Diabetes in Childhood and Adolescents

14

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14.1 Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action in tissues, or both. Diabetes mellitus (DM) is the most common endocrine disease and one of the most common chronic conditions in children. Diabetes mellitus is classified into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), other types of DM, and gestational diabetes. T1DM is the most common form of DM in children and adolescents and the presentation age start from the first year of life that increases during puberty.

T1DM is an autoimmune illness, characterized by multiple autoimmune markers even in the preclinical period, with partial or total destruction of the pancreatic islet B-cell and deficiency in insulin secretion. Consistently, genetic markers (HLA) are present, increasing or decreasing the risk of patients and their families. Potential triggers are environmental factors such as congenital rubella, enteroviral infections, casein, and cereals. Insulin is the treatment of choice to be given immediately upon diagnosis (American Diabetes Association 2018).

T2DMis an emerging disorder in children and adolescents, leaving large gaps in knowledge on the pathophysiology and treatment optimization. Patients with T2DM have insulin resistance and non-autoimmune B-cell failure. Familial T2DM, obesity, and physical inactivity are the principal risk factors.

There are other multiple types of DM: neonatal DM, endocrine and genetic illnesses, etc.

Gestational DM, is characterized by the appearance of hyperglycemia during pregnancy and should be treated immediately (Mayer-Davis et al. 2018).

14.2 Type 1 Diabetes: Diagnostics

Type 1 diabetes is characterized by the chronic immune-mediated destruction of pancreatic B-cells, leading to partial or absolute insulin deficiency. This destruction occurs at a variable rate and becomes clinically symptomatic when approximately 90% of pancreatic B-cells are destroyed.The illness progresses through three stages at variable rates:

- Stage 1: autoimmunity with normoglycemia and without clinical symptoms.
- Stage 2: dysglycemia, but asymptomatic.
- Stage 3: the symptomatic phase of the disease (Insel et al. 2015).

Type 1 diabetes mellitus in young people is usually shows characterized by polyuria, polydipsia, nocturia, enuresis, weight loss with polyphagia, and blurred vision. A plasma blood glucose level (BGL) measurement on laboratory glucose oxidase estimation is required to confirm the diagnosis, rather than a capillary blood glucose monitor. In the absence of unequivocal hyperglycemia, diagnosis must be confirmed by repeat testing with an oral glucose tolerance test (OGTT) and the diabetes-associated autoantibodies glutamic acid decarboxylase 65 (GAD), tyrosine phosphatase-like insulinoma antigen 2 (IA2), insulin autoantibodies (IAA), and

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B-cell-specific zinc transporter 8 (ZnT8). The presence of one or more of these antibodies confirms the diagnosis of type1 diabetes (Watkins et al. 2014). In its more severe form, ketoacidosis may develop and lead to stupor, coma, and, in the absence of treatment, death.

14.3 Criteria for the Diagnosis of Diabetes Mellitus

14.3.1 Glycemic Diagnostic Values (OGTT)

	Fasting blood glucose level (BGL)	2 h postload glucose level	Glycated hemoglobin (HbA1c) level
Normal	≤100 mg/dL	<140 mg/dL	<5.6%
Prediabetes IFG and/or IGT	>100 to <126 mg/dL	>140 to <200 mg/dL	5.7% to 6.4%
Diabetes mellitus	≥126 mg/dL	≥200 mg/dL + Polyuria, polydipsia, weight loss	HbA1c ≥6.5% ≥200 mg/dL casual

Information source: Diabetes Care, 2018 (American Diabetes Association 2018)
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
OGTT test: The test should be performed using a glucose load containing the equivalent of 1.75 g/kg of body weight to a maximum of 75 g

14.3.2 Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) Levels (American Diabetes Association 2018)

Impaired glucose tolerance and impaired fasting glucose levels are intermediate stages in the natural history between normal glucose homeostasis and diabetes. Patients with IFG levels and/or IGT are referred to as having "prediabetes," indicating their relatively high risk for the development of diabetes:

- FPG <100 mg/dL: normal fasting glucose.
- FPG >100 mg/dL to 125 mg/dL: IFG.
- FPG >126 mg/dL (provisional diagnosis of diabetes).

