Enhanced Recovery After Surgery
& how metabolism is key
State of the art lecture

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Örebro University Hospital
& Karolinska Institutet, Sweden

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Dublin, Ireland
March 6, 2013
Recovery After Surgery
What are we trying to achieve?

Patient back to preoperative function

• Normal gastrointestinal function
  – Normal food intake
  – Bowel movement
• Pain control
• Mobility

• No complication
Insulin & Recovery

Insulin: main anabolic hormone involved in

- All parts of metabolism
  - Glucose control
  - Fat metabolism
  - Protein

- Regulator of return of key functions
- Central to development of complications
- Affected by many perioperative treatments
Insulin & Recovery

Insulin: main anabolic hormone involved in

• All parts of metabolism
  – Glucose control
  – Fat metabolism
  – Protein

• Regulator of return of key functions

• Central to development of complications

• Affected by many perioperative treatments

• Insulin resistance: a key for understanding and enhancing recovery
Outline

• Why Insulin Resistance & Enhanced Recovery?
• Insulin resistance
  – Recovery
  – Complications
• Enhanced Recovery After Surgery (ERAS)
  – Interaction and protection against insulin resistance
  – ERAS and outcomes
Outline

• Why Insulin Resistance & Enhanced Recovery?
• Insulin resistance
  – Recovery
  – Complications
• Enhanced Recovery After Surgery (ERAS)
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  – ERAS and outcomes
Recovery After Surgery
What are we trying to achieve?

Patient back to preoperative function
- Normal GI function and food intake—energy & protein\(^1\)
  - Normal food intake
  - Bowel movement
- Pain control—pain cause insulin resistance\(^2\)
- Mobility—bed rest enhance protein breakdown\(^3\)

- No complication

Insulin resistance & complications

- Elective cardiac surgery, n= 273
- Diabetics and non diabetics

Complications increase with insulin resistance:
50% reduction in insulin sensitivity:
- 5-6 fold increase risk of complications
- 10 fold risk for infections

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

- Insulin resistance counteracts recovery
- Insulin resistance
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Postoperative Insulin resistance

Definition:
Below normal metabolic effect of insulin
• Glucose uptake
• Reduction in glucose production
• Lipolysis
• Protein breakdown / balance
Insulin sensitivity falls with the magnitude of surgery

Adopted from Thorell et al: Curr Opin Clin Nutr Metab Care 1999

**Reduction in Insulin Sensitivity (%)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Postop / Preop M-value x 100 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lap cholecystectomy</td>
<td>-20</td>
</tr>
<tr>
<td>Open hernia</td>
<td>-30</td>
</tr>
<tr>
<td>Open cholecystectomy</td>
<td>-40</td>
</tr>
<tr>
<td>Open colorectal</td>
<td>-60</td>
</tr>
</tbody>
</table>

$P < 0.001$, ANOVA

$n = 6-13$
Independent factors predicting length of stay

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

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

Thorell et al: Curr Opin Clin Nutr Metab Care 1999
Glucose uptake

Insulin regulated
Concentration regulated

Liver
Storage
Muscle
Fat
Neural tissue
Blood cells
Endothel

[B-Glucose]
Glucose uptake - meal

- Muscle
- Storage
- Liver
- Fat
- Neural tissue
- Blood cells
- Kidney
- Endothel

[B-Glucose]

Insulin regulated
Concentration regulated
Glucose uptake - stress

Insulin regulated
Concentration regulated

Liver

Muscle

Fat

Endothel

Blood cells

Neural tissue

[Glucose]
Driving forces for hyperglycemia after surgery

<table>
<thead>
<tr>
<th></th>
<th>Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>+</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>-</td>
</tr>
<tr>
<td><strong>Glucose production</strong></td>
<td>+</td>
</tr>
<tr>
<td><strong>Peripheral glucose uptake</strong></td>
<td>-</td>
</tr>
<tr>
<td>GLUT4 translocation</td>
<td>-</td>
</tr>
<tr>
<td>Glycogen formation</td>
<td>-</td>
</tr>
</tbody>
</table>

