Perioperative pathophysiology and the objectives behind Enhanced Recovery Care

Francesco Carli, MD, MPhil

McGill University

Montreal, Canada

franco.carli@mcgill.ca

ANNALS OF SURGERY
Vol. 232, No. 1, 51–57

Ann Surg 2000

A Clinical Pathway to Accelerate Recovery After Colonic Resection

Linda Basse, MD, Dorthe Hjort Jakobsen, RN, Per Billesbølle, MD, Mads Werner, MD, PhD, and Henrik Kehlet, MD, PhD

From the Department of Surgical Gastroenterology and Anesthesiology, Hvidovre University Hospital, Denmark

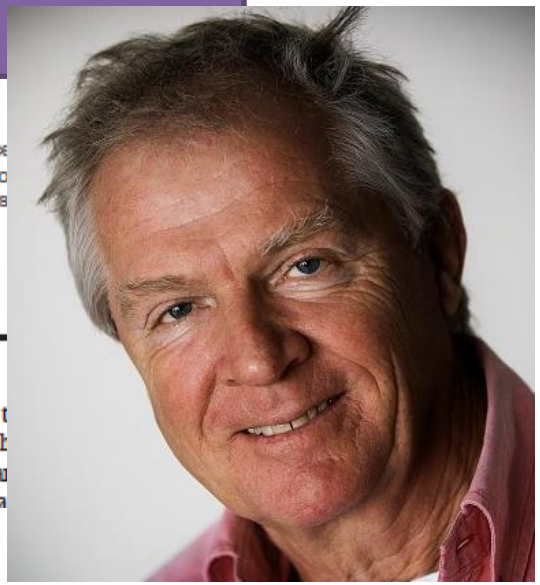
Objective
To investigate the feasibility of a 48-hour postop
program after colonic resection.

Summary Background Data
Postoperative hospital stay after colonic resecti
to 12 days, with a complication rate of 10% to 2
factors for early recovery include stress-induced
function, paralytic ileus, pain, and fatigue. It has
esized that an accelerated multimodal rehabilita
with optimal pain relief, stress reduction with re
thesia, early enteral nutrition, and early mobilizat
hance recovery and reduce the complication rate.

Methods
Sixty consecutive patients undergoing elective colonic resection were prospectively studied using a well-defined postoperative care program including continuous thoracic epidural analgesia and enforced early mobilization and enteral nutrition, and a planned 48-hour postoperative hospital stay. Postoperative follow-up was scheduled at 8 and 30 days.

Conclusion
A multimodal rehabilitation program may significantly reduce the postoperative hospital stay in high-risk patients undergoing colonic resection. Such a program may also reduce postoperative ileus and cardiopulmonary complications. These results may have important implications for the care of patients after colonic surgery and in the future assessment of open versus laparoscopic colonic resection.

- ✓ 60 patients (74 yo)
- ✓ Open colon resection + postop care program
- ✓ Epidural, early feeding and mobilization
- ✓ Median LOS 2 days
- ✓ 15% readmissions



The postoperative hospital stay after colonic resection is usually 6 to 12 days,[1–6] with a complication rate of 10% to 20%, because many patients are elderly and at high risk. The recent introduction of multimodal postoperative rehaapproximately 4 to 6 days.[6,10,11] However, in studies on t
effect of laparoscopic-assisted colonic resection, there h
rarely been a focus on revising perioperative care progra
and on including optimal analgesia, early mobilization, a

Am j Physiol 1999

Surgery-induced insulin resistance in human patients: relation to glucose transport and utilization

A. THORELL,[1] J. NYGREN,[2] M. F. HIRSHMAN,[3] T. HAYASHI,[3] K. S. NAIR,[4]
E. S. HORTON
Departments o *stitute,*
S-171 76 Stoc
Boston, Massa *ic,*
Rochester, Mi

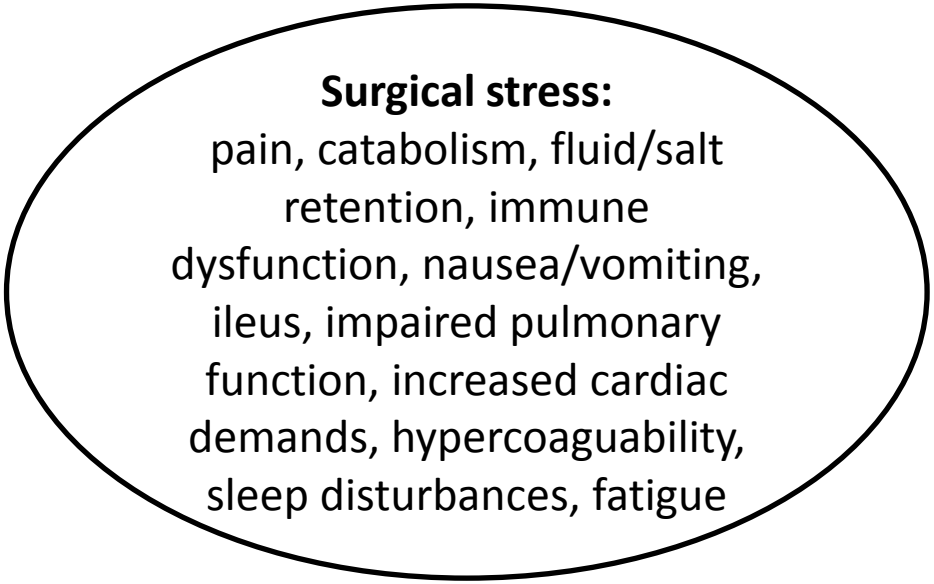
- ✓ 6 patients
- ✓ Muscle biopsies
- ✓ Insulin clamp
- ✓ Glut 4 translocation

Thorell, A., J. Nygren, M. F. Hirshman, T. Hayashi, K. S. Nair, E. S. Horton, L. J. Goodyear, and O. Ljungqvist. Surgery-induced insulin resistance in human patients: relation to glucose transport and utilization. *Am. J. Physiol.* 276 (*Endocrinol. Metab.* 39): E754–E761, 1999.—To investigate the underlying molecular mechanisms for surgery-induced insulin resistance in skeletal muscle, six otherwise healthy patients undergoing total hip replacement were studied before, during, and after surgery. Patients were studied under basal conditions and during physiological hyperinsulinemia (60 μU/ml). Biopsies of vastus lateralis muscle were used to measure GLUT-4 translocation, glucose transport, and glycogen synthase activities. Surgery reduced insulin-stimulated glucose disposal ($P < 0.05$) without altering the insulin-stimulated increase in glucose oxidation or suppression of endogenous glucose production. Preopera-

resistance is pe kely skel-
etal muscle (8). echanisms
through which al muscle
insulin resistan

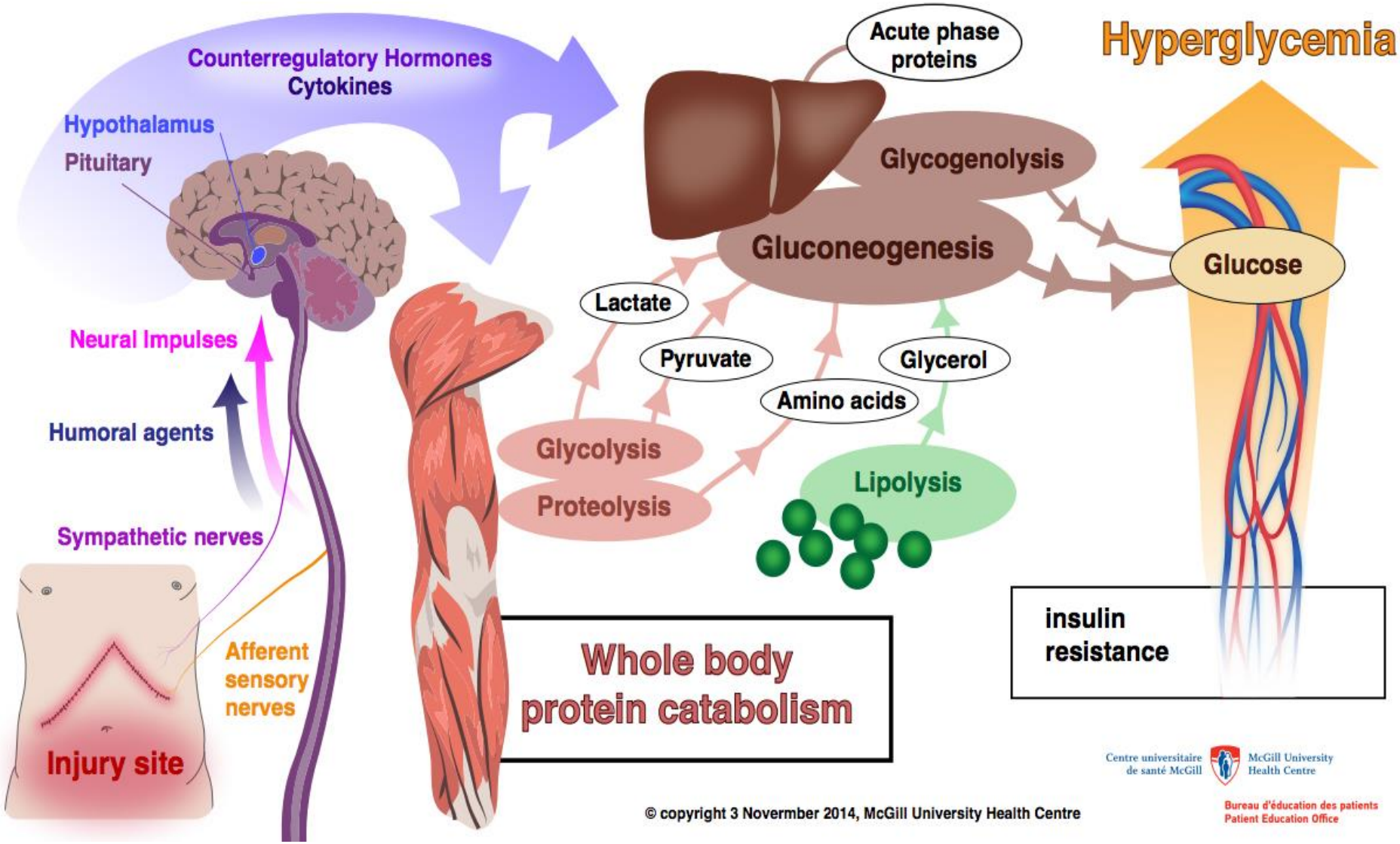
In patients derate to
severe degree, ce can be
overcome if a su infused to
maintain eugly 5) demon-
strated that bo body sub-
strate utilizatio resence of
elevated insulin gs suggest
that excessive insulin can compensate for the defects in insulin action, which is in contrast with earlier reports suggesting that stress-induced insulin resistance is due to a block in intracellular mechanisms that lead to the

