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IM - CASE RECORD

Prognostic implications of diabetes phenotyping: new concepts for an old disease

Giuseppe Daniele · Cristina Bianchi · Graziano Di Cianni · Stefano Del Prato · Roberto Miccoli

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Case presentation

Dr. Daniele: The case record presented here is that of D.S., a woman who is now 35 years. Her case report begins when she was 14 years (1987) at which time she underwent screening for diabetes because of her obesity (weight 95 kg, BMI 36 kg/m^2) and her family history of diabetes (mother and maternal grandmother). Based on her fasting glucose level (160 mg/dl), she was diagnosed with diabetes mellitus. At that time, her level of HbA1c was 7.8%. D.S. began treatment with a low calorie diet with which she obtained a moderate weight reduction (about 10–15 kg). During the following years, she has had several weight fluctuations until she reached 67 kg in 1995. Throughout that period, she had several medical visits, but there is no available information regarding her glucose levels. At 22 years of age (1996), she was admitted into the hospital following a hyperglycemic crisis, accompanied by polyuria and polydipsia. This hospitalization resulted in the diagnosis of insulin-dependent diabetes mellitus and subsequently, she began insulin treatment. On that occasion, diabetic retinopathy was found. The following years she saw an improvement in her glucose levels (HbA1c 6.5%) but a worsening of the retinopathy (diffuse microaneurysms, microhemorthages, and hard exudates) that required bilateral laser therapy. Concurrently, she developed a peripheral motor and sensory neuropathy, and then microalbuminuria but with preserved renal function. She continued insulin with four daily injections and maintained good metabolic control (HbA1c $<$ 6.5–7%), although her body weight rose continuously until she again reached 95 kg in 2000. In 2003, her HbA1c levels increased (7.8%) and she gained an additional 5 kg.

Differential diagnosis

Dr. Daniele, Dr. Bianchi: The clinical characteristics of disease at onset and during follow-up, questioned the appropriateness of the initial diagnosis and suggests a different etiology of diabetes. At that time, her β-cell function was tested in fasting and after glucagon stimulus. The results highlighted C-peptide values of 1.24 ng/ml in basal condition, and 1.47 ng/ml 6 min after the stimulus. The studies for the antibodies anti-GAD and anti IA2 were negative.

Clinical diagnosis

Dr. Daniele, Dr. Bianchi: The phenotypic characteristics, along with a moderate β-cell function reserve, and the negative antibody results, might be indicative of type 2 diabetes mellitus instead of type 1 diabetes.

Follow-up

Dr. Daniele, Dr. Di Cianni: In a patient more likely affected by type 2 diabetes, the possibility of following an alternative treatment was taken into consideration, and the patient was started on metformin therapy. Moreover,

G. Daniele · C. Bianchi · G. Di Cianni · S. Del Prato · R. Miccoli (✉)
Section of Diabetes and Metabolic Diseases,
Department of Endocrinology and Metabolism,
Ospedale Cisanello, University of Pisa,
Via Paradisa 2, 56124 Pisa, Italy
e-mail: rmiccoli@immr.med.unipi.it

obesity evaluation and treatment were carefully performed. A psychological consult found evidence of an eating disturbance. Because obesity could have strong negative effects on the control of diabetes and its complications, and considering the patient's desire to eventually pursue pregnancy, a vigorous multidisciplinary program against obesity was outlined. Finally, the patient was referred for bariatric surgery, and in July 2005, she underwent gastric banding surgery. Before surgery, she had an HbA1c value of 7.7% and a stable body weight of 108 kg. The patient continued the insulin therapy with four daily injections along with the metformin therapy. The post-surgical course went well, and in the following months, the patient registered a gradual weight loss (−30 kg after 22 months) and a significant improvement in HbA1c levels (6.8%) along with a reduced need for insulin dose (from about 40 UI/die to 20 UI/die) (Fig. 1). The gastric bands were well tolerated and functioned perfectly.

