The short term effect of repaglinide therapy on sub-optimally treated Type 2 diabetes

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Introduction

- β-cell dysfunction causes disturbed proinsulin (PI) to insulin (I) processing, resulting in hyperproinsulinaemia
- This imbalance is indicative of insulin resistance (IR) not just in Type 2 diabetes but also in those without diabetes
- An elevated PI/I ratio is indicative of increased secretory demand on β-cells
- Repaglinide, a short acting insulin sectretagogue, targets postprandial glucose excursions by stimulating insulin secretion without causing excessive hypoglycaemia, weight gain and hyperinsulinemia, more common with sulfonylureas

Aims

- To examine the effects of repaglinide on beta-cell function and levels of insulin sensitivity and resistance in Type 2 diabetes patients sub-optimally treated with metformin

Methods

- Patients (n=11) received repaglinide (starting dose 1mg TD) in addition to their metformin for 8 weeks
- A 75g OGTT was performed pre and post intervention, at 0 and 8 weeks. Samples were collected at 0, 15, 30, 45, 60 and 120 mins.
- Plasma glucose and insulin were measured using a Roche Modular Analyser locally in the routine clinical chemistry laboratory (all time points)
- Intact proinsulin was measured using a commercially available chemiluminescence assay (IV2-002; Invitron, Monmouth, UK) (0, 60 and 120 min time points)
- Insulin sensitivity (ISI) was calculated using the Matsuda Index and HOMA-IR determined using HOMA2 model

Results

- Baseline demographics for the 11 participants (7 males, 4 females) are detailed in Table 1

Table 1 Baseline demographics

Characteristic	
Age (Years)	57 ± 8.5
Weight (kg)	92 ± 19.4
HbA1c (%)	8.8 ± 1.7
HbA1c (mmol/mol)	72.9 ± 18.5
Diabetes duration (Years)	5 ± 5.6

Mean and standard deviation shown

- After 8 weeks, repaglinide produced (Figure 1):-
  - a significant reduction in glucose AUC (p=0.001)
  - a significant increase in insulin AUC (p=0.017)
  - a non-significant increase in proinsulin AUC (p=0.073)
  - no change in PI/I ratio at any timepoint