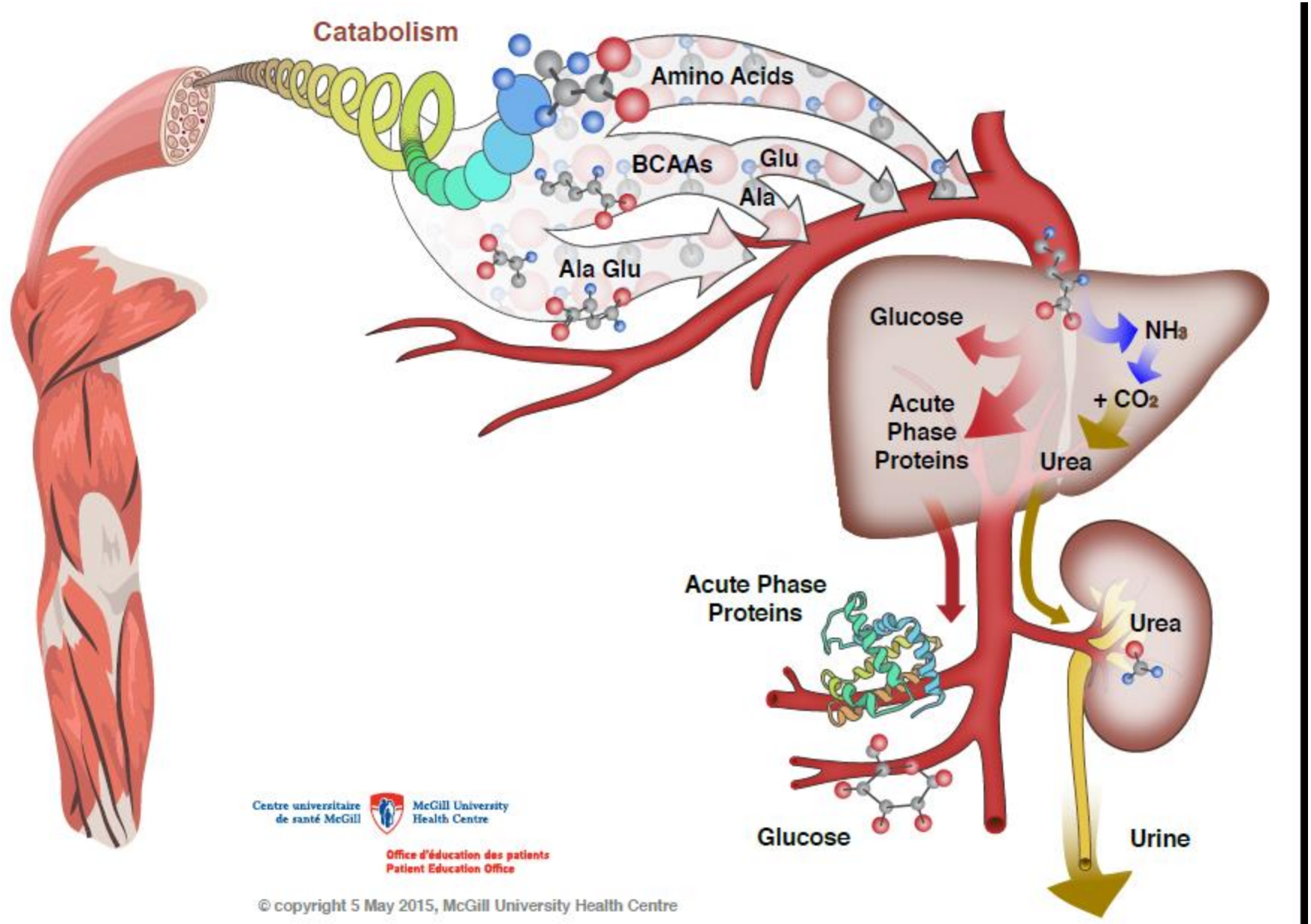
Elements of the stress response



Kehlet and Wilmore, Ann Surg 2008 (revised)

Surgery is a stressor

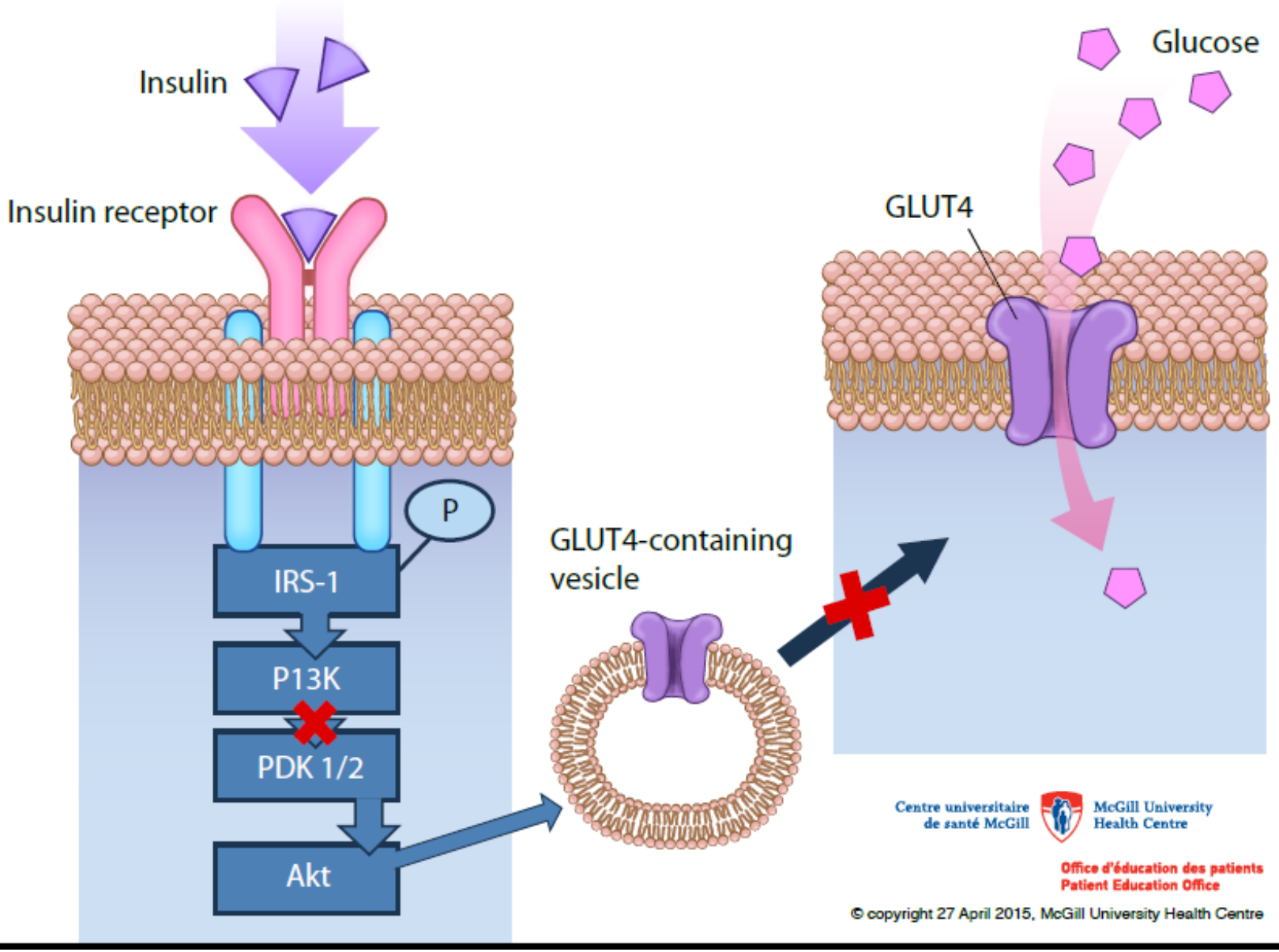




Centre universitaire de santé McGill
McGill University Health Centre

Office d'éducation des patients
Patient Education Office

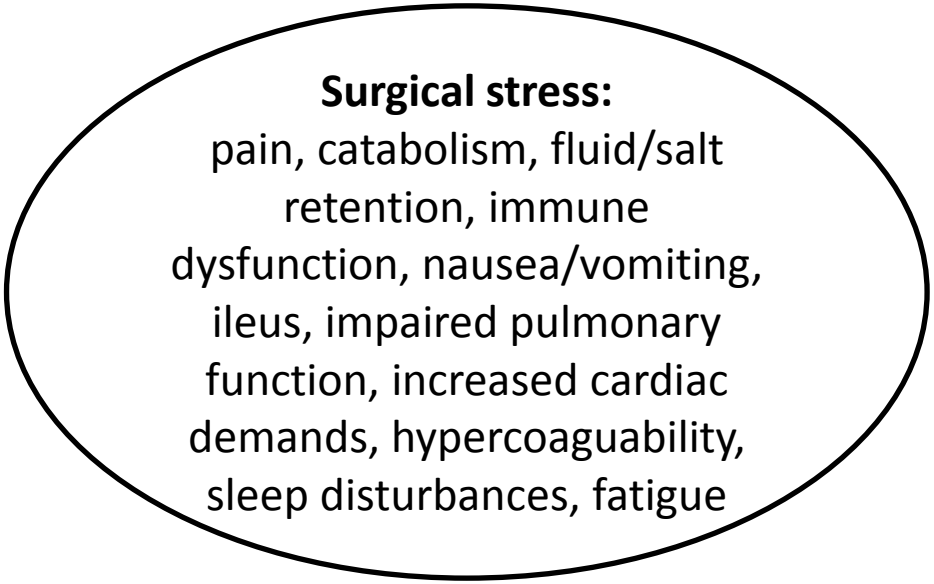
Effect of Insulin on Glucose Uptake



Centre universitaire de santé McGill
McGill University Health Centre

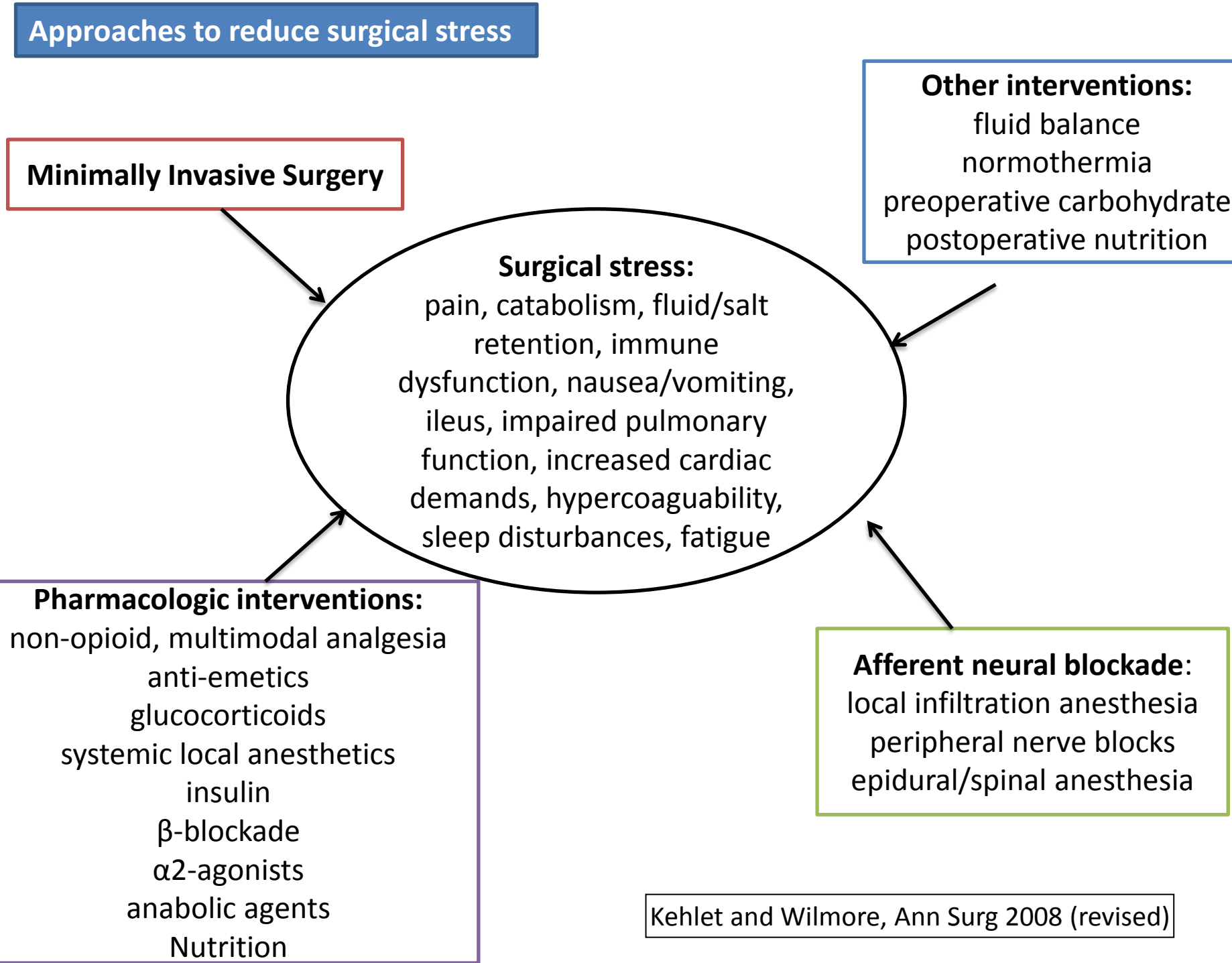
Office d'éducation des patients
Patient Education Office

