Obesity, Autoimmunity, and Double Diabetes in Youth

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A few obese youth with type 2 diabetes have evidence of islet cell autoimmunity with autoantibodies toward β-cells typical of type 1 diabetes defining what is called "double diabetes" (DD). The increasingly "obesogenic" environment that favors insulin resistance could account for the development of islet cell autoimmunity through different mechanisms. Therefore, a rising obesity trend seems to have a role (in association with other environmental factors) in the increasing incidence and the changing phenotype of type 1 diabetes in youth.

Over the past decade, it has become apparent that more cases of type 1 diabetes are diagnosed in children and adolescents who were overweight or even obese before hyperglycemia developed. Accordingly, diagnosis of type 1 diabetes is not easy to place because of the phenotypic features typically associated with type 2 diabetes. In addition, the increase of obesity observed in children may contribute to the escalation of β-cell destruction, as suggested by the accelerator hypothesis in subjects genetically susceptible to type 1 diabetes. Lifestyle modifications, including diet and exercise, which are relevant for the prevention of type 2 diabetes, may be important modifiable environmental factors also for type 1 diabetes prevention in subjects with DD.

A GRAY AREA FOR CLASSIFICATION OF DIABETES

—A few years ago, the terms "type 1 diabetes" and "type 2 diabetes" replaced "insulin-dependent diabetes" and "non-insulin-dependent diabetes," respectively. This new nomenclature reflected two distinct forms of the disease in terms of pathogenesis (1). The classification is still maintained, although other subtypes have been included in the latest classification (2). An increase in blood glucose results either from failure of the β-cells to secrete insulin (type 1 diabetes) or reduction in insulin secretion combined with insulin resistance of peripheral tissues (type 2 diabetes), or a combination of both (3). The prevalence of both types of diabetes is rapidly increasing in industrialized countries, and although much attention has focused on the increase in type 2 diabetes (4), a parallel increase in type 1 diabetes also requires explanation. Given that type 1 diabetes is mainly an autoimmune disease and type 2 diabetes an obesity- and lifestyle-related form of diabetes, the connection between diet and diabetes has traditionally focused on type 2 diabetes. However, distinctions between type 1 and type 2 diabetes are becoming blurred, both etiologically and clinically. A number of studies have suggested that differences between the two types are not always straightforward, and in many cases, common pathogenic processes may be evident (5). Not surprisingly, this has meant questioning the present classification of diabetes and the provocative proposal of declassifying the disease (6). Even the best animal model of type 1 diabetes (i.e., the NOD mouse) has some genetic background that can predispose these mice to insulin resistance before the destruction of β-cells occurs and absence of hyperglycemia (7). These observations suggest that nonimmunological processes may also be important in the cascade of events leading to β-cell destruction and, conversely, an immune-mediated process can accelerate β-cell failure in type 2 diabetes. Whatever the arguments are, both forms of diabetes are on the rise in nearly all countries; type 1 diabetes is the most prevalent chronic disease in childhood, and type 2 diabetes is reaching epidemic proportion worldwide (8,9).

Interestingly, the term DD, or "type 1.5," characterized by the occurrence of hyperglycemia in overweight/obese children and youth with the combination of markers typical of both type 2 and type 1 diabetes, has gained the attention of the scientific community (10,11). A subject may be defined as affected by DD when he/she presents features of both type 1 and type 2 diabetes; it may occur when a child with type 2 diabetes has autoantibodies to β-cells or when a child with type 1 diabetes becomes overweight/obese.

The increase in incidence of type 1 diabetes in the past decade, especially in children under 5 years old (12), can be attributed to environmental changes, either quantitative or qualitative. It is unlikely that this increase is the result of changing genetic factors in such a short period. The increase in the incidence of type 2 diabetes in children and adolescents is more likely caused by the increase in obesity and sedentary lifestyles in developed countries (13). Youth with type 2 diabetes show features of insulin resistance (obesity, acanthosis nigricans, high insulin/C-peptide levels, polycystic ovarian syndrome in girls) and typically a family history of type 2 diabetes (14). From a clinical stand point, their hyperglycemia is mild, ketosis is rare, and the management of hyperglycemia includes diet and oral hypoglycemic agents. Moreover, an increase in the number of children and adolescents with a mixture of the two types of diabetes has been reported, i.e., subjects who are obese and/or with signs

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of insulin resistance as well as positive for markers of autoimmunity to β-cells (15).

OBESITY AS AN ASSOCIATED/PRECIPITATING FACTOR FOR BOTH TYPE 1 AND TYPE 2 DIABETES IN CHILDREN—Obesity has reached epidemic proportions globally, with >1 billion adults overweight and at least 300 million clinically obese, and is a major contributor to the global burden of chronic disease and disability (16). Often, coexisting in developing countries with poor nutrition, obesity is a complex condition with serious social and psychological dimensions affecting all ages and socioeconomic groups.

