SEPTEMBER 2016

Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

"Robust" HbA_{1c} Reductions via the Combination of Lixisenatide/Insulin

A combination of lixisenatide and insulin glargine may be able to reduce HbA_{1c} to near normal (healthy) levels in patients with poorly controlled type 2 diabetes while on metformin according to clinical data from Rosenstock et al. (**p. 1579**). Significantly, the combination treatment also appears to result in concurrent weight loss, no increased hypoglycemia, and a low incidence of gastrointestinal adverse events—all of which are side effects sometimes associated with both glucagon-like peptide 1 receptor agonists (lixisenatide is one version) and long-acting insulin therapies. During the trial, the researchers compared the effects of a 2:1 ratio insulin glargine/lixisenatide combination (termed LixiLan in the article) versus insulin glargine alone, with the primary outcome of changes in HbA_{1c} over 24 weeks being the key factor. Specifically, they tested for noninferiority of the combination first and if met, then statistical superiority over insulin glargine. Secondary outcomes included changes in body weight, hypoglycemia, and safety. In short, both noninferiority and superiority of the combination were proven statistically, while at the same time body weight went down; there was no difference in the rate of hypoglycemic events (~25% in both groups); and the rates of nausea and vomiting remained low. According to the authors, the key to the effect is titration of dosing, which was calculated in the trial on the basis of insulin glargine requirements according to fasting plasma glucose levels. The gradual, incremental titration seems to have encouraged a complimentary action of the two therapies resulting in a robust HbA_{1c} reduction and a better safety profile. The authors report that when given separately neither therapy can achieve such reductions in HbA_{1c}, and the side effects usually mean that low adherence and compliance are often the results in the clinical setting. On that basis, they suggest that combining the therapies may result in highly effective outcomes.

Rosenstock et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy: the LixiLan proof-of-concept randomized trial. Diabetes Care 2016;39:1579–1586

Type 1 Diabetes Risk Assessed Through Fluctuations in β-Cell Autoantibodies

β-Cell autoantibodies are central to type 1 diabetes but their transient nature in preclinical phases may be the key to understanding (and predicting) whether full-blown type 1 diabetes will develop in children. This is according to Vehik et al. (**p. 1535**) who report this month an analysis from The Environmental Determinants of Diabetes in the Young (TEDDY) study on the development of β-cell autoimmunity in the genetically at-risk cohort of children. The prospective cohort study identified 596 children (out of ~8,500 enrolled in the study) who developed one or more autoantibodies and then monitored them every three months for changes in status in terms of autoantibodies present. Three autoantibodies were investigated: insulin autoantibody (IAA), GAD antibody (GADA), and insulinoma antigen-2 (IA-2A). Five hundred of the children were positive in consecutive visits for a single autoantibody with the rest having multiple autoantibodies (confirmed via validated analyses in two reference laboratories) at the time of initial seroconversion. The key progression then was whether reversion of antibody status occurred (β-cell autoantibodies can fluctuate, with some individuals "reversing" from positive to negative antibody status). Individuals with multiple β-cell autoantibodies that did not reverse antibody status had the highest risk of developing type 1 diabetes. Risk then decreased according to whether individuals remained single-autoantibody positive or not. Many other outcomes were also documented and these all affected risk of developing type 1 diabetes. The authors suggest that "monitoring children with single autoantibodies for at least 1 year after seroconversion is beneficial for stratification of type 1 diabetes risk." Commenting more widely on the outcomes, author Kendra Vehik told Diabetes Care: "In children less than 10 years of age reversion does occur and is likely to occur within the first year after initial seroconversion. Reversion or progression to multiple autoantibodies changes the risk of progression to type 1 diabetes. Scientists need to take note of these findings when designing trials because risk can change after one year and will have a major impact on trial outcomes."