Elements of the stress response mediated by insulin resistance

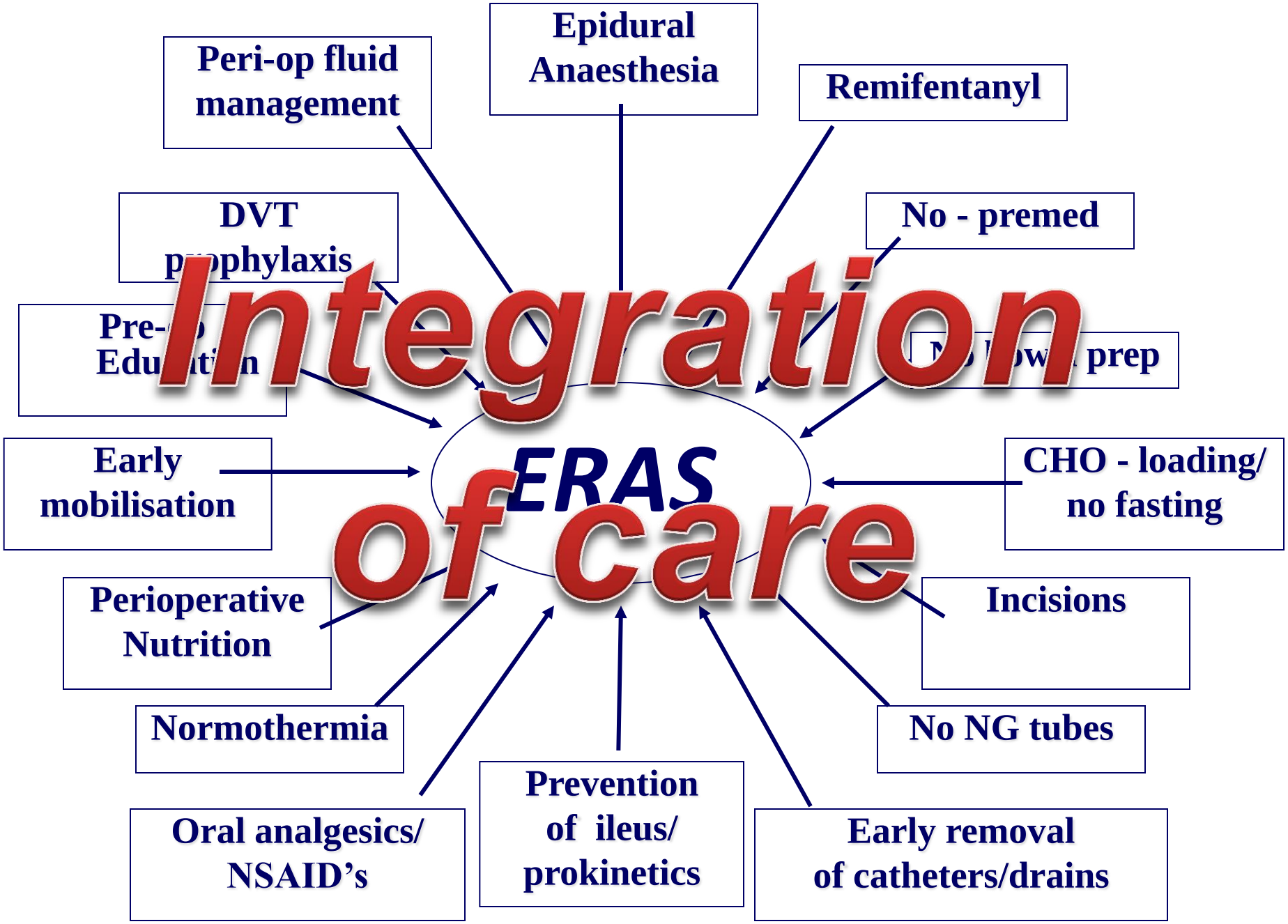


Kehlet and Wilmore, Ann Surg 2008 (revised)

Approaches to reduce surgical stress

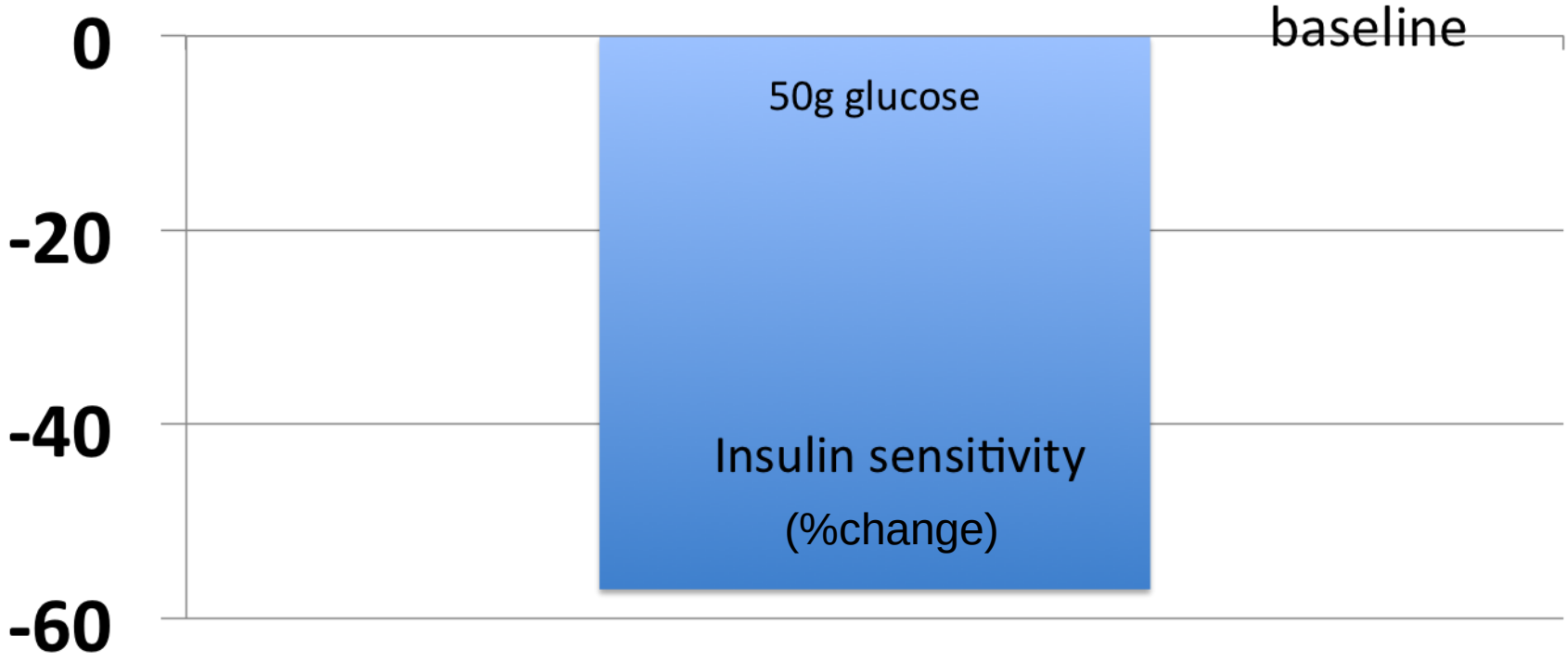


Kehlet and Wilmore, Ann Surg 2008 (revised)



Fearon et a al 2005, Lassen et al Arch Surg 2009

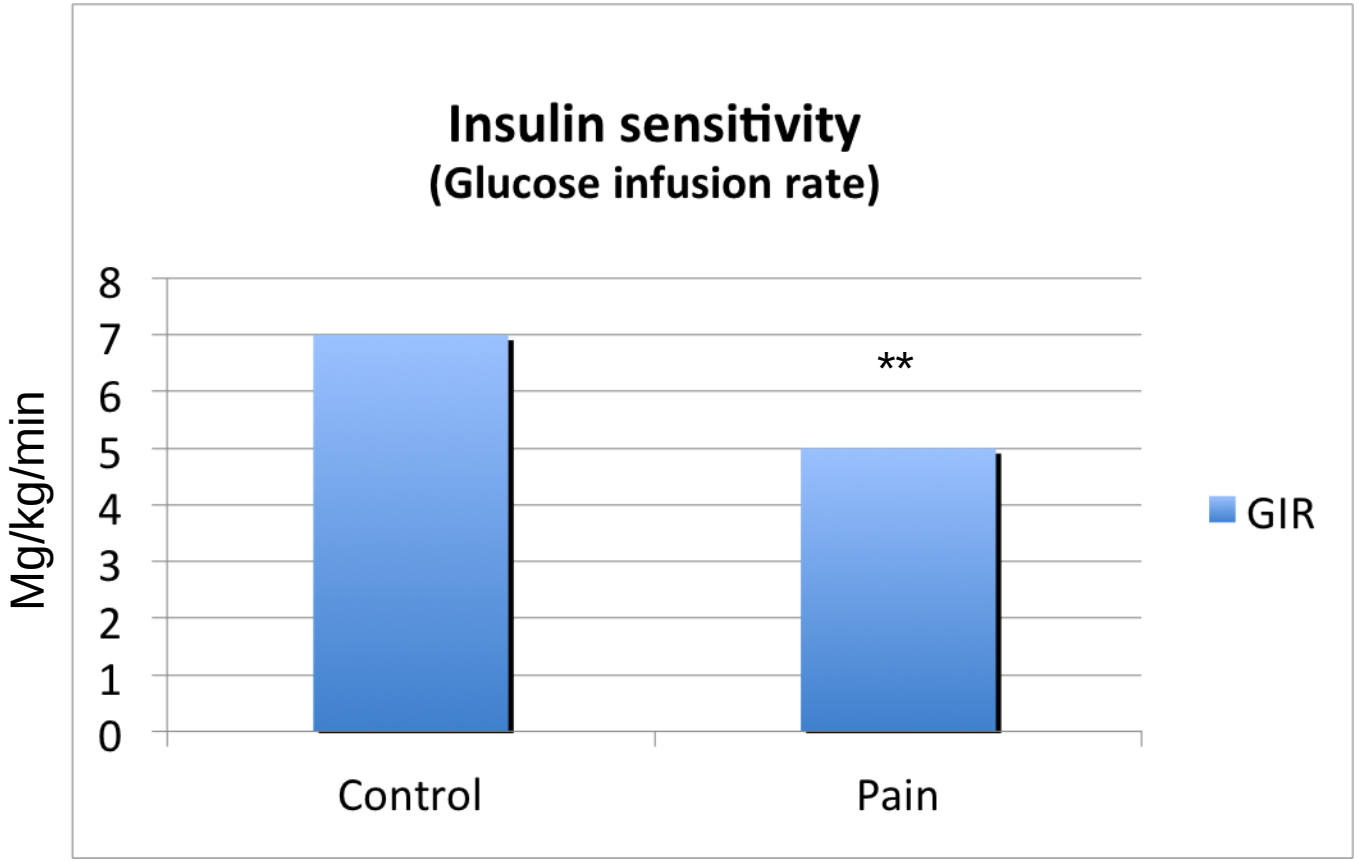
3 days Hypocaloric nutrition* cause insulin resistance



* 2000 ml 2.5% glucose

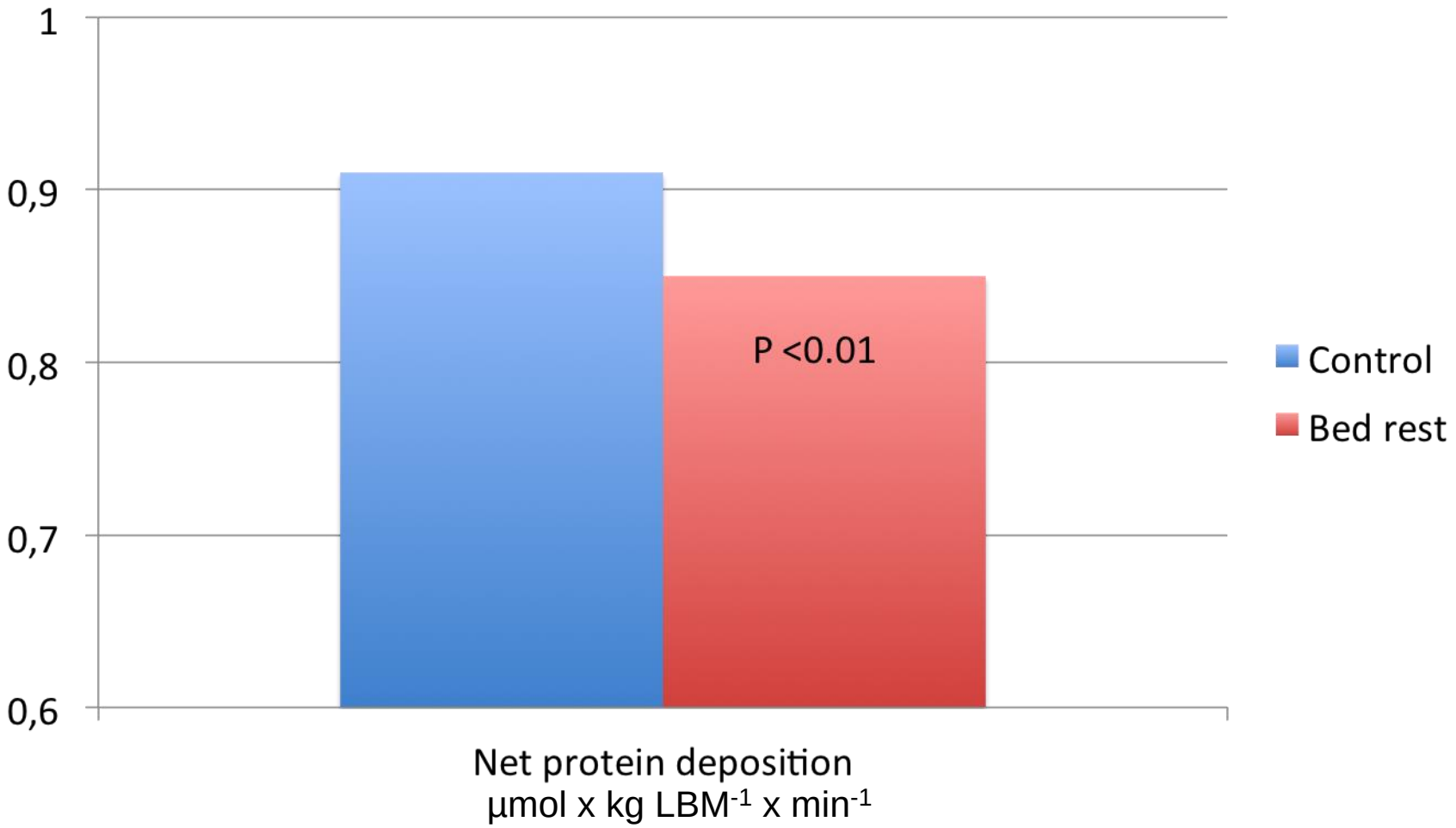
Svanfeldt M et al, Clin Nutr 2003; 1: 31-38

