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# Microvascular and Macrovascular Complications in Children and Adolescents with Type 1 Diabetes

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## 1. Introduction

Diabetes mellitus is a serious chronic disorder of childhood and represents a major public health problem. Type 1 diabetes is the predominant form of diabetes during childhood and adolescence, accounting for about 90% of cases, although the growing epidemic of obesity has been associated with an increasing number of cases of childhood-onset type 2 diabetes (Craig et al., 2009; Patterson et al., 2009).

The global incidence of type 1 diabetes is increasing worldwide, at an annual rate of 3-5%, particularly in children under the age of 5 years, and this trend leads to a significant health burden (Patterson et al., 2009). Recent studies have shown that in European countries childhood-onset type 1 diabetes is associated with three to four fold increased mortality when compared with the general population (Asao et al., 2003; Skrivarhaug et al., 2006). Similar data emerged from a long-term study of a young cohort with type 1 diabetes in the USA, where mortality was 7 times higher than in the non-diabetic population (Secrest et al., 2010a). The high mortality reported for individuals with type 1 diabetes is mainly due to diabetes-related acute and chronic complications. As recently emerged from a large population-based cohort with long-standing childhood-onset type 1 diabetes, during the first decade of diabetes acute complications, such as diabetic ketoacidosis and hypoglycemia, are the main causes of death, being responsible for about 73% of cases, whereas during subsequent decades cardiovascular (CVD) and renal diseases become the main determinants of mortality (Secrest et al., 2010b).

Diabetes vascular complications are divided in micro- and macrovascular disease. Microvascular complications include nephropathy (DN), retinopathy (DR) and neuropathy, whereas macrovascualar complications refer to cardiovascular, cerebrovascular and peripheral vascular disease (Marshall and Flyvbjerg, 2006). As a result of vascular complications, diabetes is the leading cause of blindness in working age people, is responsible for up to 40% cases of renal failure and is a major determinant of cardiovascular morbidity and mortality (Marshall and Flyvbjerg, 2006).

## 2. Microvascular complications of type 1 diabetes

Diabetic microvascular complications result from damage to the microvasculature of the kidney, retina and neurons and they generally progress throughout different stages.

**2.1 Diabetic nephropathy**

**2.1.1 Classification of diabetic nephropathy and structural kidney changes**

The changing occurring in the kidney in patients with type 1 diabetes are generally classified in five stages (Mogensen, 1999). The first stage is characterized by increases in glomerular filtration rate (GFR) and kidney hypertrophy. During the second phase subtle morphological changes occur together with progressive increases in urinary albumin excretion within the normal range. The third stage, also called incipient nephropathy, is characterized by the development of microalbuminuria, defined as an albumin excretion rate (AER) between 30-300 mg/24h or 20-200 µg/min, and by more profound structural changes. During the fourth phase there is a further increase in AER leading to macroalbuminuria (AER >200 µg/min or >300 mg/24h) and a consistent fall in GFR. Without any treatment this phase leads to the final stage of end stage renal disease (ESRD).

Typical morphological changes occurring in the diabetic kidney are represented by diffuse glomerular basement membrane thickening, mesangial expansion, hyalinosis of the mesangium and arteriolar walls, broadening and effacement of podocyte foot processes, reduction in podocyte number, glomerulosclerosis and tubule-interstitial fibrosis (Osterby, 1992). These morphological changes develop years before the clinical appearance of DN and this is an alarming aspect, given that when the disease is clinically evident some of the structural damage is already irreversible.

Thickening of the basement membrane is a common bioptic finding related to DN and is associated with loss of glycosaminoglycans and associated negative charges, with consequent increased loss of anionic albumin (Fioretto and Mauer, 2007; Fioretto et al., 1994; Mauer and Najafian, 2006). A subsequent increase in the size of membrane pores leads to the development of non-selective proteinuria. An imbalance between the production and the degradation of mesangial matrix proteins, together with an increase in mesangial cells number, is responsible for mesangial expansion in DN (Fioretto and Mauer, 2007; Mauer and Najafian, 2006).

**Stage 1**
- Hyperfiltration/hyperperfusion phase (often at diagnosis)
- Increased renal size
- AER: May be increased, but it becomes normal after starting insulin treatment

**Stage 2**
- Normoalbuminuria/Silent phase (2-5 years after diagnosis)
- Basement membrane thickening
- AER: Normal with transient increases related to poor glycemic control or exercise

**Stage 3**
- Microalbuminuria or incipient nephropathy phase (after 6-15 years)
- Further basement membrane thickening and mesangial expansion
- AER: 20-200µg/min or 30-300 mg/24h

**Stage 4**
- Overt diabetic nephropathy/Macroalbuminuria phase (after 15-25 years)
- Marked renal abnormalities, reduced renal function, increased blood pressure
- AER: >200 µg/min or >300 mg/24h

