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REVIEW

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Type 2 diabetes mellitus is becoming the most common type of diabetes in school children

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Abstract Obesity, now an epidemic in the USA, northern Europe, and Italy, is associated with several co-morbidities that shorten life expectancy, in particular type 2 diabetes mellitus (T2DM), arterial hypertension, and hyperlipidemia. The impact of obesity on mortality is evident in all ages, and is especially strong in young persons. Obesity, especially visceral obesity, associated with a sedentary lifestyle, is among the strongest risk factors for T2DM, and a diagnosis of T2DM seems to increase linearly as a function of duration of obesity. The pathogenesis of T2DM is based on a dual defect, i.e. increased insulin resistance coupled with defective insulin release. The main abnormality in obesity is increased insulin resistance, while insulin release, even though defective compared with body needs, is usually abundant.

The incidence of obesity among children aged 6-16 years is now even greater than that among adults: in Italy, figures up to 30% have been reported. As in adults, obesity is a cause, among children, of arterial hypertension, left ventricular hypertrophy, hyperlipidemia, non-alcoholic-steato hepatitis, sleep apnea syndrome (SAS), and orthopedic, psychological, and social problems. Together with an increase in body weight, there is an increase of visceral fat. Obesity in children has also led to a tremendous increase in the prevalence of impaired glucose tolerance (IGT); the percentages span from 25% in a multiethnic cohort in the USA, to 4% in Italian Caucasians. Management of obesity and of T2DM in children has to face the issue of poor compliance; there is consensus that dietary treatment of obese T2DM children is a failure, so that drugs are required; the only drug evaluated in a formal trial is metformin, that behaves in terms of efficacy and of minor side effects as in adults. In conclusion, obesity in children is not pure obesity, but is accompanied by co-morbidities that cluster to form the "metabolic syndrome" just like in the adults. If this epidemics continues and is not properly challenged, in the next decades we will face an epidemic of early cardiovascular morbidity and mortality.

Key words Type 2 dibetes • Children • Obesity • Metabolic syndrome

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Introduction

Type 2 diabetes mellitus (T2DM) is going to become the most common type of diabetes in school children. This is generally believed to be best explained by the link between obesity and T2DM. This review focuses on: (1) the interplay between obesity and T2DM in adults; and (2) the increasing knowledge of the diseases associated with obesity in school children, with emphasis on T2DM.

Obesity and diabetes in adults

Obesity is now an epidemic in the USA, in northern Europe, and in Italy [1–4]. Obesity is associated with several co-morbidities that shorten life expectancy [5]: the

impact of obesity on mortality is evident in all ages, but especially in younger ages [6]. This increase in mortality is partly mediated by increased frequency of T2DM, hypertension and hyperlipidemia [7]; congestive heart failure and coronary heart disease are now recognized as major complications of diabetes [7, 8].

In adults, obesity (especially visceral obesity) in association with a sedentary lifestyle is one of the strongest risk factors for T2DM; other risk factors include a family history of T2DM, gestational diabetes, impaired glucose tolerance (IGT), and low birth-weight [9]. Other traditional risk factors (such as belonging to selected ethnic groups) should be interpreted with caution, as these populations have experienced an impressive increase in obesity as well [10]; we can expect that other ethnic groups, once they experience economic development and hence obesity, will also experience a substantial increase in the prevalence of T2DM.

The relationship between duration of obesity (grade 3) and development of T2DM is best explained by the data in Fig. 1: the prevalence of diabetes, diagnosed on the basis of answers to questionnaries or on the results of an oral glucose tolerance test (OGTT), increases linearly as a function of years of obesity, so that among subjects with obesity for 25 years the prevalence of T2DM is about 50% [11–15].

The pathogenesis of T2DM is based on a dual defect, i.e. increased insulin resistance coupled with defective insulin release [9]; the interplay between the two defects is probably a function of body weight, as at least 3 papers have indicated that the main abnormality in obesity is increased insulin resistance, at difference from lean individuals, in whom insulin resistance is negligible and defective insulin release is the main abnormality [16–18]. At any degree of body weight, insulin release is however reduced in T2DM than in subjects with normal glucose tolerance,

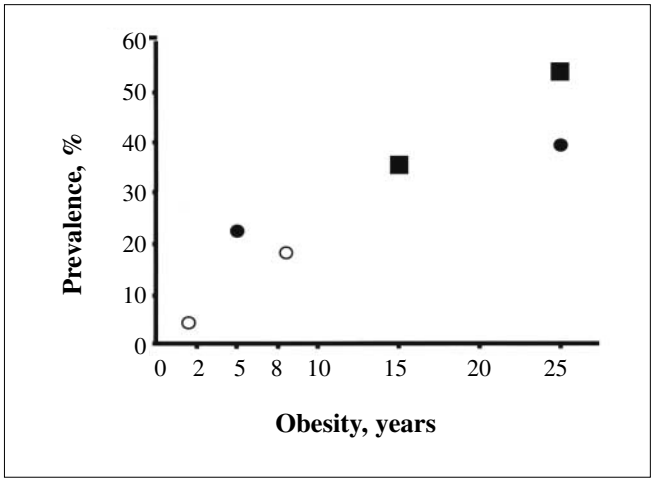

Fig. 1 Prevalence of type 2 diabetes mellitus (T2DM) among subjects with morbid obesity as a function of duration of obesity. The data are collected from references 11–15. *White circles*, self reported diagnosis of T2DM; *black circles*, T2DM diagnosed at an oral glucose tolerance test (OGTT); *black squares*, T2DM plus impaired glucose tolerance at OGTT

