



Increased amino acid provision does not lead to insulin resistance in lung cancer cachexia



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Background

- Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and has a poor prognosis.
- Reported high incidence of glucose intolerance and insulin resistance in cancer (particularly in weight-losing patients).
- Insulin resistance to amino acids can be concurrent with that of glucose¹.
- Previous studies suggest that higher provisions of amino acids can impair insulin-stimulated glucose uptake^{2,3}.

1. S. Pereira et al. *Insulin resistance of protein metabolism in type 2 diabetes*. Diabetes, (51), 2008, 56-63.
2. M. Krebs et al. *Mechanism of Amino Acid-induced Skeletal Muscle Insulin Resistance in Humans*. Diabetes, (51), 2002, 599-605.
3. M. Tremblay et al. *Overactivation of S6 Kinase 1 as a Cause of Human Insulin Resistance During Increased Amino Acid Availability*. Diabetes, (54), 2005, 2674-2684.

Hypotheses

- In cancer cachexia, there is a diminished uptake of glucose and amino acids due to insulin resistance
- Increasing provision of amino acids to post-prandial levels will adversely affect insulin sensitivity

Objectives

- To assess insulin resistance to glucose and amino acids in patients with advanced NSCLC and >5% weight loss in the past 12 months.
- To assess whether a physiological elevation of amino acids will adversely affect insulin sensitivity

Methods

- NSCLC subjects from Oncology Clinics and healthy, age & smoking history-matched controls via advertisements.
- **Experimental protocol:**
2-day admission in Clinical Investigation Unit:
Day 1: isoenergetic, isonitrogenous formula diet (based on 24h food recall), indirect calorimetry (Deltatrac), body composition (DEXA)

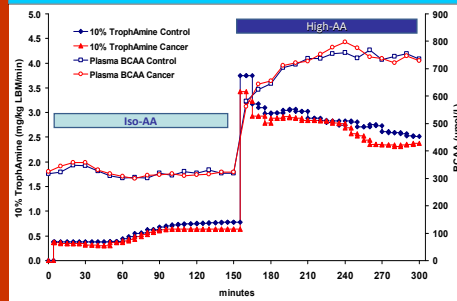
Subject Characteristics

NSCLC subjects:

- 7 men (6 adenocarcinoma, 1 squamous cell) stage III and IV
- 2 brain, 2 bone, no liver metastases
- 3 pre-, 4 post-chemotherapy (> 3 months)
- No diabetes, other metabolic disorders, anemia (Hb<100 g/L), metastases that affect organ functions, medications affecting metabolism
- Average weight loss: $8 \pm 1\%$ in 12 months

| | Control (n=8) | Cancer (n=7) |
|---|---------------|--------------|
| Age (y) | 61 ± 2 | 64 ± 3 |
| Weight (kg) | 67 ± 2 | 60 ± 3 |
| BMI (kg/m ²) | 24 ± 1 | 21 ± 1 |
| Lean body mass index (kg/m ²) | 17 ± 1 | 16 ± 1 |
| Appendicular muscle mass index (kg/m ²) | 8 ± 1 | 7 ± 1 |
| Body fat (%) | 24 ± 2 | 22 ± 2 |
| Suprailiac skinfold (mm) | 15 ± 1 | 9 ± 1† |
| Thigh circumference (cm) | 52 ± 1 | 46 ± 2† |

AA Infusion & BCAA Concentrations



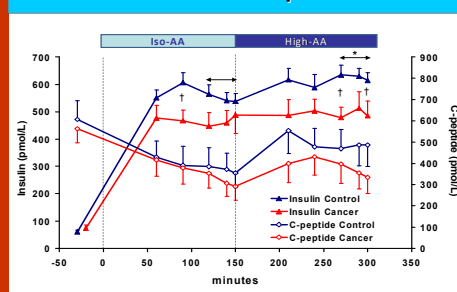
| Nutritional and metabolic data: | Control (n=8) | Cancer (n=7) |
|---------------------------------|---------------|--------------|
| Energy intake (kcal/d) | 2498 ± 181 | 1948 ± 25† |
| (kcal/kg LBM*d) | 52 ± 4 | 43 ± 2 |
| Protein intake (g/d) | 85 ± 5 | 72 ± 5 |
| (% energy) | 14 ± 1 | 16 ± 1 |
| REE (kcal/kg LBM*d) | 29 ± 1 | 31 ± 1 |
| (% of predicted) | 98 ± 2 | 107 ± 5 |

| Smoking history and physical activity: | Control (n=8) | Cancer (n=7) |
|--|---------------|--------------|
| Smoking (pack-yrs) | 22 ± 5 | 29 ± 9 |
| Quit smoking (yrs) | 16 ± 5 | 10 ± 5 |
| Handgrip strength (kg) | 44 ± 2 | 38 ± 3 |
| Physical activity (PASE questionnaire) | 178 ± 21 | 102 ± 18† |