Pain reduce Insulin sensitivity



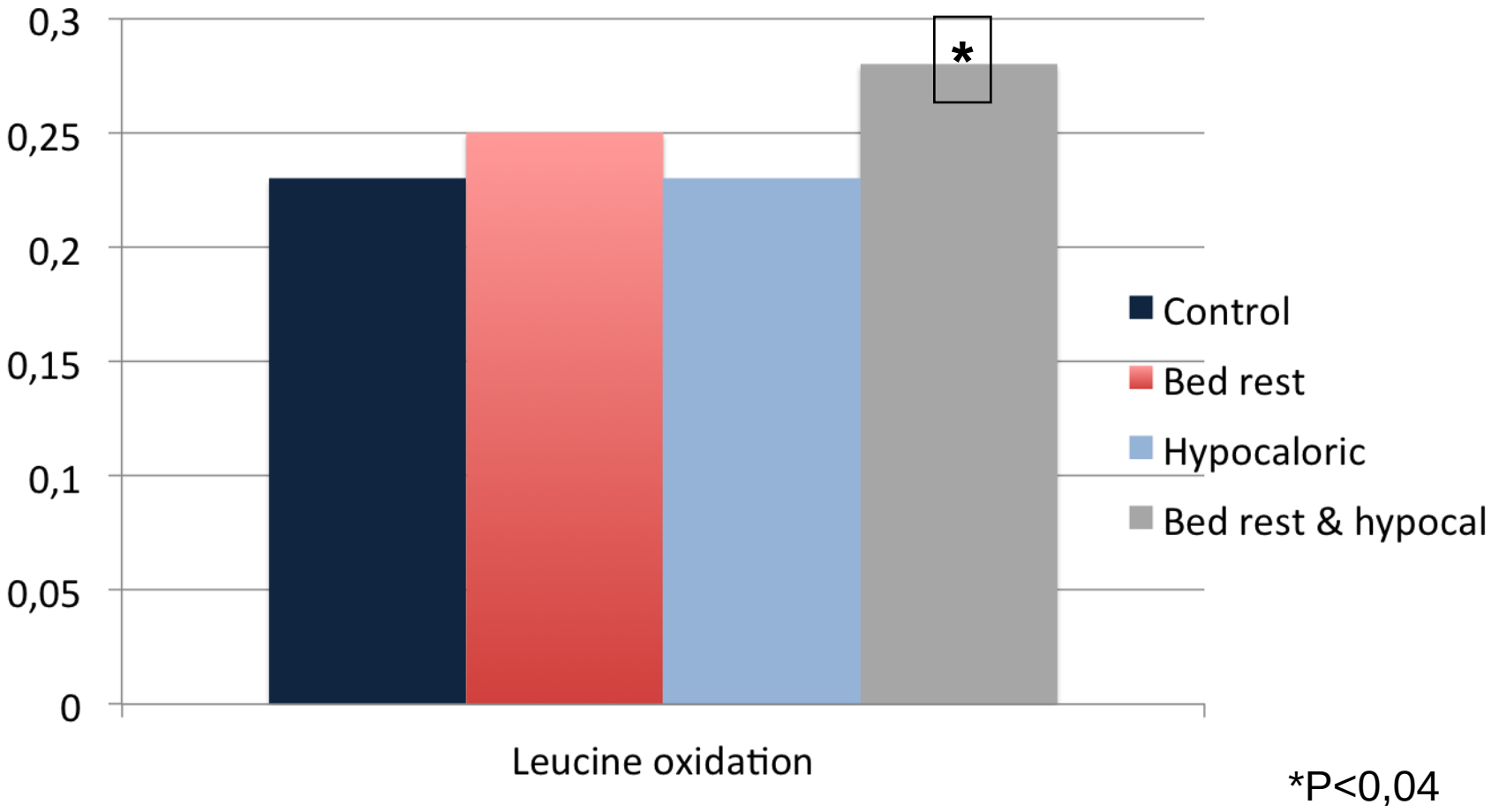
Greisen et al, Anesthesiology 2001

Effect of bed rest



Biolo G et al, Am J Clin Nutr 2007, 86: 366-77

Combined hypocarolic feeding and bed rest increase protein catabolism



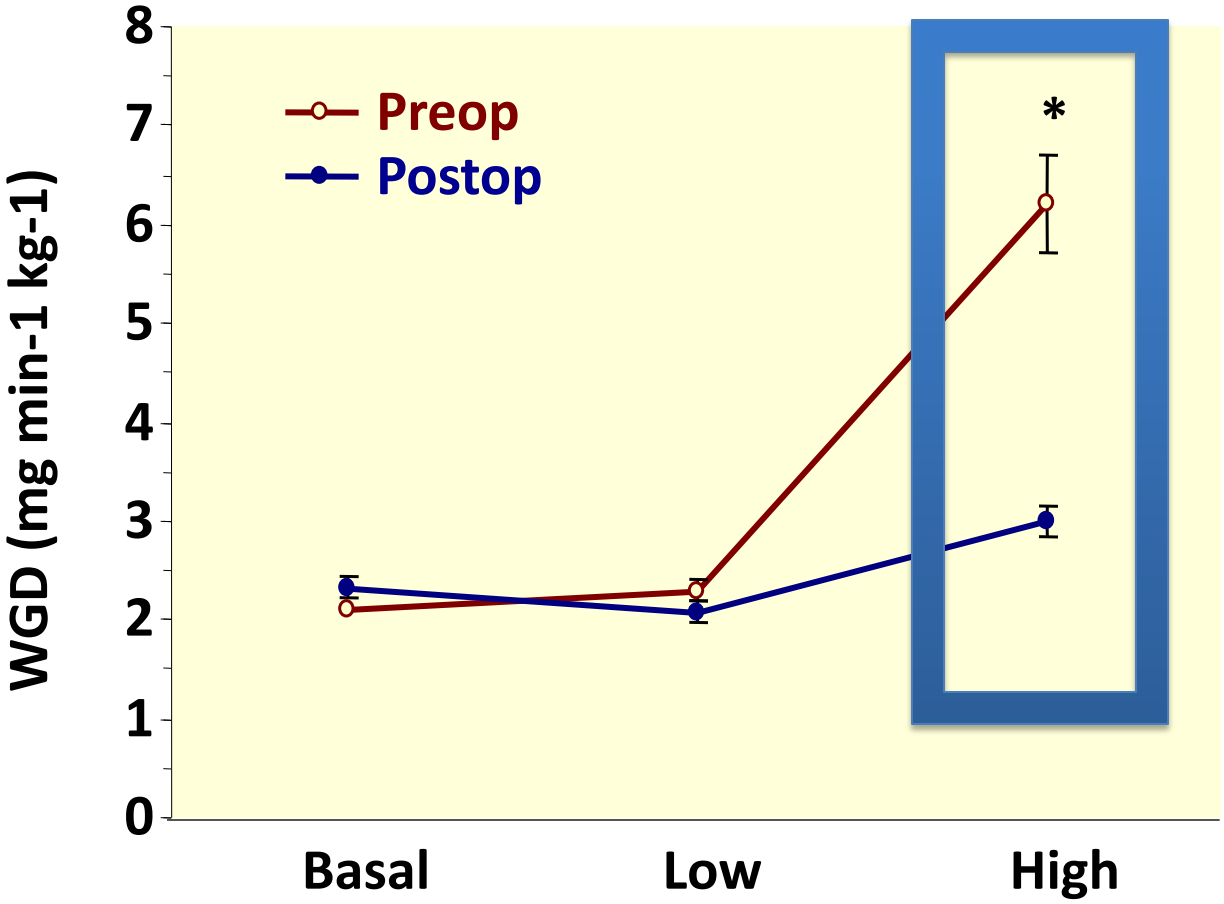
*P<0,04

Biolo G et al, Am J Clin Nutr 2007, 86: 366-77

Metabolic changes

	Day	Night
Hormones	Insulin +	Insulin – Glucagon Cortisol
Substrates	Storage	Breakdown
Utilization	CHO > Fat	Fat > CHO

Resistance is in uptake

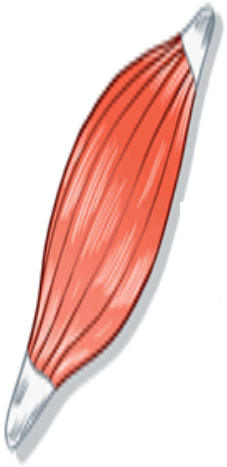


Clamp

P-Insulin µU/ml	10	30	65

Nygren et al, Clin Sci 1996

Insulin resistance muscle



- **Reduced glucose uptake**
- **Reduced glycogen storage**
- **Increased protein catabolism**