- 2-hour post-load plasma glucose level: 140 mg/dL, normal glucose tolerance.
- 2-hour post-load plasma glucose level: 140–200 mg/dL, IGT.
- 2-hour post-load plasma glucose level: >200 mg/dL, diabetes.

14.3.3 Epidemiology of Type 1 Diabetes

Overall, approximately 96,000 children under 15 years of age are estimated to develop type 1 diabetes annually worldwide.

The incidence varies between different countries, within countries, and between ethnic populations with the highest incidence rates observed in Finland (50/100,000), Europe (10–20/100,000), Northern Europe (30/100,000), and Canada (45/100,000). In Asia, the incidence is very low in Japan (2/100,000) and China (1/100,000) (Harjutsalo et al. 2013; Karvonen et al. 2000).

14.4 Treatment of Children and Adolescents with Diabetes

14.4.1 Treatment Consists of Insulin, Nutrition, Education, Exercise, and Psychosocial Support

14.4.1.1 Insulin

Children and adolescents with type 1 diabetes are dependent on insulin for survival and should have access to adequate amounts of at least regular insulin (short acting) and NPH insulin (intermediate-acting insulin).

Human insulins. Currently, children are administered human insulins instead of porcine or bovine insulin due to their low immunogenicity.

Regular insulin (short acting). Usually identical to human insulin, it is still used as premeal bolus injections, given 20–30 min before meals together with intermediate-acting insulin NPH, twice daily (Danne et al. 2002).

14.4.1.2 Insulin Analog: Basal Insulin and Rapid Acting Insulin

Basal insulin analogs include glargine and detemir. They have a more predictable effect compared to that of NPH, with less variations in its effect, but they are more expensive (50% to 100%). In general, it is possible to use them once or twice daily.

Rapid-acting insulin analogs include aspartic, glulisine, and lispro. They have a rapid and shorter duration of action than that of regular insulin.

They can be used immediately before or after meals, and nocturnal hypoglycemia may also be reduced due to its short duration of action.

Regular and rapid-acting insulins can be given subcutaneously or intravenously, but NPH and basal analogs should only be administered subcutaneously.

Injection Site. The usual sites of injection are the lateral aspect of the arm, buttocks, lateral thigh, and abdomen. The abdomen has faster absorption, but lipohypertrophy (accumulation of fat) is very frequent.

Storage of Insulin. Unused insulin should be stored in a refrigerator (4–8 °C) and never be frozen or receive direct sunlight or warming.

Devices for Insulin Administration. Disposable insulin syringes and pen injectors containing insulin in prefilled cartridges, in small size (5–6 mm), are available.

Continuous subcutaneous insulin infusion is possible with the use of external pumps (DCCT 1994). This method permits a more physiological insulin replacement therapy. Motivation appears to be the most important factor for the success of this form of therapy (Danne et al. 2018).

Daily insulin dosage depends on several factors: age, weight, puberty, monitoring of blood glucose and glycated hemoglobin levels, nutritional intake and distribution, exercise, intercurrent illness, etc.

Initially, the total daily insulin dose is often <0.5 IU/kg/day, prepubertal children require 0.6–1 IU/kg/day, and during puberty, requirements are above 1–2 IU/kg/day. The "best" dose of insulin is that which achieves the best glycemic control (70–180 mg/dL) without hypoglycemia and good growth, weight, and height according to the children's chart.

There are different regimens of distributing the insulin dose in relation to the type of insulin, lifestyle (diet, exercise, school, work, commitments, etc.), and residual insulin secretion.