| Clinical laboratory results: | Control (n=8) | Cancer (n=7) |
|--|---------------|--------------|
| C-reactive protein (mg/L) | 1.2 ± 0.4 | 14.4 ± 5.3‡ |
| Hemoglobin (g/L) | 148 ± 4 | 138 ± 7 |
| White blood cells (10 ⁹ /L) | 5.7 ± 0.5 | 8.5 ± 1.8 |
| Albumin (g/L) | 41 ± 1 | 38 ± 1 |
| Platelets (10 ⁹ /L) | 251 ± 13 | 264 ± 22 |
| Testosterone (pmol/L) | 30 ± 3 | 25 ± 3 |
| Cortisol am (nmol/L) | 311 ± 28 | 370 ± 45 |
| Growth hormone (µg/L) | 0.6 ± 0.2 | 1.8 ± 0.6 |
| Urea (mmol/L) | 4.9 ± 0.2 | 3.4 ± 0.3† |
| Creatinine (µmol/L) | 72 ± 3 | 78 ± 3 |

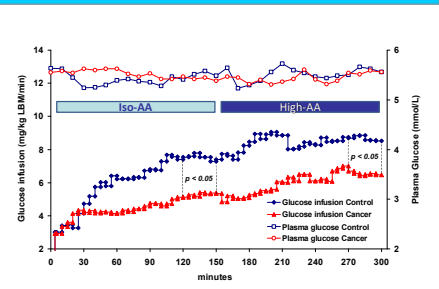
Mean ± SEM. †p<0.05 vs. control group by independent t-tests, ‡p<0.01 vs. control group by Mann-Whitney

Insulin & C-Peptide

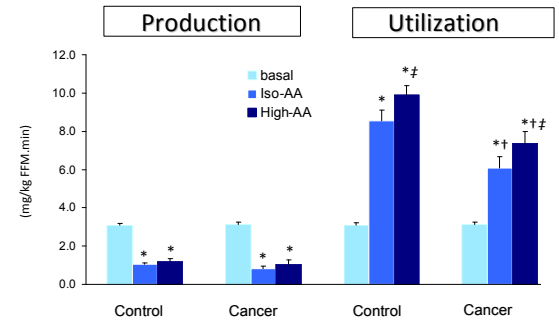


Results

Glucose Infusion & Concentrations



Glucose Kinetics



Summary

Patients with NSCLC and mild cachexia vs. well-matched controls exhibit:

- ↓ Energy intake, anthropometric measures, and physical activity
- Normal fasting insulin, glucose production (EGP), glucose, FFA & AA
- Inflammation but no hypermetabolism

In response to insulin with fasting AAs (Iso-AA):

- **Impaired** insulin-stimulated peripheral uptake of glucose and As
- Normal suppression of EGP and lipolysis

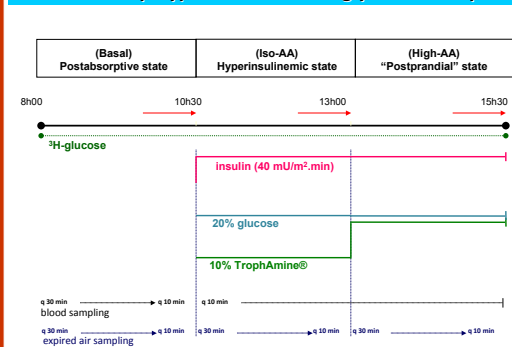
In response to insulin & postprandial AAs (High-AA):

- **Impaired** insulin-stimulated glucose uptake
- Normal insulin-stimulated uptake of amino acids

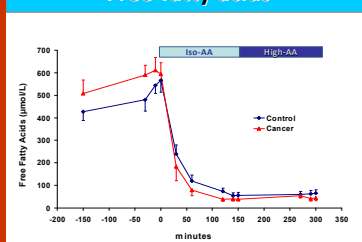
Novel Findings:

- Instead of anticipated impairment of glucose uptake from High-AA, both groups increased glucose utilization (albeit lower in cancer)
- NSCLC subjects reached a lesser hyperinsulinemia with the same infusion rates

Two-step hyperinsulinemic euglycemic clamp



Free-fatty acids



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Conclusion

Providing high availability of amino acids, equivalent to a physiological postprandial state (≈25g protein) did not impair insulin action on glucose metabolism; rather it enhanced glucose uptake.

Therefore, the presence of insulin resistance should not be viewed as a deterrent to recommending higher protein intakes in patients with cancer cachexia.