

Module 17.2

Insulin Resistance and Glucose Control

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Learning Objectives

- Understand the mechanisms behind insulin resistance (IR) and how this may relate to recovery;
- How IR affects glucose metabolism;
- How IR can be avoided and how it should be treated;
- Insights to the relationship between hyperglycaemia and complications in surgery.

Contents

1. How insulin resistance develops
2. Metabolic and clinical outcomes from treating insulin resistance
3. Changes in glucose metabolism
4. Proactive approach to insulin resistance
5. Treating insulin resistance with insulin
6. Modern fasting guidelines

Key Messages

- The counter regulatory hormones and inflammatory response to surgery cause insulin resistance;
- Resistance to insulin develops within minutes and remains for days to weeks;
- Insulin resistance is the cause of hyperglycaemia;
- Hyperglycaemia increases complications and mortality in postoperative critically ill patients, and has been associated with prolonged length of stay in uncomplicated surgery;
- Treatment with insulin during TPN to maintain normoglycaemia also normalizes FFA levels, substrate oxidation and nitrogen losses;
- Insulin resistance can be avoided or minimized by the use of epidural anaesthesia and analgesia, minimal invasive surgery and by preoperatively preparing metabolism with carbohydrates instead of overnight fasting;
- Preoperative carbohydrate loading as opposed to overnight fasting has been shown to reduce nitrogen losses, retain lean body mass and improve muscle strength;
- If insulin resistance has developed and hyperglycaemia is present, available data suggests that insulin should be given to keep blood glucose levels between 4.5 and 6.1 mM in post operative critically ill patients;
- Modern fasting guidelines recommend patients to drink clear fluids up until 2 hours and allow solids 6 hours before anaesthesia and surgery.

1. How insulin resistance develops

Surgery and trauma initiates the release of stress hormones and cytokines (1). Catecholamines, cortisol, glucagon and growth hormone independently cause IR, and potentiate each other. Cytokines such as Interleukin 6 and TNF- α also cause insulin resistance.

IR affects all parts of metabolism and also other endocrine systems. Hyperglycemia and elevations of FFA levels are typical signs of insulin resistance. Protein breakdown increases and negative nitrogen balance is also associated with insulin resistance.

2. Metabolic and clinical outcomes from treating insulin resistance

When the effectiveness of insulin is reinstated by the use of iv insulin, these metabolic disturbances are reversed (2). More importantly, in critically ill surgical patients, this treatment was shown to reduce mortality by over 40%, due to reductions in sepsis, need of assisted ventilation, renal failure and polyneuropathy (3) (Fig. 1).

Other studies have suggested that the degree of insulin resistance is an independent factor explaining the variation in length of stay after uncomplicated surgery (1) (Fig. 2, Fig. 3).

Normalization of glucose in ICU reduces mortality & morbidity

Prospective randomized trial

1548 consecutive postop ICU patients

Target glucose 4.5-6.1 mM vs. treat >12mM

- Mortality ICU ↓ 43%
- Mortality in hospital ↓ 34%
- Bacteremia ↓ 46%
- Ventilatory support ↓ 37%
- Renal failure ↓ 41%
- Polyneuropathy ↓ 44%

Fig. 1 G van den Berghe, N Engl J Med 2001

Insulin resistance & length of stay

Retrospective analysis of LOS for 53 patients with uneventful postop course.

The relative change in insulin sensitivity relates to LOS. The absolute change had no relation to LOS

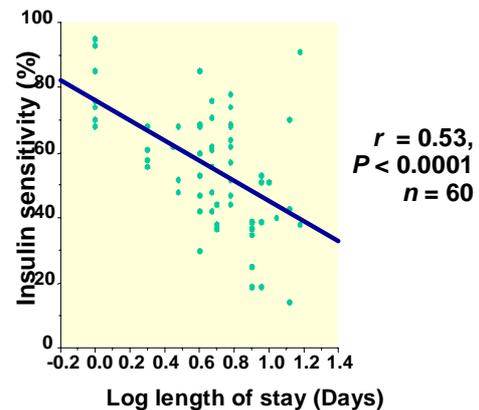


Fig. 2 Thorell et al: Curr Opin Clin Nutr Metab Care 1999

Factors predicting length of stay

- Type of surgery
- Perioperative blood loss
- Postoperative insulin resistance

$R^2 = 0.71$, $p < 0.01$,

sequential multiple regression analysis

Fig. 3

Thorell et al: Curr Opin Clin Nutr Metab Care 1999

Glucose metabolism Postoperative vs Type 2 diabetes

	Postop	Type 2 DM
Hyperglycemia	+	+
Insulin sensitivity	-	-
Glucose production	+	+
Peripheral glucose uptake	-	-
GLUT4 translocation	-	-
Glycogen formation	-	-