Childhood obesity is one of the most serious public health challenges of the 21st century. It has become a global problem that is steadily affecting many low- and middle-income countries, particularly in urban settings. The number of overweight children under the age of 5 years is estimated to be over 42 million worldwide (17). Rates of childhood obesity have increased greatly between 1980 and 2010 (18). Currently, 10% of children worldwide are either overweight or obese (19). Childhood obesity is already epidemic in some areas and on the rise in others.

Diabetes and obesity are twin interrelated epidemics that threaten to engulf the world's health care systems over the next decades. The prevalence of both is growing at an alarming rate, with up to 400 million people likely to develop diabetes in the next 15–20 years unless action is taken (18). Both diabetes and obesity are associated with significant mortality and morbidity from macrovascular disease, and both type 1 and type 2 diabetes carry the extra burden of the specific microvascular complications of retinopathy, neuropathy, and nephropathy. Whereas diabetes was a rare disease in the developing world 50 years ago, rates are soaring even in the poorest countries. In Asia, China alone has >92 million people diagnosed with the condition and nearly 150 million more showing early symptoms. This increase can be attributed to rapid economic growth and urbanization that has affected public health by changing diets and encouraging more sedentary lifestyles (19).

Diabetes is the third most common chronic disease of childhood (20). However, major gaps exist in knowledge of the types, frequency, pathophysiology, natural history, and processes of care. Until the past decade, types of diabetes other than type 1 diabetes were rarely diagnosed in children and adolescents. Recently, several reports described type 2 diabetes as a pediatric disease (21). However, outside of some American Indian groups and limited data in African American and Hispanic populations (22), there are virtually no population-based studies of childhood type 2 diabetes, and population prevalence of type 2 diabetes is unknown.

To date, there are no gold standard definitions of different types of diabetes presenting in youth. Clinical phenotypes at onset frequently overlap. Obesity and diabetic ketoacidosis can be found in both type 1 and type 2 diabetes (23). Age at diagnosis poorly differentiates between types (24).

To address these issues, SEARCH for Diabetes in Youth (SEARCH) was initiated in 2000. The primary aims of SEARCH are as follows: *1*) to estimate the population prevalence and incidence of type 1, type 2, and other types of diabetes overall and by age, sex, and race/ethnicity; 2) to develop efficient and practical approaches to the classification of diabetes type for prevalent and incident cases; and 3) to describe and compare clinical presentation and course of type 1 diabetes, type 2 diabetes, and other types of diabetes.

First results highlight the importance of characterizing this form of diabetes in youth. As expected, the most recent results of the SEARCH study show that most youths affected by type 2 diabetes are obese. Youth with type 1 diabetes have a higher prevalence of overweight, but not obesity, than nondiabetic youths. Future studies of obesity among youths with diabetes of all types will clarify the impact of obesity on diabetes, both as a risk factor and as a comorbidity (25).

THE ACCELERATOR HYPOTHESIS AS A CRITICAL FACTOR FOR DIABETES INCREASE—The accelerator hypothesis (26,27) believes that body mass is central to the development and rising incidence of diabetes. The hypothesis originally proposed three accelerators of β-cell loss, which recently have been reduced to two, without altering the premise. The first is insulin resistance, which not only accelerates the apoptosis of β-cells in its own right by making them work harder metabolically, but also renders them more immunogenic. The second accelerator is a hierarchy of responsive genes, whose reactivity modulates the gradient of β-cell declining function. Control of weight gain and its associated insulin resistance could be the means of reducing both type 1 and type 2 diabetes development (28). The accelerator hypothesis predicts an earlier onset of diabetes in heavier people and views type 1 and type 2 diabetes as the same disorder of insulin resistance set against different genetic backgrounds (29). None of the two accelerators leads to diabetes in the absence of weight gain (30), a trend that the hypothesis deems central to the rising incidence of all types of diabetes in the industrially developed and developing world. Weight gain causes an increase in insulin resistance, resulting in the weakening of glucose control. Therefore, an increasing body weight in the industrialized world has been accompanied by an earlier onset (i.e., acceleration) of diabetes.

The accelerator hypothesis is supported by several epidemiological case-control and population-based cohort studies. A study from Norway found almost linear correlation between the incidence rate of type 1 diabetes and birth weight (31). The risk of type 1 diabetes was higher by more than twofold in children with birth weight >4,500 g compared with newborns with the lowest birth weight (<2,000 g). In the Childhood Diabetes in Finland Study, children <15 years of age who developed type 1 diabetes were heavier and taller throughout childhood than birth date– and sex-matched control subjects (32). In this nationwide case-control study, a 10% increment in relative weight was associated with a 50–60% increase in the risk of type 1 diabetes before 3 years of age and a 20–40% increase from 3 to 10 years of age. The most recent epidemiological observations suggest that high birth weight could possibly result from a moderating effect on intrauterine growth of HLA genotypes conferring a high risk of diabetes (33). There are other data consistent with the hypothesis that the age at presentation of type 1 diabetes is associated with fatness (34) but not confirmed by other studies (35). Longitudinal studies will be important to further elucidate the accelerator hypothesis, and in this respect, a randomized controlled trial to reduce insulin resistance in at-risk children of type 1 diabetes should be implemented (36). Moreover, the accelerator hypothesis seeks to explain how a rising risk (insulin resistance) reduces the need for a genetic contribution to

modulate the risk and leads to convergence of the phenotype. It will remain a hypothesis until a suitably controlled intervention to reduce blood glucose is shown to slow conversion from risk to disease in children susceptible to type 1 diabetes (37).

OUR OWN STUDIES

Effect of different diets on diabetes development

To indirectly test the accelerator hypothesis, we evaluated the effects of a reduced amount of food (4 g/day) instead of the "ad libitum" diet on the development of diabetes in the NOD mouse model. The relationship between body weight and onset of diabetes was examined in the context of weight at birth, weight changes since birth, and weight at disease onset. Furthermore, we tested the hypothesis that a diet with a lower protein and a greater starch amount could also affect disease development.

Female NOD mice were randomly allocated to two different groups: group A reduced food intake with 4 g/day using a high-nutrient diet (RM3) and group B reduced food intake with 4 g/day using a diet poor in protein and rich in starch (RM1). Mice were weighed regularly throughout their lifespan and tested weekly for urinary glucose (>56 mmol/L), as a sign of development of diabetes. At diabetes onset, mice were removed from the experiment and their diabetes status was confirmed by a blood glucose reading of ≥11.5 mmol/L. At the end of the study, no significant difference was observed between group A and group B in terms of weight at birth (10.3 ± 2 vs. 10.6 ± 1.9 g), weight changes since birth considering the pre-diabetes phase (24.9 ± 2.1 vs. 23.6 ± 2.1 g), and weight at disease onset (23.7 ± 2.1 vs. 21.5 ± 3.5 g). However, incidence of diabetes was significantly reduced in group A (20.8%) compared with group B (45.8%, $P = 0.001$) (38).

Because mice exposed to a high-starch diet did not increase in body weight, we cannot rule out the accelerator hypothesis to explain the differences in the two groups of mice. However, the incidence of diabetes was significantly reduced in the group fed with a diet poor in starch and rich in protein, suggesting that this type of diet may be effective in preventing β-cell loss and insurgence of diabetes by modulating the autoimmune response toward β-cells.

Islet cell autoimmunity in the young population and DD

A few obese youth with type 2 diabetes have evidence of islet cell autoimmunity with autoantibodies toward β-cells (39). The increasingly "obesogenic" environment that favors insulin resistance could account for the development of islet cell autoimmunity through different mechanisms. Glucotoxicity accelerates β-cell apoptosis and, by increasing β-cell immunogenicity, further accelerates β-cell apoptosis in subjects genetically predisposed to intense immune response.

Recent data have shown that the prevalence of type 1 diabetes autoantibodies in normal schoolchildren differs between different population groups ranging between 0.5 and 1.8% (40,41). To throw new light on this hypothesis, we investigated islet cell autoimmunity in a population of obese youth with normal glucose tolerance ($n = 251$), impaired glucose tolerance ($n = 113$), and type 2 diabetes ($n = 15$). Children were of different races including Caucasian, African American, and Hispanic American. We found that GAD autoantibodies were detectable in 2.4% of obese children/adolescents with normal glucose tolerance; none of these subjects were Caucasian (42).

Prevalence of DD: a preliminary study

Few data are available in literature on the prevalence of DD in a Caucasian population (43). We designed a questionnaire in which clinical and laboratory data were collected from consecutive cases of diabetic patients aged between 5 and 30 years attending diabetes outpatient clinics in the Lazio region (continental Italy). Unpublished data included information on date of diagnosis, presence of at least one islet cell–related autoantibody, weight, height, waist circumference, blood pressure, cholesterol, triglycerides, HbA_{1c}, basal C-peptide, and type of antidiabetic therapy. In our study, we arbitrarily define an overweight/obese subject with hyperglycemia, positivity for GAD or other antibodies and high baseline C-peptide secretion (>0.3 nmol) as affected by DD; a subject positive for GAD or other antibodies and C-peptide <0.3 nmol as affected by type 1 diabetes; a subject positive for GAD or other antibodies and C-peptide >0.3 but <0.6 nmol as affected by "possible type 1 diabetes"; a subject negative for GAD or other antibodies and C-peptide >0.6 nmol a subject affected by type 2 diabetes.

