Table 1. Outcomes.

Outcome Measure	SPT	CLT	p value
Time in target (110-200 mg/dL overnight; hours)	3.20±0.77	5.30±0.66	0.12
Time >300 mg/dL overnight (hours)	1.30±0.42	0.18±0.08	0.035
AUC >200 mg/dL overnight (mg/dL*hours)	384±84	162±40	0.049
Number of interventions for hypoglycemia	4.0	5.0	1.0
Peak postprandial glucose (mg/dL)	353±24	367±23	0.71
12:00 PM glucose (mg/dL)	273±24	189±18	0.009

CLT maintained tight glucose control without increasing the incidence of hypoglycemia and improved pre-lunch blood sugars, leading the investigators to conclude that it has the potential to improve diabetes care for very young children.

The Precocious "AGE'ing" Effect of Type 1 Diabetes in Children

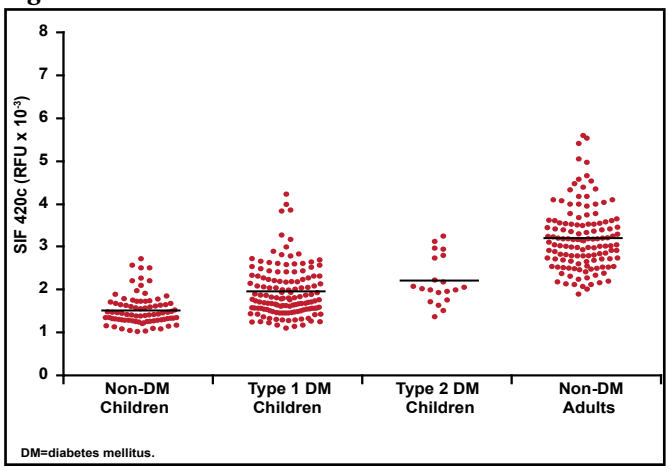
Written by Phil Vinall

Type 1 diabetes mellitus increases the formation of long-lived complexes, known as advanced glycation endproducts (AGEs), which can contribute to the development of complications in patients with diabetes [Genuth S et al. *Diabetes* 2005]. AGEs accumulate naturally in tissues over time, and tissue burden is a function of chronological age. Shreepal Shah, MD, Louisiana State University, New Orleans, Louisiana, USA, presented results of the "The Precocious "AGE'ing" Effect of Type 1 Diabetes in Children" study, which examined the relationship between chronological age and type 1 diabetes on skin AGEs in children. The study results indicated that a large proportion of children with type 1 and type 2 diabetes have precocious accumulation of skin AGEs, as estimated by skin-intrinsic fluorescence (SIF), compared with children and adults without diabetes.

The study was conducted in children with established type 1 (n=133; mean age 13 years) and type 2 diabetes (n=20; mean age 15 years) and healthy children (n=91; mean age 10 years) and adults (n=129; mean age 40 years) without diabetes. The mean duration of diabetes was 6 years for patients with type 1 diabetes and 4 years for those with type 2 diabetes. History of, or current smoking was cause for exclusion. Skin AGEs were estimated noninvasively by measuring SIF using a Scout DS® device using procedures previously described by Felipe et al. [Felipe DL et al. *Diabetes Care* 2011]. The goal of the study was to assess accumulated skin AGEs, estimated from SIF, from children with diabetes compared with individuals who did not have diabetes.

In individuals without type 1 diabetes, SIF, stimulated at 420λ (SIF 420c), increased with chronological age. When adjusted for chronological age and gender, SIF 420c was higher in children with type 1 and type 2 diabetes compared with children without diabetes (Figure 1). Forty-three percent of children with type 1 diabetes and 55% with type 2 diabetes had SIF values that were comparable with those of the adults (who were approximately 27 years older) without diabetes. SIF was associated with HbA1C or hemoglobin glycation index in the children with diabetes, but mean blood glucose levels were not.

Figure 1. SIF 420c.



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Many children with type 1 and type 2 diabetes have estimated skin AGE levels that are comparable with those that would be observed naturally only in adults aged 20 to 40 years. The investigators estimated that 4 to 6 years of diabetes duration is comparable with ~30 years of chronological aging. The authors speculated that factors that predispose individuals to precocious accumulation of skin AGEs may also predispose them to precocious development of diabetes complications.

Abatacept in Patients with New-Onset Type 1 Diabetes: One-Year Follow-Up

Written by Phil Vinall

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that is driven by activated T-lymphocytes. To be fully active, immune T-cells need a costimulatory signal in addition to the main antigen-driven signal. A previous study showed that abatacept, a costimulation modulator that prevents full T-cell activation, slowed reduction in

β-cell function over 2 years in individuals with recent-onset T1DM [Orban T et al. *Lancet* 2011]. Tihamer Orban, MD, Joslin Diabetes Center, Boston, Massachusetts, USA, presented 1-year follow-up data from the previous 2-year study [NCT00505375].