Fig. 4

Adopted from Ljungqvist et al, Clin Nutr 2001

Insulin sensitivity and magnitude of operation

Factors that influence postoperative insulin resistance:

- The type of surgery
- Factors that did not affect postop IR:
- Gender
- Preop insulin sensitivity

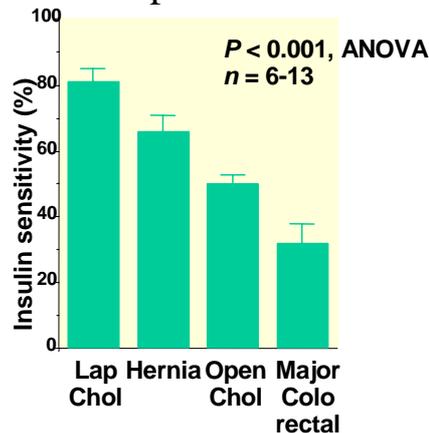


Fig. 5

Thorell et al: Curr Opin Clin Nutr Metab Care 1999

Time course of insulin resistance

Patients undergoing open cholecystectomy with uneventful postop course

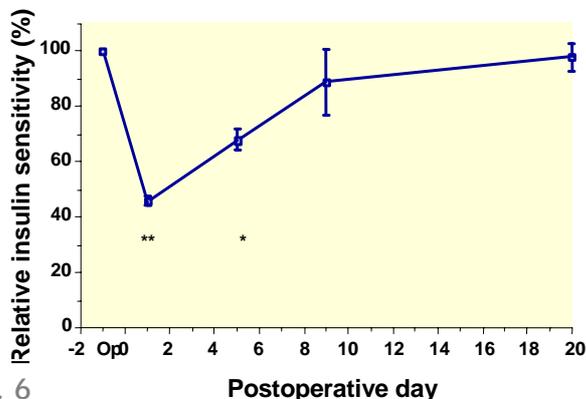


Fig. 6

Thorell et al: Curr Opin Clin Nutr Metab Care 1999

3. Changes in glucose metabolism

Within minutes of the trauma, changes in all parts of metabolism begin to occur. The overall reaction is a change to catabolism.

Hyperglycaemia develops due to a simultaneous increase in glucose production, while glucose uptake in insulin sensitive cells (mainly muscle and fat tissue) becomes resistant to the action of insulin.

In muscle, the main target tissue for insulin, this hormone has reduced capacity to stimulate specific glucose transporting proteins facilitating glucose uptake, and glycogen formation is also blocked. This change may remain for several weeks after a colorectal operation and seems associated with muscle function (4).

It is interesting to note that the changes occurring in glucose metabolism after surgery in otherwise healthy patients are very similar to those developing over years in patients with diabetes mellitus type 2 (5) (Fig. 4).

The degree of IR is related to the magnitude of the operation (1) and remains for about 2-3 weeks after uncomplicated medium size upper abdominal surgery (6) (Fig. 5, Fig. 6).

4. Proactive approach to insulin resistance

There are a few known ways to proactively minimize post-operative insulin resistance (Fig. 7). The placement and activation of a thoracic epidural before the onset of the operation has been shown to reduce postoperative IR by about 40% in abdominal surgery (7). This was associated with marked reductions of circulating catecholamine and cortisol levels. Minimal invasive surgical techniques also reduce postoperative insulin resistance markedly, probably by reducing the level of traumatic injury to the body (8) (Fig. 8).

Pain is another factor that increases insulin resistance in itself (9). This is yet another argument for the use of continuous epidural analgesia after major surgery, since this has been shown to provide better pain control than intravenous opioids (10) including PCA (11).

Finally, it has been shown that preparing metabolism for the stress of surgery by boosting insulin sensitivity using a carbohydrate load instead of remaining in the overnight fasted state results in an approximately 50% reduction in insulin resistance in a several surgical procedures and in hip replacement (12) (Fig. 9).

The latter method is by far the best studied, and has been shown to affect both of the two main driving forces behind hyperglycaemia.

