Comparative Study between Traditional Fasting versus Overnight Infusion of Lipid or Carbohydrate on Fatty Acyl Co-A and Insulin in Obese Patients undergoing Elective First Time On-pump Coronary Artery Bypass Grafting

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Abstract

This is study to dysfunction of skeletal muscle mitochondria and development of oxidative stress. Insulin resistance occurs both in the liver and in extrahepatic tissues mainly muscle. Endogenous glucose production is increased and the uptake of glucose in the periphery is reduced Insulin resistance is the central feature of the endocrine response to surgical tissue trauma triggering metabolic changes known as the catabolic response to surgery that can be manifested as muscle protein loss and sodium and water retention, with suppression of anabolic hormone that can end up with hypoalbuminaemia, pulmonary congestion, hyperglycemia and delayed wound healing with consequent prolonged postoperative hospital stay Insulin resistance in adipose tissue leads to increased lipolysis which increase free fatty acid flux which further aggravates insulin resistance in liver and muscle through generation of metabolites, altering the insulin signaling pathway. In truth, reducing accelerated lipolysis is a target for the treatment of insulin resistance. After all, the overnight high free fatty acids are candidates for beta oxidation that is a powerful stimulus to hepatic gluconeogenesis which may lead to insulin resistance The reduced insulin sensitivity can be reflected on skeletal muscles and adipose tissue and can lead to decreased utilization of the high glucose level in the blood with hyperglycemia as an end result .

Keywords

EMP-MCT- ACTH- DHA-Carbohydrat

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AMP	Adenosine monophosphate
MCT	Medium chain triglycerides
CPT	Carnitine palmitoyltransferase
GLUT	Glucose transporter
ACTH	Adrenocorticotrophic hormone
GH	Growth hormone
TSH	Thyroid stimulating hormone
LH	Luteinizing hormone
FSH	Follicle stimulating hormone
CRF	Corticotrophin releasing factor
IGF	Insulin-like growth factors
FFA	Free fatty acids
CHO	Carbohydrate
GLN	Glutamine
PDC	Pyruvate dehydrogenase complex
ATP	Adenosine triphosphate
PDK	Pyruvate dehydrogenase kinases
mRNA	messenger RNA
CRP	C-reactive protein
IL	Interleukin
PONV	Postoperative nausea and vomiting
TPN	Total parenteral nutrition
MCFA	Medium chain fatty acid
MCT	Medium chain triacylglycerides
LCFA	Long chain fatty acid
LCT	Long chain triacylglycerides

MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
SRBP	Sterol regulatory element-binding proteins
PPAR	Peroxisome proliferator-activated receptor
AA	Arachidonic acid
LTB	Leukotriene B
RQ	Respiratory quotient
TCA	Tricarboxylic acid
G6P	Glucose-6- phosphate
VLDL	Very low density lipoproteins
BMI	Body mass index
ACC	Acetyl CoA carboxylase
CABG	Coronary artery bypass grafting
GLUT	Glucose transporter
TG	Triglycerides

Introduction

The adverse metabolic effects of preoperative fasting have been studied comprehensively. In brief, fasting results in depletion of liver glycogen reserves, increased whole-body protein catabolism, elevation of plasma fatty acyl Co-A concentrations and increased resting energy expenditure [(1)].

Metabolic response to surgery and other trauma involves an increased metabolic rate and a state of hypermetabolism. Thus, substrate oxidation is markedly increased, resulting in an accelerated catabolic situation characterized by a net breakdown of glycogen, fat and protein. Although insulin levels are often increased, blood glucose levels also increase due to the development of insulin resistance. Conventional preoperative fasting time may aggravate insulin resistance and cause hyperglycemia, especially because it is frequently longer than the expected 6-8 hours and may be as long as 10-16 hours [(2)].

Following surgery, the effect of insulin on its receptors is affected leading to decreased glucose uptake by cells. Hence the end result will be postoperative hyperglycemia. This is due to dysfunction of skeletal muscle mitochondria and development of oxidative stress. Insulin resistance occurs both in the liver and in extrahepatic tissues mainly muscle. Endogenous glucose production is increased and the uptake of glucose in the periphery is reduced [(3)].