Adopted from Ljungqvist et al, Clin Nutr 2001
Driving forces for hyperglycemia after surgery similar to diabetes

<table>
<thead>
<tr>
<th></th>
<th>Postop</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Glucose production</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Peripheral glucose uptake</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GLUT4 translocation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Glycogen formation</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Adopted from Ljungqvist et al, Clin Nutr 2001
Normalizing insulin action normalizes metabolism

Insulin infusion to normalize:

• Blood glucose

Also controlled:

• FFA
• Urea excretion
• Substrate utilization after major surgery

Insulin resistance the key to catabolism

Outline

• **Insulin resistance counteracts recovery**
• **Insulin resistance is central to stress metabolism**
  – Recovery
  – Complications
• **Enhanced Recovery After Surgery (ERAS)**
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Glucose uptake - stress

Liver

Muscle

Fat

Neural tissue

Blood cells

Endothel

Too little

[Glucose]

Too much

Kidney

Insulin regulated

Concentration regulated
Insulin resistance muscle

- Reduced glucose uptake
- Reduced glycogen storage
- Increased protein catabolism
Insulin resistance muscle

Energy supply
- Reduced glucose uptake
- Reduced glycogen storage
- Increased protein catabolism

Lean body mass
- Muscle function

Mobilisation
Insulin important for wound healing

- 6 patients studied twice, >40% burn injury
- Placebo – randomised - cross over design
- Hyperinsulinemia
  - 400-900 microunits/ml for 7 days or placebo
- Glucose infusion to normoglycemia

- Donor-site healing time reduced
  - from 6.5 to 4.7 days, p < 0.05

EJ Pierre et al, J Trauma 1998
# Impaired Recovery

<table>
<thead>
<tr>
<th>Postop (days)</th>
<th>Tissues/cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness</td>
<td>muscle</td>
</tr>
<tr>
<td>Infections</td>
<td>leukocytes</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>blood vessels</td>
</tr>
<tr>
<td>Renal failure</td>
<td>kidney</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>nerve tissue</td>
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</table>
Outline

• **Insulin resistance counteracts recovery**
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mRNA of inflammatory pathway genes up-regulated in skeletal muscle

Witasp et al, Clin Nutr 2009
Intracellular gene reactions to surgery

Endocrine signaling

Inflammatory signaling

Insulin signaling/glucose uptake

Witas et al, JCEM 2010: 95: 3460-9
## Complications

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<td>muscle</td>
</tr>
</tbody>
</table>
Why these organs/cells?

Tissues unprotected to glucose uptake:

• Uncontrolled inflow of glucose
• No storage
• Overflow of glycolysis
• ROS production
• Block of glycolysis & Krebs cycle
• Altered gene expression
• Enhanced inflammatory response
• Vicious circle
Vicious circle

Stress of surgery
Stress hormones
Cytokines

Insulin resistance
Hyperglycemia
Enhanced inflammation
ROS production
Glucose levels in ERAS & outcomes after surgery

- 120 Consecutive patients
- Colorectal surgery
- No history of diabetes
- Preop HbA1c – above or below 6.1
- 26% pathologically high (≥ 6.1 mM)
- Glucose 5 times daily postop
- CRP and complications (30 day follow up)

Gustafsson et al, BJS 2009: 96; 1358-64
Glucose after major elective surgery

N = 120
1500 kcal/d

Gustafsson et al, BJS 2009: 96; 1358-64
HbA1c, Glucose control and postop complications

Gustafsson et al, BJS 2009: 96; 1358-64

Complications

- HBA1c > 6.1: OR 2.9, P < 0.05
- HBA1c ≤ 6.1: OR 2.3, P = 0.13

Infections

- HBA1c > 6.1: % of patients
- HBA1c ≤ 6.1: % of patients
Postoperative insulin resistance increase the risk for complications