Insulin resistance muscle

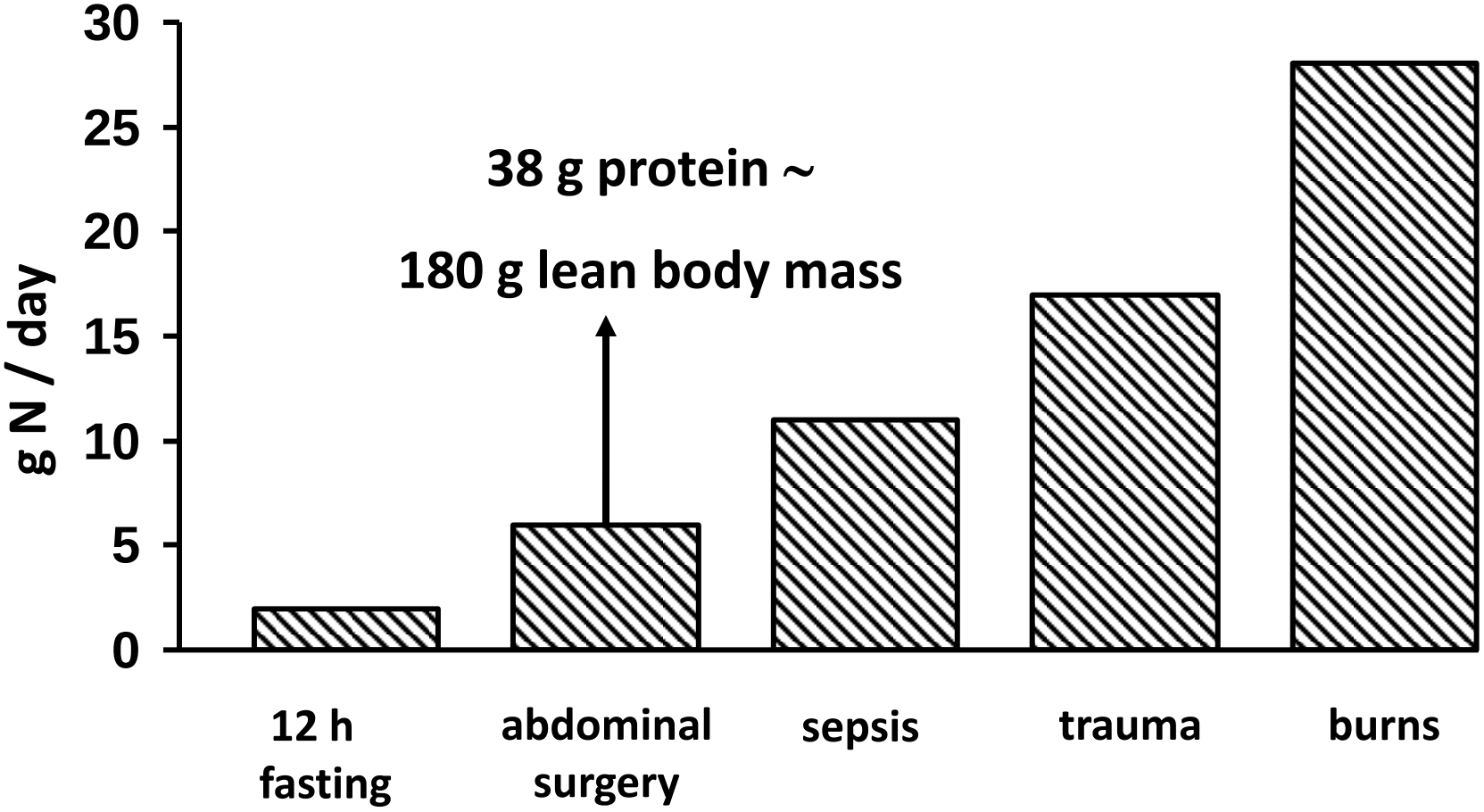
Energy supply ↓ glucose uptake

Lean body mass ↓ glycogen storage

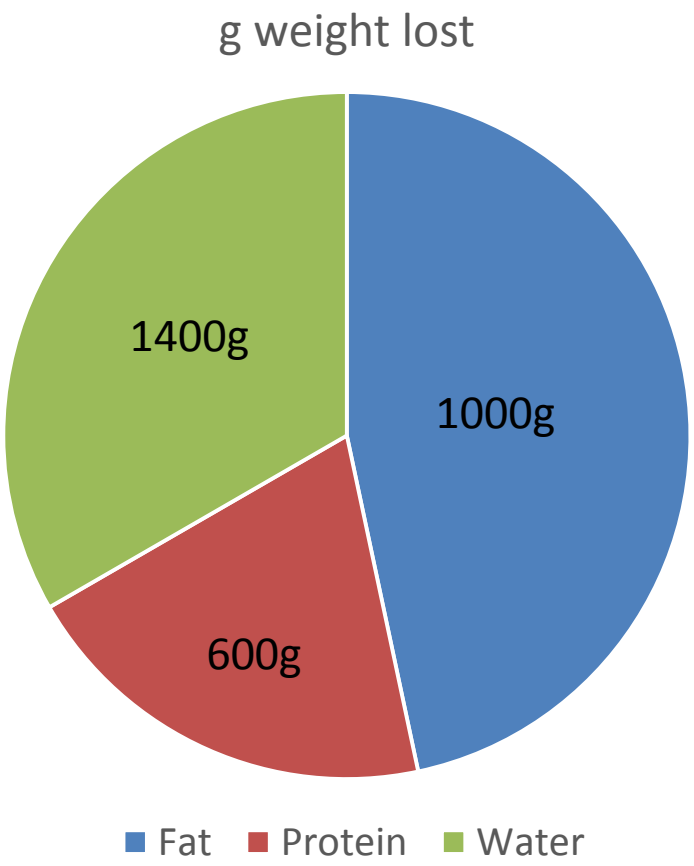
- **Muscle function** ↓ bo m

Mobilisation ↓

Stress and protein loss



Postoperative Catabolism

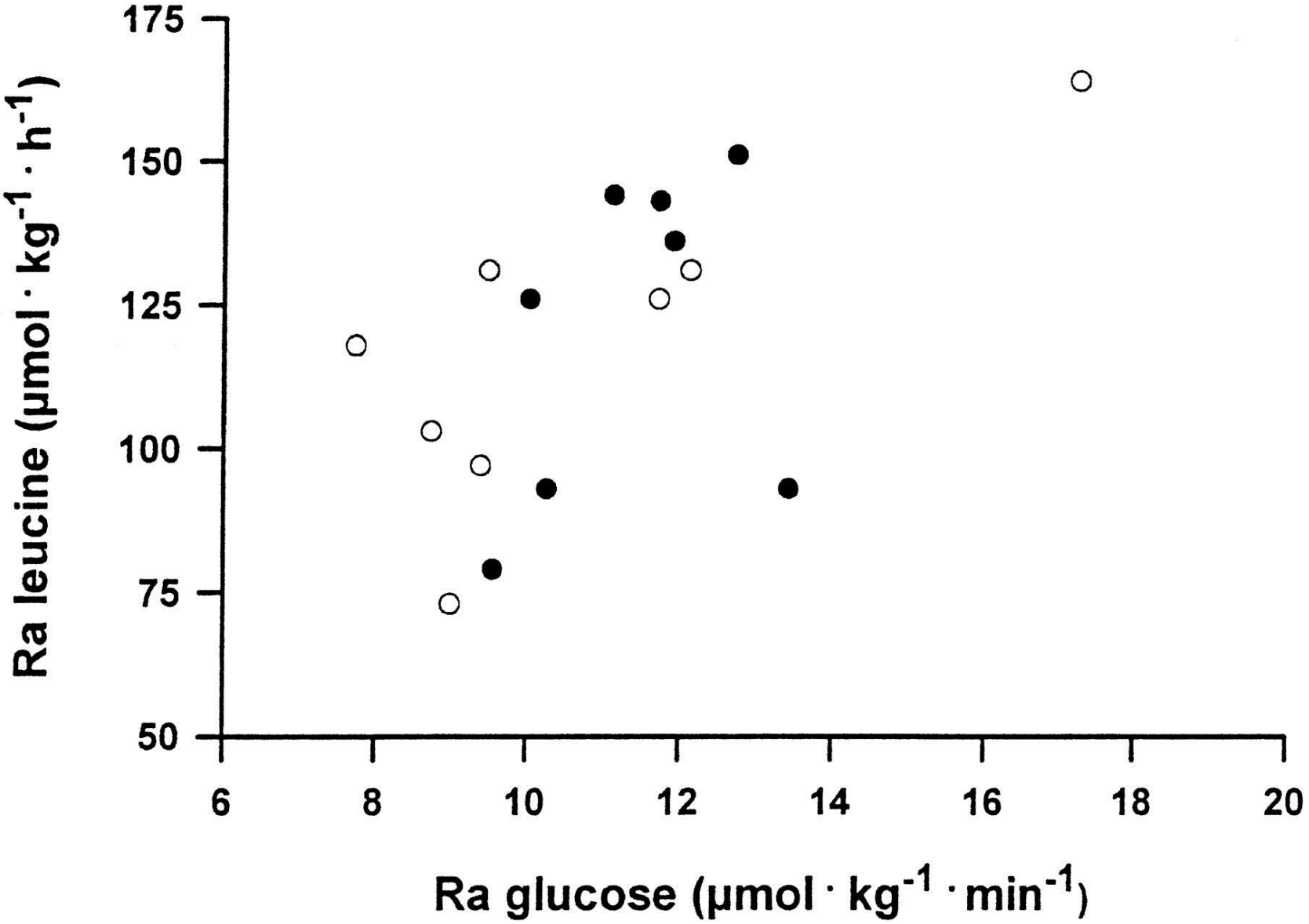


Hill et al. WJS. 1993

Nitrogen loss

minor surgery	40 g	**1.2 kg**
gastrointestinal tract surgery	100-150 g	**3 – 4.5 kg**
sepsis	200 g	**6 kg**
burns	300 g	**9 kg**

1 g of nitrogen is 30 g hydrated lean tissue



Carli F, Schricker T, Metabolism, 2001

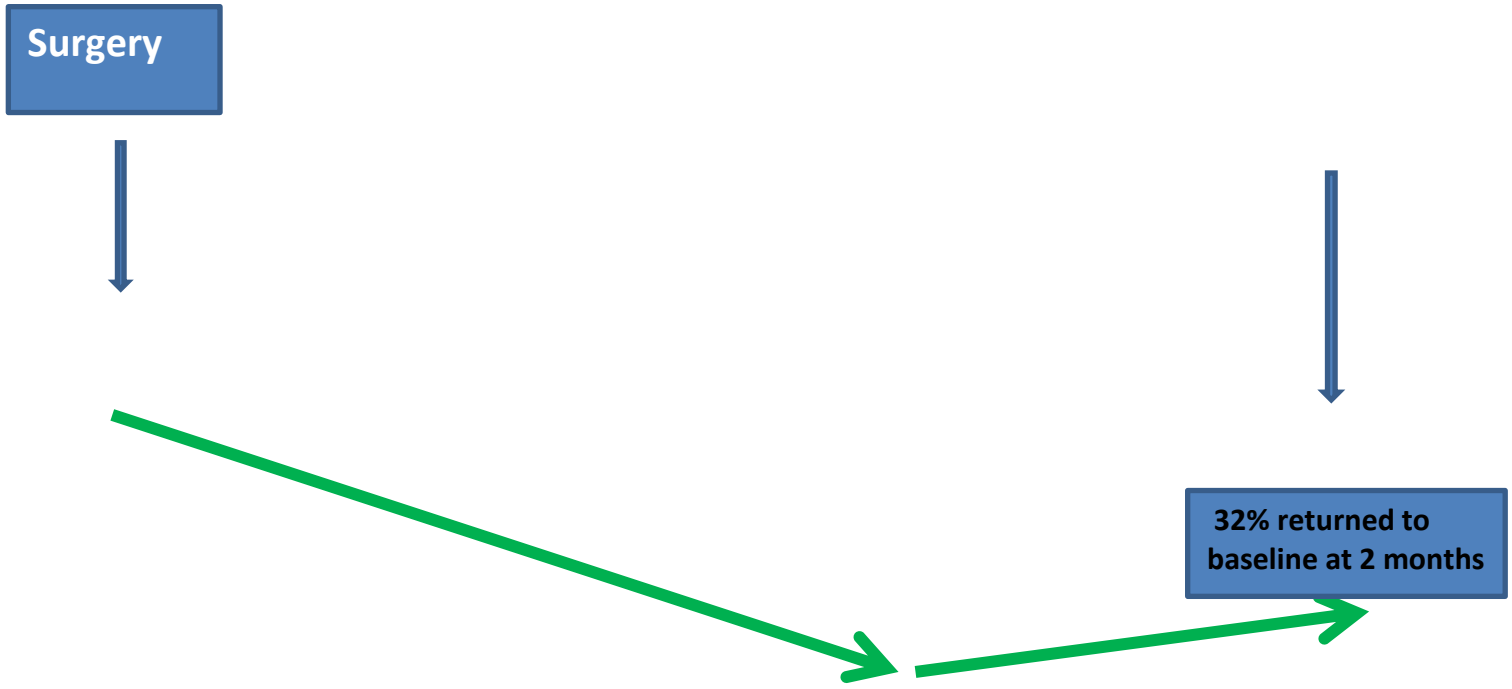
Influence of body composition profile on outcomes following colorectal cancer surgery

Br J Surg 2016

- 805 patients for colorectal cancer surgery
- Lumbar skeletal muscle index (LSMI), visceral adipose tissue (VAT by analysis of CT images).
- Myosteatosis associated with prolonged LOS
- **Muscle depletion independent risk for complications and long LOS**
- Myopenia is an independent prognostic effect on cancer survival for patients with colorectal cancer.

