Diabetes Remission Clinical Trial (DiRECT): Changes in Hepatic VLDL1-TG Production and Intrapancreatic Fat during Weight Maintenance Phase

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Type 2 diabetes is characterized by excess hepatic and intrapancreatic fat deposition. Liver-derived Very Low Density Lipoprotein-Triglyceride (VLDL1-TG) delivers fat to all peripheral tissues. Relative changes in VLDL1-TG production and intrapancreatic fat were investigated in a sub-group of the prospective, randomized Diabetes Remission Clinical Trial (DiRECT). Individuals with complete datasets at 12 months (n=45) were included. Detailed metabolic tests were carried out at baseline, 4 months, and 12 months after low calorie diet (825-853 kcal/day). Intra-organ fat was quantified using 3-point Dixon MRI, VLDL1-TG production was quantified using a competitive blocking non-isotopic method, and insulin secretion was measured by the Stepped Insulin Secretion Test with Arginine (SISTA).

Weight loss induced major changes in liver and intrapancreatic fat with 69% remission of diabetes (responders, defined as HbA1c <6.5%). This was followed by weight regain between 4-12 months in responders (82.3±2.8 to 85.4±3.2kg, p=0.001) and non-responders (84.5±3.2 to 89.6±3.3kg, p<0.0001). However, liver fat, VLDL1-TG production, and intrapancreatic fat remained stable in responders (2.5 ±1.9 to 2.9±0.6%, p=0.20; 386.7±30.2 to 428.5±21.2 mg/kg/day, p=0.14; and 8.0±0.5 to 7.7 ±0.4%, p=0.26, respectively). In contrast, these parameters increased in non-responders (2.7±0.5 to 6.2 ±1.8%, p=0.02; 460.2±39.8 to 596.2±36.6 mg/kg/day, p=0.001; and 6.7±0.3 to 7.0±0.4%, p=0.18, respectively). The recovered first phase insulin secretion in responders continued to improve between 4-12 months (0.13±0.02 to 0.17±0.04 nmol/min/m^2, p=0.17). There was no change in the non-responders (0.03±0.01 to 0.03±0.01 nmol/min/m^2, p=0.98).

These data are consistent with VLDL1-TG being the link between liver fat and intrapancreatic fat, and a major modulator determining remission of type 2 diabetes.