Cardiovascular risk onset in children and adolescents with diabetes mellitus

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Contributor: Ida Pastore

The prevalence of diabetes mellitus is rising among children and adolescents worldwide. Cardiovascular diseases are the main cause of morbidity and mortality in diabetic patients. We review the impact of diabetes on establishing, during childhood and adolescence, the premises for cardiovascular diseases later in life. Interestingly, it seems that hyperglycemia is not the only factor that establishes an increased cardiovascular risk in adolescence. Other factors have been recognized to play a role in triggering the onset of latent cardiovascular diseases in the pediatric population. Among these cardiovascular risk factors, some are modifiable: glucose variability, hypoglycemia, obesity, insulin resistance, waist circumference, hypertension, dyslipidemia, smoking alcohol, microalbuminuria and smoking. Others are unmodifiable, such as diabetes duration and family history. Among the etiological factors, subclinical endothelial dysfunction represents one of the earliest key players of atherosclerosis and it can be detected during early ages in patients with diabetes. A better assessment of cardiovascular risk in pediatric population still represents a challenge for clinicians, and thus further efforts are required to properly identify and treat pediatric patients who may suffer from cardiovascular disease later in early adulthood.

Keywords: adolescents ; cardiovascular risk ; children ; diabetes mellitus.

1. Introduction

The prevalence of the two most common forms of diabetes, type 1 (T1D) and type 2 (T2D) is increasing worldwide, even in the pediatric population, rapidly becoming an urgent public health problem [1][2][3]. The International Diabetes Federation has estimated that T1D affects more than 1,100,000 children and adolescents, with an annual incidence of about 128,900 worldwide [1]. Until the early 1990s, T2D was believed to be almost an exclusive condition of adulthood, but its prevalence in adolescents is increasing in many countries [1]. Even if the estimates are not as precise as for T1D, in the United States, 20,262 adolescents are diagnosed with T2D, and by 2050, a fourfold increase will occur [3][4]. In addition, prediabetes affects nearly 5% of children aged between 6 and 10 years [5]. These growing trends are largely due to the spread of a more western lifestyle. Physical inactivity, increased calorie intake and reduced energy expenditure all facilitate overweight and obesity onset in children [6]. These conditions affect almost all children with T2D, and are common also in the pediatric population, with T1D having a prevalence of up to 34% [7][8][9]. A recent study was conducted in a population of 708 children who were positive for one of the circulating diabetes autoantibodies, but were not diabetic. The study revealed that the children who tested negative for HLA haplotypes predisposing to T1D and had an elevated body mass index (BMI) progressed to multiple autoantibodies positivity and had an increased risk of developing T1D [10]. Younger patients with T2D showed an impaired insulin secretion and detectable circulating autoantibodies [11][12]. Moreover, children and adolescents with T2D, when compared to adults with T2D, showed a higher and faster loss of beta-cells activity, which makes achieving optimal metabolic compensation more difficult [13][14][15].

2. Inflammation in Children and Adolescents with Diabetes

An early appearance of a pro-inflammatory state may be a key player in conditioning the onset of CV disease later in life [16]. Central obesity and physical inactivity are both associated with a pro-inflammatory state and are very common in young patients with obesity, with T2D and with T1D [9][11][13][17][18]. Obesity and T2D are characterized by a state of systemic chronic low-grade inflammation, that triggers a vicious circle involving insulin resistance, oxidative stress and endothelial dysfunction and lays the basis for early and accelerated atherosclerosis [16]. A low-grade inflammation is also observed in lean children with T1D, while increased levels of pro-inflammatory cytokines are described, either in T1D or T2D [19][20]. Continuous systemic chronic inflammation from childhood accelerates plaque formation and contributes to its growth [19]. Nearly 700 adolescents aged between 10 and 17 years who had a recent diagnosis of T2D were studied, and a detrimental inflammatory profile that worsened over time was shown [21]. Indeed, the inflammatory state was only