The most frequently used regimens are as follows: one or two injections of human insulin such as intermediate-action NPH or long-acting insulin analogue, glargine or detemir, and human regular or analogue rapid-acting insulin, such as lispro and aspartic, before each main meal (breakfast, lunch, and main evening meal).

Insulin adjustments should be made until target blood glucose (BG) and HbA1c levels are achieved (Neu et al. 2015).

Hypoglycemia should be avoided in children <6 years old, which could induce severe cognitive impairment. Children with persistently poor glycemic control (HbA1c >9%) should be assessed by a specialized pediatric diabetes team aimed at improving glycemic control should be consider to enhance chronically poor metabolic control and prevent acute and chronic complications. (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee) (Delahanty and Halford 1993).

14.4.1.3 Nutrition

Nutritional management is one of the cornerstones of diabetes care and education. Children with type 1 diabetes should follow a healthy diet; this involves consuming a variety of foods from the four food groups (grain products, vegetables, fruits, milk and alternatives, and meat and alternatives). Appropriate matching of insulin to carbohydrate content may allow increased flexibility and improved glycemic control (Cameron et al. 2013).

Nutrition therapy should be individualized based on the child's nutritional needs, eating habits, and lifestyle and must ensure normal growth and development without compromising glycemic control.

Features suggestive of eating disorders and celiac disease should be systematically studied.

Evidence suggests that it is possible to improve diabetes outcomes through attention to nutritional management and an individualized approach to education (Martin et al. 2012).

14.4.1.4 Education

Children with new-onset type 1 diabetes and their families require education regarding diabetes. Education must include insulin action and administration, blood glucose and ketone testing, dosage adjustment, prevention of diabetic ketoacidosis, and preventive treatment of hypoglycemia, nutrition therapy, and exercise.

Health care providers should initiate conversations with children and their families about school, career choices, psychological issues, etc.

Interdisciplinary teams providing education should include, as a minimum, a pediatric endocrinologist/diabetologist, diabetes specialist nurse, a dietician, and a psychologist (Komatsu et al. 2005).

14.4.1.5 Exercise

Physical activity is an essential component of treatment. Playing games and sports offer psychological benefits for all age groups with type 1 diabetes. Unfortunately, exercise can increase the risk of hypoglycemia. The management of hypoglycemia during and after doing exercise adds to the complexity of the treatment (Braatvedt et al. 1997).

The goal of hypoglycemia treatment is to prevent it, reducing the doses of insulin or consuming more carbohydrates. In mild or moderate hypoglycemia, some juice or liquid with sugar is enough to restore the blood glucose level to 100 mg/dL.

Diabetes should not limit the patient's ability to excel in a chosen sport. Many famous athletes have proved this. Camps for children with diabetes that include counseling on nutrition and insulin adjustment for exercise can result in improved glycemic control (Hilliard et al. 2013).

14.4.1.6 Psychosocial Support

Psychosocial support must be provided at diagnosis and regularly thereafter. The treatment will only be effective if the

family and patient are able to implement it. For the impact of psychosocial factors on the treatment plan, it is necessary to work with the individual and family to overcome barriers or redefine goals as appropriate, especially as the youth grows, develops, and acquires the need for greater independent self-care (Reynolds and Helgeson 2011).

Young people with DM appear to have a greater incidence of depression, anxiety, psychological distress, and eating disorders compared to their healthy peers (Young et al. 2013; Winkley et al. 2006).

Mental health professionals should be available not only to interact with patients and families at clinic visits to conduct screening and more complete assessment of psychosocial functioning, but also to support the diabetes team in the recognition and management of mental health and behavior problems (Cryer 2008).

14.5 Complications

14.5.1 Acute Complications

14.5.1.1 Hypoglycemia

Hypoglycemia is the most common acute complication of type 1 diabetes. Its risk presents a major physiological and psychological barrier to achieving optimal glycemic control (Rewers et al. 2014). A blood glucose of 65 mg/dL has been accepted as a level for defining hypoglycemia; however, 70 mg/dL is used as the threshold value for initiating treatment because of the potential for glucose to fall further (Jones 2018).