Insulin resistance is the central feature of the endocrine response to surgical tissue trauma triggering metabolic changes known as the catabolic response to surgery that can be manifested as muscle protein loss and sodium and water retention, with suppression of anabolic hormone that can end up with hypoalbuminaemia, pulmonary congestion, hyperglycemia and delayed wound healing with consequent prolonged postoperative hospital stay [(4)].

Insulin resistance in adipose tissue leads to increased lipolysis which increase free fatty acid flux which further aggravates insulin resistance in liver and muscle through generation of metabolites, altering the insulin signaling pathway. In truth, reducing accelerated lipolysis is a target for the treatment of insulin resistance. After all, the overnight high free fatty acids are candidates for beta oxidation that is a powerful stimulus to hepatic gluconeogenesis which may lead to insulin resistance [(5)].

There are many methods to detect insulin resistance. Using fasting insulin and glucose levels serves as measures of insulin sensitivity and secretion [6].

The reduced insulin sensitivity can be reflected on skeletal muscles and adipose tissue and can lead to decreased utilization of the high glucose level in the blood with hyperglycemia as an end result [7].

Nonetheless, carbohydrate preloading in patient with insulin resistance carries the possibility of the dysfunction of Adenosine monophosphate (AMP) protein kinase that would lead to impaired handling of carbohydrate especially if they were subjected to additional stress of cardiopulmonary bypass [8].

Medium chain triglycerides (MCTs) are saturated fats with 8-10 carbon atoms. It does not need carnitine palmitoyltransferase 1(CPT 1) enzyme to get entry into mitochondria for oxidation. Therefore it can be of beneficial effect in patients with insulin resistance who have a defect in the carnitine shuttle system. Some studies found that it reduces insulin resistance in humans [9]. On the opposite side other studies demonstrated no effect of MCTs on insulin concentration or blood glucose [10]. Whereas, 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 same study suggested the role of fish oil in activating the AMP kinase with its consequences on blood glucose homeostasis [11].

It was stated previously that for patients with metabolic syndrome, preoperative infusion of lipid emulsion enriched with medium chain triglycerides and fish oil resulted in reduction of postoperative insulin level with normal blood glucose and triglycerides compared to preoperative infusion of carbohydrates [12].

Endocrinal and metabolic consequences of surgery

The stress response is the neuroendocrine, metabolic and inflammatory changes which occur after surgery or trauma. This results in substrate mobilization, muscle protein loss, salt and water retention, with decreased anabolic hormone secretion. There is activation of the sympathetic nervous system, immunological and hematological changes. Generally, the magnitude of the metabolic response is proportional to the severity of the surgical trauma. These changes are useful to aid survival of the patient by mobilizing substrates, limiting tissue damage, destroying infectious organisms and activating repair processes. Psychological and behavioural changes may accompany the physiological events [13].

Table 1 [4]
Changes occurring during the stress response

Physiological	• Hormonal • Metabolic • Immunological • Haematological
Psychological	• Malaise (fatigue)
Behavioural	• Reluctance to move

- **Endocrinal changes :**

The hypothalamic–pituitary axis and the sympathetic nervous system are activated by somatic and autonomic afferent nerve input from the area of trauma or injury. There is a failure of the normal feedback mechanisms which control hormone secretion. [4]

i. Pituitary gland:

a. ACTH

The anterior pituitary gland is controlled by hypothalamic releasing or inhibiting factors, which are secreted from the hypothalamus into the hypothalamic–hypophyseal portal circulation. The hypothalamus has direct neural control of the posterior pituitary gland. The secretion of the anterior pituitary hormones { ACTH and GH } is stimulated by hypothalamic releasing factors, corticotrophin releasing factor (CRF) and somatotrophin respectively . Increased vasopressin (antidiuretic hormone) release from the posterior pituitary, in addition to CRF, stimulates the production of ACTH and b-endorphin from the anterior pituitary. The net result is increase in the level of ACTH which stimulates cortisol production within a few minutes of the start of surgery. The production of ACTH is far in excess of that required to produce a maximum adrenocortical response [14].

b. Growth hormone:

Growth hormone has mixed catabolic and anabolic effects but increased secretion after surgery has only a minor physiological role and its diabetogenic effects are not thought to be important in the perioperative period. GH promotes glycogenolysis and lipolysis while glucose uptake and utilization by cells are inhibited. However, it may have a more important role in preventing muscle protein breakdown and promoting tissue repair. This is achieved by increasing the production of

polypeptides in the liver, which are known as somatomedins or insulin-like growth factors (IGFs). The main one is somatomedin C (or IGF-1), which reduces protein catabolism. There has been considerable interest in the potential role of recombinant growth hormone or IGFs in improving wound healing, but evidence is inconclusive [15].

c. b-Endorphin and prolactin:

b-Endorphin is a peptide produced from anterior pituitary and increased concentrations during surgery reflect its stimulation, while prolactin has a major role during pregnancy and lactation. The secretion of prolactin is under inhibitory control via prolactin release inhibitory factor and the perioperative increased prolactin secretion occurs by release of this inhibitory control. The physiological effects of increased secretion of both hormones during surgery are unknown, but they may alter immune function [16].

d. Vasopressin:

The production of this hormone from the posterior pituitary is increased during surgery. It has an anti-diuretic effect. It is also an important vasopressor and enhances haemostasis. ACTH release is enhanced by vasopressin [16].

e. TSH, LH and FSH :

The secretion of other hormones, thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH) does not change significantly. The importance of the changes in gonadotrophin production and testosterone after surgery is uncertain. Testosterone concentrations are decreased for several days as are oestrogen values in females [17].

ii. Adrenal :

a. Catecholamines

Catecholamines are released from the adrenal medulla in response to hypothalamic stimulation. The secretion of catecholamines is increased during stress and surgery which results in marked activation of the sympathetic nervous system. This is the cause of tachycardia and hypertension which may occur in stress and surgery [18].

b. Cortisol:

The normal baseline value of cortisol is 400 nmol/ litre , which can increase to >1500 nmol/ litre within 4–6 h of the start of major surgery. The normal negative feedback mechanism fails to occur and concentrations of ACTH and cortisol remain persistently high. The magnitude and duration of the increase correlate well with the severity of the insult and the response is not abolished by the administration of corticosteroids. The metabolic effects of cortisol are enhanced with skeletal muscle protein breakdown to provide gluconeogenic precursors and amino acids for protein synthesis in the liver, and stimulation of lipolysis. Glucose utilization is impaired, which is known as an 'anti-insulin effect' leading to further hyperglycaemia. There is also sodium and water retention and potassium loss due to its mineralocorticoid effects. Cortisol also has well recognized anti-inflammatory effects mediated by decreased levels of inflammatory mediators such as leukotrienes, cytokines and prostaglandins [19].

iii. Pancreas (Insulin and glucagon) :

Insulin is an anabolic hormone which is usually secreted in response to hyperglycaemia to enhance glucose utilization and glycogen synthesis. It also inhibits lipolysis and reduces muscle protein loss. Trauma and surgery cause inhibition of the b-cells in the pancreas by the alpha 2-adrenergic inhibitory effects of catecholamines and this leads to failure of the body to secrete insulin in response to trauma. Therefore low insulin level activates phosphorylase enzyme that enhances glycogenolysis which helps to rise up the blood sugar level and thereafter insulin secretion tends to increase in response to hyperglycaemia as long as tissue trauma is extensive with sympathetic nervous system stimulation. However, cytokine release in addition to secretion of glucocorticoids would down regulate the glucose receptors in muscle and adipose tissue and consequently insulin resistance ensues which further leads to increased blood sugar level [(20)].

iv. Thyroid hormones :

Thyroxine (T4) and tri-iodothyronine (T3) are secreted by the thyroid, in response to TSH. T3 is five times more active than T4. They are highly bound in the circulation to albumin, thyroxine-binding pre-albumin and thyroid-binding globulin. They stimulate oxygen consumption and may increase the metabolic rate and heat production. Circulating concentrations are inversely correlated with sympathetic activity and after surgery there is a reduction in thyroid hormone production, which returns to normal over a few days. Postoperatively T4 may be monodeiodinated to reverse T3 instead of T3 and this may help to reduce the overall metabolic rate [(17)].