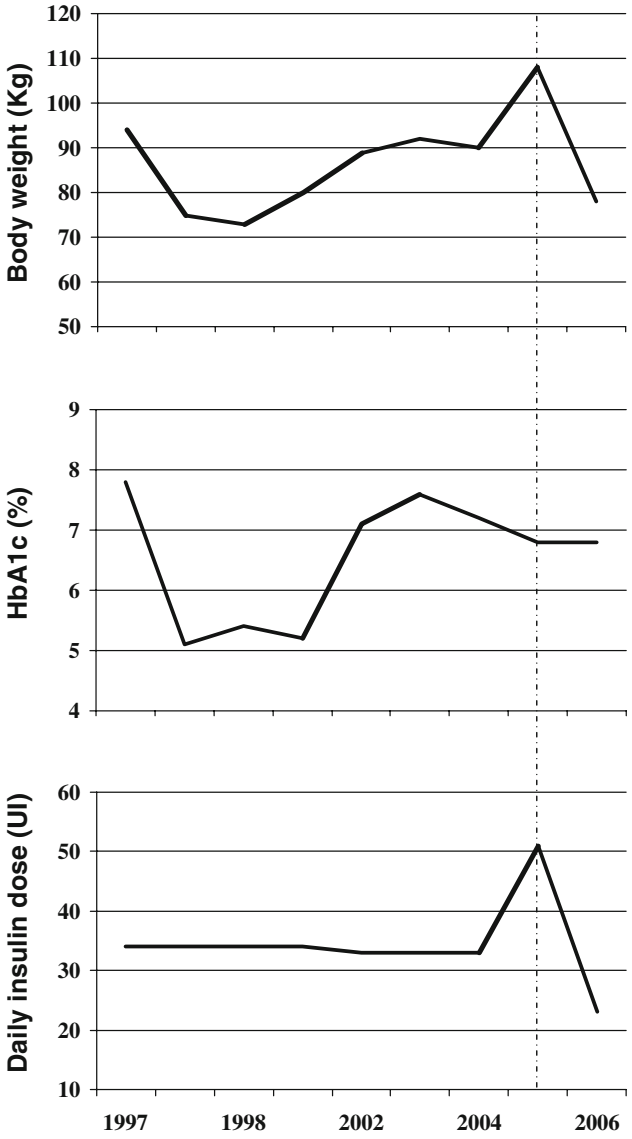

Fig. 1 Body weight, HbA1c levels and daily insulin dose during the 10-year follow-up period. *Dotted line* indicates bariatric surgery

Discussion

Dr. Daniele, Dr. Del Prato, Dr. Miccoli: The case reported here is useful to discuss several aspects regarding both the diagnosis and treatment of diabetes.

The etiologic classification of hyperglycemic syndromes identifies two main types of diabetes, type 1 and type 2 diabetes [1]. Recently, other categories of diabetes have been defined, including type 1a, type 2b, type 1 1/2, LADA (latent autoimmune diabetes of adult), double diabetes, hybrid diabetes, MODY (maturity onset diabetes of the young) and LADY (latent autoimmune disease in youth) [2, 3].

Type 1 diabetes, or immune-mediated, represents 5–10% of all cases of diabetes [2]. It is characterized by β-cellular destruction associated with an autoimmune process, which is evidenced in 85–90% of presenting cases by the presence of the antibodies anti-insula, anti-GAD, anti-IA2, and anti-IA2β. Patients with type 1 diabetes have an elevated risk of other associated autoimmune diseases such as celiac disease, Graves' disease, Hashimoto's thyroiditis, Addison's disease, and pernicious anemia. A small percentage of patients (idiopathic type 1b) of African and Asian descent do not present with signs of autoimmune disorders. Although type 1 diabetes can occur at any age, it most frequently develops in childhood and adolescence, usually associated with ketoacidosis. In other patients, it manifests in a slower onset of hyperglycemia and develops into ketoacidosis following an infection or stress trigger. Classic symptoms of the disease are polyuria, polydipsia, asthenia, and weight loss. A distinctive characteristic of type 1 diabetes is in the almost complete absence of C-peptide [2].

