It's Time to Mow the GRAS in Type 1 Diabetes

Desmond A. Schatz,[1] S. Robert Levine,[1] and Mark A. Atkinson[1,2]

Tommy (fictitious name, but a true story) did not pick a run-of-the-mill school science fair project, such as seeing whether plants grew better with Bach versus Metallica, powering a radio with a potato, or testing the absorbency of various paper towel brands. Tommy, one of our patients with type 1 diabetes, had a different motivation. His project was designed to test whether a simple dietary modification, the addition of ground grapefruit rind, would improve postprandial glucose values. This was not a randomized controlled trial with statistical power; indeed, his mother served as the data safety monitoring board, institutional review board, and the Food and Drug Administration equivalent granting regulatory approval. Yet, even with the $N = 1$, the results were eye-opening. His simple experiment demonstrated improved diabetes management.

This observation some 3 years ago, combined with many other like reports over the years, has convinced us that it is time to readdress this issue of large-scale clinical testing for Generally Recognized As Safe (GRAS)-like agents in settings of type 1 diabetes. Evaluating the ability of these agents to enhance glycemic control, and/or improve anti-inflammatory/antioxidant/immunomoregulatory status, could identify a safe and cost-effective approach to improving lives and perhaps attenuate disease-associated complications. GRAS-like agents refers to agents covered under the Food and Drug Administration's GRAS and dietary supplement (i.e., the Dietary Supplement Health and Education Act) regulations and, in a few cases, other constituents such as probiotics and helminthes.

This was not a new idea for us, for those in the clinical research and practice communities, or for patients with type 1 diabetes. Indeed, many GRAS-like agents have been tested in type 1 diabetic patients in situations ranging from those anecdotal in design to efforts involving controlled clinical trials. Examples include coenzyme Q10, garlic, magnesium, and chromium (rev. in 1). With a majority of studies evaluating the benefits of these practices having been (perceived or realized) as negative or neutral within the medical community as a whole, a logical question would be, "What's changed and why would we now posit the need to revisit their potential use?" To this, we would assert that changes in the "landscape in type 1 diabetes care"—including more than a generation of far too many unfulfilled promises seeking more mainstream bio-pharmaceutical solutions, all pursued with vigor while GRAS-like agents promise was incompletely explored—now demand it.

Significant large-scale efforts have taken place over the last decade in an attempt to prevent and reverse type 1 diabetes (e.g., National Institutes of Health [NIH] TrialNet, Immune Tolerance Network, European Nicotinamide Diabetes Intervention Trial) (2). While such efforts have resulted in improvements in our knowledge of the natural history of the disease (both immunological and metabolic), and there is certainly cause for optimism that one form of therapy may eventually cure the disorder, the sobering reality is that no means exists, today, to practically or with assurance reverse type 1 diabetes (3). Yet, with current research emphasis on intervening in new-onset patients, a continuing "numbers" problem exists—one that has been largely ignored but deserves attention. Nearly all studies seeking to reverse type 1 diabetes require patients to be enrolled and subject to treatment within a 3-month window from the time of diagnosis. Based on NIH SEARCH for Diabetes in Youth study data (4), approximately 18,000 individuals under age 20 years are diagnosed with type 1 diabetes in U.S. each year, meaning that at any point in time only an estimated 4,500 individuals are trial eligible. It could be considered remarkable, in a way, that so much of our clinical trial efforts to halt progression of type 1 diabetes are directed at this exclusive (and quite small) group when perhaps as many as 1.5 million individuals in the U.S. live with established disease—a population for which little cure-focused research is afforded, outside of islet and/or pancreas transplantation, which is indicated for an equally narrow population of patients. Hence, reason number one to look at GRAS-like agents again: a large portion of the clinical enterprise associated with type 1 diabetes research focuses on a small minority of subjects and not the population as a whole.

Second, any such listing for rationale would fall short if we failed to highlight the "S" in GRAS: safety. Within the last decade, a growing number of therapies within the diabetes universe (albeit, nearly all used for type 2 diabetes) have either not been approved or, once granted approval, have subsequently been withdrawn from the market for safety concerns (5). Beyond this, some of the more successful immunosuppressive regimens capable of attenuating loss of C-peptide in new-onset type 1 diabetes are of questionable broad-based applicability because of issues of safety, as well as the limited ability of health care providers to respond to potential adverse events if administered in a private-practice setting.