**Stage 5**
- End stage renal disease phase (after 25-30 years)
- Advanced glomerulopathy; marked decreased renal function, hypertension
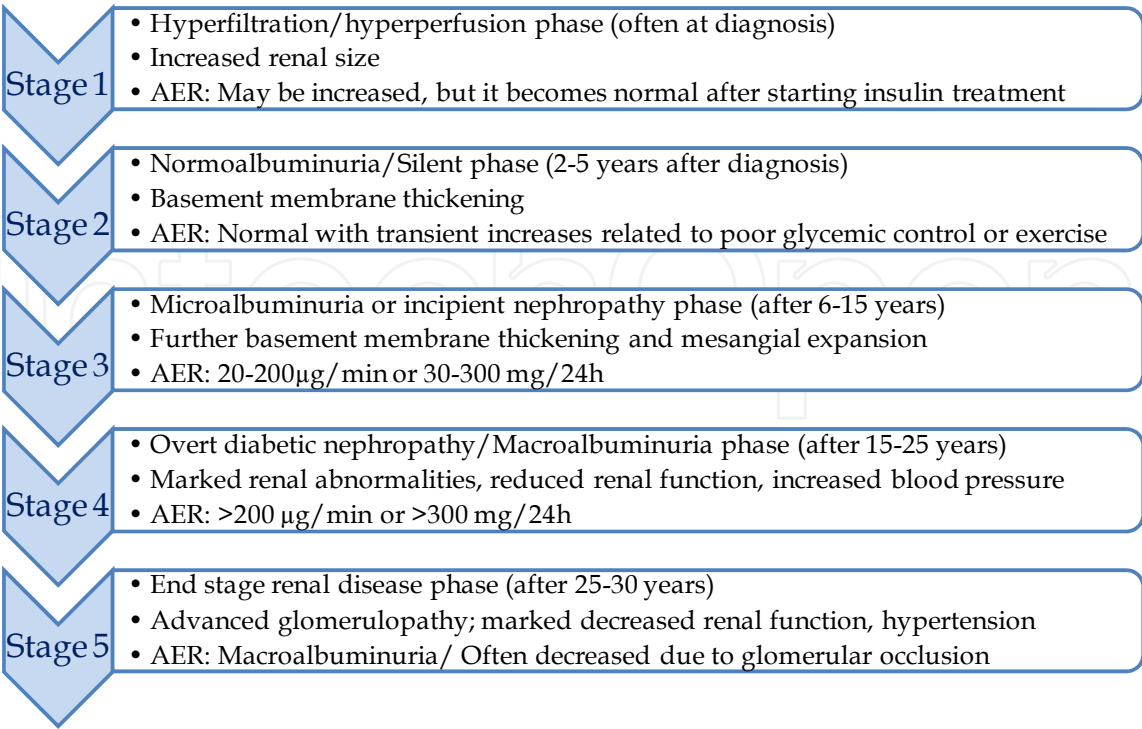- AER: Macroalbuminuria/ Often decreased due to glomerular occlusion

Fig. 1. Stages of diabetic nephropathy

Changes in the podocyte is another key feature of DN (Mauer and Najafian, 2006). Podocytes are highly specialised epithelial cells, interconnected by foot processes, which delimit the slit diaphragm, the main size-selective barrier in the glomerulus. The first detectable alteration in podocytes in the context of DN is a broadening and effacement of their foot processes (Kriz et al., 1998), which leads to a decrease in their density and number and a detachment from the glomerular basement membrane. The last phenomena are directly correlated to levels of albumin-creatinine ratio (ACR) and to the decline in GFR (Fioretto and Mauer, 2007). Podocytes can also undergo hypertrophy, apoptosis and increased synthesis of collagen IV, whereas there is a decreased synthesis of proteins, such as nephrin (Fioretto and Mauer, 2007).

Another characteristic of DN is the hyalinosis of the afferent and efferent arterioles in the glomerulus, due to the accumulation of complement components, fibrinogen, immunoglobulins, albumin and other plasma proteins (Fioretto and Mauer, 2007). Hypertrophy and sclerosis of the iuxtaglomerular apparatus is another frequent finding in DN (Mauer and Najafian, 2006).

### 2.1.2 Epidemiology of diabetic nepropathy

DN affects about one third of people with type 1 diabetes after a disease duration of 20 years and represents an important determinant of mortality (Jones et al., 2005). This has been recently confirmed in patients with both childhood-onset and adult-onset type 1 diabetes (Groop et al., 2009; Orchard et al., 2010). In a large cohort of adults with type 1 diabetes the presence of microalbuminuria, macroalbuminuria and ESRD was associated with 2.8, 9.2, and 18.3 times higher standardized mortality ratio, respectively (Groop et al., 2009). Similarly, Orchard *et al*. reported a standardized mortality ratio of 6.4, 12.5 and 29.8 for individuals with microalbuminuria, proteinuria and ESRD, respectively, in a cohort with childhood-onset type 1 diabetes followed longitudinally for 30 years (Orchard et al., 2010).

The natural history of DN has changed over the last decades and, whereas earlier landmark studies indicated that patients with microalbuminuria had a 60-85% risk of progressing to overt proteinuria within 6-14 years (Mogensen and Christensen, 1984; Parving et al., 1982; Viberti et al., 1982), more recent studies have reported a rate of progression of 30% over 10 years, and an increasing number of cases of regression to normoalbuminuria (31 to 58%) (de Boer et al., 2011; Hovind et al., 2004; Perkins et al., 2003). Regression to normoalbuminuria has been associated with a better metabolic control, a better lipid and blood pressure profile as well as with non-modifiable risk factors, such as younger age and shorter duration of microalbuminuria (Hovind et al., 2004; Perkins et al., 2003). These data are encouraging and highlight the positive effect of improvements in treatment, particularly glycemic (1993) and blood pressure control (Lewis et al., 1993), in influencing the natural history of DN. However, this changing trend may be also related to an overestimation of the rate of progression in earlier studies.

With regards to young people with childhood onset type 1 diabetes, recent studies from Sweden (Nordwall et al., 2004) and Australia (Mohsin et al., 2005) have shown a decreasing trend in DN. However, these positive results have not been consistently reported. In fact, data from Iceland (Tryggvason et al., 2005) and the UK (Amin et al., 2009) indicated an unchanged trend in the incidence of microalbuminuria and DN over the last decades.