but this simply means that insulin release is not enough for body needs, otherwise they would not be diabetic [19]. This difference between obese and non-obese diabetes has practical implications, meaning that in obese patients endogenous insulin is usually enough to control glucose metabolism, with the aid of lifestyle modifications and drugs that enhance insulin release or improve insulin resistance; in contrast, in lean patients endogenous insulin is scanty since diagnosis, and this is the main reason why, sooner or later, exogenous insulin is required [16, 20, 21].

The full blown picture of obese diabetes is probably best characterized as "metabolic syndrome", in which obesity, diabetes, hypertension, hyperlipidemia, hyperuricemia and a pro-coagulatory state cluster to magnify the cardiovascular risk [22].

Treatment of T2DM is aimed at controlling symptoms and preventing of complications, and targets for obese and non-obese patients are the same. The American Diabetes Association has clearly indicated that blood glucose levels, both fasting and post-prandial, are important, with the resulting normalization of glycated hemoglobin and disappearance of glycosuria; also blood lipids should be corrected, as well as blood pressure, and body mass index [23]. Various drugs are now available to control blood glucose levels, lipid levels, and arterial blood pressure, and to reduce body weight.

In the UK Prospective Diabetes Study (UKPDS), prevention of complications has been obtained in obese patients with intensive treatment with metformin [24], and even more effective was the anti-hypertension treatment of naive patients with either ß-blockers or inhibitors of angiotensin converting enzyme (ACE) [25]. It should be noted that, as happens in non-diabetic individuals, more than one drug is required to effectively control blood pressure. In subjects with pre-existing cardiovascular complications, some combinations of drugs (mainly angiotensin receptor antagonists and ACE inhibitors) are more effective than other combinations in preventing new events [26–28].

The importance of body mass index (BMI) as a primary target for intervention has hardly been understood for a long time, in spite of the fact that in obese patients treated with diet alone, diet and exercise, or diet and behavioral treatment it is possible to observe decreases of HbA_{1c} greater than those observed in trials using hypoglycaemic drugs [21, 29]. When body weight decreases, improvement of glucose metabolism is associated with enhancement of insulin sensitivity, while insulin release is not affected or is decreased; together with this, several other risk factors decrease, such as blood lipids, fibrinogen, arterial blood pressure [21]. However, most studies have been of duration up to 1 year [29], and this conflicts with the notion that obesity is a chronic condition and with recommendations of the World Health Organization (WHO) for a long-term strategy targeted at ensuring sustained weight loss and preventing weight regain [30]. In fact, there is evidence that cyclical weight loss followed by regain of body weight (the weight cycling or "yo-yo" effect) can be by itself a risk factor for cardiovascular disease [31].

Two considerations have paved the way for bariatric surgery in morbid obesity: (1) with massive obesity it is virtually impossible to reach a body weight target useful to manage co-morbidities [32]; and (2) weight cycling is extremely common [31]. The literature is rich in details about two surgical approaches: gastric bypass, a major surgical procedure, and laparoscopic gastric banding (LAGB). With both procedures, the effective part of the stomach is reduced to a cavity of 30 ml, and BMI stabilizes (starting from >40 kg/m^2) to ≤35 kg/m^2 [33–35]. The longest follow-up, 14 years, showed that arterial blood pressure, blood glucose, and HbA1c normalized in more than 80% of patients with abnormalities at baseline [33]. Even more promising is the fact that gastric bypass, vertical banded gastroplasty, and LAGB all reduced the prevalence of impaired fasting glucose (IFG), and prevented the progression of IGT to T2DM [13, 15]. Less evident is the preventive role towards progression of arterial hypertension [15], but there is evidence that mortality and especially cardiovascular mortality are less in surgically treated obese patients than in diet-treated obese patients [36]. This observation most likely mirrors the fact that weight loss is more durable in the former than in the latter. Prevention of T2DM has also been successfully attempted, in obese subjects with IGT, through modification of lifestyle [37–39], or through the use of drugs such as metformin [39, 40], troglitazone [41], and acarbose [42].