Avoiding insulin resistance and hyperglycemia

- Minimal invasive surgery
- Epidural anesthesia
- Pain relief
- Metabolic preparation

Fig. 7

Insulin resistance Effect of surgical technique

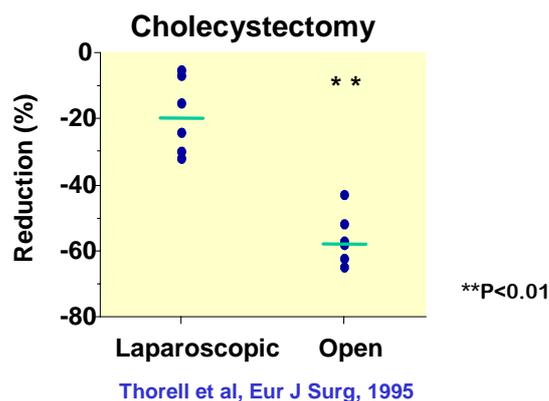


Fig. 8

Preoperative CHO reduces postop insulin resistance

Summary of 4 prospective trials of the effect of preoperative CHO loading. Left to right: iv glucose 20%, oral 12.5%, iv glucose 20% + insulin, oral 12.5% CHO drink.

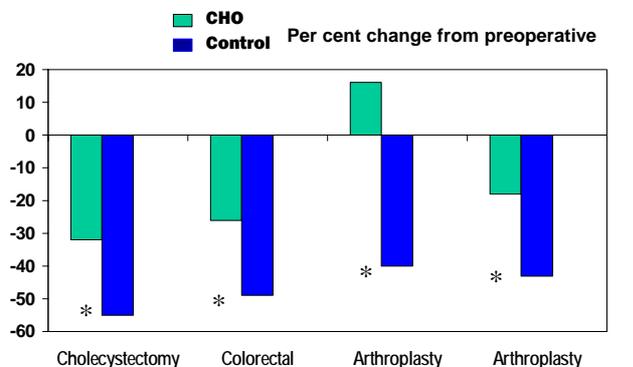


Fig. 9

Preoperative CHO + EDA maintains normoglycemia during enteral feeding

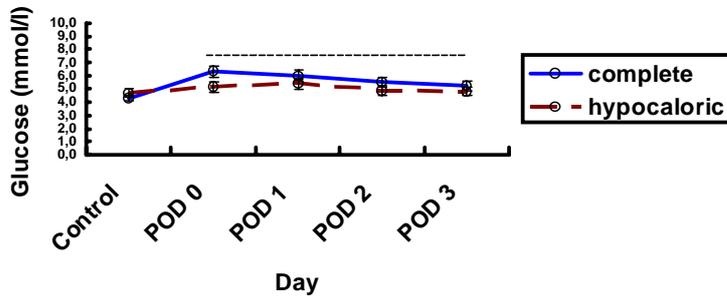


Fig. 10 Soop M et al, Br J Surg, 2004

Preoperative carbohydrates reduce glucose production and enhance glucose uptake (13). When this treatment is combined with epidural analgesia for several days after major colorectal surgery, insulin resistance can be minimized to levels seen after laparoscopic cholecystectomies.

In this situation, it is possible to provide complete enteral nutrition while glucose levels remained below 6.1 mM without any need of exogenous insulin (14) (Fig. 10).

In addition to these effects on glucose metabolism, preoperative carbohydrate treatment has been shown to affect protein metabolism and muscle function by reducing nitrogen losses (15) (Fig. 11), retaining lean body mass (16) (Fig. 12) and improving muscle strength (4) (Fig. 13).

Preoperative 20% glucose infusion and urea losses

Prospective randomized trial comparing the effects of 20% glucose infusion (5 mg/kg/min), known to increase insulin levels as after a meal, and a 5% glucose infusion (1 mg/kg/min) overnight before abdominal surgery.

