-Smirnov test) was presented as median (range) and analyzed with the Kruskal-Wallis test as appropriate. SPSS V15.0 for Windows (SPSS, Inc., Chicago, Il, United States) was used for statistical analysis. A minimum sample size of 63 (21 per a treatment group) will be needed to demonstrate a difference in the mean insulin levels of 4mcg/ml or more between the groups, assuming a standard deviation in the data to be analyzed of 4 based on published results from an earlier study by Amr Abdelmonem [9], statistical power of 90% (error of 0.1) and an al-pha value of 0.05. We assumed that a change of such magnitude in insulin levels to be clinically significant.

Outcome parameters:

Serum insulin at the start of infusion (T1) and 1 hour before induction (T2), on admission to ICU (T3), after 24 hours of admission (T4), and 48 hours of admission by ELISA technique using Stat Fax-2100, Awareness technology INC device. Also random blood sugar was measured at T1, T2, T3, and T4.

Results

1- Demographic data:

Study population were comparable regarding their preoperative demographic characteristics (Table 1).

2- Insulin level:

Baseline insulin levels showed no significant difference among the three study groups. At T2, insulin levels were significantly lower in the L-group [3 (2.5-6) μu/ml] compared to the C-group [25.5 (12-40) μu/ml] and the G-Group [15.8 (12-38) μu/ml]. Same significant difference remained at both T3 and T4. Between C-and G-groups, T2
and T3 levels were comparable. At T4, insulin levels were significantly higher in the G-group [35.5 (19-60) µu/ml] compared to the C-group [18.5 (18-29) µu/ml]. At T5, insulin levels were comparable among the three study groups (Table 2).

3- Random blood sugar:
Baseline readings were comparable among the three study groups being; (105.7±15.4), (103.9±14.5), and (113.3±17.8) for control, glucose and lipid groups respectively (Table 3). At T2, T3 and T4 the figures in the L group decreased significantly compared to those of the other two (Table 3); Fig. (1). Blood sugar in the L group decreased significantly at T3 and T4 when compared to the baseline values of the same group Fig. (2) while, the only significance between the C group and the G group was noted only at T4 where they were lower in the C group compared to the G group.

Random blood sugar values were significantly higher in the C and the G groups at T2, T3 and T4 when compared to baseline values of the same group Fig. (2).

Table (1): Demographic characteristic (data are presented as mean ± SD and numbers).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C Group</th>
<th>G Group</th>
<th>L Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.3±9.3</td>
<td>51.7±4.0</td>
<td>48.9±9.2</td>
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<tr>
<td>Weight (Kg)</td>
<td>100.3±11.7</td>
<td>98.7±10.9</td>
<td>99.7±8.4</td>
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<tr>
<td>Height (centimeters)</td>
<td>168.2±8.2</td>
<td>166.2±2.7</td>
<td>168.9±9.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.6±2.2</td>
<td>35.6±2.3</td>
<td>35.3±2.3</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>(12/9)</td>
<td>(13/8)</td>
<td>(12/9)</td>
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Table (2): Insulin level [median (IQR)].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C Group</th>
<th>G Group</th>
<th>L Group</th>
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<tbody>
<tr>
<td>Insulin T1(μu/ml)</td>
<td>10.5 (3-18)</td>
<td>8.5 (8-23)</td>
<td>11 (9-14)</td>
</tr>
<tr>
<td>Insulin T2</td>
<td>25.5 (12-40)</td>
<td>15.8 (12-38)</td>
<td>3 (2.5-6)†</td>
</tr>
<tr>
<td>Insulin T3</td>
<td>15.5 (7-45)</td>
<td>14 (9-33)</td>
<td>4.8 (4.2-11)†</td>
</tr>
<tr>
<td>Insulin T4</td>
<td>18.5 (18-29)</td>
<td>35.5 (19-60)*</td>
<td>6 (4-16)†</td>
</tr>
<tr>
<td>Insulin T5</td>
<td>22 (17.5-26.5)</td>
<td>44 (4.5-60)</td>
<td>20 (10-25)</td>
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</tbody>
</table>

*: Denotes statistical significance compared to C group. †: Denotes statistical significance compared to G group.