partially reverted by pharmacological therapy [21] In children and adolescents with diabetes, pro-inflammatory abnormalities may play a prognostic role for the development of diabetic complications and may represent novel pharmacological targets [22]. Previous studies, although not conclusive, demonstrated increased levels of C-reactive protein, interleukin-6, tumor necrosis factor-α, leptin, and decreased levels of adiponectin in children and adolescents with diabetes [23][24][25][26][27][28]. Interestingly, pro-inflammatory marker levels seem to also be elevated in lean adolescents with diabetes and good glycemic control [29][30]. Interestingly, the role of diet in modifying the inflammatory profile in children with diabetes is still debated; while in children with obesity, it only seems to be more evident [31][32]. More recently, a putative role for microbiome in the activation of gut and systemic inflammation was suggested in children and adolescents with diabetes [33]. This is of particular interest, especially in children and adolescents in which a pro-inflammatory state may persist over time, and may exert a detrimental effect on the CV system [16]. Interventional studies on the effect of prebiotics on gut microbiota are needed to elucidate their role in improving inflammatory state, insulin resistance and glycemic control.

3. Early Treatment of Children and Adolescents with Diabetes

In pediatric patients with diabetes, CV risk begins early and grows over time, and thus maintaining an optimal glycometabolic control in the long term is mandatory [34][35]. In the management of children and adolescents with diabetes, a pivotal role is played by health education [34]. The identification of a nutritional educational plan, with the aim of managing the intake of nutrients is essential [34]. Regular physical activity improves glycemic control, insulin sensitivity, lipid profile, body composition, wellbeing and cardiovascular health [36]. Therapeutic strategies used in the treatment of young patients with T1D and T2D partially differ from those used in adults [34]. Indeed, insulin therapy is recommended in children and adolescents with T1D, while metformin, insulin and liraglutide are approved for clinical use in children and adolescents with T2D [34]. Intensive insulin therapy allows one to achieve glycemic control, while it can facilitate weight gain, central adiposity, rises in blood pressure, and a more atherogenic lipoprotein profile [37][38]. In young patients with T2D, a more aggressive treatment with metformin and rosiglitazone results in a better durability, with beneficial consequences also on the development of micro- and macro- complications [39][40]. Recently, a secondary analysis of the same population demonstrated that metformin ameliorates lipoprotein profile, glycemic control, blood pressure and BMI, suggesting the role of metformin in improving CV parameters [41]. Data from a pediatric diabetes consortium registry analyzing young patients with T2D demonstrated the durability of metformin monotherapy in those with lower HbA1c and a more recent onset of the disease [42]. A growing number of studies showed that metformin enhances insulin sensitivity and reduces insulin dose in youth with T1D, but also improves vascular markers [36][43].

The sodium glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) are two classes of anti-diabetic drugs that have demonstrated to exert cardioprotective effects in multiple cardiovascular and renal outcomes trials in adults with T2D, on primary and secondary prevention [44][45][46][47]. Moreover, their effectiveness and safety are also being tested in the treatment of patients with T1D [48][49]. Recently, Tamborlane et al.

demonstrated the efficacy of liraglutide in children and adolescents with diabetes aged between 10 to 17, but they also observed an increased number of gastrointestinal adverse effects [50].

In line with these observations, novel antidiabetic therapies should be tested as a treatment of young patients, either with T1D or T2D, with the aim not only of optimizing glycemic control, but also of mitigating their CV risk. Further studies are needed to evaluate SGLT2i and GLP1RA efficacy and safety in large cohorts of young patients with diabetes. Current guidelines recommend the use of drugs to control hypertension and dyslipidemia after changes in lifestyle in children and adolescents with diabetes [35][51]. However, there is concern about the use of statins and antihypertensive drugs in this population, for the lack of large intervention trials in the young and their teratogenic effect. More recently, regenerative therapy has proven to be a useful and innovative strategy in preventing and treating vascular complications in diabetes. Even further clinical trials are required; these therapies might be of particular interest in the young, who have a higher cellular regenerative capacity than adults [52][53].

4. Conclusions

CV disease still remains the leading cause of mortality in diabetes, and the onset of diabetes in pediatric age results in an increased risk for lifelong CV disease. The prevention, or at least the delay, of diabetic complications still represents a challenge for clinicians and caregivers of pediatric patients. If targeted early, cardiovascular complications may be potentially reversible, so interventions should be initiated as soon as possible to avoid the establishment of potentially untreatable CV disease. The CV risk in children and adolescents not only results from the deleterious effects of

hyperglycemia, but also can be mediated by others CV risk factors, such as dyslipidemia, hypertension, albuminuria, overweight or obesity. Efforts are needed to better understand the pathophysiology of CV risk in children and adolescents with T1D and T2D, to avoid CV diseases in patients with diabetes.

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