Vehik et al. Reversion of β-cell autoimmunity changes risk of type 1 diabetes: TEDDY study. Diabetes Care 2016;39:1535–1542

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Deaths Due to Type 2 Diabetes in China: Epidemiological Analyses

A 23-year follow-up of the Da Qing Diabetes Prevention Study cohort suggests that while impaired glucose tolerance (IGT) is associated with increased risk of death, much of this excess risk is actually attributable to the development of type 2 diabetes. The study by Gong et al. (**p. 1550**) compared mortality before and after the development of diabetes in 542 Chinese individuals with IGT who had taken part in the diabetes prevention trial that started in 1986. Researchers followed up on the individuals over the next 23 years. Another 512 individuals who had been screened in the original study but had normal glucose tolerance (NGT) were used as a comparison group. According to the authors, a straight comparison of the NGT versus IGT groups revealed a 70% higher death rate in the IGT group. Within this group, 32% died during the follow-up period with the majority of deaths (~75%) occurring after progression to type 2 diabetes (note: 79% of the cohort did progress to type 2 diabetes). After adjusting for age, death rates were considerably lower before the onset of type 2 diabetes compared with after the onset of type 2 diabetes. To confirm the effect of diabetes, the authors then used a modelling approach to account for a range of potential confounding factors and concluded that diabetes likely accounts for a 73% increased risk of death when glucose intolerance is present. The latest estimates from the International Diabetes Federation suggest China has the largest population globally with diabetes and the rates of prediabetes currently run at nearly 50% of the population. According to study authors Guangwei Li and Ping Zhang: "The excess mortality associated with IGT is seen mainly after the development of type 2 diabetes, thus delaying or preventing the development of type 2 diabetes may be expected to lower mortality risk. Lifestyle interventions are effective in preventing or delaying type 2 diabetes in persons with prediabetes, thus widely implementing such interventions in China and rest of the world may reduce deaths associated with diabetes."

Gong et al. Changes in mortality in people with IGT before and after the onset of diabetes during the 23-year follow-up of the Da Qing Diabetes Prevention Study. Diabetes Care 2016;39:1550–1555

Blunted Insulin Action After Injection Into Lipohypertrophic Tissue

A common complication of diabetes, lipohypertrophy, may have major implications for insulin absorption and action and consequently may lead to a deterioration in postprandial glucose control, according to Famulla et al. (**p. 1486**). Using a combination of euglycemic clamp/mixed-meal tests, the authors assessed the pharmacodynamic response and postprandial glucose control of insulin lispro injection into normal adipose tissue and into lipohypertrophic tissue. The crossover study focused on 13 patients with type 1 diabetes. Specifically they showed that both insulin absorption and effect were impaired, and consequently blood glucose levels were approximately 25% higher when injected into lipohypertrophic tissue in comparison with injections into normal tissue. In addition, intraindividual (day to day) variability of insulin concentrations were nearly fivefold higher following injection into lipohypertrophic tissue. Lipohypertrophy refers to the development of a fatty lump under the skin at the site of repeated insulin injections. Users of injectable insulin are usually advised to rotate injection sites to avoid lipohypertrophy. The authors highlight the consequences of injecting into such tissues, pointing out that two patients had virtually no response in terms of insulin levels when injecting into lipohypertrophic tissue and that both experienced hyperglycemia following the mixed-meal test. They suggest that users should avoid injecting into such tissue and that patients with lipohypertrophy should be educated to ensure they rotate injection sites. Commenting more widely on the study, author Tim Heise said: "Many patients with long-standing insulin therapy suffer from lipohypertrophy. Our results show a substantial deterioration of and a high variability in insulin absorption from the altered tissues impeding insulin titration. We urgently need more clinical research on the impact of lipohypertrophy on clinical outcomes and in particular on procedures and tools to reduce the incidence of lipohypertrophy. This is especially the case in patients on insulin pumps who might be particularly affected by the erratic insulin absorption from lipohypertrophic tissues."

Famulla et al. Insulin injection into lipohypertrophic tissue: blunted and more variable insulin absorption and action and impaired postprandial glucose control. Diabetes Care 2016;39:1486–1492

DOI: 10.2337/dc16-ti09