A simple model-based test for insulin sensitivity compares well with the euglycaemic hyperinsulinaemic clamp

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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].

Early diagnosis of insulin resistance can reduce the burden of further complications and save lives and cost. Current diagnostic methods are too expensive and complicated to be useful in widespread population screening (euglycemic 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

Test design

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

The test is designed to measure the same metabolic effect as the gold standard euglycaemic hyperinsulinaemic clamp.

Design goals:
Simple, low intensity, high accuracy, low cost, physiological dosing

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
5. Determine β-cell function from C-peptide data

Diagnostic outcome

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

Type 2 diabetes
- Low insulin sensitivity (6.7 x 10⁻⁴ mU/l/min)
- Insignificant 1st phase insulin response
- Elevated glucose concentrations

Impaired Fasting Glucose (IFG)
- Low insulin sensitivity (3.2 x 10⁻⁴ mU/l/min)
- Impaired 1st phase insulin response
- Elevated insulin secretion throughout
- Slow decay of glucose concentration

Normal Glucose Tolerant (NGT)
- High insulin sensitivity (11.7 x 10⁻⁴ mU/l/min)
- Healthy 1st phase insulin response
- Elevated insulin secretion throughout
- Rapid decay of glucose concentration

Performance

1. Model validation on euglycemic clamp data [3]
   a) Correlation clamp
   ISI vs. model S, 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
   - Difference not statistically significant (P=0.5, P=0.52)

   Part 2: Repeatability
   - Same dose on same individual on a different day

References
[1] International Diabetes Federation (www.idf.org)