Dr. Xavier Pi-Sunyer

Abnormal regulation of glycemia (“dysglycemia”) has an extremely long time course, from its earliest stage, labeled pre-diabetes, to the onset of Type 2 diabetes (T2D), the development of clinically detectable microvascular changes and measurable atherosclerosis, to clinically manifest complications with attendant morbidity and mortality. The Diabetes Prevention Program (**DPP**) focused on the pre-diabetes stage of dysglycemia and demonstrated powerful beneficial effects of lifestyle intervention (ILS) and metformin (MET), compared with placebo, in preventing or delaying the onset of diabetes mellitus over a 3-year period in a high risk population (n=3234). The DPP also described the role of phenotypic and genotypic risk factors associated with diabetes development, the factors that influenced the success of the interventions and health economic implications of diabetes prevention. On the basis of these results, the DPP lifestyle program has been widely implemented. The DPP Outcomes Study (**DPPOS**) explored the longer-term effects of T2D prevention, bridging the period between pre-diabetes and T2D over 11 years of follow-up, to examine outcomes that required more time to develop than the relatively brief 3 years of DPP (n=2776). DPPOS showed longer-term salutary effects of the original interventions on T2D prevention and on cardiovascular disease (CVD) risk factors. Prevention was cost-saving with MET and cost-effective with ILS. Although the aggregate microvascular outcome was not significantly reduced by either active intervention, those in whom T2D was prevented had a 28% *lower* risk of developing microvascular complications compared with those who developed T2D. The risk of complications was associated with T2D duration and HbA1c levels. The proposed project (**DPPOS Follow-up**), will study the DPPOS cohort for 10 more years, taking advantage of the long-term randomized exposure to MET and the densely phenotyped and genotyped DPPOS cohort (n=2776), including ~1500 patients with known T2D duration and ~1200 who have not developed T2D, to address yet unanswered questions about long-term exposure to MET and ILS initiated early in the course of dysglycemia. DPPOS Follow-up will examine outcomes that are of increasing public health concern in an aging population with pre-diabetes and T2D, including the development of CVD, cancer, and concomitant quality of life. The **overarching goals** of DPPOS Follow-up are to examine efficiently: 1) the putative benefits of metformin therapy begun early in the prediabetic phase on risk for CVD and cancer; 2) the very long-term effects of T2D prevention with ILS and MET by intention-to-treat on further development of diabetes, and on traditional and more recently recognized complications of dysglycemia; and 3) the modern day clinical course of dysglycemia and its associated complications, based on both categorical diagnoses (pre-diabetes vs. diabetes) as well as a continuum, including a careful analysis of interactions with DPP interventions as well as established and novel risk factors.