Table (3): RBS (mean ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C Group</th>
<th>G Group</th>
<th>L Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBS T1 (mg/dl)</td>
<td>105.7±15.4</td>
<td>103.9±14.5</td>
<td>113.3±17.8</td>
</tr>
<tr>
<td>RBS T2</td>
<td>146.4±46.5</td>
<td>180±54.6</td>
<td>104±17.8†</td>
</tr>
<tr>
<td>RBS T3</td>
<td>227.3±66.6</td>
<td>202.4±58.6</td>
<td>91.6±11.2†</td>
</tr>
<tr>
<td>RBS T4</td>
<td>139.9±26.9</td>
<td>159.9±16.2</td>
<td>102.4±19.3†</td>
</tr>
</tbody>
</table>

*: Denotes statistical significance compared to C group. †: Denotes statistical significance compared to G group.

Discussion
In this study we demonstrated that pre-operative overnight infusion of lipid emulsion enriched with medium chain triglycerides and fish oil resulted
in significantly lower serum insulin level and random blood sugar compared to both pre-operative carbohydrate infusion and conventional pre-operative fasting.

Recently many animal studies in experimental stress showed that even brief fasting is sufficient for alteration of body metabolism from the fed to the fasting state with reduction in glycogen reserves and hence altering reactions to stress. Providing patients with macronutrients in the few hours preceding surgery is thus fundamental to simply prepare the metabolism to be anabolic rather than catabolic during the perioperative period and reduce the metabolic stress response [10].

The metabolic consequences of overnight fasting come from low insulin level and high glucagon, which are responsible for glycogenolysis, gluconeogenesis, lipolysis, and finally proteolysis. This fast milieu stands for the stress response that signifies fasting before surgeries [11].

In this study, preloading our patients with lipid emulsion resulted in significantly controlled blood sugar level as well as low insulin levels when compared with either fasting or glucose loading where the blood sugar level as well as insulin level increased significantly even when compared with base line values of the same groups.

In consistent with our findings, a randomized study in Toronto of 26 patients undergoing coronary artery bypass grafting and 12 patients having spinal surgery who received oral carbohydrate supplements in the evening and two hours before surgery showed no improvement in post-operative insulin sensitivity. The patients who received the carbohydrate supplements did, however, have lower blood glucose and higher insulin levels than the traditionally fasted patients [12]. Though different methodology concerning adding insulin to glucose preload, Lazar et al., [13] demonstrated a beneficial effect of pre-operative glucose-insulin-potassium infusion on the myocardial performance for patients undergoing urgent CABG surgeries. In addition, Nygren et al., [14] demonstrated a significant improvement in insulin sensitivity for patient's undergone total hip replacement who received glucose insulin infusion preoperatively compared to those who didn't receive the treatment.

Indeed, in 2011 the Joint British Diabetes Societies guideline on the management of adults with diabetes undergoing surgery stated:

“The Enhanced Recovery Partnership Programme recommends the administration of high carbohydrate drinks prior to surgery. This may compromise blood glucose control and is not recommended for people with insulin treated diabetes.” [15].

On the contrary, a randomized double-blind placebo controlled trial in Germany amongst 160 patients undergoing elective cardiac surgery, including 31 with non-insulin treated type 2 diabetes, reported that blood glucose levels, gastric fluid volume and insulin requirement did not differ between groups. However, patients receiving a carbohydrate load required less intra-operative inotropic support after initiation of cardio-pulmonary bypass weaning (p<0.05). This study provided no details on how well controlled the patients were or the presence of complications, but did specifically exclude patients with type 1 diabetes after initial recruitment [16].

Actually the controversy concerning the effect of carbohydrate loading can be explained by the type of patients who can receive carbohydrate load before surgery. After all, our patients who had ischemic attacks and diagnosed as coronary artery disease patients may lack metabolic flexibility which is defined by the preference for fat-oxidation during fasting and for carbohydrate in response to glucose. In truth, one of the main factors that affect metabolic flexibility and its consequences on the abnormal response to glucose intake is insulin sensitivity [17].

The abnormal response to insulin was evident in our study through patients in the carbohydrate group who received glucose and their insulin was increased and yet, their blood glucose increased as well. Even though, traditional fasting did show an abnormal response to insulin thanks to the increase in the free fatty acids release from adipocytes and interestingly a long time ago it was stated that hyperinsulinemia increases lactate production through glycolysis by conversion of pyruvate by lactate dehydrogenase in virtually all human tissues, both through anaerobic as well as aerobic conditions and this lactate is a precursor of glucose [18].