### 2.1.3 Early manifestations of diabetic nephropathy in youth with type 1 diabetes

Microalbuminuria is the most common abnormal finding in children and adolescents with type 1 diabetes, whereas overt proteinuria is found in less than 1–1.5% of them (Jones et al., 1998; Schultz et al., 1999b). Microalbuminuria often develops during puberty, whereas its prevalence during prepubertal years is rare (Janner et al., 1994; Lawson et al., 1996; Norgaard et al., 1989; Rudberg et al., 1993). The overall prevalence of microalbuminuria in youth with type 1 diabetes ranges between 4 and 26% (Bojestig et al., 1996; Cook and Daneman, 1990; Dahlquist and Rudberg, 1987; Joner et al., 1992; Jones et al., 1998; Mathiesen et al., 1986; Moore and Shield, 2000; Norgaard et al., 1989; Olsen et al., 2000; Rudberg et al., 1993; Schultz et al., 1999b). This large variation in the prevalence of microalbuminuria is due to differences in study design, duration of diabetes, age range, and glycemic control. Most studies investigating microalbuminuria have been cross-sectional and clinic based, with only a few being longitudinal, but mainly with a retrospective design. Jones *et al.* (Jones et al., 1998) reported a prevalence of 14.5% during 8.5 years of diabetes duration, whereas Rudberg *et al.* (Rudberg et al., 1993) reported a prevalence of 24% after 15 years diabetes duration. The most recent data from the Oxford Regional Prospective Study (ORPS), a population-based inception cohort of children with type 1 diabetes, has shown a cumulative prevalence of microalbuminuria of 25.7% after 10 years and of 50.7% after 19 years of diabetes duration (Amin et al., 2008).

After puberty, rates of rise in albumin excretion tend to decline and, longitudinal studies suggest that microalbuminuria is persistent in only 50% of adolescents; whereas in the other 40-50% urinary albumin excretion returns into the normal range after 3-10 years from the onset of microalbuminuria (Amin et al., 2008; Gorman et al., 1999). However, with longer follow-up cases of transient or intermittent microalbuminuria may become persistent. In addition, although urinary albumin excretion may return into the normal range, the renal morphological changes associated with microalbuminuria can persist and increase the risk of its recurrence and progression (Steinke and Mauer, 2008). Few data are available on the rate of progression of microalbuminuria to macroalbuminuria in young people with type 1 diabetes. The ORPS has shown a progression rate of around 13% after 3.2 years from the onset of microalbuminuria, a rate similar to that reported in adults (Amin et al., 2008).

Another renal abnormality often detected in youth with type 1 diabetes is increased GFR (Amin et al., 2005; Rudberg et al., 1992). Hyperfiltration, which has been associated with increased renal size often precedes the onset of microalbuminuria (Amin et al., 2005; Rudberg et al., 1992). In some, although not all studies, increased GFR has emerged as an independent predictor of microalbuminuria, and a recent meta-analysis has reported a 2.7 increased risk of developing microalbuminuria associated with hyperfiltration (Magee et al., 2009).

## 2.2 Diabetic retinopathy
### 2.2.1 Classification and structural changes

DR begins with the appearance of non-proliferative retinal abnormalities, which then progress to sight-threatening proliferative lesions (Aiello et al., 1998; Williams and Pickup, 2004) . The early stage of DR is characterised by the development of capillary microaneuryms, which consist in small blind outgrowths of retinal capillaries developing in areas where the wall is weakened (Aiello et al., 1998; D'Amico, 1994; Williams and Pickup, 2004). As the retinal damage progresses, there is the appearance of non-proliferative abnormalities, including

hemorrhages, exudates and the development of vascular obstruction, intraretinal microvascular abnormalities, and infarction of the retinal nerve fibers causing cotton wool spots (Aiello et al., 1998; D'Amico, 1994; Williams and Pickup, 2004). Although this stage is not sight-threatening, it is highly predictive of progression to more advanced stages of retinopathy. Proliferative retinopathy is characterized by the development of new vessels, secondary to ischemia, on the surface of the retina and/or the optic disc (Aiello et al., 1998; D'Amico, 1994; Williams and Pickup, 2004). These new vessels can bleed into the vitroretinal space, and cause visual loss. In addition, the subsequent formation of fibrous tissue can cause tractional retinal detachment (Williams and Pickup, 2004). This stage is associated with a high risk for visual impairment related to hemorrhages and retinal detachment.

Diabetic macular oedema can complicate both non-proliferative and proliferative retinopathy and is a serious cause of vision loss in patients with diabetes (Ciulla et al., 2003). It is characterized by increased microvascular permeability and deposition of hard retinal exudates (Ciulla et al., 2003). This stage involves the breakdown of the blood-retinal barrier, with leakage of plasma from small blood vessels in the macula. Swelling of the macula is then followed by deposition of hard retinal exudates as a consequence of deposition of lipids and lipoproteins following plasma re-absorption (Ciulla et al., 2003).

| Proposed disease severity level | Dilated ophthalmoscopy findings |
|---|---|
| No apparent retinopathy | No abnormalities |
| Mild nonproliferative DR | Microaneurysms only |
| Moderate nonproliferative DR | More than just microaneurysms, but less than severe nonproliferative DR |
| Severe nonproliferative DR | No signs of proliferative DR, with any of the following:<br>- More than 20 intraretinal hemorrhages in each of four quadrants<br>- Definite venous beading in two or more quadrants<br>- Prominent intaretinal microvascular anomalies in one or more quadrants |
| Proliferative DR | One or more of the following:<br>- Neovascularization<br>- Vitreous or preretinal hemorrhage |

Table 1. International clinical DR disease severity scale

Retinal damage in diabetes is mainly due to leakage of retinal blood vessels and inadequate retinal perfusion (Aiello et al., 1998; D'Amico, 1994; Williams and Pickup, 2004). It has been suggested that one of the initial alterations in the retinal hemodynamic is represented by retinal vasodilatation and hyperperfusion, due to hypoxia and increased release of nitric oxide (Joussen et al., 2004). This is followed by an impairment of the retinal vascular autoregulation with increased tension in the epithelial wall and increased vascular permeability, which, in turn, cause vascular leakage and aneurysm formation (Kohner et al., 1995; Scherrer et al., 1994).

