A Simple, High-Resolution Model-Based Insulin Sensitivity Test - Analysis, Benchmark and Clinical Pilot

Thomas Lotz¹, J Geoffrey Chase¹, Kirsten A McAuley², Geoffrey M Shaw³, Juliet Berkeley³ and Jim I Mann²

¹Centre for Bioengineering, University of Canterbury, Christchurch, New Zealand
²Edgar National Centre for Diabetes Research, Dunedin, New Zealand
³Dept of Intensive Care Medicine, Christchurch Hospital, Christchurch, New Zealand

1.0 Introduction

Type 2 Diabetes affects more than 230 million people worldwide and is responsible for 3.5 million deaths annually [1]. About 215,000 New Zealanders are estimated to have type 2 Diabetes and an equal number are insulin resistant, prior to developing the disease [2]. Costs for the NZ public health system: $540 million in 2006, expected to rise over $1.8 billion by 2021 [2]. Similar numbers and scales hold worldwide [1].

Early diagnosis of insulin resistance can reduce the burden of further complications and save lives. Current diagnostic methods are too expensive and complicated to be useful in widespread population screening (euglycaemic clamp, IVGTT), or not accurate enough to give more than a high/low result (HOMA, OGTT).

Insulin resistance rises up to 10 years prior to diagnosis.

2.0 Test design

Provide complete diagnostic information about:
- Insulin sensitivity
- β-cell function

Design goals:
1.) Simple, low intensity, 2.) high accuracy, 3.) low cost, and 4.) physiologically dosed (and thus measured)

The protocol:
1. Low dose bolus of glucose (10g) and insulin (1U)
   - Reduce endogenous regulatory effects
   - Improve clinical practicability and safety
2. 30 min timed sampling of glucose, insulin and C-peptide
3. Fit metabolic models
   - Only transient data from 10 - 30 minutes post bolus
   - Identification requires only few samples
4. Determine insulin sensitivity from model parameter $S_i$
5. Determine β-cell function from C-peptide data

3.0 Diagnostic outcome

Test outcome on 3 exemplary subjects spanning the range from NGT to Type 2 Diabetes:

- **Normal Glucose Tolerant (NGT)**
  - High insulin sensitivity ($11.7 \times 10^{-4}$ mU/l/min)
  - Healthy 1st phase insulin response
  - Rapid decay of glucose concentration

- **Impaired Fasting Glucose (IFG)**
  - Low insulin sensitivity ($3.2 \times 10^{-4}$ mU/l/min)
  - Impaired 1st phase insulin response
  - Elevated insulin secretion throughout
  - Slow decay of glucose concentration

- **Type 2 diabetes**
  - Low insulin sensitivity ($6.7 \times 10^{-4}$ mU/l/min)
  - Insignificant 1st phase insulin response
  - Significant b-cell damage
  - Elevated glucose concentrations

4.0 Performance

1. Model validation on euglycemic clamp data [3]
   - a) Correlation clamp $ISI$ vs. model $S_i$, r=0.97
   - b) Change in insulin sensitivity in intervention study by McAuley et al. [4]

2. Clinical Pilot study
   - 17 subjects, 43 tests
   - **Part 1:** Effect of dose on outcome
     - Low dose: 5g glucose / 0.5U insulin
     - Medium dose: 10g glucose / 1U insulin
     - High dose: 20g glucose / 2U insulin
   - **Part 2:** Repeatability
     - Same dose on same individual on a different day

3.0 Repeatability

- **Model-based insulin sensitivity testing**
  - Higher repeatability 6.0% (MSD 4.9)
  - Range 1.7% - 24.7%

References: