EDITORIALS

Are Children the Future of Type 2 Diabetes Prevention?

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The lifetime risk of type 2 diabetes is now more than one in three in the general U.S. population, and one in six adolescents is now obese, suggesting that prevention should start in childhood.[1,2] Many consider diabetes and obesity to be "common-source" epidemics that are rooted in our culture, as evidenced by national trends toward larger portion sizes and more meals built around calorically dense fast food, sugar-sweetened drinks, and sedentary behavior.[3,4] Fighting such a powerful wave with purely clinical and adult-based approaches to prevention may seem like pasting a small bandage on a gaping wound. Rather than focusing on adults who may be set in their ways, we should perhaps target our youth, who may represent a better hope for changing the norms, habits, attitudes, and preferences that define our culture's collective energy balance.

At the same time, we should not naively assume that approaches targeted to youth will result in effective policy for the prevention of type 2 diabetes. Despite the devastating effects of type 2 diabetes, the prevalence among youths (about 1 case per 2400 U.S. youths 10 to 19 years of age) is low enough that even highly effective interventions would need to be applied to thousands of youths to prevent just a few cases.[5] Therefore, efforts to prevent diabetes that target youths would require substantial payback in adulthood through reduced levels of diabetes and other illnesses. Bridging the wide gap between risk factors in youth and the prevention of illness in adults needs not only evidence that risk factors track strongly from childhood to adulthood, but also efficient interventions with sustainable effects across life stages.

The article by Franks et al. in this issue of the *Journal*[6] shows that among Pima Indian youths 5 to 19 years of age, obesity and 2-hour glucose levels below the threshold for impaired glucose tolerance, but above normal levels, were associated with a rate of death in young adulthood and middle age that was about twice that of peers without diabetes. The Pima Indians are sometimes considered to be unrepresentative of the U.S. population because they have an especially high risk of diabetes. However, the prevalence of impaired glucose tolerance among persons in the current study (4%) is similar to the current prevalence in the general population of U.S. adolescents (3%) and is far less than the prevalence among obese adolescents in the United States (9.5%).[7] Since the trends with respect to obesity and diabetes among the Pima Indians have been a reliable harbinger for trends in the rest of the U.S. population during recent decades, the present study should intensify the debate about whether interventions that are initiated during childhood and young adulthood can affect our broader diabetes epidemic.

Several aspects of the findings of Franks et al. should inspire new investigations. First, childhood cholesterol and blood-pressure levels were not predictive of death, perhaps indicating that they do not track into adulthood as persistently as obesity and impaired glucose tolerance do. Alternatively, these risks may follow patients into adulthood, but primary care clinicians can then detect and manage elevated blood pressure and lipid levels with drugs, whereas they are ill equipped to manage obesity and impaired glucose tolerance ("prediabetes"). Second, associations related to impaired glucose tolerance should not necessarily be generalized to impaired fasting glucose, as it is defined by the American Diabetes Association. Impaired fasting glucose in adults is associated with the development of diabetes and with death, but whether this association holds true in the

case of youths is not clear. In addition, a recent study showed that among adolescents, elevated glucose levels were no more predictive of later diabetes than either body-mass index or systolic blood pressure — reminding us that the best predictors of imminent diabetes among adults may be different from the best predictors of long-term risk of diabetes among youths.[8] Third, since most of the deaths from endogenous causes among the population studied in the article occurred before the participants were 45 years of age, this study examined only premature death. The mortality rates were more than twice those of the general U.S. population and were inordinately affected by deaths from liver disease, a finding that merits further study.[9] We should not assume that follow-up into the seventh and eighth decades of life, when most people die of more typical causes, would yield similar associations between impaired glucose tolerance and death. Finally, these and other authors suggest that the life spans of future generations may be affected by the epidemics of obesity and diabetes; this might not be so, given the improvements in care and in the treatment of risk factors — improvements that continue to push life spans to record highs and that have ironically contributed to the growing prevalence of type 2 diabetes.[10,11] The more pressing question raised by this study, however, is whether increased rates of central obesity, elevated insulin levels, and impaired glucose tolerance among youths will result in increased cases of type 2 diabetes, illness, and disability in future generations.

