Neurocognitive Decline Unrelated to Mild Cognitive Impairment in Type 1 Diabetes

Written by John Otrompke

Patients with type 1 diabetes (T1D) experienced a gradual decline in certain cognitive functions, but the decline was not comparable to mild cognitive impairment, which is a precursor of dementia. The decline in brain volume loss was associated with higher baseline systolic blood pressure (SBP), while a decline in executive function was associated with baseline elevated HbA1C in patients with T1D, according to Eelco van Duinkerken, PhD, Vrije Universiteit Medical Center, Amsterdam, The Netherlands, who presented the 4-year follow-up data.

The study of cognitive decline compared the brain function of 25 patients with T1D and 25 matched controls. All participants had to be free of diseases affecting the brain and psychiatric comorbidities, and had to be right-handed. To explore the theory that microangiopathy is related to cognitive decline, all diabetic patients had proliferative retinopathy as a marker of angiopathy, and diabetes duration of at least 10 years.

At baseline, the mean age for all was ~45 years (range, 18 to 56 years), and the mean duration of diabetes was 35 years. The SBP was 133.9 mm Hg in the diabetes group, compared with 126.9 mm Hg in the control group (p=0.045). The baseline HbA1C values were 7.9% and 5.4% (p<0.001) in the diabetes and control groups, respectively.

There was no difference in general cognitive ability, information processing speed, or attention at follow-up. The researchers noted a slight increase in performance over time in patients with diabetes, but not in the control group; however, this lacked statistical significance.

However, an accelerated decrease in executive function was found in T1D patients relative to the controls, which was ascertained by asking the subjects to identify the color of ink or state how many animals they could think of in 2 minutes.

The changes in brain volume from baseline to follow-up (mean, 4.28 years T1D group; 4.73 years control group) are measured by MRI. The decrease in brain volume was 1.34% in the patients with T1D compared with 0.68% in the control patients (p=0.036).

The brain volume loss was most notable in the frontal and central areas of the right hemisphere, which are associated with executive function performance (p=0.021).

While the baseline SBP was found to correlate with brain volume loss and baseline elevated HbA1C was found to correlate with executive function loss, there was no correlation with severe hypoglycemic events. The change in brain volume was not seen in speed-related domains, as some researchers had theorized.

T1D patients with angiopathy face the possibility of progressive cognitive decline, which is unrelated to mild cognitive impairment.

Metformin/Pioglitazone/Exenatide Triple Therapy Superior to Stepwise Add-On Conventional Therapy in Newly Diagnosed Type 2 Diabetes

Written by Muriel Cunningham

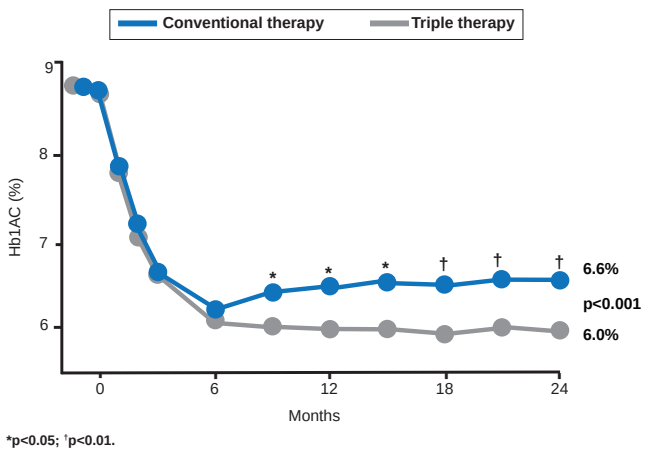
Muhammad Abdul-Ghani, MD, PhD, University of Texas Health Science Center, San Antonio, Texas, USA, presented the results of the Durability of Combination Therapy With Exenatide/Metformin Versus Conventional Therapy in New Onset T2DM study [NCT01107717] that evaluated the effects of a triple-therapy regimen versus stepwise add-on conventional therapy in patients with newly diagnosed type 2 diabetes. In this open-label study, 155 patients were randomized to triple therapy or stepwise add-on conventional therapy, with a goal of achieving an HbA1C of <6.5%. "We hypothesized that starting people with new-onset diabetes on agents that correct core defects known to be present in subjects with type 2 diabetes will produce a greater, more durable, and safer reduction in HbA1C," explained Dr. Abdul-Ghani.

Triple therapy comprised metformin 1000 mg/day, pioglitazone 15 mg/day, and exenatide 5 µg BID. At Month 1, dosages were increased to metformin 2000 mg/day, pioglitazone 30 mg/day, and exenatide 10 µg/day. Pioglitazone was increased to 45 mg/day at Month 3 if glycemic targets (fasting plasma glucose [FPG] <100 mg/dL and HbA1C <6.5%) were unmet. Patients randomized to conventional therapy started with metformin 1000 mg/day. Medication adjustments were made at specific time points if glycemic targets (FPG <100 mg/day and HbA1C <6.5%) were not met: Month 1—metformin increased to 2000 mg/day and glyburide initiated at 5 mg/day; Month 2—glyburide increased to 10 mg/day; Month 3—glargine insulin initiated at 10 units/day. Glargine dosage was increased each week by 10 units/day if FPG remained >100 mg/dL.