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

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

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

<table>
<thead>
<tr>
<th>Glucose level</th>
<th>Outcome</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate (161-200 mg/dl) (8.9-11.1 mmol/l)</td>
<td>Surgical site infection</td>
<td>1.44 (1.10-1.87)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>1.37 (1.00-1.87)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Severe (&gt;200mg/dl) (&gt;11.1 mmol/l)</td>
<td>Pneumonia</td>
<td>1.55 (1.10-2.18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Re operation</td>
<td>1.37 (1.02-1.87)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Jackson et al, JACS 214; 2012
Hyperglycemia impairs immune function

- Correlation between hyperglycemia and incidence of infection
- Diabetics with poor glucose control
  - Abnormal granulocyte adherence
  - Reduced chemotaxis
  - Lower phagocytosis
  - Abnormal microbiocidal function

All above improved by glucose control

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Fast track surgery ≈> ERAS

• Multimodal approach to recovery - H Kehlet, DK
• A pioneer in fast track surgery

• Inspiration and early collaborator in ERAS

• ERAS – focus on patient recovery – not speed per se

*Fearon K et al, Clin Nutr 2005,
Enhanced Recovery After Surgery Study Group

• Best practice in perioperative care:
  – colon resection,
  – rectal resection,
  • liver, gastric, pancreas, gynaecology, urology…..

• Aims: Enhance recovery

• Means:
  – *Reduce the stress of surgery*
  – *Support of function*

• Evidence Based Protocol*

3 brand new guidelines 2012

Guidelines for Perioperative Care in Elective Colonic Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations

U. O. Gustafsson · M. J. Scott · W. Schwenk · N. Demartines · D. Roulin · N. Francis · C. E. McNaught · J. MacFie · A. S. Liberman · M. Soop · A. Hill · R. H. Kennedy · D. N. Lobo · K. Fearon · O. Ljungqvist

Guidelines for Perioperative Care for Pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society Recommendations

World J Surg
DOI 10.1007/s00268-012-1771-1

Guidelines for Perioperative Care in Elective Rectal/Pelvic Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations

J. Nygren · J. Thacker · F. Carli · K. C. H. Fearon · S. Norderval · D. N. Lobo · O. Ljungqvist · M. Soop · J. Ramirez
3 new guidelines 2012

Available free
www.erassociety.org
ERAS
Making radical changes

**Surgeon:**
- No bowel prep
- Food after surgery
- No drains
- Early removal u-catheter
- No iv fluids, no lines
- Early discharge

**Anesthetist:**
- Carbohydrates no fasting
- No premedication
- Thoracic Epidural Anesthesia
- Balanced fluids
- Vasopressors
- No or short acting opioids

*All evidence based!*
Enhanced Recovery After Surgery
ERAS

Standardized protocol for perioperative care

• Reduce stress
• Support function

• Evidence based care
• Integrated view
• Standards
• Follow up – audit
Enhanced Recovery After Surgery

Patients journey

Clinic

Preop

Surgery

Anesthesia

HDU

Ward

Home

Recovery

Audit compliance & outcomes
• Issues remain, but new insights and possibilities
• Insulin resistance counteracts recovery
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• ERAS presents EBM protocols to enhance recovery
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ERAS

- Peri-op fluid balance
- Epidural Anaesthesia
- Short acting anaesthetics
- DVT prophylaxis
- Pre-op counselling
- Early mobilisation
- Early postop oral feeding
- Maintaining body temperature
- Oral analgesics/NSAID’s
- Prevention of ileus/prokinetics
- Early removal of catheters/drains
- No - premed
- No bowel prep
- Preop CHO/no fasting
- Surgical technique
- No NG tubes