Early structural abnormalities in the retinal microvasculature are characterised by thickening of the basement membrane, loss of endothelial cells and pericytes and increased capillary permeability (Kohner et al., 1995). An important characteristic of retinopathy is the loss of pericytes from the retinal capillaries (D'Amico, 1994; Feng et al., 2007; Frank, 2004). Pericytes are contractile cells which have an important role in the regulation of the capillary blood flow and their loss has been associated with the development of retinal microaneurysms (Feng et al., 2007; Kuwabara and Cogan, 1963). The loss of pericytes, associated with that of capillary endothelial cells, contributes to the disruption of the integrity of the blood–retinal barrier. Thickening of the capillary basement membrane and deposition of extracellular matrix components are additional mechanisms contributing to the alterations in the retinal blood flow (Feng et al., 2007).

Retinal leukostasis has been also associated with DR and, in particular, with capillary occlusion and the consequent appearance of retinal areas of non perfusion (Aiello et al., 1998; D'Amico, 1994; Williams and Pickup, 2004). These alterations contribute, in turn, to retinal ischemia, which is a potent stimulus for vascular neoformation (Miyamoto and Ogura, 1999).

### 2.2.2 Epidemiology of retinopathy

DR is the leading cause of blindness in people of working age in Western countries (Ciulla et al., 2003). The prevalence of DR increases with age and its was approximately 17.7 per 100 people with diabetes in the year 2005 (Deshpande et al., 2008). DR can be diagnosed already after 5 years from the onset of diabetes, and almost all patients will show variable degrees of DR after 20 years diabetes duration.

Recent data from the Wisconsin Epidemiologic Study of DR have shown that the 25-year cumulative incidence of visual impairment in adults with type 1 diabetes was 13% and that of severe visual impairment was 3%. Patients with onset of diabetes during more recent years have a lower prevalence of visual impairment when compared with those diagnosed in the past, independently of duration of diabetes (Klein et al., 2010). This is in agreement with some other recent studies reporting a declining incidence of retinopathy and other microvascular complications (Nathan et al., 2009; Nordwall et al., 2004).

### 2.2.3 Early manifestations of retinopathy in youth with type 1 diabetes

Early stages of DR can be detected in young people with type 1 diabetes, as shown by a population based study from Australia, where early background retinopathy was detected in 24% of the study population after 6-year diabetes duration (Donaghue et al., 2005). Similarly, in a Swedish study retinopathy was detected in 27% of young patients after 13 years of duration (Nordwall et al., 2006). Children with type 1 diabetes under the age of 10 years are at minimal risk of DR, but the prevalence rate increases after 5 years from diagnosis in post-pubertal patients (Klein et al., 1984). In an incident cohort, early retinopathy was detected in 12% of prepubertal children compared to 29% of adolescents, after 6 year type 1 diabetes duration (Donaghue et al., 2005). Interestingly, adolescents with type 1 diabetes have a higher risk of progression to sight-threatening DR when compared to adults and the progression may be particularly rapid when glycemic control is poor (Maguire et al., 2005). As for DN, cases of regression have also been reported for DR (Maguire et al., 2005).

## 2.3 Diabetic neuropathy

Diabetic neuropathy is the most common neuropathy in industrialized countries, and it is associated with a wide range of clinical manifestations (Tesfaye et al., 2010). Diabetic neuropathy is defined as a clinical or subclinical disorder, without any additional causes other than diabetes, and can be either somatic or autonomic (Boulton et al., 2005). Early diagnosis and treatment of diabetic neuropathy are important given that peripheral neuropathy is associated with a high risk of feet injury in patients with type 1 diabetes (Boulton et al., 2005). In addition, diabetic autonomic neuropathy can lead to a significantly increased morbidity and mortality, mainly when involves the cardiovascular system (Boulton et al., 2005).

### 2.3.1 Classification and epidemiological data of diabetic neuropathy

Chronic distal symmetric polyneuropathy (DPN) is the most common form of diabetic neuropathy and affects 30-50% of patients with type 1 diabetes and can be asymptomatic in up to 50% of them (Tesfaye et al., 2010). DPN implies symmetric damage of peripheral small sensory and large motor nerve fibres. It generally starts from the most distal end of the feet and then extend proximally over time and can lead to foot ulceration and amputation of lower limbs (Boulton et al., 2005). Dysfunction of peripheral small nerve fibres is characterised by parasthesiae, burning, and deep aching pain. If larger nerve fibres are affected, vibration, light touch and joint position senses are impaired, and tendon reflexes are absent (Boulton et al., 2005). Less common forms of diabetic somatic neuropathy include focal or multifocal neuropathies, which are characterized by entrapment of a peripheral nerve commonly the median, ulnar or peroneal nerve (Boulton et al., 2005).

Diabetic autonomic neuropathy is a disorder of the autonomic nervous system in the context of diabetes and can affect the cardiovascular, gastrointestinal, urogenital systems and the sudomotor function (Tesfaye et al., 2010). Autonomic neuropathy can be observed in around 20% of asymptomatic patients with diabetes (Tesfaye et al., 2010). Clinical symptoms of autonomic neuropathy do not generally occur until long after the onset of diabetes. Subclinical autonomic dysfunction can, however, occur within two years of diagnosis in patients with type 1 diabetes (Boulton et al., 2005). Dysautonomic features may reflect the involvement of different systems and manifest as postural hypotension and orthostatic lightheadedness, gastroparesis, gastric fullness, early satiety, sexual dysfunction, bladder dysfunction, gustatory sweating or anhidrosis and pupillomotor dysfunction (Boulton et al., 2005).