In the current study, there was no rise in the blood glucose and insulin as well in our patients who received the lipid emulsion. Turner et al., [19], Han et al., [8] and Eckel et al., [20] have demonstrated the role of medium chain triglycerides in increasing insulin sensitivity. Furthermore, fish oil was found to prevent the decline in GLUT 4 which is the transporter of glucose to the skeletal muscles and same study suggested the role of fish oil in
activating the AMP kinase with its consequences on blood glucose homeostasis [21].

In addition, we could relate our results to the effects of lipid emulsion containing medium chain triglycerides to direct beta oxidation in the mitochondria without overloading the blood with free fatty acid that could represent a burden on the beta cells of pancreas that induce gluconeogenesis and overload the circulation with glucose [22].

Conclusion:
Obese patients who underwent coronary artery bypass grafting surgeries, comparing conventional fasting, preoperative carbohydrate infusion, and pre-operative infusion of lipid emulsion enriched with medium chain triglycerides and fish oil, had controlled levels of blood sugar at lower insulin levels that was in favor of the use of lipid emulsion as pre-operative macronutrient load.

References
8- Practice guidelines for pre-operative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: Application to healthy patients un-d ergoing elective procedures: An updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology. Mar., 114 (3): 495-511, 2011.
دراسة مقارنة بين الصيام التقليدي مقابل تسريب طوال الليل من الدهون أو الكريوهيدرات على مستوى الأنسولين والسكر الشهري في الدم في مرئي السمنة الذين يخضعون لعملية تغيير شرايين القلب للمرة الأولى على مضخة الشريان التاجي

لقد تم دراسة الآثار السلبية الناتجة عن الصيام قبل الجراحة بشكل كامل، والاختيار، وجد أن الصيام يؤدي إلى استنزاف احتياطيات الجليكوغين في الكبد، وزيادة هرم البروتين بالجسم، وارتفاع تركيزات آسيل كر آ A-1 الدهنية.

وقد أثبت أن استجابة عمليات التمثيل الغذائي للجراحة وغيرها من الصدمات تتم على زيادة معدل الأرض. وعلى الرغم من أن كثير من الأحيان يتم زيادة مستويات الأنسولين، وزيادة مستويات السكر في الدم أيضًا نتيجة زيادة مقدار الأنسولين. أيضا، الصيام التقليدي قبل الجراحة قد تزيد مقدار الأنسولين وتسبب ارتفاع السكر في الدم، وخاصة لأنه في كثير من الأحيان يطول وقت الصيام عن 6-8 ساعات المفتوحة.

وقد يكون ما 21-16 ساعة.

بعد الجراحة، يتغير مفعول الأنسولين على مستقبلاته بما يؤدي إلى انخفاض امتصاص الجلوكوز من قبل الخلايا. ومن هنا جاءت النتيجة النهائية التي ستكون ارتفاع السكر في الدم بعد العمليات الجراحية. وتحدد مقدار الأنسولين في كل من الكبد والأنسجة خارج الكبد والأنسجة في العضلات.

كمسح للجزء الأول من فصل مسماً الكبد والأنسولين تحمل إمكانية التنقل من أنيونين أميد (AMP) بروتين kinase، الذي من شأنه أن يؤدي إلى ضعف في معالجة الكريوهيدرات خاصة إذا تعرض لضغط إضافي من مضخة الشريان التاجي.

ومع ذلك، اعتمد الكريوهيدرات مسبقاً في المريض مع تفاعل الأنسولين تجلب إمكانية التنقل من أنيونين أميد (AMP) بروتين kinase، الذي من شأنه أن يؤدي إلى ضعف في معالجة الكريوهيدرات خاصة إذا تعرض لضغط إضافي من مضخة الشريان التاجي.

فإن موجود للعديد من الكريوهيدرات، وهو ليس في حاجة للكريوهيدرات، وبالتالي (CPT) للدخول إلى الميتوكوندريا للأكسدة. وبالتالي، فإن إمكانية التنقل في مسار الذي يعني من مصنع الدهون الذي لديه خلايا النظام الكاربئي، ووجدت بعض الدراسات أنه يمكن أن يكون من مصنع الدهون في الإنسان، على الجانب الآخر أظهرت دراسات أخرى عدم وجود أي تأثير على تركيز الأنسولين أو الجلوكوز في الدم. في حين تم العثور على أن زيادة السمك يمكن أن يؤدي إلى ارتفاع في ناقل الجلوكوز إلى العضلات.