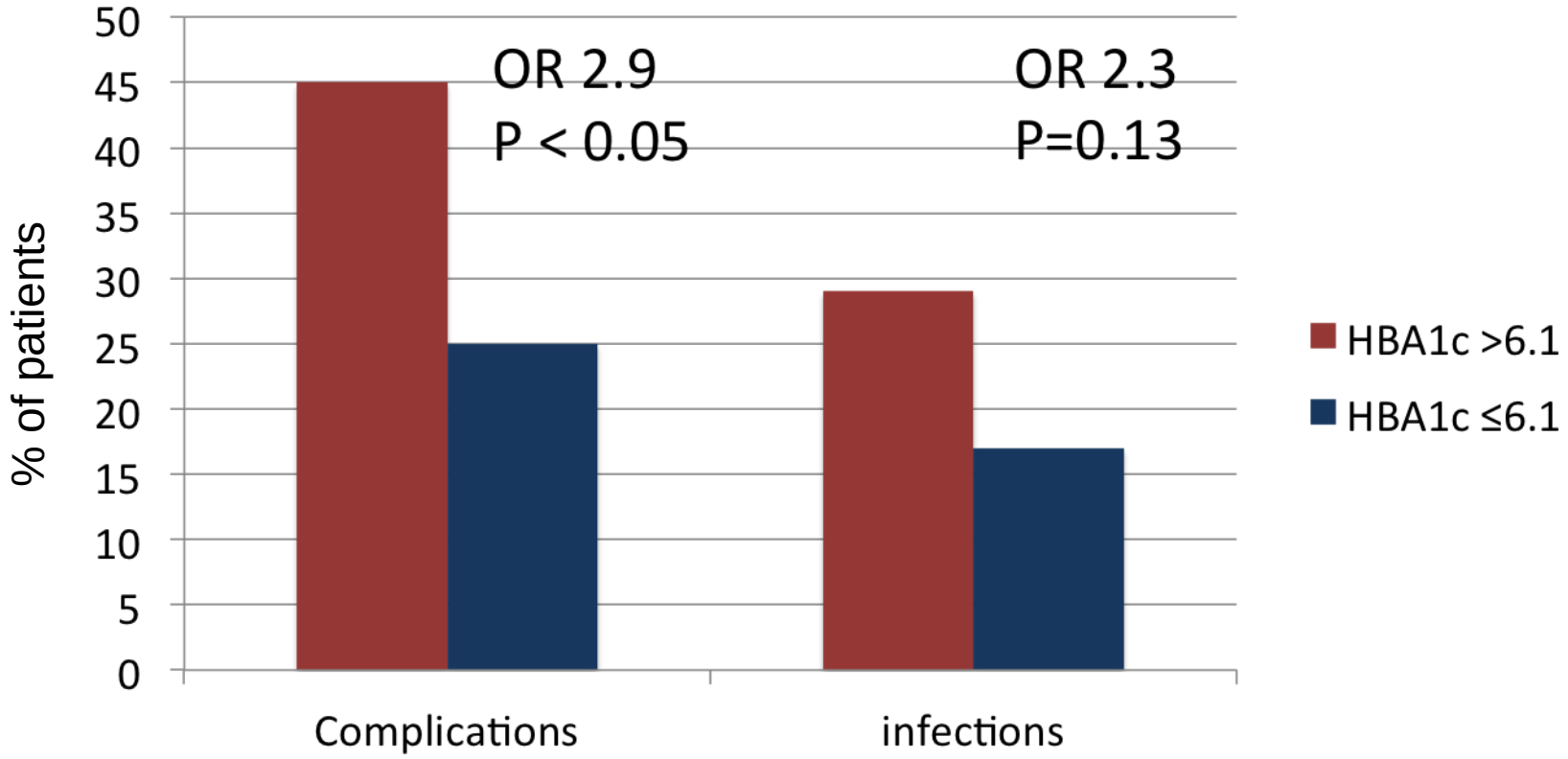
Loss of functional capacity after surgery for colorectal cancer

(Chao L, Surg Endosc 2013)



Impact of insulin resistance on recovery

HbA1c, Glucose control and postop complications



Gustafsson et al, BJS 2012

Postoperative insulin resistance increase the risk for complications

273 patients open cardiac surgery, insulin sensitivity determined at the end of op

Complication	OR for every decrease by 1 mg/kg/min (Insulin sensitivity)	P value
Death	2.33 (0.94-5.78)	0.067
Major complication	2.23 (1.30-3.85)	0.004
Severe infection	4.98 (1.48-16.8)	0.010
Minor infection	1.97 (1.27-3.06)	0.003

The ORs were adjusted for potential confounders

Sato et al, JCEM 2010; 95: 4338-44

Operative Day glucose & outcomes

Colorectal cancer patients, n= 7,576

Glucose level	Outcome	Odds ratio (95% CI)	p value
Moderate (161-200 mg/dl) (8.9-11.1 mmol/l)	**Surgical site infection**	1.44 (1.10-1.87)	<0.01
	Pneumonia	1.37 (1.00-1.87)	<0.05
Severe (>200mg/dl) (>11.1 mmol/l)	**Pneumonia**	1.55 (1.10-2.18)	<0.01
	Re operation	1.37 (1.02-1.87)	<0.05

Jackson et al, JACS 2013

Increasing hyperglycemia greater risk & longer stay

TABLE 5. Independent Risk Factors Associated With Reoperation and Length of Hospital Stay in Nondiabetic Patients

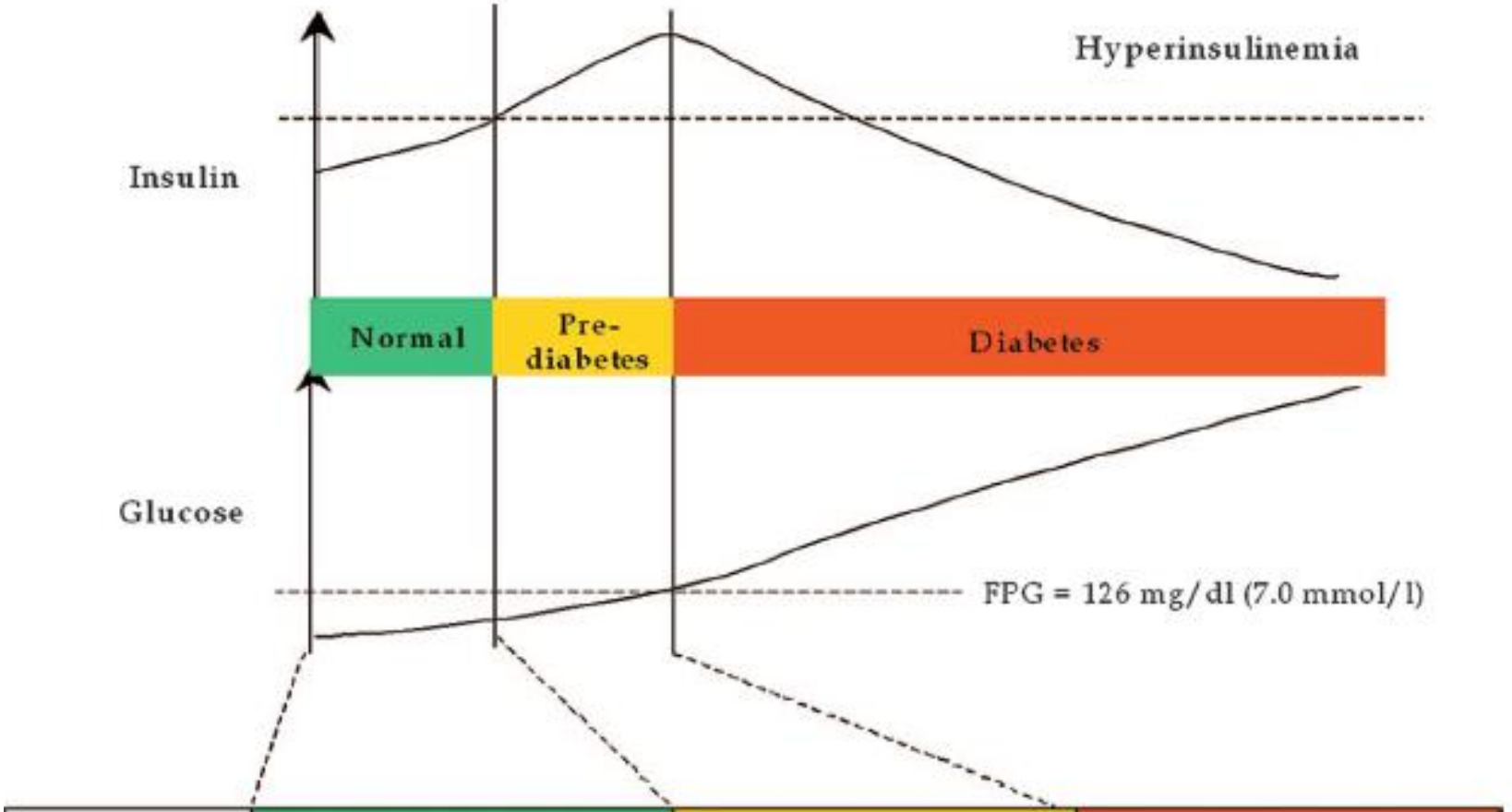
Characteristic	OR	95% CI	*P**
Reoperation			
Steroid use	2.29	0.66–7.93	0.19
Age <50 yr	0.70	0.41–1.18	0.18
ASA ≥3	0.62	0.36–1.09	0.09
Emergency surgery	3.80	1.48–9.76	**0.005**
Surgery time ≥180 min	1.26	0.74–2.16	0.40
Hyperglycemia group			Overall 0.007
Normoglycemia (reference)	1.0		
Mild hyperglycemia	2.10	1.05–4.20	**0.036**
Severe hyperglycemia	3.83	1.63–9.01	**0.002**
Characteristic	**Medians Ratio***	**95% CI**	***P*†**
Length of stay			
Steroid use	1.03	0.83–1.28	0.77
Age <50 yr	0.95	0.89–1.02	0.15
ASA score ≥3	1.21	1.13–1.30	**<0.001**
Emergency surgery	1.53	1.26–1.86	**<0.001**
Surgery time ≥180 min	1.30	1.21–1.40	**<0.001**
Hyperglycemia Group			Overall <0.001
Normoglycemia (reference)	1.0		
Mild hyperglycemia	1.16	1.08–1.26	**<0.001**
Severe hyperglycemia	1.28	1.14–1.43	**<0.001**

Reoperation

Length of stay

Kiran et al, Ann Surg 258; 2013

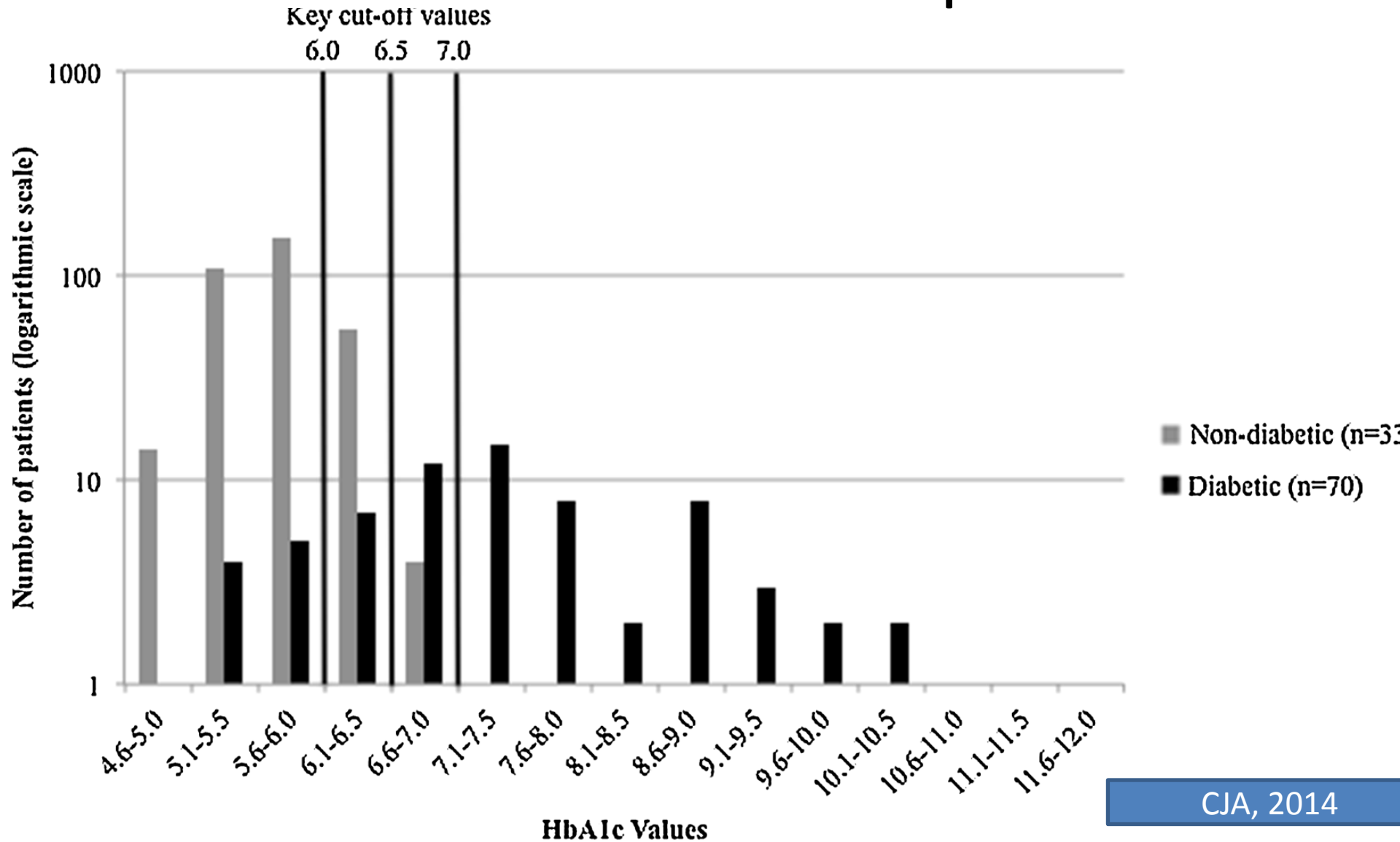
Development of Diabetes



Fasting Plasma Glucose	<100mg.dl-1 (<5.6mmol.dl-1)	IFG: 100-125 mg.dl-1 (5.6-6.9 mmol.l-1)	≥126mg.dl-1 (7mmol.dl-1)
2hr Post OGTT	<140 mg.dl-1 (<7.8 mmol.dl-1)	and/or IGT: 140-199 mg.dl-1 (7.8-11.0 mmol.l-1)	≥200 mg.dl-1 (≥11.1 mmol.l-1)

