

Pathophysiology of Remission in Type 2 Diabetes: The Diabetes Remission Clinical Trial (DiRECT)

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DiRECT is a prospective, randomised study of type 2 diabetes of <6 years duration. In the intervention group, weight loss was induced using a liquid diet replacement (825-853 kcal/day) for 3-5 months with withdrawal of all anti-diabetic drugs on day 1. A subgroup underwent 3-point Dixon MRI of liver and pancreas fat and measurement of hepatic very low density lipoprotein triglyceride (VLDL1-TG) metabolism and first phase insulin secretion, before and after 3-5 months. Those with HbA1c <48mmol/mol (<6.5%) after weight loss (n=37; responders) were compared with those remaining >48mmol/mol (n=16; non-responders). At baseline, the two groups were similar (age 53.3±1.2 vs. 53.6±2.2 years, weight 100.3±2.8 vs. 98.2 ±3.9kg, BMI 34.9±0.7 vs. 34.9±1.2kg/m²) but not duration of diabetes (2.7±0.3 vs. 3.8±0.4 years, p=0.04) nor HbA1c 57.1±1.8 vs. 62.5±2.3 mmol/mol; p<0.07).

Weight decreased similarly in responders (100.3±2.8 vs. 84.2±2.3kg; p<0.0001) and in non-responders (98.2 ±3.2 vs. 84.3 ±3.6kg (p<0.0001). HbA1c changed only in responders (57.1±1.8 to 41.2±0.6 mmol/mol, p<0.0001; 62.5±2.3 to 63.8±4.7 mmol/mol, p=0.77, respectively). Decreases occurred in liver fat in responders and non-responders (16.7±1.6 to 3.4±0.7%, p<0.0001 and 15.0±2.7 to 2.4±0.5%, p<0.0001), plasma VLDL1-TG concentration (0.69±0.07 to 0.44±0.06 mmol/l, p=0.001 and 0.64±0.10 to 0.46±0.11 mmol/l, p=0.15), and intra-pancreatic fat (8.7±0.4 to 7.8±0.4%, p<0.0001 and from 7.6±0.5 to 6.7±0.4%, p=0.001). In contrast, first phase insulin secretion increased in responders only (0.05±0.01 to 0.12±0.02, p<0.0001 vs. 0.02± 0.01 to 0.02±0.01, p=0.98, respectively).

Failure of first phase insulin secretion response but not differential lipid or hepatic responses characterises non-responders. De-differentiation of beta cells in early type 2 diabetes is not reversible in all, despite removal of the metabolic stress. Such individuals are characterised by longer duration of diabetes even in early type 2 diabetes.