

## **The diet resistant phenotype and its predictive value in choice of weight treatment strategies.**

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The Core program at the Ottawa Hospital Bariatric Centre is a standardized, 6 month lifestyle modification course consisting of weekly sessions and 6 or 12 weeks of total meal replacement with Optifast 900 (Nestle). We have maintained an extensive data base on a cohort of 3,249 obese subjects enrolled in this program. Notably, these subjects demonstrate a three-fold variation in weight loss after controlling for the usual predictors for weight loss, initial body weight, gender and age. We have defined subjects in the upper quintile of rate of weight loss (ROWL) in response to the initial 6 wk 900 kcal/d meal replacement formula as obese diet responsive (ODS) and those in the bottom quintile as obese diet resistant (ODR).

In support of *the hypothesis that weight loss success has important molecular determinants*, we have demonstrated, that in comparison to ODR subjects, ODS subjects exhibit: 1) increased proton leak in skeletal muscle mitochondria 2) up-regulation of gene sets involved in energy metabolism in skeletal muscle e.g. OXPHOS, 3) increased proportion of type I oxidative muscle fibers and 4) increased expression of OXPHOS genes in blood samples collected *prior to the initiation of energy restriction*.

Identification of patients least likely to respond to conventional interventions would conserve limited funding resources for bariatric surgery and expedite surgical procedures for those who require them most. Ultimately a better understanding of the diverse genetic and biochemical determinants of adiposity, short-term and long-term response to energy restriction and of capacity for weight loss maintenance, will lead to more effective and individualized treatment regimens.

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