Hypoglycemia is classified as symptomatic and asymptomatic, mild, moderate, or severe. The symptoms result from adrenergic activation (shakiness, pounding heart, and sweatiness) and neuroglycopenia (headache, drowsiness, and difficulty concentrating), and behavioral changes (irritability, agitation, quietness, and tantrums). In children, severe hypoglycemia is most often defined as an event associated with a seizure or loss of consciousness (Karges et al. 2017). Common clinical precipitants for hypoglycemia are excessive insulin doses, missed meals, exercise in adolescents, and alcohol ingestion. Risk factors include young age, previous severe hypoglycemic events, and hypoglycemic awareness. A lower HbA1c level is a risk factor, but now is less common with contemporary therapy (Clarke et al. 2008). Severe hypoglycemia requires urgent treatment in a hospital with intravenous glucose administration (10% glucose, 2–3 mL/kg). At home, IM or SC glucagon injection should be given (<12 years old, 0.5 mg; >12 years old, 1 mg). If the blood glucose level is nearly 70 mg/dL, glucose control can be accomplished by giving glucose tablets or sweetened fluids. In 10 or 15 min, the blood glucose level should be retested and the treatment repeated if there is no response. Milder hypoglycemia should be treated with oral glucose (10–15 g) or 100 mL of sweet drink or juice, followed by additional carbohydrates (bread, cookies) (Willi et al. 2003). New technologies including continuous glucose monitoring (CGM) and pump therapies offer the potential to reduce the impact of hypoglycemia (Bui et al. 2010).

14.5.1.2 Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with type 1 diabetes mellitus (T1DM). Among the different types of diabetes, the prevalence of type 1 diabetes in youth did not significantly change over time (30.2%). The overall prevalence was highest in the 0- to 4-year age group and lowest in the 15- to 19-year age group. The high prevalence at diagnosis in many countries indicate a need for increased awareness of the signs and symptoms of type 1 diabetes and better access to health care (Neu et al. 2009).

Mortality is predominantly related to the occurrence of cerebral edema; only a minority of deaths in DKA is attributed to other causes. Cerebral edema occurs in 0.3% to 1% of all episodes of DKA, and its etiology, pathophysiology, and ideal method of treatment are poorly understood.

Definition

Diabetic ketoacidosis (DKA) is a metabolic derangement characterized by the triad hyperglycemia, acidosis, and ketosis that occurs in the presence of very low levels of effective insulin action, together with elevations in counterregulatory hormones including glucagon, catecholamine, cortisol, and growth hormone (Roche et al. 2005). This leads to increased glucose production by the liver and kidney and impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolarity. The increased lipolysis, with ketone body production, causes ketonemia, metabolic acidosis, and loss of electrolytes and water that can lead to dehydration, shock, and death.

Diagnosis

Early recognition of the classical triage of polydipsia, polyuria, and polyphagia with weight loss is essential; vomiting, pain in the stomach, and rapid breathing (Kussmaul), together with compromised circulation and decreased level of consciousness, are early signs. The biochemical criteria for the diagnosis of DKA include hyperglycemia >200 mg/dL, with bicarbonate level < 15 mmol/L, and/or pH <7.30 (venous). DKA is generally categorized by the severity of the acidosis, varying from mild pH <7.30 and bicarbonate level 15 mmol/L to moderate pH <7.2 and then severe pH <7.1 and bicarbonate level < 5 mmol/L, associated with glycosuria, ketonuria, and ketonemia (Savage et al. 2011).

Treatment

In general, it is necessary to use 0.9% saline during the first 2 h but at different infusion rates, from 10 mL/kg/L to 20 mL/kg/h. After the first 2 h, the amount of fluids to be infused should not exceed 3 L/m2/day. The fluid infused is saline, either 0.9% or 0.45%, and 5%–10% glucose solution, corresponding to the glycemic value. Potassium supplementation is performed at different rates at 20–40 mEq/L. Bicarbonate is exceptionally used according to the pH DKA severity (Metzger 2010).