| | **Autonomic neuropathy** |
|---|---|
| **Peripheral neuropathies** | - *Cardiovascular:* Postural hypotension, resting tachicardia, exercise intolerance |
| *Generalized symmetric polyneuropathies* | |
| - Acute sensory | - *Genitourinary:* Bladder dysfunction, Erectile dysfunction |
| - Chronic sensorimotor | |
| - Autonomic | - *Gastrointestinal:* Gastric paresis, constipation/diarrhea, fecal |
| *Focal and multifocal neuropathies* | inconinence |
| - Cranial | - *Sudomotor:* Gustatory sweating, Anhidrosis, Heat intolerance, Dry skin |
| - Truncal | |
| - Focal limb | - *Metabolic:* hypoglycemia unawareness |
| - Proximal motor | - *Pupillomotor dysfunction* |

Table 2. Neuropathies in diabetes

Diabetic neuropathy is characterized by a reduction in the number of fibers, degeneration of the myelin sheath as well as changes affecting the endoneurial connective tissue, vessels and perineurium (Greene et al., 1992). The process of nerve demyelination may progress to Wallerian degeneration, in which the nerve axon is also injured and the distal part of the axon dies (Greene et al., 1992).

### 2.3.2 Early signs of diabetic neuropathy in youth with type 1 diabetes

In the most comprehensive epidemiological studies involving both adult and pediatric patients, DPN was detected in 9 to 58% of the study populations (Boulton et al., 2005). Data on autonomic neuropathy indicate a prevalence ranging from 14% to 75%, with a high number of youth with type 1 diabetes presenting suclinical signs of autonomic dysfunction, even after a short duration of T1D. This variability across different studies is mainly related to differences in the characteristics of the study cohorts as well as to the use of different testing modalities and different criteria and cut off values (Trotta et al., 2004; Verrotti et al., 2009).

## 3. Macrovascular complications of type 1 diabetes

Patients with type 1 diabetes have an increased risk of developing cardiovascular disease (CVD) relative to the nondiabetic population, and premature atherosclerosis represents the main cause of morbidity and mortality in type 1 diabetes populations (Laing et al., 2003).

There is extensive evidence in support of the concept that atherosclerosis begins early in life (Ross, 1993) and therefore identification of CVD risk factors and preventive strategies should be started during childhood and adolescence (Dahl-Jorgensen et al., 2005). Children and adolescents with type 1 diabetes represent a high risk population with regards to CVD, given that cardiovascular risk factors are common among them (Dahl-Jorgensen et al., 2005; Margeirsdottir et al., 2008; van Vliet et al.) and they can contribute to their poor long-term prognosis (Skrivarhaug et al., 2006). A recent study has shown that as many as 86% of youth with type 1 diabetes has at least one, 45% at least two and 15% at least three CVD risk factors, including high HbA1c, high blood pressure, dyslipidemia, smoking and family history of CVD events (Margeirsdottir et al., 2008). These data are alarming given that it is well known that CVD risk factors can persist or track over time (Berenson, 2002) and therefore contribute to the overall burden associated with type 1 diabetes.

### 3.1 Early signs of macrovascular disease in youth with type 1 diabetes

The early stages of the atherosclerotic process are silent, but autopsy studies have detected early structural alterations in the arteries of youth, where they have been associated with the same risk factors than in adults (Berenson et al., 1998). The earliest recognizable pathologic intimal lesions are the fatty streaks, which make their appearance in the aorta of children even before 3 years of age (McGill et al., 2000; Williams et al., 2002). Fatty streaks represent an early manifestation of lipid accumulation in the vessel wall and they have been associated with increased cholesterol levels as well as with hyperglycemia (McGill et al., 2000).

Technology progresses over the last years have made possible to look for early surrogate markers of atherosclerotic vascular disease. These markers are represented by structural alterations such as increased intima-media thickness as well as functional changes represented by decreased flow-mediated dilatation and increased arterial stiffness, as detected by pulse wave velocity (Dahl-Jorgensen et al., 2005).

Several studies have consistently shown that children and adolescents with type 1 diabetes present signs of endothelial dysfunction, as measured by flow-mediated dilation in the brachial artery (Jarvisalo et al., 2004; Singh et al., 2003). In addition, increased aortic and carotid intima-media thickness has been reported in children with type 1 diabetes (Harrington et al., 2010; Jarvisalo et al., 2001). Besides, markers of inflammation and oxidative stress are significantly increased in youth with type 1 diabetes when compared with age-matched controls and they can mediate vascular damage (Snell-Bergeon et al., 2010).

Progression of CVD in youth with type 1 diabetes can be more aggressive than in adults with diabetes, therefore highlighting the importance of early preventive strategies (Dahl-Jorgensen et al., 2005).

| Early manifestations of CVD in youth with type 1 diabetes |
| --- |
| • Increased inflammatory markers |
| • Increased oxidative stress |
| • Increased intima-media thickness |
| • Decreased flow-mediated dilatation |
| • Increased pulse wave velocity |

Table 3. Early manifestations of CVD in youth with type 1 diabetes

## 4. Pathogenesis of micro- and macrovascular complications

Vascular complications in the context of diabetes are the result of an interplay between hemodynamic and metabolic factors and the consequent activation of common intermediate pathways, associated with increased synthesis and release of growth factors, cytokines, chemokines and oxidant species, which are all final mediators of vascular damage (Cooper, 2001).

A strong association exists between the presence of micro- and macrovascular complications in people with type 1 diabetes (Girach and Vignati, 2006). In particular, it is well known that DN is a key risk factor for cardiovascular complications and many patients with renal impairment die of CVD-related causes even before developing ESRD (Groop et al., 2009). In addition, there is growing evidence suggesting that increases in albumin excretion, even within the normal range, in the general population as well as in people with type 1 diabetes, represents a determinant of CVD (Klausen et al., 2004). The link between micro- and macrovascular disease could be represented by endothelial dysfunction, as an underlining feature of both processes, as well as by a certain degree of inflammation, which has been associated to the presence of both micro- and macrovascular complications (Schalkwijk and Stehouwer, 2005).

