Future Intervention Trials in Type 1 Diabetes

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The recently completed trials using insulin (U.S.) and nicotinamide (Europe) were not effective in preventing type 1 diabetes (1,2), but they leave an important legacy of goodwill among their collaborators and expertise in the conduct of such trials and a network through which more may be carried out.

A commentary on the trials has recently been published (3), and its authors urge “a different combination.” Concerned that too little is known of early immune interactions to intervene effectively in infancy, when the disease is thought to start, they propose trials of combination or “cocktail” therapy to achieve immunosuppression in newborn patients. The ultimate benefit to the pre-diabetic patient would come if it were possible to improve β-cell survival in the context of reduced inflammation. Antigen-based therapies, monoclonal antibodies, and other immunoregulatory and immunosuppressive agents are listed, built around confident assertions that type 1 diabetes “has an autoimmune basis” and that, given the success of combination therapy in cancer, AIDS, and systemic lupus erythematosus, “why should type 1 diabetes be any different?”

But what if type 1 diabetes is different? What if the paradigms are different? And they may be because, despite an immense research effort, the doubling of the incidence of type 1 diabetes over the past 25 years in most industrialized countries still goes without explanation. What if β-cell damage, driven by some lifestyle factor, drives the immune response?

A summary of intervention trials presented to the 2003 International Diabetes Federation meeting in Paris identified the principal requirements for future trials: safety (which is paramount), a viable hypothesis, and evidence that they may be expected to work. In all three respects, lifestyle intervention is arguably a prime candidate. It is safe, likely to prove effective, and underpinned by a clear hypothesis.

The Accelerator Hypothesis asserts that type 1 and type 2 diabetes are one and the same disorder of insulin resistance, set against different genetic backgrounds (4). Insulin resistance, a product of modern lifestyles, accelerates the loss of β-cells in both type 1 and type 2 diabetes, whereas autoimmunity—driven by β-cell upregulation induced by the insulin resistance in those with a particular set of immune response (HLA) genes—accelerates the loss still further. The difference between type 1 and type 2 diabetes may mainly be one of a difference in tempo of the β-cell lesion. Type 1 diabetes, the hypothesis argues, is a subset of type 2 diabetes (although some believe the converse to be true) and predictably more and more difficult to distinguish from it as the tempo of type 2 diabetes quickens and its age at presentation falls. The concepts of “type 1.5 diabetes” and “double diabetes” are conceptualizations of the same convergence in pathogenesis (5,6), and the whole area of type 1 diabetes, type 2 diabetes, autoimmunity, and insulin resistance has recently been the subject of editorial critique (7).

The Accelerator Hypothesis has already faced its first tests of viability in both animals and humans. In the BB rat, the incidence of type 1 diabetes falls when food intake is limited rather than available ad libitum (8). In humans, the members of two sizeable and independent cohorts with childhood type 1 diabetes were not only heavier than their peers, and by implication more insulin resistant, but crucially, their age at presentation was inversely related to their body mass—true acceleration (9,10). Lifestyle intervention to lower insulin resistance has already been shown to reduce progression to type 2 diabetes by nearly 60% (11,12). Lifestyle change should arguably rank high among interventions proposed for type 1 diabetes by targeting factors already shown to influence its progression in humans.

What is the evidence that lifestyle change will be likely to prevent type 1 diabetes at a public health level? The signs may be all around us. The highest order of proof is the response to intervention and that, in a natural intervention of colossal scale, industrialized nations have shifted their BMI some 20% during the past 25 years (13,14). Few would contest that insulin resistance resulting from this rise in body weight underlies the corresponding rise in type 2 diabetes that has occurred over the same duration (15,16) or that excess nutrition and underactivity are the principal lifestyle factors responsible. It is sometimes forgotten, however, that type 1 diabetes has shown a parallel rise over the same period, doubling its incidence in the same populations (17,18).

Although there is no certainty that lifestyle change and insulin resistance have caused the rise in type 1 as well as type 2 diabetes, there is strong circumstantial evidence in favor of the association and a safe intervention on hand to test it. So why have intervention panels so far not sought to trial lifestyle changes in the prevention of type 1 diabetes, as they have for type 2? One reason is logistics. Because its prevalence is only some 10%
of that of type 2 diabetes, conducting trials of type 1 diabetes implies international recruitment and more time to completion. The Accelerator Hypothesis had not cast type 1 diabetes in the mold of type 2 diabetes when the Diabetes Prevention Trial-1 and European Nicotinamide Diabetes Intervention Trial were conceived in the early 1990s. Since then, however, associations between insulin resistance and type 1 diabetes have become clearer (19, 20), and a way forward has opened up.

There may be sound reason to consider immune intervention in type 1 diabetes (3), as immune insulitis undoubtedly accelerates the loss of β-cells. However, if insulin resistance is a driver of β-cell damage and the immune response to it, there may be yet more reason to reduce insulin resistance by insulin sensitizers or behavioral change. Lifestyle intervention has proved effective in type 2 diabetes. The parents of high-risk children are likely to ensure compliance, and markers of intervention impact such as simple anthropometry, body composition by dual-energy X-ray absorptiometry or bioimpedance, autoantibody titers, and insulin resistance by homeostasis model assessment are well established in children. Given the evidence available, now seems an appropriate time to judge the merits of lifestyle change or insulin-sensitizing drugs alongside more speculative, and possibly more risky, interventions when planning the next type 1 diabetes prevention trial.

References