Regular or rapid-acting insulin analogue is infused using an automated syringe injected directly in the fluid solution starting from the second to third hour, mostly according to the DKA severity. The insulin infusion rate is 0.05–0.1 U/k/h to rate DKA severity and to evaluate DKA management follow-up needs. The administration of insulin could also be done subcutaneously (Control and Complications Trial Research Group 1994).

14.6 Microvascular and Macrovascular Complications

Childhood and adolescence are periods during which intensive education and treatment may prevent or delay the onset and progression of complications in later adult life (Mogensen et al. 1995). Clinically evident diabetes-related vascular complications are rare in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of the disease. Longer duration of diabetes at older age and puberty are risk factors for complications.

The long-term complications of diabetes include micro- and macrovascular complications. The microvascular complications are nephropathy, retinopathy, and neuropathy.

14.6.1 Nephropathy

Nephropathy is defined as persistent proteinuria >500 mg/24 h or albuminuria >300 mg/24 h and is usually associated with hypertension and a diminishing glomerular filtration rate (GFR). End-stage renal failure may occur many years later and requires dialysis or kidney transplantation. Early detection of diabetic nephropathy and timely treatment of blood pressure have a pivotal role in the prevention of end-stage renal failure in young people and adults with diabetes (Schultz et al. 2000).

Annual screening for albuminuria with a random spot urine sample for albumin to creatinine ratio should be considered once the child has type1 diabetes for 5 years (Hietala et al. 2010). The estimated glomerular filtration rate should be evaluated initially and then based on age, diabetes duration, and treatment.

14.6.2 Treatment

When persistently elevated, urinary albumin to creatinine ratio (>30 mg/g) should be evaluated with at least two or three urine samples, and treatment with an ACE inhibitor should be considered and the dose titrated to maintain blood pressure within the age-appropriate normal range.

14.6.3 Retinopathy

Adolescents have a higher risk of progression to vision-threatening retinopathy (severe nonproliferative retinopathy or proliferative retinopathy) compared with that of adults (Bragge et al. 2011). The progression may be rapid, especially in those with poor glycemic control. Biomicroscopy fundus slit examination through dilated pupils by an ophthalmologist and mydriatic seven-field stereoscopic retinal photography and fluorescein angiography OCT specifically reveal macular edema (Mohamed et al. 2007).

Once sight-threatening retinopathy is detected, laser therapy consists of multiple discrete outer retinal burns throughout the mid- and far peripheral area, sparing the central macula (Šimunović et al. 2018). Diabetic cataracts have been reported in patients with type 1 diabetes close to or even preceding diagnosis. Surgical removal may be required (Russell and Zilliox 2014).

14.6.4 Neuropathy

Neuropathy is a polyneuropathy caused by diffused damage to all peripheral nerve fibers—motor, sensory, and autonomic. Patients usually complain of numbness, prickling, burning, and/or paresthesia of the hands or feet (Guy et al. 2009).

14.6.5 Macrovascular Disease (CVD)

The mortality and morbidity of CVD are markedly increased in diabetic individuals compared with that in the nondiabetic population. Hypertension has a greater impact on CVD, and blood pressure control to <130/80 mmHg reduces cardiovascular morbidity. Atherosclerosis starts in childhood and adolescence and cardiovascular events are strongly associated with poor glycemic control. Cholesterol plays an important role in the initiation and progression of atherosclerosis. High