Type 2 diabetes accounts for 90–95% of all cases of diabetes, and manifests primarily in adulthood [2]. It is the result of a combination of insulin-resistance and a relative β-cell failure. The occurrence of hyperglycemia may be occasional, for example in conjunction with a cardiovascular event. The C-peptide levels are normal or elevated with this type of diabetes [2]. Only 10–15% of patients present with antibodies (anti-GAD) that can be seen as a sign of future insulin dependence [2]; in this case the diabetes is defined as LADA.

New evidence has opened the discussion of a possible common acquisition that would redefine the two distinct pathologies of type 1 and type 2 diabetes. This includes the directly proportional relationship between body weight and the risk of type 1 diabetes, the increase in incidence of type

2 diabetes in adolescents and of diabetes type 1 in children under 5 years of age, and the occasional presence of autoantibodies in patients with type 2 diabetes. Based on these considerations, a hypothesis has been made showing a continuum between type 1 and 2 diabetes with a considerable superimposition for the onset age [4]. According to a recent hypothesis, a complicated interaction between genetic factors (genotype HLA involvement in the immune response) and non-genetic factors (i.e. insulin resistance) is the basic mechanism of the β-cell hyper-stimulation that causes the β-cell to become immunogenic and the target of autoimmune reactions. From this viewpoint, the individual factors accelerate the development of diabetes and therefore the β-cell deficit that would determine the onset age of the disease. Furthermore, the insulin-independence is not an entity of the diagnosis but only a temporary state that will eventually lead to insulin-dependence.

In the case of our patient, symptoms of diabetes were not present, and so she was treated by diet only while a deeper study of the disease was not performed, particularly a screening of diabetes complications. Presumably based on the practices at the time, the disease must have been labeled as insulin-independent and, therefore, thought to be less serious, so the patient received minimal treatment. A more accurate phenotypic evaluation was performed during the following years when the etiological classification of the disease was established which definitively excluded type 1 diabetes and gave the differential diagnosis of monogenic diabetes (Table 1). Although this form only represents 1–2% of diabetes cases [2], the diagnosis allows for appropriate therapy, screening, and genetic counseling. For example, patients with some specific mutations respond well to therapy with sulfonylurea while heterozygous cases of certain genes do not indicate any special treatment. The family history of diabetes in three consecutive generations, the age and symptoms at onset, and also the insulin independence of our patient could have indicated monogenic diabetes at the time the patient first showed up. Nevertheless, the obesity of the patient, the persistence of moderate residual β-cell function, the absence of autoantibodies oriented the diagnosis towards type 2 diabetes, associated with obesity of class II-III (Fig. 2).

Based on the recent guidelines from America Diabetes Association (ADA) [6], patients with diabetes type 2, like the patient presented here, should be treated at the time of diagnosis with a low-calorie diet and metformin when the HbA1c is above 7%. The level of HbA1c should be used to guide future treatment decisions taking into consideration the most effective agent or insulin therapy if the HbA1c is at or above 8.5% or if secondary symptoms to hyperglycemia are present [5].

After approximately 10 years of what was likely inadequate treatment, acute metabolic complications and chronic microvascular complications appeared in our patient. The last decade has shown an increase in the presence of type 2 diabetes in childhood through adolescence that runs parallel to an increase in the prevalence of obesity in the same age group. Further review of epidemiological studies has shown that the onset of type 2 diabetes in adolescence can be associated with a higher morbidity and mortality [6]. In fact, in these subjects microvascular complications (retinopathy, nephropathy, and neuropathy) may be present at the time of diagnosis [7], and are qualitatively similar but rapidly progressive in comparison with these symptoms in adolescents with type 1 diabetes. Moreover, obesity, hypertension, dyslipidemia, and NAFLD (non-alcoholic fatty liver disease) can be associated with a higher cardiovascular risk although the data to prove this is lacking. In any case, type 2 diabetes must be quickly diagnosed to prevent subsequent β-cell failure [8] and the development of micro-macrovascular complications by reducing insulin resistance through weight loss and antidiabetic drugs.