Bagri H, Carli F, Anesthesiology

High rate of preoperative HbA1C in non diabetic colorectal patients



CJA, 2014

Preoperative Insulin Resistance and the Impact of Feeding on Postoperative Protein Balance: A Stable Isotope Study

J Clin Endocrinol Metab, November 2011, 96(11):E1789–E1797

Francesco Donatelli, Davide Corbella, Marta Di Nicola, Franco Carli, Luca Lorini, Roberto Fumagalli, and Gianni Biolo

	Before Surgery	After Surgery
IS	5.6	5.4
IR	5.9	4.1

mc/kg/h

J Clin Endocrinol Metab, November 2011, 96(11):E1789–E1797

Patients at risk of development of IR

- Elderly
- Cancer
- Frail
- Obese
- Depressed

Bagry H, Carli F, Anesthesiolooy 2008

Strategies to Impact on Insulin Resistance

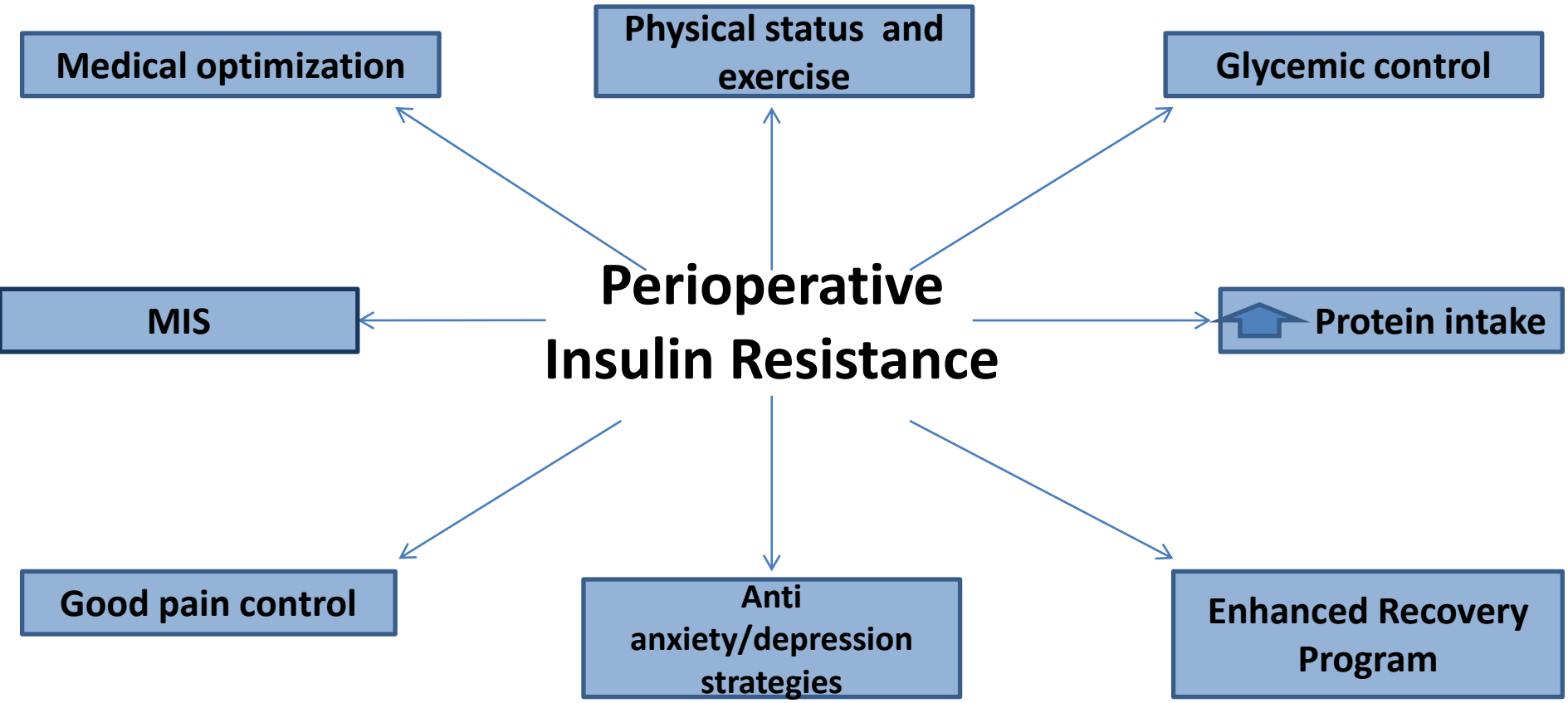


Table 1. Clinical Strategies Thought to Directly or Indirectly Modulate the Surgical Stress Response and Nutritional Outcome

	Hormonal	Metabolic	Inflammatory
Minimally invasive surgery	✓	✓	✓
Neural blockade	✓	✓	✓
Opioid-sparing pain control	✓		
Prevention of hypothermia	✓	✓	
Perioperative fluid management	✓		
Anabolic agents (*e.g.*, growth hormone)	✓	✓	
Glucocorticoids	✓	✓	✓
β-blockade	✓	✓	
α2-agonists	✓		✓
Exercise	✓	✓	✓
Carbohydrate loading	✓	✓	✓
Immunonutrition		✓	✓
Early oral nutrition	✓	✓	✓
Adequate dietary protein		✓	
Insulin (glycemic control)	✓	✓	✓

Gillis C, Carli F, Anesthesiology 2015

The effects of a 2 week modified high intensity interval training program on the homeostatic model of insulin resistance (HOMA-IR) in adults with type 2 diabetes

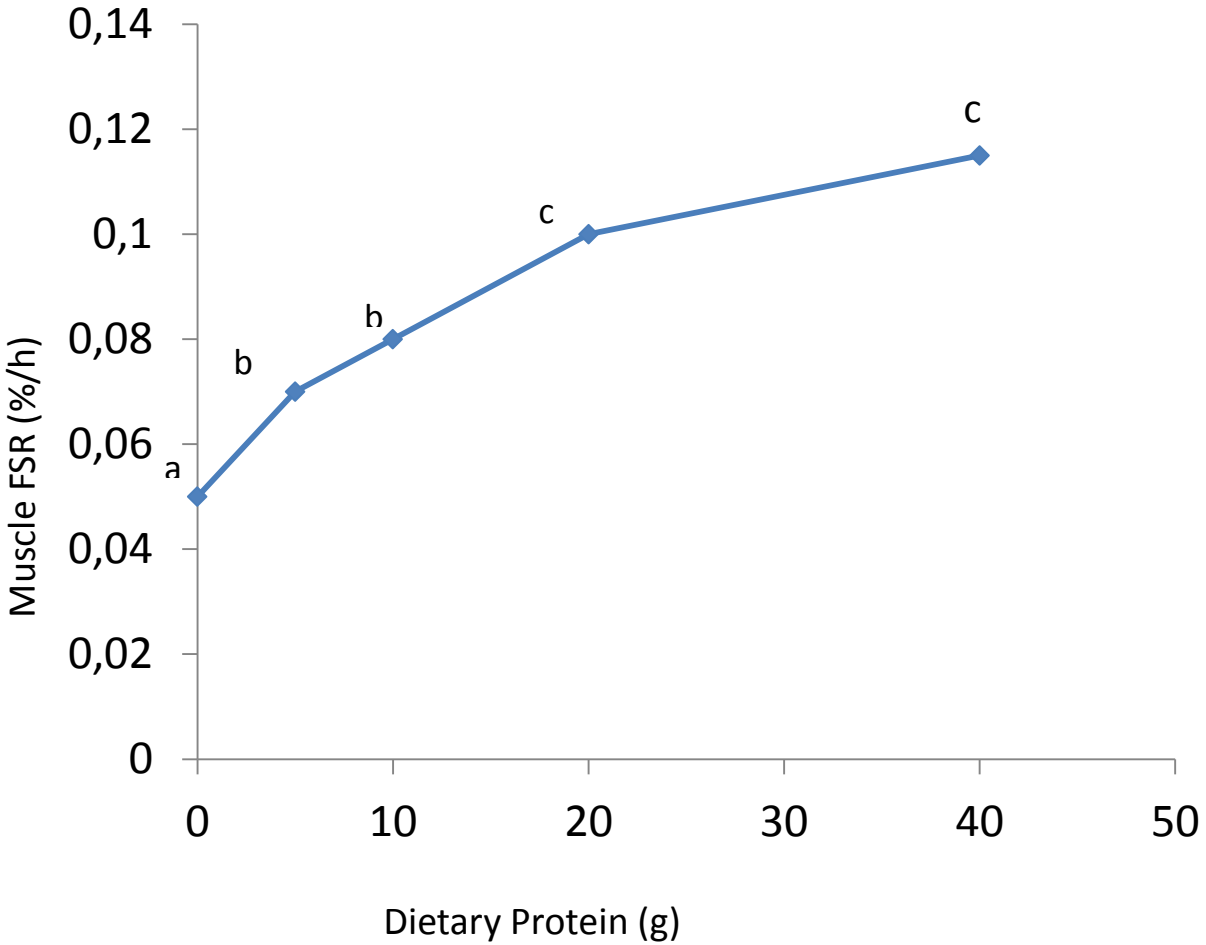
J Sports Med Phys Fitness. 2014

- 6 individualized training sessions of HIT (4x30 seconds at 100% of estimated maximum workload followed by 4 minutes of active rest) over 2 weeks
- HOMA-IR calculated from fasting glucose/fasting insulin
- Decreased all parameters of glucose
- Better glucose utilization

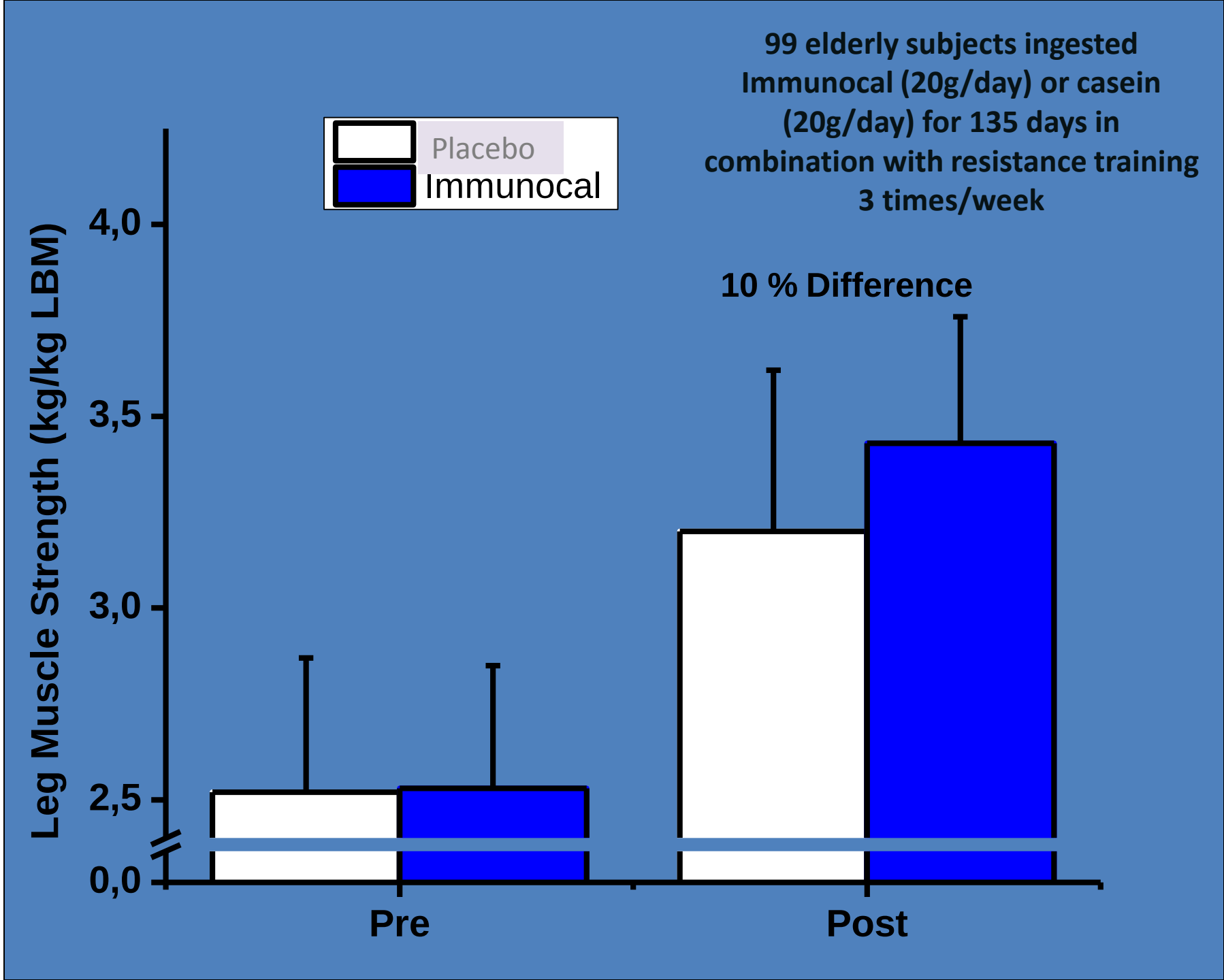
The effects of high-intensity interval (HIT) training on glucose regulation and insulin resistance: a meta-analysis
Obes Rev, 2015

