IRS1 Gene Variations Modify Insulin Resistance Response to Various Diet Types (DIRECT Study)

Durst, Ronen[1]; Tirosh, Amir[2]; Meiner, Vardialla[3]; Schwarzfuchs, Dan[2]; Shpitzen, Shoshi[4]; Schurr, Dan[4]; Eliav, Osnat[4]; Stampfer, Meir J[5]; Leitersdorf, Eran[6]; Shai, Iris[2]

[1]Hadassah Hebrew University Medical Center, Cardiology, Jerusalem, Israel; [2]Ben Gurion Univesrity of the Negev, Daniel Abraham Center for Health and Nutrition, Departments of Epidemiology, Faculty of Health Sciences, Beer Sheva, Israel; [3]Hadassah Hebrew University Medical Center, Department of Genetics, Jersualem, Israel; [4]Hadassah Hebrew University Medical Center, Center for Research Prevention and Treatment of At, Jerusalem, Israel; [5]Harvard Medical School, Departments of Epidemiology and Nutrition Harvard, Boston, USA; [6]Hadassah Hebrew University Medical Center, Center for Research Prevention and Treatment of At, Internal Medicine Department, Faculty of Medicine, Jerusalem, Israel

Background: In the 2-year Dietary Intervention Randomized Controlled Trial (DIRECT) study, participants were randomized to low-fat, Mediterranean, or low-carbohydrate diets and followed up for metabolic parameters. It is currently unknown whether genetic variants influence insulin resistance dietary response. Common genetic variants in the Insulin receptor substrate 1 (*IRS1*) gene have been recently associated with insulin resistance and hyperinsulinemia. We examined whether the best-associated variant of IRS1 modifies the long-term changes in insulin resistance and body weight among participants of the DIRECT study.

Methods and Results: We genotyped *IRS1* rs2943641 in 263 overweight adults randomly assigned to either low fat, low carbohydrate or Mediterranean diets. We assessed the progress in fasting insulin, insulin resistance (HOMA-IR) and weight loss by genotypes. There was significant interactions between *IRS1* rs2943641 genotype and dietary intervention on changes in fasting insulin (P=0.004 for interaction) and HOMA-IR (P=0.013 for interaction) at 2 years. For example: participants with CC genotype had greater decreases in insulin resistance (HOMA-IR) than those without this genotype in the low-fat diet group, while an opposite effect was observed on the non-wild type allele carriers (CT+TT) (P=0.01). No such interaction was seen on body weight. Our results recapitulated the recently published results of the Pound Loss cohort. [1]

Conclusions: There is a genetic predisposition affecting insulin levels and insulin resistance after dietary intervention. This is demonstrated by different response to various types of diet among carriers of the wild type and non-wild type *IRS1* rs2943641 allele.

1. Qi, Q., et al., Insulin Receptor Substrate 1 Gene Variation Modifies Insulin Resistance Response to Weight-Loss Diets in a 2-Year Randomized Trial: The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) Trial. Circulation, 2011. 124(5): p. 563-71.