In the case reported above, in spite of the alternative approach to the treatment of diabetes, the problem of obesity persisted as a considerable co-morbidity throughout the case during the following years. A significant variation

Table 1 Clinical characteristics of type 1, type 2 and monogenic diabetes

Characteristics	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes
Genetics	Polygenic	Polygenic	Monogenic
Age	Usually chilhood	Usually adulthood	Often postpubertal except MODY2 and neonatal diabetes
Onset	Most often acute, rapid	Often insidious	Variable
Familiy history	+/−	++	+++
Obesity	Reflects the background risk	Very common	Reflects the background risk
Ketosis	Common	Rare (1/3 of newly diagnosed adolescent)	Rare in MODY common in neonatal diabetes
Autoimmunity	Yes	No	No
C-peptide (nmo/l)	Decreased/absent	Normal/increased	Normal/reduced

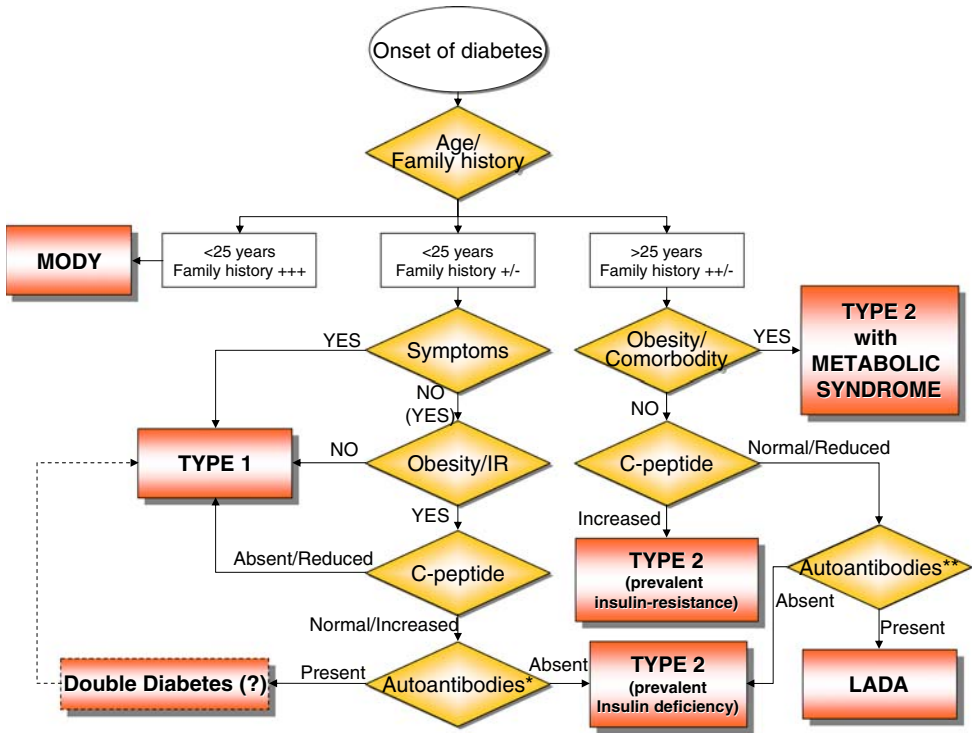

Fig. 2 Flow-chart for diffential diagnosis of type 2 diabetes. *Asterisk* represents *ICA* (cytoplasmic islet cell antibodies), GAD (to GAD65) and IA2 (to tyrosine phosphatase IA-2) antibodies. If age < 10 years IAA (insulin) autoantibodies. *Double asterisks* represent GAD (to GAD65) and *ICA* (cytoplasmic islet cell antibodies) antibodies. *IR* insulin resistance

in weight accompanied considerable modifications in the dosage of insulin with limited results in terms of metabolic control. Because of the effects of obesity on insulin-resistance, weight loss is an important therapeutic objective for overweight or obese individuals with prediabetes or diabetes [9]. Psychological evaluation of our patient demonstrated an eating disorder that led to an alternative treatment of obesity and, thus, diabetes. The ADA suggests that gastric reduction surgery can be an effective weight loss treatment for obesity, and may be considered in people with diabetes who have BMI $\geq$ 35 kg/m^2 [10] (Table 2). In accordance with this indication, gastric banding surgery was proposed for our patient.