The epidemic of obesity in school children

A new drama is going on: the prevalence of obesity children aged 6–16 years is even greater than that among adults: in Italy, figures up to 30% have been reported [4]. As in adults, obesity is a cause, among children, for arterial hypertension, left ventricular hypertrophy, hyperlipidemia, non-alcoholic steatohepatitis, sleep apnea syndrome (SAS), and orthopedic, psychological, and social problems [43]. Together with an increase of body weight, an increase of visceral fat has been reported [44, 45]. In the Bogalusa Heart study [46], 11% of 9167 school children were obese (>85th percentile of BMI), and the risks for hypertension, hyperlipidemia and hyperinsulinemia were 3- to 12.6-fold greater than those for children <85th percentile. More importantly, 58% of children had at least one of the three previously mentioned risk factors [46]. In an Italian study of 710 obese children, 13%–35% had associated abnormalities in arterial blood pressure, serum, fibrinogen, lipidemia, uricemia or C-reactive protein [47].

Furthermore, prevalence of T2DM has increased to 4.09% in young Pima Indians and to 0.45% in Native Americans and Canadians, compared to a 0.17% prevalence of T1DM [48]. In Ohio, 33% of all diabetic children are now affected by T2DM [49], and in the period from 1990 to 1998 the incidence and prevalence of T2DM have increased by 46%, as opposed to the 5% increase in incidence of T1DM [50]. A full-blown picture of "metabolic syndrome" has been reported in about 4% of all adolescents and in up to 30% of overweight adolescents in the United States [51]. Phenotypic and autoimmune characteristics of patients at diagnosis indicate that we are dealing with "classic" T2DM (Table 1) [52–54]. In keeping with what happens in adults [16–18], insulin-requiring children have a more serious impairment of insulin release than children treated with oral agents [55, 56]. Low birth-weight and the catch-up growth in the first 6 years of life are probably as important in the development of the full-blown picture of T2DM as the current body weight at 6 years [57]. Early detection of T2DM is recommended by the American Diabetes Association in obese children aged >10 years, with at least one additional risk factor such as family history of T2DM, belonging to

Table 1 Clinical and autoimmune characteristics of children at diagnosis of alleged type 1 and type 2 diabetes mellitus. Children were of African-American, Hispanic, or White ethnicities. The meta-analysis was performed using data from references 52–54. Values are percentages of children studied, unless otherwise indicated

	T2DM	T1DM	Significance (p)
Children, n	48+44+37	39+199	
Age at onset, years[a]	13–14	9–10	<0.001
Family history of T2DM, %[a]	50–61	0–16	<0.01
Family history of T2DM in the mother, %	39	10	<0.001
BMI, kg/m^2	31	18	<0.001
Ketoacidosis at onset, %	45	76	<0.001
Insulin treatment 1 year after onset, %	50	100	<0.05
Islet cell antibodies, %	8	71	<0.01
GAD antibodies, %	21	76	<0.001
Insulin autoantibodies, %	31	77	<0.01

[a] Values are ranges

BMI, body mass index; *GAD*, glutamic acid decarboxylase

ethnic minorities and hyperlipidemia. It has been proposed that at least 2.5 million children should be screened for T2DM in the USA [58].

Obesity in children has also led to a tremendous increase in the prevalence of IGT: the percentages span from 25% in a multiethnic cohort in the USA [59], to 4% in Italian caucasians [47]. Both figures are extremely high, although there are at present only hypotheses to explain this difference, such as variations in ethnicity, diet and heritage.

Management of obesity and T2DM in children has to face the issue of poor compliance. In the study of Pinelli et al. [60], only 70% of the studied cohort was still in a nutritional intervention program 2 months after starting; after 2 years only 6% still participated. There is a consensus that dietary treatment of obese T2DM children is a failure, so that drugs are required [61]. The only drug evaluated for use in children in a formal trial is metformin, which has an efficacy and side effect profile similar to that in adults [62].

The only good news is that parental supervision usually results in good metabolic control [63]. As in adults, there are pioneering reports on the efficacy of bariatric surgery (biliointestinal diversion) for the most severely obese children (BMI = 60 kg/m^2); two series reported effective control of body weight for up to 14 years, and disappearance, at least 1 year after surgery, of co-morbidities such as arterial hypertension, diabetes, and SAS [64, 65]. This approach, however, is hardly considered or even ignored by pediatricians, who actually recommend changes in eating patterns, limitations of specific foods, low-fat diets and physical activity for all age groups [66]; this last approach is considered to be of benefit in the prevention of type 2 diabetes, even in spite of marginal decreases of body weight and of visceral fat [67].

What should be done? More public health authorities, family doctors, and pediatricians should be concerned about this epidemic of obesity, as obesity in children is not pure obesity, but is accompanied by co-morbidities that cluster to form the "metabolic syndrome" just like in adults. If this epidemic continues and is not properly challenged, in the next decades we will face an epidemic of early cardiovascular morbidity and mortality [46]. The dimensions of this new epidemic cannot be predicted at present, as emerging countries will soon follow what is happening in Western societies. Prevention and education can no longer be post-poned [68].

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