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4-T: Treating to Target in Type 2 Diabetes One-Year Results

Most patients are likely to need more than one type of insulin to achieve target glucose levels in the longer term, according to the one-year results of the 4-T Study (Treating to Target in Type 2 Diabetes).

In discussing the study, Michael Roden, MD, Medical University of Vienna, Austria, noted that the rationale for the 4-T trial was that there is still uncertainty about which strategy of insulin treatment is most favorable for type 2 diabetics who still produce insulin and exhibit fasting hyperinsulinemia. "The 4-T Study is important," Prof. Roden said, "because it directly compares the efficacy and safety of three analog insulin regimens for one year under matched conditions of oral antidiabetic therapy."

Jonathan Levy, MD, Oxford Centre for Diabetes, UK, described the 4-T protocol. In 4-T, 708 men and women aged ≥18 years with type 2 diabetes were randomly assigned to one of three open-label Novo Nordisk regimens: BID biphasic insulin (NovoMix 30), TID prandial insulin (NovoRapid) or once-daily basal insulin (Levemir) before bed, with a morning injection added if necessary. The primary outcome was the HbA1c levels achieved by each regimen.

Patients were required to have had type 2 diabetes for at least one year, HbA1c levels between 7.0-10.0%, body mass index ≤40 kg/m^2, and be currently taking sulfonylureas or metformin. Insulin titration was according to an online Trial Management System giving a single algorithm for all groups. Doses were increased if one-third or more glucose values were above target and reduced in the presence of hypoglycemia. Patients were educated as to how to adjust dosing between visits (7 from randomization to 1 year with 8 interim telephone contacts).

At baseline, mean age was ~62 years; mean diabetes duration was 9 years; HbA1c was 8.5%; and mean fasting plasma glucose was 9.6 mmol/L. The median insulin starting dose was 15 U/day (range 10-24), 77% of patients received >10 U/day, 37% >20 U/day, and 5% >40 U/day. No grade 3 hypoglycemic events occurred within 2 weeks of starting insulin. Adherence to dose adjustment recommendations (±10%) was 89.7%, 80.4%, and 90.2% for the biphasic, prandial and basal insulin groups, respectively. Significantly more patients in the basal group (17.9%; p<0.001) required a second insulin formulation versus those in the biphasic (8.9%) or prandial groups (4.2%).

Primary outcome results were presented by Rury Holman, FRCP, Oxford Centre for Diabetes, Endocrinology and Metabolism, UK (Table 1).

Table 1. 4-T One-year HbA1c Levels.

Regimen	Mean HbA1c % (± SD)	Change from baseline % (± SD)	p value
Biphasic	7.3 (0.9)	-1.3 (1.1)	
Prandial	7.2 (0.9)	-1.4 (1.0)	0.08 vs biphasic
Basal	7.6 (1.0)	-0.8 (1.0)	<0.001 vs biphasic or prandial

Significantly more patients had HbA1c <6.5% while taking prandial (23.9%) or biphasic (17.0%) insulin versus basal insulin (8.1%; p=0.001). Weight gain was highest in the prandial group (5.7 kg; p<0.005 vs biphasic) and lowest in the basal insulin group

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(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."

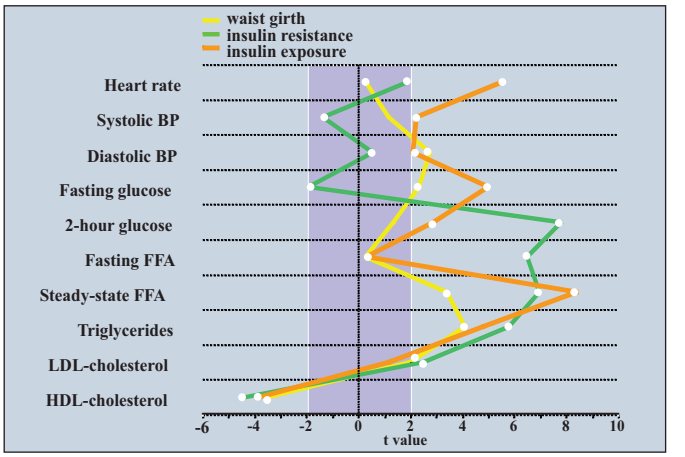
Cardiometabolic Risk Related to More Than Insulin Resistance

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.