Bariatric surgery is emerging as a prominent form of treatment for obesity and, more recently, for diabetes. An elevated percentage of diabetic subjects are overweight or morbidly obese. The obesity also represents an important risk factor for cardiovascular disease, and is often associated with type 2 diabetes, dyslipidemia, hypertension, non-alcoholic hepatopathy steatosis, subclinical inflammation, and endothelial dysfunction. Several studies on surgical interventions have shown that treatment of obesity, especially that of grade III, can improve diabetes and other metabolic conditions. The reduction of caloric intake mediates anatomical modifications of the intestine that represents the main effect of bariatric surgery [11].

Table 2 Clinical recommendations for bariatric surgery in type 2 diabetes

Recommendation	Level of evidence
Bariatric surgery should be considered for adults with BMI 35 kg/m2 and type 2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy	B
Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring	E
Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI of 30–35 kg/m2, there is currently insufficient evidence to generally recommend surgery in patients with BMI 35 kg/m2 outside of a research protocol	E
The long-term benefits, costeffectiveness, and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed randomized controlled trials with optimal medical and lifestyle therapy as the comparator	E

Modified from Ref. [10]

Restrictive surgery, like gastroplastic, gastric banding, the combination of the previous two operations, and vertical gastrectomy (sleeve) slow the gastric emptying process by creating a reservoir. Gastric bypass Roux-en-Y and the

biliopancreatic diversion with duodenal switch are usually completed in combination with restrictive vertical gastrectomy to reduce food absorption by excluding a large part of the intestine.

In a meta-analysis involving 136 studies encompassing a total of 22,094 diabetic patients, bariatric surgery led to complete remission of diabetes in 48% of patients after gastric banding, 84% of patients after gastric bypass Roux-en-Y and in 95% after biliopancreatic diversion [12]. Furthermore, in the case of the malabsorptive procedures, the diabetic remission was verified in the weeks following the surgery, which suggests a metabolic effect independent of weight modification. It is possible that the duodenum and the proximal part of the ileum have a role in the physiopathology of diabetes through the regulation of the incretin system in order to maintain glucose homeostasis [13]. A recent hypothesis proposes that there is an imbalance towards the anti-incretinic system with a reduction of insulin secretion and action, and β-cell growth in patients with type 2 diabetes. In bypassing the duodenum and portions of the ileum through malabsorptive bariatric surgery, the balance between these systems is restored by the exaggerated contact between nutrients and the distal regions of the ileum and colon. The β-cell function, unlike BMI, should represent a predictive factor of bypass surgery for the treatment of diabetes. In our patient, the positive outcome of gastric banding surgery has permitted a rapid weight reduction (around 30 kg), better control of diabetes (HbA1c -1%) and a significant reduction in insulin need.

In conclusion, the phenotypic characteristics are important tools to the correct etiological diagnoses of diabetes, and allow the correct formulation of prognosis and treatment. The early onset of type 2 diabetes in adolescence is related to an increased risk of severe and premature microvascular complications, and therefore an early screening for retinopathy, nephropathy, and other co-morbidities should be performed from the time of the diabetes diagnosis, as well as to permit an accurate, follow-up. At diagnosis, the intensive life style approach should be the first intervention unless other metabolic abnormalities are present. Metformin is useful in controlling glucose-metabolism. Finally, bariatric surgery, when indicated, can be an effective alternative approach for the treatment of obesity and diabetes.

Epilogue

Dr. Di Cianni: In January 2007, D.S. underwent her first pregnancy. A strict home blood glucose monitoring allowed her to reach HbA1c values of less than 6%, with a weight gain of 10 kg by the end of the pregnancy. During the 36th week she had a rise in blood pressure and edema in the lower limbs which were associated with thrombocytopenia and a worsening of albuminuria. These elements all suggested pre-eclampsia and D.S. was admitted to the obstetric ward. Finally, she delivered a normal baby boy weighing 3.2 kg, after induced labor.

Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

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