- Fifty Studies, 250 pts
- > 2 weeks supervised HIT, 90% VO2 peak
- Decreased fasting glucose
- Decreased fasting insulin
- Better insulin sensitivity
- Average body fat loss of 1.3 kg

Increase in muscle protein synthesis following exercise with whey proteins, increased insulin sensitivity



Burke LM. *Med Sci Sports Exerc*. 2012;44(10):1968-77


99 elderly subjects ingested Immunocal (20g/day) or casein (20g/day) for 135 days in combination with resistance training 3 times/week
Placebo
Immunocal
10 % Difference
Leg Muscle Strength (kg/kg LBM)
4,0
3,5
3,0
2,5
0,0
Pre
Post

In-Hospital Exercise Program






The effect of perioperative glucose control on postoperative insulin resistance☆

Christina Blixt[a,b,*], Christian Ahlstedt[a,b], Olle Ljungqvist[c], Bengt Isaksson[b,d], Sigridur Kalman[a,b], Olav Rooyackers[a,b]

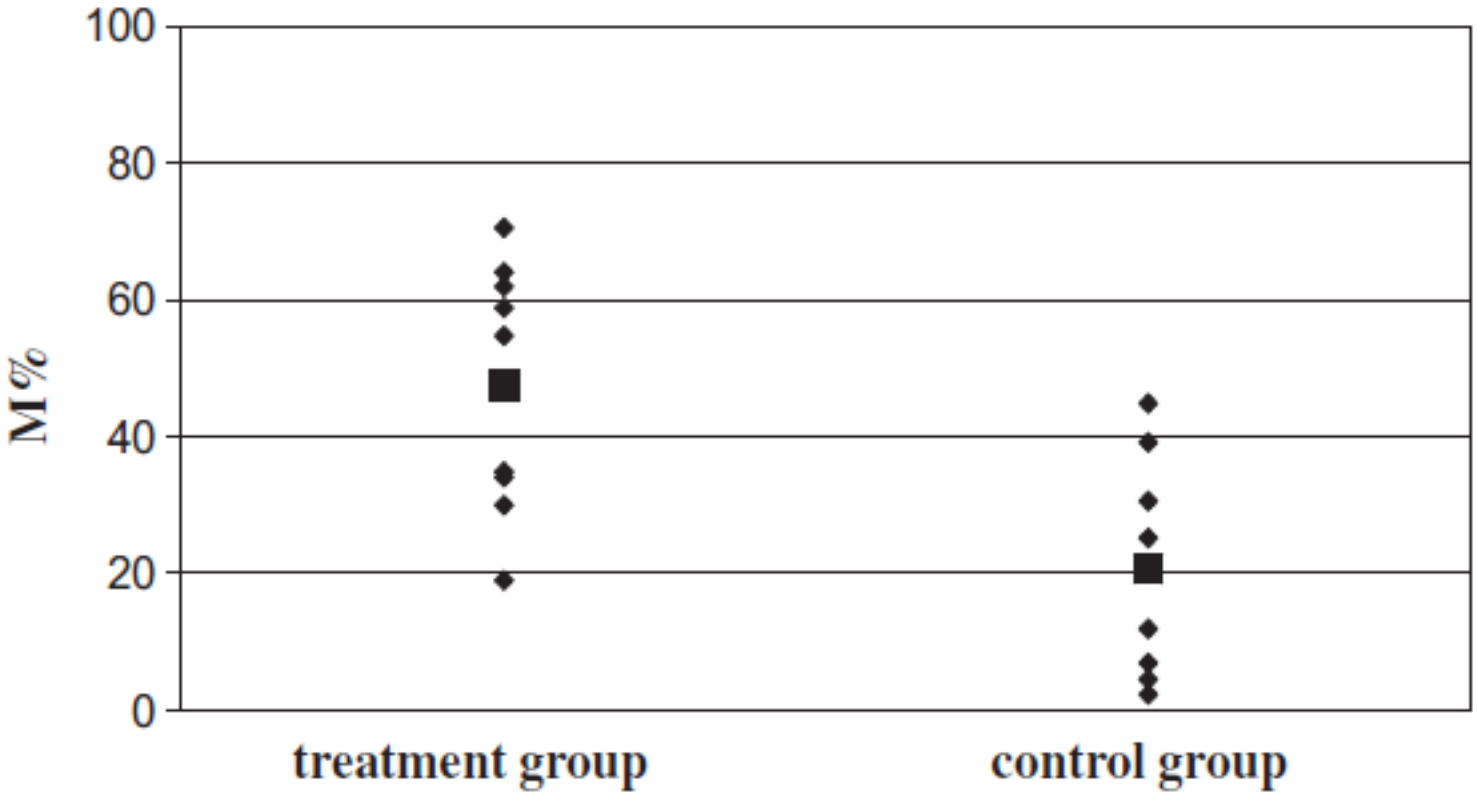
Clinical Nutrition 2012

- Hepatectomy
- BG treated (6-8 mmol/l) vs BG control > 8mmol/l
- Hyperinsulinemic normoglycemic clamp before and after surgery to measure insulin resistance

The effect of perioperative glucose control on postoperative insulin resistance☆

Christina Blixt [a,b,*], Christian Ahlstedt [a,b], Olle Ljungqvist [c], Bengt Isaksson [b,d], Sigridur Kalman [a,b], Olav Rooyackers [a,b]

Clinical Nutrition 2012



Keeping the B S <8mmol/l with insulin impacts on postop insulin resistance

Recent Metformin Ingestion Does Not Increase In-Hospital Morbidity or Mortality After Cardiac Surgery

Anesth Analg 2007;104:42–50

- 1284 diabetic patients
- Received metformin within 8-24 h of surgery
- Comparison with non-metformin therapy
- Propensity score analysis

Factor	Metformin-treated	Nonmetformin-treated	Odds ratio (95% CI)	*P*-value
Mortality	3 [0.7% (0.1, 2.0%)]	6 [1.4% (0.5, 2.9%)]	0.5 (0.1, 2.0)	0.51
Cardiac morbidity	2 [0.5% (0.1, 0.2%)]	6 [1.4% (0.5, 2.9%)]	0.3 (0.1, 1.7)	0.29
Prolonged intubation	7 [1.6% (0.6, 3.2%)]	23 [5.2% (3.3, 7.7%)]	0.3 (0.1, 0.7)	0.003
Renal morbidity	2 [0.5% (0.1, 0.2%)]	7 [1.6% (0.6, 3.2%)]	0.3 (0.1, 1.4)	0.18
Neurologic morbidity	6 [1.4% (0.5, 2.9%)]	7 [1.6% (0.6, 3.2%)]	0.9 (0.3, 2.6)	0.78
Infection morbidity	3 [0.7% (0.1, 2.0%)]	14 [3.2% (1.7, 5.3%)]	0.2 (0.1, 0.7)	0.007
Overall morbidity	15 [3.4% (1.9, 5.5%)]	34 [7.7% (5.4, 10.6%)]	0.4 (0.2, 0.8)	0.005

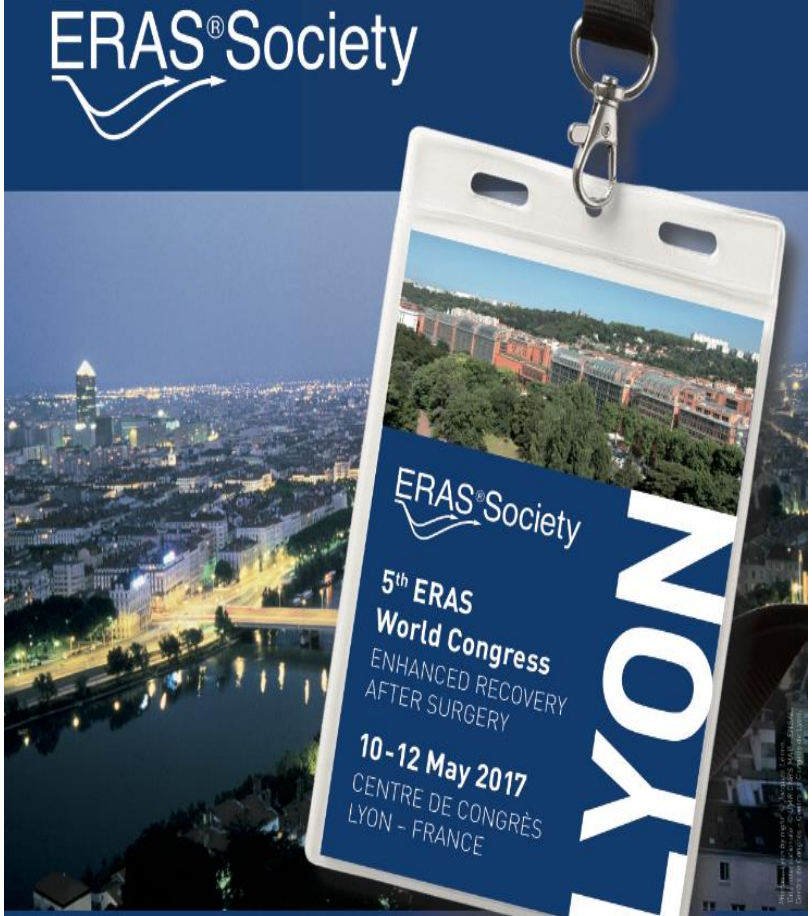
	Metformin-treated		Nonmetformin-treated		
Outcome	*N*	Median (25th, 75th%)	*N*	Median (25th, 75th%)	*P*-value
Initial tracheal intubation time (h)	443	7.8 (5.1, 13.2)	443	8.5 (2.6, 13.1)	0.11
Total tracheal intubation time (h)	443	8.1 (5.1, 13.7)	443	8.8 (5.8, 14.3)	0.047
Hospital length of stay (days)	443	7 (5, 8)	443	6 (5, 8)	0.60
Cardiac output[a]	443	5.3 (4.4, 6.4)	443	5.4 (4.4, 6.4)	0.68
pH[a]	442	7.4 (7.4, 7.4)	442	7.4 (7.4, 7.4)	0.08
Pco_2 (mm Hg)[a]	442	41 (37, 45)	442	39 (36, 43)	<0.001
Po_2 (mm Hg)[a]	442	146 (109, 190)	442	153 (116, 197)	0.29

Metformin and recovery

Take home message

- Metabolic response to surgery remains the pivotal concept which guides clinicians to identify therapeutic modalities
- Insulin resistance appears to be an important pathogenic mechanism which impacts on outcomes beyond LOS.
- We should continue to focus on physiology to explain other possible mechanisms which control surgical metabolism and recovery

ERAS® Society



SAVE THE DATE
10-12 May 2017

For more information,
please contact the Congress Secretariat

5th ERAS World Congress
c/o MCI Suisse SA
75, rue de Lyon, 1211 Geneva 13 – Switzerland
Phone +41 22 33 99 726 / Fax +41 22 33 99 631
Email eras@mci-group.com

Thank you

Enhanced Recovery Society of Canada
Société de réhabilitation rapide du Canada