(1.9 kg; p<0.001 vs the prandial and biphasic groups). Median insulin doses (U/kg/day) were 0.53 for biphasic, 0.61 for prandial and 0.49 for basal insulin. Mean hypoglycemic events (≥ grade 2) were significantly greater with prandial insulin (12.0 per patient per year) than with biphasic (5.7) or basal (2.3).

Prof. Holman concluded that regimens using biphasic or prandial insulin reduced HbA1c to a greater extent than basal, but were associated with greater risks of hypoglycemia and increased weight gain.

Closing his analysis of 4T, Prof. Roden recommended that for patients with HbA1c above target despite maximal doses of metformin plus sulfonylureas, "Add basal insulin because it is as effective as biphasic and prandial insulin to decrease HbA1c, at least when HbA1c is ≤8.5%."

Prof. Roden concluded, "Long-term randomized controlled trials comparing different insulins and oral antidiabetes drugs regarding macrovascular endpoints are still lacking to allow supporting one specific therapeutic regimen in type 2 diabetes."

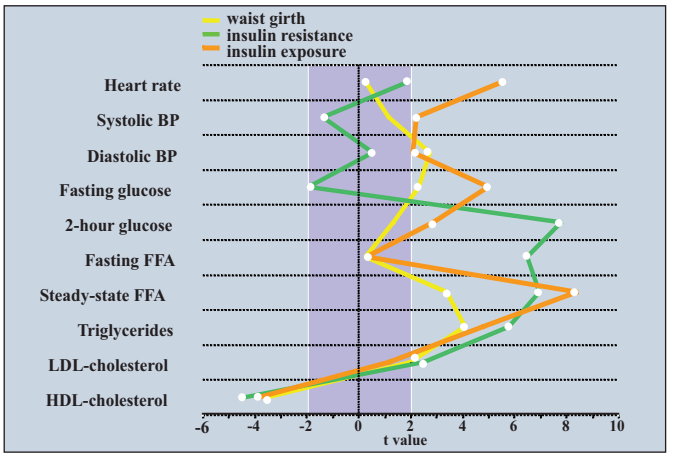
Cardiometabolic Risk Related to More Than Insulin Resistance

Results from the European RISC (Relationship Between Insulin Sensitivity and Cardiovascular Risk) study presented by Mark Walker, MD, Newcastle University, UK, suggest that insulin resistance is not the sole underlying driver of cardiometabolic risk. Insulin exposure and obesity are also independent contributors. Furthermore, the lack of physical activity promotes the development of insulin resistance, and total activity of any kind (more than the intensity of the exercise) improves insulin sensitivity.

RISC evaluated the relative contributions of cardiometabolic risk factors in a prospective study of 1,308 normal healthy adults (mean age 43; range 30-60 years) from 14 European countries. To measure insulin resistance, investigators used euglycemic clamp testing, which measures insulin resistance by balancing insulin infusions with glucose infusions. The participants also underwent oral glucose tolerance tests.

In the multivariate analysis, four traits independently predicted the cardiovascular risk score: body mass index (BMI), waist measurement, insulin resistance, and insulin exposure (Figure 1).

Figure 1. Independent Associations of Insulin Resistance, Hyperinsulinemia and Waist.



Baseline BMI and waist circumference were independently associated with most of the conventional cardiovascular risk factors. Insulin sensitivity was positively associated with postprandial free fatty acids, triglycerides, and LDL-cholesterol, and negatively associated with HDL. Insulin exposure was related to higher levels of heart rate, blood pressure, and fasting plasma glucose, and to poorer lipid profiles. Insulin resistance and hyperinsulinemia were often found in isolation and were not necessarily dependent on each other.

Physical activity was quantitatively assessed by accelerometer, which subjects wore for 5-8 days. Total amount of physical activity (total counts per day) at the end of 5 days—more than the intensity—was associated with improvement in insulin sensitivity and less arterial wall thickening.

The most active patients had the greatest insulin sensitivity. "The good news is that even for obese patients, this was true, and that you do not have to vigorously exercise to benefit," Dr. Walker noted.

In a 3-year follow-up of 784 subjects, 1% of this healthy middle-aged population had developed diabetes, 8% had impaired glucose tolerance, 13% developed hypertension, and 11% developed central adiposity. Impaired beta-cell function was associated with a three-fold risk of developing diabetes or pre-diabetes, and a two-fold risk of developing abdominal obesity at 3 years.

RISC will follow these subjects until 2014 to determine whether insulin resistance at baseline can independently predict cardiovascular disease as measured by carotid intimal thickness.