Patients were followed every 3 months after the first 3 months. Changes could be made to medications if FPG was <60 mg/dL or in cases of hypoglycemia. Patients were considered treatment failures if they had HbA1C levels >6.5% on two consecutive visits 3 months apart despite maximum therapy. The primary endpoint was the difference in HbA1C between the triple-therapy and conventional-therapy groups.

Participants were ~47 years of age, with duration of diabetes of ~5 months, and an initial mean HbA1C of 8.6% (range, 6.6% to 14.0%). HbA1C decreased sharply in both treatment groups by the 6-month time point. HbA1C remained below 6.5% for the triple-therapy arm from 6 to 24 months, but it gradually increased to 6.6% at 24 months in the conventional-therapy arm (Figure 1).

Figure 1. Change in HbA1C Over Time



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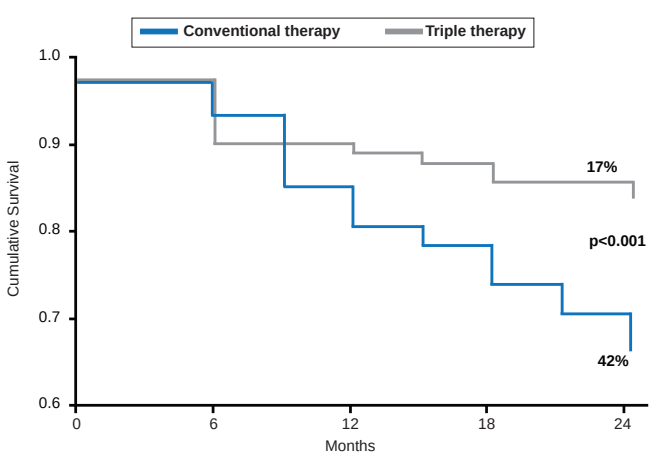
Additional analyses indicated that 60% of patients in the triple-therapy group achieved an HbA1C <6.0% versus 27% in the conventional-therapy group (p<0.001). At 24 months, significantly fewer patients in the triple-therapy group (17%) were considered treatment failures compared with the conventional-therapy group (42%; p<0.001; Figure 2).

Figure 2. Time to Treatment Failure



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Patients in the triple-therapy group lost a mean of 1.2 kg whereas those in the conventional-therapy group gained a mean of 4.1 kg at 24 months (p<0.001). Significantly fewer hypoglycemic events occurred in the triple-therapy group (15%, 0.27 events per patient-year) versus the conventional-therapy group (46%, 2.1 events per patient-year; p<0.0001).

Dr. Abdul-Ghani concluded that initiating triple therapy with metformin/pioglitazone/exenatide at diagnosis achieves a greater and more durable reduction in HbA1C with less risk of hypoglycemia compared with the stepwise add-on conventional therapy.

Insulin Dose Not Linked to Cardiovascular Mortality in the ACCORD Trial

Written by Muriel Cunningham

Previously published results from the Action to Control Cardiovascular Risk in Diabetes study [ACCORD; ACCORD Study Group. *N Engl J Med* 2008] showed an increased risk of all-cause and cardiovascular (CV) mortality in the intensive control group (HbA1C target, <6.0%) compared with the less intensive group (HbA1C target, 7.0% to 7.9%). "This brought a huge puzzle to the diabetes community, to figure out why we were seeing this result," said Elias S. Siraj, MD, Temple University School of Medicine, Philadelphia, Pennsylvania, USA. Several post hoc analyses have been conducted to date to determine what factors may have influenced this outcome [ACCORD Study Group. *N Engl J Med* 2008; Bonds DE et al. *BMJ* 2010; Riddle MC et al. *Diabetes Care* 2010; Seaquist ER et al. *Diabetes Care* 2012]. These analyses did not find a conclusive link between the ACCORD results and factors such as hypoglycemia, low HbA1C, the rapid decline in HbA1C during the first year of the study, weight gain, and specific medication use.

To better understand the findings of this study, ACCORD investigators hypothesized that higher doses of exogenous insulin may be associated with the CV mortality results from the ACCORD trial. To investigate this idea, data for insulin exposure and CV mortality from 10,163 patients were analyzed. HRs and 95% CIs were calculated, and multivariable Cox regression performed to choose the most appropriate baseline covariates and models.

The updated average total, basal, and bolus insulin doses were significantly higher in the intensive-control arm (all p<0.0001). In addition, there was a significant linear association between the updated average HbA1C level and updated average insulin dose in both groups (both p<0.0001). Four different Cox proportional hazards models were employed to determine HRs for CV mortality. The first model controlled for the following 14 baseline covariates: age, history of CV disease, heart failure, QT-index, baseline HbA1C value, high-density lipoprotein, amputation, presence of peripheral neuropathy, serum