Third, many of the studies performed with GRAS-like agents have been undertaken by companies whose post-study marketing efforts often, but not exclusively, leave the medical professional with (rightly or wrongly) questions of their validity—for reasons ranging from seemingly outlandish claims of benefits to promotion on late-night cable television ads. Safe and efficacious GRAS-like agents could be within our reach, but their potential is tainted by our understandable bias against a product pitched by infomercial.

Fourth, we will soon be approaching the 20th anniversary of the results reporting for the NIH Diabetes Control

From the [1]Department of Pediatrics, University of Florida, Gainesville, Florida; and the [2]Department of Pathology, University of Florida, Gainesville, Florida.
Corresponding author: Mark A. Atkinson, atkinson@ufl.edu.
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and Complications Trial (DCCT) effort (6). Although some difficulties in implementation of DCCT guidelines remain today, clear improvements in diabetes management have occurred for many with type 1 diabetes. Additional improvements in glycemic control have also occurred through the availability of insulin analogs, alternative modes of insulin delivery, glucose detection devices, improved educational methods, and more (7). Yet, the costs of those improvements can be quite significant and difficult to administer. GRAS therapies (if successful) could provide a relatively low-cost improvement to this extensive armamentarium, both in the U.S. and other developed countries, as well as in third world nations in dire need of cost-conscious improvements in diabetes care (8).

Fifth and finally, there are also the questions of access and delivery for any new therapeutic. Sadly, we are not of the belief that adequate attention has been directed at the practicality of providing care to those in need in a public health care setting (i.e., outside of academic medical centers). Beyond this, are public and private payers going to be willing to provide the hundreds of millions—if not billions—of dollars necessary to extend the use of any of the current wave of putative agents, designed for improving glycemia in new-onset type 1 diabetic patients, to all patients who might benefit? Until such time occurs, our own belief is that GRAS-like therapies provide a potentially attractive option for testing.

Having contended that a GRAS-like initiative is warranted, the next obvious questions would be, "What would you test and in which populations?" We would posit that options for testing could include—but not be limited to—the following compounds, either alone or in combination: γ-aminobutyric acid, grapefruit extract, omega-3 fatty acids, vitamin D, glutathione, nitro fatty acids, *Trichuris suis* ova, and probiotics. Any such list could certainly be modified subject to available data suggesting potential therapeutic benefit. As to which populations testing is warranted, one group that would certainly be of interest is the large cohort of often ignored individuals with type 1 diabetes who, based on their ability to produce C-peptide, might particularly benefit from GRAS-like therapies. In the NIH's DCCT trial, a nontrivial percentage (i.e., ~11%) of individuals with disease from 5–15 years postdiagnosis were noted to produce an appreciable quantity of C-peptide (≥0.02 pmol/mL) (Fig. 1) (6). While this group is usually thought rare, not often considered is that by sheer number (i.e., 11% of 1.5M equates to some 165,000 persons) they eclipse the aforementioned population size of recent-onset subjects eligible for most disease reversal or islet β-cell preservation efforts. Additional subject groups worth testing for the benefits of GRAS therapy would also include the aforementioned group with recent-onset disease, established type 1 diabetic patients independent of their ability to produce C-peptide, as well as those who do not yet have type 1 diabetes but are at high risk for the disease as the result of the presence of disease associated autoantibodies. Indeed, we consider testing within this later group seeking disease prevention a particularly attractive option given many of the arguments for GRAS therapies previously mentioned in this editorial (e.g., safety, cost, ease of delivery). Although the goals and outcomes for studying each of these groups would certainly