The primary study was a multicenter, double-blind, randomized, controlled trial in which subjects (n=112) aged 6 to 45 years (mean 14 years) who were recently diagnosed with T1DM were randomly assigned (2:1) to receive abatacept (10 mg/kg, maximum 1000 mg per dose) or placebo infusions intravenously on Days 1, 14, and 28 and monthly thereafter for a total of 27 infusions over 2 years. Dr. Orban reported on the effects of discontinuing costimulation modulation with abatacept on preservation of β-cell function in patients from this study who were followed for 1 year after infusions were stopped.

The follow-up analysis included 93 subjects (64 from the abatacept group and 29 from the placebo group). C-peptide 2-hour AUC means, adjusted for age and baseline C-peptide, at 36 months were 0.215 (95% CI, 0.168 to 0.265) and 0.135 (95% CI, 0.0692 to 0.205) nmol/L for the abatacept and the placebo groups, respectively (p=0.033). This difference was similar to the difference observed during the treatment phase of the trial. The C-peptide decline from baseline remained parallel with an estimated 9.5-month delay with abatacept. HbA1C was lower in abatacept-treated patients (p<0.001), with no difference in insulin use. A treatment effect was observed only for race and CDR3 status.

Data from this follow-up study indicate that costimulation modulation with abatacept slows the decline in β-cell function in recent-onset T1DM beyond drug administration and leads to lower HbA1C levels. These results suggest that abatacept may be useful in prevention studies in individuals who are at high risk of T1DM and/or as a component in studies that use a combination of different treatment strategies. Further trials are needed to test whether or not a shorter course of abatacept treatment would be sufficient to achieve similar beneficial effects.

Explaining the UKPDS Legacy Effect

Written by Phil Vinall

Ten years of follow-up observations from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated virtually identical HbA1C levels in subjects who were randomly assigned to 2 different glucose control strategies (intensive or conventional). However, subjects who received intensive glucose control remained at a significantly lower risk of diabetic complications. This continuing benefit of earlier improved glucose control has been termed the type 2 diabetes legacy effect [Chalmers J, Cooper ME. *N Engl J Med* 2008], an influence that is similar to the metabolic memory that has been described for type 1 diabetes [Stumvoll M et al. *N Engl J Med* 1995]. Marcus Lind, MD, University of Gothenburg, Gothenburg, Sweden, presented data that examined the degree to which historical HbA1C values contribute to later reductions in the risks of myocardial infarction (MI) and all-cause mortality. An additional aim was to elucidate the time-dependent impact of earlier HbA1C values on a year-by-year basis.

Continuous hazard functions for death and MI from diagnosis of type 2 diabetes in relation to age, sex, HbA1C, and original treatment assignment (intensive/conventional) were estimated in 3849 individuals from UKPDS. These data were then evaluated for different HbA1C levels during a preceding time interval to determine the degree to which they might explain the death and MI legacy effects.

Older age, male sex, and HbA1C, but not treatment group, were all found to be significantly (all p<0.001) related to MI and death. The model was used to estimate the impact of a 1% reduction in HbA1C from each of 2 time periods (at diagnosis and 10 years after diagnosis) on the risk of death and MI. For all-cause mortality, the results indicate the reduction in risk from the legacy effect is almost 3 times stronger when the HbA1C reduction is achieved early (at diagnosis) compared with later (after 10 years), and this effect is mostly because of the lower HbA1C levels at the earlier time points. The pattern is similar, but the effects of early reduction are somewhat less potent for MI.

The model was used to predict the relative reduction in the probability of death for a 50-year-old man with newly diagnosed type 2 diabetes and an HbA1C of 8% in 2 different scenarios: immediate (at diagnosis) reduction of HbA1C by 1% and waiting 10 years for the same HbA1C reduction. Reducing the HbA1C by 1% (to 7%) at diagnosis will result in an 18.6% risk reduction for death compared with only a 6.6% risk reduction if the HbA1C reduction is delayed for 10 years. Similar relationships in risk reduction and timing of the HbA1C reduction were seen when the model was applied to MI and to women.

Statistical modeling of UKPDS data confirmed that earlier HbA1C levels continue to contribute to the risk of diabetic complications, as seen in the Diabetes Control and Complications Trial [The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993]. The long-term impact of achieved HbA1C levels explains to a large extent the sustained reductions in the risk of death and MI that were seen in the UKPDS post-trial monitoring period. Thus, early intensive, optimal, glycemic control is essential to minimize the long-term risk of diabetic complications.