We analyzed data from 161 consecutive Caucasian diabetic subjects. Based on our definition of DD, we found a prevalence of 4.96% of subjects with this form of diabetes (P.P., C.G., C. Bizzarri, unpublished data). There is clearly the need for larger studies in different populations to better characterize this form of diabetes.

In some young patients, it is sometimes difficult to place diagnosis of type 1 or type 2 diabetes on clinical grounds. To differentiate these entities, studies to assess the presence of autoantibodies to β-cell antigens may help to define the type of diabetes. Islet cell autoimmunity (in particular, GAD antibodies) appears to occur more frequently in overweight/obese children from African American/Hispanic descent (see PREVALENCE OF DD: A PRELIMINARY STUDY).

Furthermore, increasing obesity and poor fitness have led to a remarkable increase of type 2 diabetes in youth and young adults and to what is called DD (10,11).

DOUBLE DIABETES AS A RESULT OF A CHANGING ENVIRONMENT

—Subjects with DD are overweight or obese and, because of insulin resistance, they may require a high insulin dose. Moreover, they may suffer from high blood pressure and an abnormal lipid profile. Teenage girls and women may have polycystic ovary syndrome, including several hormonal abnormalities leading to amenorrhea and hirsutism.

In DD, it is clear that one important factor is excessive weight gain causing insulin resistance, and this is what places a subject with type 1 diabetes into the DD category. Moreover, subjects with type 1 diabetes and a family history of type 2 diabetes are more likely to develop insulin resistance if they gain excessive body weight, as postulated by the accelerator hypothesis. According to the accelerator hypothesis, the increase in incidence of type 1 diabetes observed in young children is due to excessive weight gain and the development of insulin resistance, a phenomenon associated with type 2 diabetes. Insulin resistance puts the β-cells under stress by forcing them to produce more insulin. Stressed β-cells are more likely to experience autoimmune injury, which can lead to their destruction and the development of type 1 diabetes in an individual genetically at

risk. This result suggests that weight gain can accelerate development of type 1 diabetes in people who might get it later in life if they had maintained a healthy weight. Obesity and insulin resistance might also partially explain why there is an increase in the total number of cases of type 1 diabetes. Excess body weight can induce the immune system to destroy the insulin-producing cells when that might not have occurred without the excess body weight.

COULD THE RISING INCIDENCE OF AUTOIMMUNE DIABETES BE RELATED TO ENVIRONMENTAL CHANGES OTHER THAN OBESITY?

—Other environmental factors have been investigated for their potential role in increasing the incidence of type 1 diabetes. Birth weight and the risk of childhood-onset type 1 diabetes has been evaluated in several studies. A recent meta-analysis (44) evaluating 29 European studies demonstrated that children who are heavier at birth have a significant and consistent, but relatively small, increase of type 1 diabetes. Children with birth weight >4.0 kg had an increased risk of 10% compared with children weighing 3.0–3.5 kg. Increased early growth also has been associated with increased risk for type 1 diabetes in various European populations (45). Height and weight were significantly increased from 1 month after birth in type 1 diabetic patients compared with control subjects. A recent study showed a significant linear increase in the risk of childhood type 1 diabetes across the range of maternal ages: a 5% increase in type 1 diabetes for 5 year increase in maternal age. However, the authors concluded that only a small percentage of the new cases of type 1 diabetes are attributable to an increase in maternal age at the time of delivery (46). Overall, there is increasing evidence that environmental factors other than obesity have a role in explaining the rising incidence of type 1 diabetes, but their exact impact has yet to be established.

In conclusion, there is a new challenge for both diabetes research and clinical practice represented by the increasing incidence of all types of diabetes and the changing phenotype of the disease in childhood and adolescence. It is difficult, at this stage, to recognize whether DD is a real new emerging form of diabetes or does it simply reflect the rising trends in obesity in the population. The more likely explanation is that the rising obesity trend seems to have a role (in association with other environmental factors) in explaining the increasing incidence and the changing phenotype of type 1 diabetes in youth. On the other hand, the only certainty is that we have to cope with a diabetes phenotype (DD), which makes both diagnosis and consequently the therapeutic approach difficult for these patients who are mostly diagnosed in the pediatric age-group.

Long-term studies are needed where networking and integrated management with different specialists can tackle this alarming condition.

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