Fearon et al, Clin Nutr, 2005
ERAS

- Peri-op fluid balance
- Epidural Anaesthesia
- Short acting anaesthetics
- DVT prophylaxis
- Pre-op counselling
- Early mobilisation
- Early postop oral feeding
- Preventing ileus/prokinetics
- Oral analgesics/NSAID's
- Maintaining body temperature
- Preop CHO/no fasting
- No premed
- No bowel prep
- Surgical technique
- No NG tubes
- Early removal of catheters/drains

Fearon et al, Clin Nutr, 2005
ERAS elements to reduce insulin resistance

Preoperative
• Preoperative carbohydrates
• Epidural anesthesia

Postoperative
• Pain control
• Early postop feeding
Preoperative CHO reduces postop insulin resistance

Nygren et al: Curr Opin Clin Nutr Metab Care 2001
EDA reduces postoperative insulin resistance

Uchida, Br J Surg 1988

- Epinephrine
- Cortisol
- Insulin sensitivity

Postoperative change (%)

* p<0.05
** p<0.01

IV Opiates
EDA

Uchida, Br J Surg 1988
Insulin sensitivity improved with pre op Carb, EDA + post op feed

Epidural - less paralysis

EDA vs. Iv opiates

Jorgensen Cochr Database Syst Rev 2004
ERAS: oral intake development
(mean intake postop day 1-4)
Insulin sensitivity

Day before surgery

ERAS Care

Dinner, normal sleep

Bowel prep
No nutrition

Traditional care
Insulin sensitivity

Morning of surgery

ERAS Care

- Dinner, normal sleep
- Carbohydrate treatment
- Overnight fasting
- Bowel prep
- No nutrition

Traditional care
Insulin sensitivity

Anesthesia start

ERAS Care

Dinner, normal sleep
Carbohydrate treatment
Thoracic Epidural

Preoperative sedation
Overnight fasting
Bowel prep
No nutrition

Traditional care
Insulin sensitivity

Reaction to surgery

ERAS Care

Dinner, normal sleep
Carbohydrate treatment
Thoracic Epidural

Surgery

Overnight fasting
Preoperative sedation
Bowel prep
No nutrition

Greater drop without Epidural

Traditional care
Insulin sensitivity

Afternoon of surgery

ERAS Care

Dinner, normal sleep
Carbohydrate treatment
Thoracic Epidural

Immediate feeding & mobilisation

Surgery

NPO iv low caloric fluids

Preoperative sedation
Overnight fasting
Bowel prep
No nutrition

Traditional care
Insulin sensitivity

Days after surgery

ERAS Care

- Dinner, normal sleep
- Immediate feeding & mobilisation
- Carbohydrate treatment
- Thoracic Epidural
- Oral feeding & mobilisation
- Preoperative sedation
- Overnight fasting
- Slow return to feeding and mobilisation
- Bowel prep
- No nutrition
- NPO iv low caloric fluids

Traditional care

Ljungqvist, JPEN 2012
Insulin sensitivity

Days after surgery

ERAS Care

- Dinner, normal sleep
- Immediate feeding & mobilisation
- Carbohydrate treatment
- Thoracic Epidural
- Oral feeding & mobilisation
- Slow return to feeding and mobilisation
- Surgery

Traditional care

- Preoperative sedation
- Overnight fasting
- Bowel prep
- No nutrition

ERAS Society

- NPO iv low caloric fluids
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• Issues remain, but new insights and possibilities
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  – Minimize insulin resistance & support anabolism
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Real life Adherence to Best practice

The German "Prevalence" Study in ICU

- 92% adherence to best practices

M M Levy, ASPEN 2007
Implementing change
Adherence to Best practice

The German "Prevalence" Study

92% 4%

Use of low tidal volume

M M Levy, ASPEN 2007
ERAS: Audit the change

Audit compliance & outcomes
ERAS implementation

**Primary Operation**
- Sigmoid resection: 24%
- Ileoceleal/rectal anastomosis: 23%
- Anterior resection of rectum: 19%
- Left hemicolectomy: 7%
- Reversal of Hartmann’s proctocolectomy: 5%
- Abdominoperineal resection: 4%
- Other large/small bowel surgery: 3%
- Total/Subtotal colectomy: 1%
- Proctocolectomy with anus exploration only: 1%

