Caloric intake that exceeds energy expended and its consequences, particularly development of type 2 diabetes mellitus, is emblematic of a climate change for modern medicine — a phenomenon so complex, embedded in culture and economics, and intertwined with conflicts between individual freedom and societal health that solutions are difficult to envision. Chronic caloric surplus (rather than obesity itself) is a central cause of epidemic type 2 diabetes,1 but differences in response to energy excess,2-4 disproportionately present among disadvantaged youth, increase susceptibility to type 2 diabetes in early life. Indeed, the percentage of type 2 diabetes in cases of new-onset diabetes in adolescence has increased from 3% a few decades ago to approximately 50% today.5 Because complications increase with the duration of diabetes, it is critical to improve prevention and treatment strategies for affected youth.

In an impressive effort, the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study, now reported in the Journal, randomly assigned 699 young people with type 2 diabetes to test how well metformin alone, metformin plus rosiglitazone, and metformin plus an intensive lifestyle-intervention program maintained glycemic control (a glycated hemoglobin level of <8%) for a minimum of 2 years.6 The recruitment and retention of demographically representative participants and the implementation of a lifestyle-intervention program in children and adolescents is laudable. However, the results of the study were discouraging — 52% of participants treated with metformin alone had treatment failure, metformin plus lifestyle intervention did not significantly improve glycemic control and achieved targeted weight loss in only 31% (and this weight loss was apparently transitory in many participants), and the addition of rosiglitazone to metformin improved durable glycemic control, but 39% still had treatment failure. Furthermore, the failure rate with metformin monotherapy appeared higher than that in recently diagnosed adult patients. Thus, these data imply that most youth with type 2 diabetes will require multiple oral agents or insulin therapy within a few years after diagnosis.

Do these results put a nail in the coffin of lifestyle modification and endorse add-on drugs to treat type 2 diabetes in children? Reasons to resist this notion may lie in the study design and analysis. The study's focus on the comparison of metformin alone with metformin plus lifestyle change or metformin plus rosiglitazone, without comparison of the two combination treatments, overshadows the fact that failure rates of the metformin-plus-lifestyle and metformin-plus-rosiglitazone groups did not differ significantly. With regard to secondary outcomes, participants in the metformin-plus-lifestyle group gained less fat mass than those in the metformin-plus-rosiglitazone group, a result that could reduce the risk of other diseases associated with obesity. In addition, possible sex7 and racial differences in the effect of lifestyle change on glycemic control hint that effective strategies to prevent type 2 diabetes and slow its progression may vary.

Critics may conclude that the lack of meaningful weight loss in most participants in the metformin-plus-lifestyle group points to poor adherence, rather than representing an indictment of lifestyle change itself. Because changes in eating and activity habits were calculated to decrease baseline weight by 7 to 10%,8 most participants clearly did not adopt these habits, and the feasibility of lifestyle change was evaluated...
Hormonal Contraceptives and Arterial Thrombosis — Not Risk-free but Safe Enough

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The link between combined estrogen–progestin oral contraceptives and venous and arterial thrombosis was made soon after these products were marketed, in the early 1960s.1-3 By 1970, the doses of estrogen in combined estrogen–progestin oral contraceptives had already been lowered on the basis of epidemiologic data showing that formulations with higher estrogen doses were associated with increased vascular risks.4 Studies published in 1995 and 1996 showed that increases in the risk of venous thromboembolism were greater with newly marketed estrogen–progestin oral-contraceptive formulations containing desogestrel and gestodene than with formulations...