It will be important to convert these results into effective prevention policies. Impaired glucose tolerance, impaired fasting glucose, and elevated glycated hemoglobin levels are practical targets among adults not only because they indicate a high risk of diabetes but also because structured lifestyle interventions can be highly effective.[12] Segregated interventions may not work as well among youths because the long incubation period from risk factor to disease and unclear positive-predictive value for the development of diabetes and its complications make for inefficient risk stratification and allocation of intervention resources.[8]

The dilemma raised by epidemiologic data — that interventions that are targeted to youths need to be extraordinarily sustainable to pay off later in life — requires us to revisit the common sources of the epidemics of obesity and diabetes. Fortunately, there is active discussion about what the most promising interventions are. Schools, families, and social groups are all potential targets. The HEALTHY study (ClinicalTrials .gov number, NCT00458029), a 3-year cluster-randomized intervention trial involving more than 6000 sixth graders from 42 schools, will provide a unique, rigorous test of a model intervention to reduce glucose levels and other risk factors that incorporates thoroughly integrated nutritional, physical-activity, behavioral, and social-marketing components.[13] Other experts suggest that we must reach far outside the schoolhouse to find out whether focusing policies on culturally embedded risk factors — sugar-sweetened beverages, calorically dense foods, excessive television and video watching, the high price and limited availability of healthy foods, and community designs that discourage physical activity — can be as fruitful as targeting tobacco, saturated fat, and trans fats has been for the prevention of cardiovascular disease.[3] Targeting food policies to prevent type 2 diabetes has proved to be difficult, however, because the quantity of what we eat may be as damaging as its quality. Finally, we should be mindful that the wellspring of most chronic diseases is not captured by single physiological risk factors or specific exposures. Because variation in the rates of illness and death among persons in specific places, social classes, and communities in the United States and elsewhere in the world is as great as the difference between persons with and persons without impaired glucose tolerance, our search for ways to alter the common source must continue.[14]

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Fistula First, Stent Graft Second

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A growing number of patients in the United States undergo efficient hemodialysis through autogenous arteriovenous fistulas or prosthetic arteriovenous grafts. Unfortunately, these vascular conduits are fraught with complications, and failing access remains the leading cause of hospitalization for patients undergoing dialysis.[1]

The superiority of autogenous arteriovenous fistulas as compared with prosthetic arteriovenous grafts is well established. Fistulas have a far lower risk of failure and a reduced requirement for revision as compared with prosthetic grafts. In 1997, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommended a goal of arteriovenous fistula formation in 50% of all new patients undergoing hemodialysis. In 2005, the Center for Medicare and Medicaid Services raised the target to 66% in the breakthrough initiative that has become known as "Fistula First."[2]

Unfortunately, a substantial number of patients lack suitable veins for the creation of autogenous fistulas and require placement of prosthetic grafts. The high rate of graft failure in such patients leads to increased cost of treatment and periodic loss of access. Ameliorating the problem of graft stenosis has been the subject of intense investigation over the past decade. The study by Haskal and colleagues in this issue of the *Journal*[3] provides hope that, as we enter the new decade, patients with arteriovenous grafts may experience a brighter future.

The major cause of failure of prosthetic arteriovenous grafts is stenosis at the venous anastomosis of the graft. Attempts to prevent or reduce the incidence of this problem through surgical or pharmacologic means have been largely unproductive. In a recent report in the *Journal*, pharmacologic treatment with dipyridamole and aspirin resulted in only a small (5-percentage-point) difference in restenosis as compared with placebo.[4]

Balloon angioplasty has been the standard treatment for stenosis of a venous anastomotic graft. Yet the benefit of angioplasty is offset by a high rate of restenosis within weeks or a few months after the procedure. To date, randomized, controlled trials have not shown a substantial prolongation of graft patency after angioplasty, findings that have led to controversy regarding the merit of surveillance and early intervention.[5]

A variety of innovative percutaneous techniques have been used to treat anastomotic graft stenoses, such as cutting balloons, cryoballoons, and bare-metal stents. None of these interventions have significantly prolonged graft patency as compared with conventional balloon angioplasty in appropriately sized, prospective, randomized, controlled trials.[6,7]

The study by Haskal et al. appears to be the first large, randomized, controlled trial to clearly demonstrate superiority of an approach over balloon angioplasty. Their data reveal that treating a venous outflow stenosis with a stent graft more than doubles the rate of graft patency, and sub-