### 4.1 Glycemic control

Chronic hyperglycemia is known to activate several deleterious pathways implicated in the damage of vessels: protein glycation, increased glucose flux through alternative polyol and hexosamine pathways, increased oxidative stress, which then stimulate secondary intracellular signaling pathways leading to production of growth factors, cytokines and inflammatory factors (Brownlee, 2001).

Several epidemiological studies have shown a direct and strong association between long-term glycemic control, as expressed by HbA1c levels, and the risk of developing nephropathy, retinopathy and neuropathy (Amin et al., 2008; Danne et al., 1998; Gallego et al., 2008; Nordwall et al., 2009). In addition, HbA1c has been shown to be a key determinant also of early signs of atherosclerosis (McGill et al., 1995).
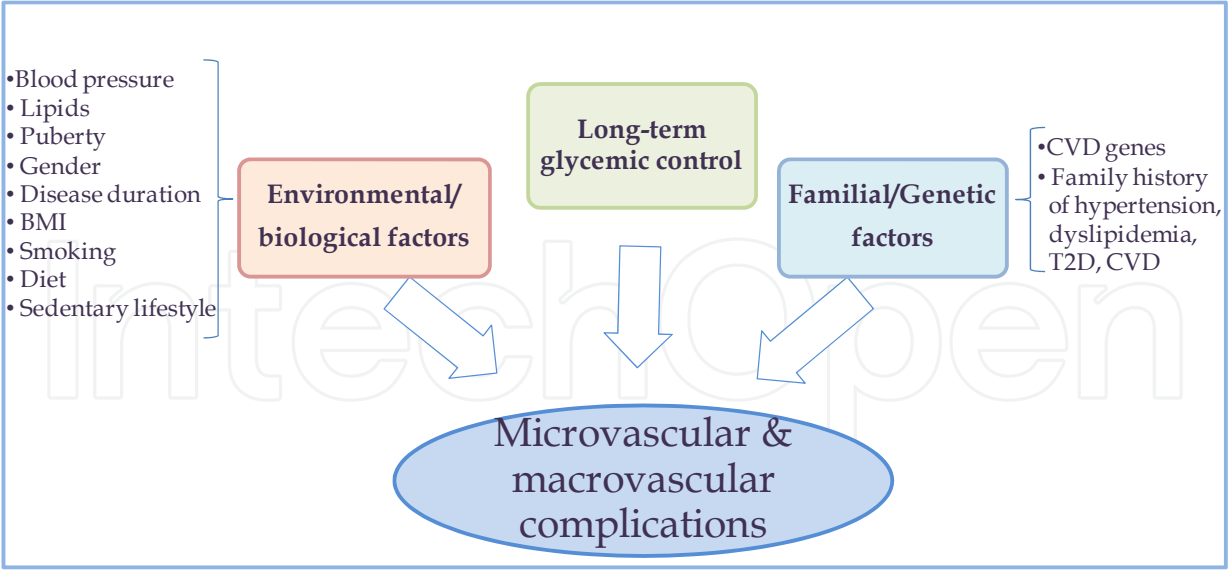
Fig. 2. Risk factors for the development of vascular complications in adolescents with type 1 diabetes

The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) studies have clearly shown the beneficial effect of strict glycemic control in reducing the risk of microvascular and macrovascular complications in subjects with type 1 diabetes (1993; 2003). In the adolescent cohort of the DCCT, a positive effect of improved glycemic control on complication risk was obtained. Intensive insulin therapy reduced the risk for the development and progression of DR by 76% and 54%; the occurrence of microalbuminuria and proteinuria by 39% and 54% and that of clinical neuropathy by 60% when compared to the conventional treated group (1994). Data from the DCCT/EDIC study also showed that intensive insulin therapy reduced the risk for any cardiovascular disease by 42% and of nonfatal myocardial infarction, stroke or death from CVD cause by 57% (Nathan et al., 2005). The beneficial effect of intensive insulin treatment in patients with childhood-onset type 1 diabetes also emerged from the Oslo study, where long-term glycemic control predicted coronary atherosclerosis (Larsen et al., 2002).

In addition, the EDIC study raised the important concept of 'metabolic memory'; in other words although after the end of the DCCT HbA1c levels became comparable between the intensively and conventionally treated groups, patients belonging to the first group still kept an advantage from prior better HbA1c levels (2003). Therefore, the EDIC data highlighted the need of implementing intensive management as soon as type 1 diabetes is diagnosed. This was further supported by recent data related to DR, showing that, although at year 10 of the EDIC there was still a decrease in DR progression risk in the intensively treated adult group, in the adolescent cohort retinopathy progression at year 10 of the EDIC did not differ between the previous DCCT intensively and conventionally treated groups, thus indicating loss of the metabolic memory (White et al., 2010). Interestingly, 79% of the difference in the metabolic effect between adults and adolescents after 10 years from the end of the DCCT was due to the difference in mean HbA1c levels during the DCCT between the two cohorts. This 1% difference, which did not seem to play a major role during the DCCT and early EDIC years with regards to the outcomes, seems to be a major player in the long run (White et al., 2010).

### 4.2 Blood pressure and plasma lipids

Elevated blood pressure and alterations in its circadian rhythm are common findings in people with type 1 diabetes and have been associated with the risk of developing vascular complications (Gallego et al., 2008; Marcovecchio et al., 2009b; Tesfaye et al., 1996). Increases in blood pressure have been found to precede or occur concomitant with the appearance of microalbuminuria in adolescents with type 1 diabetes (Marcovecchio et al., 2009b; Schultz et al., 2001). Similarly, higher than normal systolic and diastolic blood pressure independently contribute to the development of DR (Gallego et al., 2008). Blood pressure has been also associated with early markers of atherosclerosis (Dahl-Jorgensen et al., 2005).