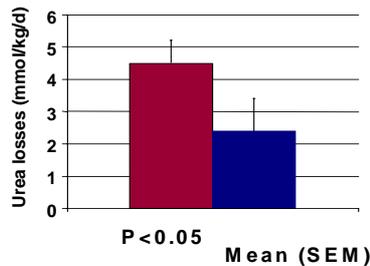


Fig. 11 Crowe Br J Surg 1984

Preoperative CHO retains lean body mass

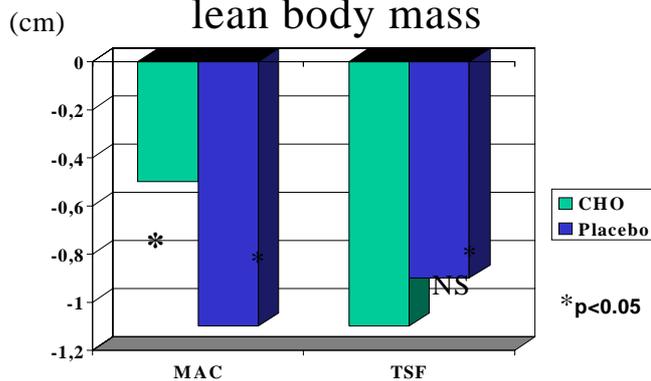


Fig. 12 Yuill et al: Clin Nutr 2005

From a nutritional point of view, the report indicating reduced PONV after laparoscopic cholecystectomies comparing preoperative oral carbohydrates to overnight fasting (18) is interesting (Fig. 14), while there was no significant difference to placebo in this or in another study of similar kind (19).

5. Treating insulin resistance with insulin

In postoperative patients with a need of ventilatory support in the ICU, tight control of blood glucose levels (4.5 - 6.1 mM) has been shown to reduce drastically complications and mortality (Fig. 15).

Further studies showed that it was the prevailing glucose level and not primarily the insulin given that had the effect. Importantly, a post hoc analysis showed that normoglycaemia (blood glucose < 6.1 mM) gave the best effect on overall outcomes including mortality.

Even glucose levels between 6.1 and 8.3 mM was associated with increased mortality and morbidity (20). This suggests that normoglycaemia should be the target glucose level for these

patients. To what extent hyperglycaemia exists in the ordinary postoperative patient, and how this may affect outcomes remains to be investigated.

Preoperative oral CHO retains quadriceps muscle function

Prospective randomized trial, comparison between patients given CHO alone or CHO and amino acids (same result) versus overnight fasted patients

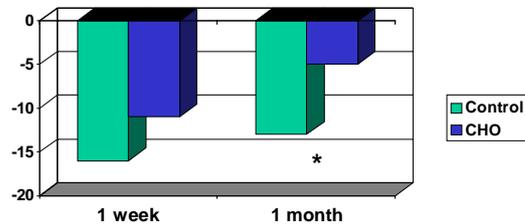


Fig. 13 Henriksen MG et al Acta Anaesth Scand 47; 191-197, 2003

Observed late (12-24h) PONV Laparoscopic cholecystectomy

	No	Yes	Totals
CHO	54	1	55
Placebo	55	4	59
Fasted	50	8	58
Totals	159	13	172

P = 0.05, Chi square, CHO vs, fasted

Fig. 14 Hausel J et al, Br J Surg 2005

Hyperglycemia & risk of ICU mortality

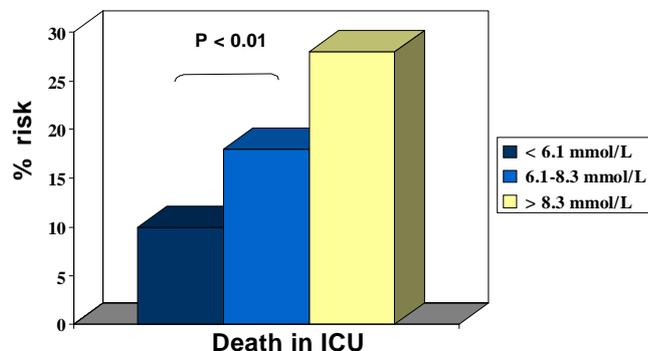


Fig. 15 G. Van den Berghe et al, Crit Care Med, 31:2, 2003

Principles of modern fasting guidelines

Elective surgery:

- Free intake of clear fluids until 2h before anesthesia
- Intake of solids until 6h before anesthesia

Exceptions:

- Patients with known GI transit delay for any reason
- Emergency surgery

Fig. 16

O Ljungqvist & E Söreide, Br J Surg, 2003

6. Modern fasting guidelines

Over the last 2 decades the traditional routine of overnight fasting before elective surgery has been questioned, challenged and proven not to provide any additional safety over allowing patients to drink freely of clear fluids up until 2 hours before elective anaesthesia and surgery (21) (Fig. 16).

In fact, many of the most common preoperative discomforts primarily thirst and to some extent headaches and hunger, can be avoided when the patient is allowed to drink in the morning

before surgery.

Many European and North American Anaesthesia Societies have therefore updated their fasting guidelines and generally recommend that patients drink clear fluids up until 2 hours before anaesthesia. Solids, however, empty from the stomach much slower, and should not be taken later than 6 hours before anaesthesia. Patients with known slow gastric emptying for any reason should best be treated with more restriction, and generally be kept fasted for longer periods of time to reduce the risk of aspiration.

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