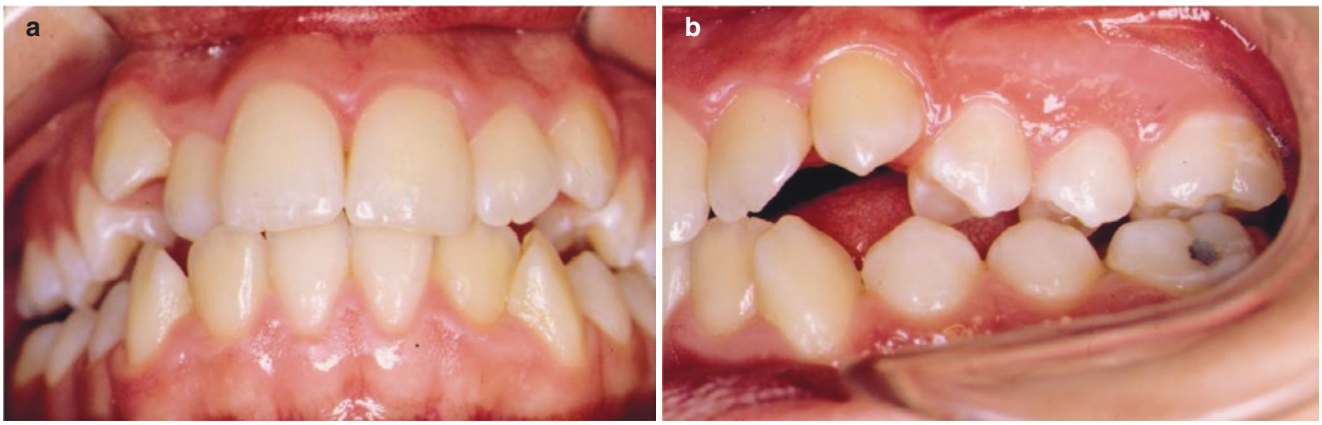

Fig. 14.1 (**a**, **b**) The following case is a 12-year-old patient diagnosed with type 1 diabetes since she was 6 years old

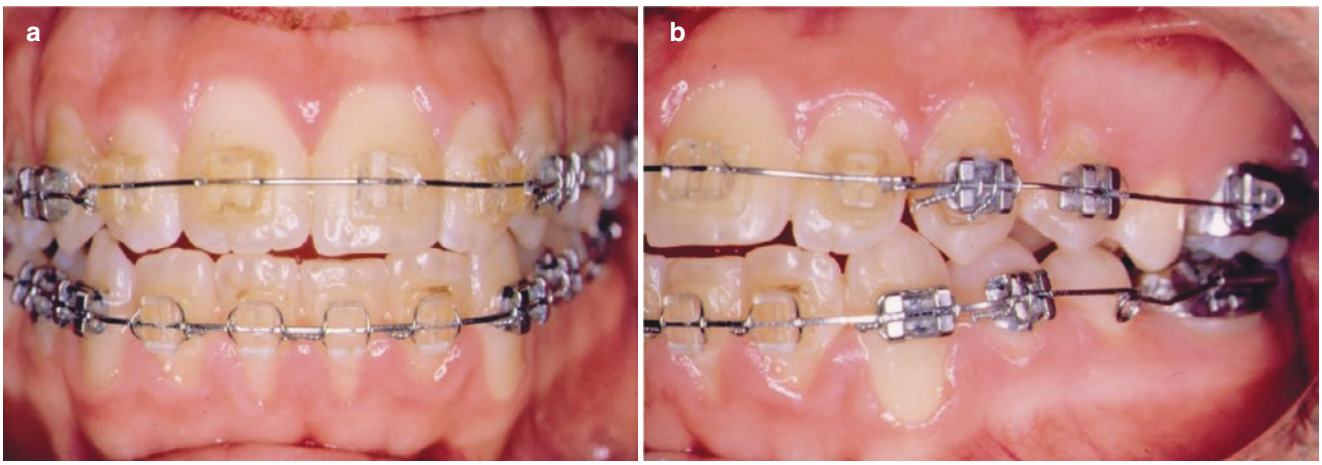

Fig. 14.2 (**a** and **b**) Although the periodontal inflammation of the gums was constantly controlled, it was present throughout the entire treatment

LDL cholesterol is defined as >100 mg/dL and triglycerides >150 mg. If present, then interventions to improve metabolic control, dietary changes, and increased exercise should be instituted. If the above interventions do not lower the LDL cholesterol to <130 mg/dL, statins should be considered in children aged >10 years (42).