Lipid abnormalities have also been linked to the development and progression of micro- and macrovascular complications in adolescents with diabetes (Dahl-Jorgensen et al., 2005; Kordonouri et al., 1996; Marcovecchio et al., 2009a).

### 4.3 Duration and age at onset of type 1 diabetes

Duration of diabetes is another major determinant of complication risk. Although vascular complications rarely appear before puberty, prepubertal duration of diabetes is an important determinant for their development (Coonrod et al., 1993; Orchard et al., 1990). Patients with type 1 diabetes from early childhood and especially those diagnosed under five years of age seem to have slightly delayed onset of persistent microalbuminuria during the first 10 to 15 years duration compared with patients diagnosed later in childhood or during puberty. However, this initial protective effect of a younger age at diagnosis disappears over time (Amin et al., 2008; Donaghue et al., 2003). After 15 years of diabetes duration the risk of developing microalbuminuria is similar between subjects diagnosed with diabetes before 5 years of age when compared with those diagnosed between 5-11 years of age or after the age of 11 years, suggesting that age at the onset of diabetes does not influence the overall risk for microalbuminuria (Amin et al., 2008). A recent study has highlighted that also for DR, although patients diagnosed at a young age have a longer time free of proliferative retinopathy, this advantage then gradually disappears and youth diagnosed before the age of 15 years have a higher risk of proliferative retinopathy when compared with those diagnosed when aged 15-40 years (Hietala et al., 2010).

### 4.4 Puberty

Puberty is an important factor implicated in the development and progression of vascular complications. Poor glycemic control is a common finding among adolescents with type 1 diabetes (1994; Holl et al., 2003). In addition, puberty is associated with a decrease in insulin sensitivity, and adolescents with type 1 diabetes are more insulin resistant when compared with healthy controls (Dunger, 1992). Rapid growth, hormonal and metabolic changes characterise this period of life and can influence complications risk (Dunger, 1992).

### 4.5 Gender

A gender dimorphism has been reported for vascular complications. In particular, during adolescence the risk for microalbuminuria is higher in female than in male subjects with comparable glycemic control (Amin et al., 2008; Jones et al., 1998), whereas among adults with type 1 diabetes the risk is higher for males (Hovind et al., 2004). These differences have been related to variations in the hormonal milieu and to a higher degree of insulin resistance in girls (Schultz et al., 1999a).

### 4.6 Other factors

Genetic factors represent another important contributing factor for the development of vascular complications, as suggested by their familial clustering, and by the observation that only a subset of patients with poor glycemic control develop severe long-term complications (1997). Family history of cardiovascular risk factors is associated with increased risk of microvascular complications in the offspring (Monti et al., 2007; Seaquist et al., 1989).

A high body mass index (BMI) represents another potential risk factor for microvascular complications in youth with type 1 diabetes (Stone et al., 2006). In addition, obesity is a well-known risk factor for cardiovascular disease (Dahl-Jorgensen et al., 2005).

Environmental factors, including diet and lifestyle, can also contribute to the risk of developing vascular complications. Smoking in people with type 1 diabetes has been associated with an increased risk of developing vascular complications (Chase et al., 1991; Mohamed et al., 2007).

## 5. Management of microvascular and macrovascular complications

### 5.1 Screening

Diabetic microvascular and macrovascular complications are often asymptomatic during their early stages, and once symptoms develop, they may be difficult to reverse. Therefore, longitudinal repeated screening for vascular complications initiated during early adolescence is currently recommended

The American Diabetes Association (ADA) recommends to start screening in patients with type 1 diabetes aged 10 years or older after a disease duration of 3-5 years, with yearly follow-up (Silverstein et al., 2005). The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening from the age of 11 years in those with 2 year diabetes duration and from 9 years in those with a 5 year duration for both nephropathy and retinopathy (Donaghue et al., 2007). Measurement of urinary albumin excretion is the basis for early detection of microalbuminuria and can be achieved with: 1) 24-hour urine collection; 2) overnight timed urine collections; 3) albumin-creatinine ratio (ACR) or albumin concentration on a early morning spot urinary sample (Donaghue et al., 2007). 24-hour or timed urine collections are often difficult to collect in children and adolescents. Assessing ACR in early morning urines is the easiest method to carry out in an office setting and it generally provides accurate information (Donaghue et al., 2007).

With regards to DR, several techniques can be used, including direct and indirect ophthalmoscopy, stereoscopic digital and color film based fundus photography, mydriatic or nonmydriatic digital color or monochromatic single-field photography. The best technique to identify and grade retinopathy is represented by retinal photography, through dilated pupils, but dilated indirect ophtalmoscopy associated with biomicroscopy is an acceptable alternative (Ciulla et al., 2003).

In contrast to well-established criteria for when starting screening for DN and DR, it is unclear when to commence screening for neuropathy. History and physical examination are generally the recommended methods of screening (Donaghue et al., 2007). Clinical examination, including history of pain, paresthesia, numbness and physical examination of ankle reflexes and vibration and light touch sensation, is a fundamental part of screening, although not being as sensitive or specific as nerve conduction studies (Donaghue et al., 2007). Autonomic neuropathy can be assessed with specific autonomic nerve tests, such as heart rate response to deep breathing, standing from a lying position, Valsalva maneuver, heart rate variations at

rest, QT interval, postural changes in BP and pupil responses to light and dark adaptation (Donaghue et al., 2007). These tests need to be carefully standardized and therefore they are largely used as screening methods for complications at a population level.