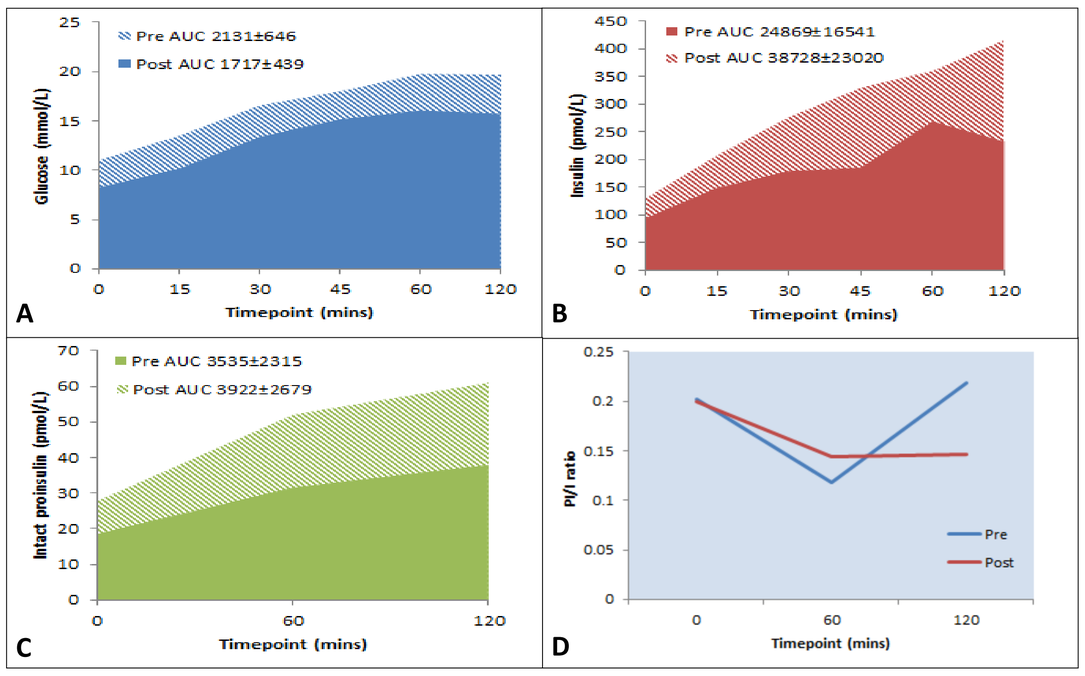

Figure 1

Plots showing A) Glucose AUC, B) Insulin AUC, C) Proinsulin AUC and D) PI/I ratio

- In a subset of patients termed 'responders' (n=5), an improvement (decrease) in PI/I ratio (>10% at 60 mins post-prandial) was observed, with no significant difference in other clinical or biochemical measures (Figure 2)

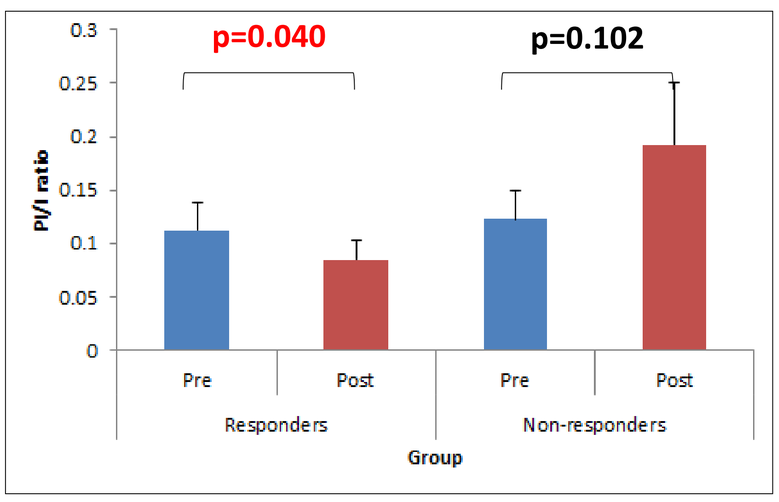

Figure 2

PI/I ratio categorised by response

- However, the 'responder' group exhibited lower insulin sensitivity (Matsuda Index) and higher HOMA-IR at baseline and 8 weeks (Figure 3)

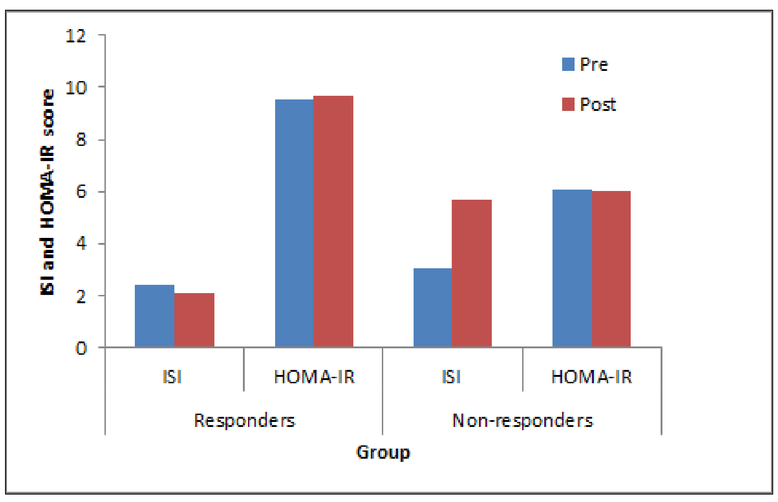

Figure 3

ISI and HOMA-IR categorised by response

Conclusions

- Repaglinide improved PI/I ratio in only a subset of patients, independent of insulin sensitivity or resistance
- An alternative treatment strategy may benefit 'non-responders' to prevent beta-cell exhaustion