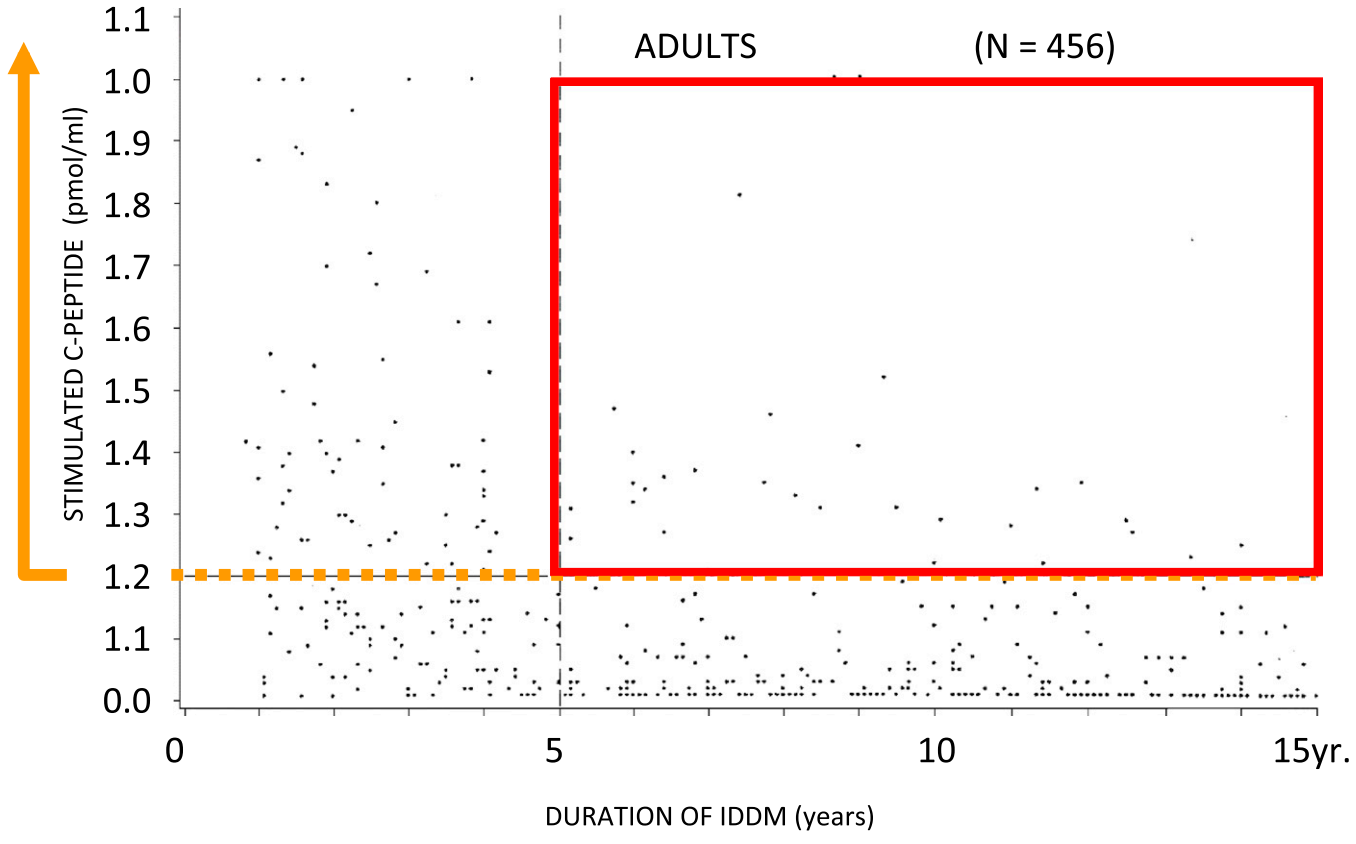

FIG. 1. Effects of duration of type 1 diabetes on residual β-cell function: observations during eligibility testing for the DCCT. Stimulated C-peptide as a function of type 1 diabetes duration. Eleven percent of adults with a disease duration of greater than 5 years had a stimulated C-peptide of greater than 0.02 pmol/mL (those meeting this standard are noted in the red box; those with stimulated C-peptide above this range regardless of disease duration are noted with a gold line). Adapted from the DCCT Research Group. J Clin Endocrinol Metab 1987;65:30–36.

be different, we believe it remains of significant question and interest whether GRAS-like therapies would afford clinical and quality-of-life benefits to such populations.

We recognize that launching any large-scale (including population-based) clinical trial initiative represents a daunting challenge. Fortunately, a number of efforts have either been formed or are undergoing development whose design provides a network of type 1 diabetic patients or subjects at increased risk for the disease and potentially amenable to GRAS-based testing. These would include the Type 1 Diabetes Exchange organized and supported by the Helmsley Trust, the Brehm Coalition for Type 1 Diabetes Research, as well as the highly successful TrialNet program. Beyond this, we would also think that improvements to this field would occur through increased interactions between agencies dedicated to the care of those with type 1 diabetes (e.g., NIH National Institute for Diabetes and Digestive and Kidney Diseases, the American Diabetes Association, the Juvenile Diabetes Research Foundation, etc.) and institutes with much in the way of experience with GRAS/Dietary Supplement Health and Education Act initiatives (i.e., National Center for Complementary and Alternative Medicine).

Within the professional ranks, we believe there may be a lingering intellectual resistance and perhaps a fear with attempts to move forward in this realm, given concerns that individuals agreeing to such a cause would be considered "unprofessional." Our hope is that the opportunities for testing, combined with the need for safe interventions having a reduced cost, would at least in part overcome such cautions and allow the type 1 diabetes research field to "mow the GRAS" and test what these agents could do for those with or at increased risk for the disease.

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