**Complications (Primary and Follow-up)**
- Nausea or vomiting: 15%
- Wound infection: 13%
- Urinary tract infection: 10%
- Urinary retention: 9%
- Other: 5%
- Anastomotic leak: 4%
- Cardiac arrhythmia: 4%
- Renal dysfunction: 4%
- Other EDA-related complications: 4%

**LOS & ICU (Average)**
- Primary Stay: 9.3 days
- Readmission: 0.6 days
- Total Stay: 9.8 days
- Intensive Care: 0.3 days

Admission Records in Selection: 183 of 183
Before ERAS: Outcomes

Compliance

Primary Operation

Complications (Primary and Follow-up)

LOS & ICU (Average)
Before ERAS: Compliance
After ERAS: Outcomes

Primary Operation

<table>
<thead>
<tr>
<th>Operation</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmoid resection</td>
<td>23%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Left hemicolectomy</td>
<td>11%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Abdominoperineal resection</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other large/small bowel surgery</td>
<td>3%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Other stoma procedures</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total/Subtotal colectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctocolectomy w/ anus</td>
<td></td>
<td></td>
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</tbody>
</table>

ERAS Compliance: 71%

Complications (Primary and Follow-up)

<table>
<thead>
<tr>
<th>Complication</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea or vomiting</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td></td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td></td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Obstipation or diarrhea</td>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Other respiratory complications</td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Other EDA-related complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar atelectasis</td>
<td></td>
<td></td>
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LOS & ICU (Average)

<table>
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<tr>
<th>Component</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Stay</td>
<td>8.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Readmission</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Total Stay</td>
<td>8.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Intensive Care</td>
<td></td>
<td>0.2</td>
</tr>
</tbody>
</table>
After ERAS: Compliance
Length of stay & Readmissions vs. ERAS compliance

Gustafsson et al, Arch Surg, 2011
Complications & Symptoms vs. ERAS compliance

Gustafsson et al, Arch Surg, 2011
ERAS Compliance vs LOS

N = 3369
19 centers
8 countries
ERAS reduce length of stay

Length of stay reduced by 2.5 days

Meta analysis 452 patients, 6 RCTs, 4 countries

Varadhan et al, Clin Nutr 2010
ERAS reduce complications

Complications down by half

Meta analysis 452 patients, 6 RCTs, 4 countries

Varadhan et al, Clin Nutr 2010
Metabolic response to surgery in traditional perioperative care

- N losses
- N balance
- Energy exp
- Glucose
- Insulin
- Insulin sens

Postoperative change (%)

Traditional
Metabolic response to surgery in traditional perioperative care vs. ERAS protocols

- N losses
- N balance
- Energy exp
- Glucose
- Insulin
- Insulin sens

Postoperative change (%)

- Traditional
- ERAS protocols
Insulin resistance counteracts recovery

Insulin resistance is central to stress metabolism
  - Reduces healing and muscle function recovery
  - Closely related to common postoperative complications

ERAS presents EBM protocols to enhance recovery
  - Interaction and protection against insulin resistance
  - Structured interactive audit increase compliance and improve outcomes by minimizing metabolic stress
Conclusions

Enhanced Recovery After Surgery is achieved by

• Using Evidence Based Protocols for perioperative care

ERAS

• Improves outcomes
  – Faster return of function
  – Reduce complications

A Key mechanism:

• Minimize insulin resistance
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• Metabolism and Nutrition is back on the surgical agenda
2nd ERAS World congress

Valencia Spain
April 23-26, 2014

World class speakers

BJS Henrik Kehlet Lecture

Pre congress course: Implementation

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