14.6.6 Orthodontic Procedures

It is possible to achieve normalization of tooth position as well as improvements in functional problems in children or teenagers with any type of diabetes. As described previously, this endocrine disorder is typically associated with gingivitis and periodontitis. It is for this reason that a thorough control of dental hygiene is required to lessen the risk of infections since, in diabetic patients, gingival tissues respond, with difficulty, to pathogens that are normally present in the mouth (Fig. 14.1).

Gingivitis is typically observed in this type of patient. This particular case is worse since there is a lack of space for proper tooth eruption.

After 18 months of treatment, the objectives, sought from the orthodontic perspective, were achieved. What needs to be kept in mind is that, in spite of the parents' efforts, many adolescent patients rebel against treatment for diabetes as well as orthodontics (Fig. 14.2).

From the orthodontic point of view, the objectives decided at the beginning of treatment have been accomplished: correction of dental midline and placement of the upper canines and normalization of crossbite, overjet, and gingival line.

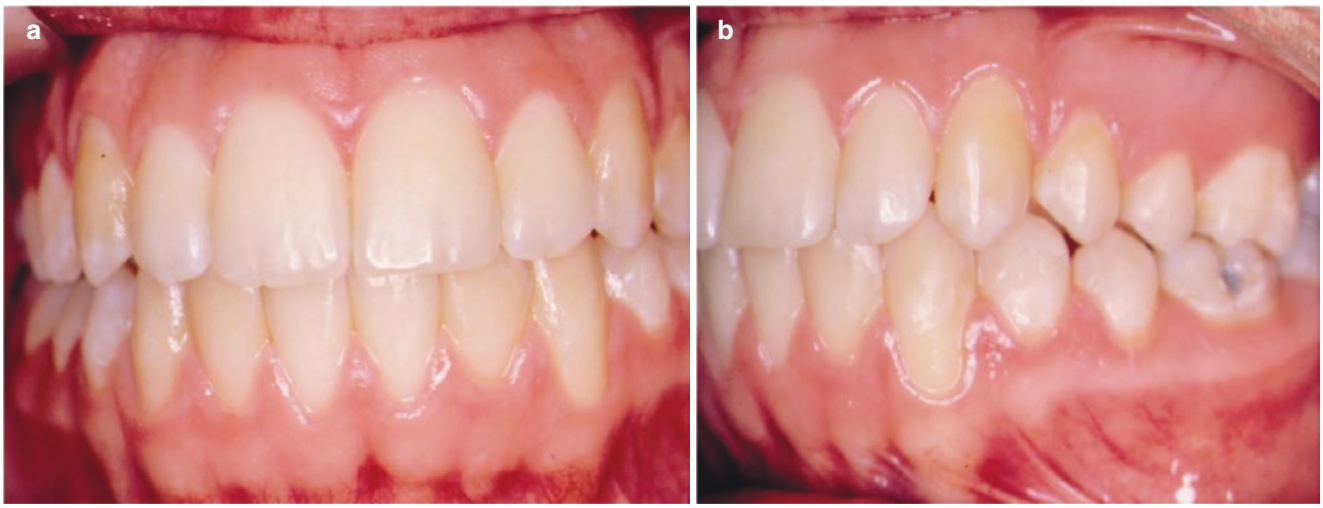

Fig. 14.3 Final photographs confirm the excellent results achieved, even though in a diabetic patient (**a**, **b**)

Monthly periodontal follow-up was recommended in order to normalize gingival tissues (Fig. 14.3).

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