Additional screening concerns risk factors for CVD, such as dyslipidemia and hypertension. Blood lipids should be checked soon after diagnosis and if normal then repeated after 5 years (Donaghue et al., 2007). Office blood pressure should be assessed annually and in case of abnormal values, hypertension needs to be confirmed by ambulatory blood pressure monitoring.

| |
|---|
| **When to start**<br>• Microvascular complications: at age 11 with 2 year duration of type 1 diabetes or from age 9 with 5 year duration (for nephropathy and retinopathy; unclear for neuropathy)<br>• Macrovascular complications: after 12 years |
| **Screening Method:**<br>*1) Diabetic nephropathy*<br>• Annual albumin-creatinine ratio in a spot urine sample or first morning albumin concentration<br>*2) Diabetic retinopathy*<br>• Annual dilated fundus ophthalmoscopy or fundal photography<br>*3) Diabetic neuropathy*<br>• History and physical examination<br>• Nerve conduction and autonomic tests<br>*4) Macrovascular disease*<br>• Annual assessments of blood pressure<br>• Assessment of lipid levels every 5 years |

Table 4. Screening for micro- and macrovascular complications in youth with type 1 diabetes

## 5.2 Interventions

Improving glycemic control is the cornerstone of treatment strategies aiming at reducing the development and progression of microvascular and macrovascular complications. The DCCT and EDIC study clearly showed the importance of a strict glycemic control both in adults and in adolescents with type 1 diabetes (1994). The importance of keeping HbA1c within targets has also been highlighted by other studies, but similarly to the DCCT, subsequent studies have confirmed the difficulties encountered when dealing with young people with type 1 diabetes (Holl et al., 2003; Petitti et al., 2009). Tight glycemic control in the DCCT and subsequent studies was associated with a higher risk of complications, such as hypoglycemia and weight gain (1994). In addition, poor compliance is an important issue to be taken into account in adolescents with type 1 diabetes. Furthermore, other factors besides insulin therapy are relevant for metabolic control, such as dietary habits, education, family interactions, cultural and psychological aspects (Holl et al., 2003), and therefore they need to be taken into account in order to define a successful treatment plan.

Treatment with angiotensin converting enzyme inhibitors (ACEIs) is recommended when hypertension is confirmed (Donaghue et al., 2007). ACEIs are treatment of choice in adults with microalbuminuria, based on evidence that their use decrease the rate of progression and even increase rates of regression of microalbuminuria (Lewis et al., 1993). A beneficial

effect of anti-hypertensive treatment, and in particular of treatment with ACEIs, has also been demonstrated for DR (Chaturvedi et al., 1998). The EURODIAB Controlled Trial of Lisinopril in type 1 diabetes showed a significant effect of lisinopril in reducing by around 50% the progression of retinopathy in normotensive and normo- or microalbuminuric patients (Chaturvedi et al., 1998). However, there is no universal recommendation for the use of ACEIs in children and adolescents with microalbuminuria. The ADA recommends to start treatment with ACEIs in presence of persistent microalbuminuria (Silverstein et al., 2005). Similarly, the recent ISPAD guidelines suggest to use ACEIs or angiotensin receptor blockers in presence of persistent microalbuminuria, in order to prevent progression to proteinuria (Donaghue et al., 2007), even though the lack of evidence in this context is acknowledged.

Dyslipidemia should be managed firstly with improvements in glycemic control and dietary changes and, in case of persistence of high cholesterol levels, treatment with statins should be considered, although there is no enough evidence of their use in children apart from those with familial hypercholesterolemia  (Donaghue et al., 2007). However, in adults statins have been shown to be effective in the primary and secondary prevention of major cardiovascular events  (2002).

Adolescents with type 1 diabetes need to be persuaded to avoid smoking. In addition, it is of paramount importance also to avoid increases in BMI, given that adiposity is a well known risk factor for cardiovascular complications, and in some studies it has also been associated with microvascular complications of type 1 diabetes (Donaghue et al., 2007).

| Targets to reduce diabetic vascular complications |
|---|
| • HbA1c: ≤7.5% (without severe hypoglycemia) |
| • LDL cholesterol: <2.6mmol/l |
| • HDL cholesterol: >1.1mmol/l |
| • Triglycerides: <1.7mmol/l |
| • Blood pressure: <90th percentile for age, sex and height |
| • BMI <95th centile |
| • Avoid smoking |
| • Physical activity: moderate: >1hr/day |
| • Sedentary activities: <2hr/day |
| • Healthy diet |

Table 5. Recommendations to reduce diabetic vascular complications (ISPAD guideline 2006-2007)

New potential therapeutic possibilities for the treatment of vascular complications are emerging and they include drugs targeting specific pathways implicated in their pathogenesis. These include inhibitors of aldose reductase, inhibitors of protein kinase C, antagonists of advanced glycation end-products, glycosaminoglycans, inhibitors of growth factors and anti-oxidants (Soro-Paavonen and Forbes, 2006). Up to now, there are no definitive data to recommend the use of these new potential therapies but the overall objective of targeting specific metabolic and hemodynamic pathways implicated in the pathogenesis of diabetic vascular complications could lead to validation of these classes of drugs and discovery of novel pharmaceuticals.

## 6. Conclusions

The risk for micro- and macrovascular complications is high in young patients with childhood-onset type 1 diabetes and their development negatively influence their long-term prognosis.

Early identification of risk factors and prevention of diabetes complications are of paramount importance in children and adolescents. Diabetic vascular complications are often asymptomatic during their early stages, and once symptoms develop, it can be difficult to reverse them. Therefore, screening for vascular complications started during early adolescence, as currently recommended, is essential. Identification of risk factors and subclinical signs of complications is of paramount importance for the early implementation of preventive and therapeutic strategies, which could change the course of vascular complications and improve the prognosis of youth with diabetes. Efforts should be made for optimizing glycemic control, to keep blood pressure and lipid levels within target levels, to avoid smoking, promote exercise and a healthy diet. Future studies are required to test the efficacy and safety of new therapies, which could target specific metabolic or hemodynamic pathways implicated in the pathogenesis of diabetic complications.

Further advances in genomics, proteomics and in other 'omics' and the integration of the findings of these different sciences will hopefully allow a better understanding of the pathogenesis of diabetic vascular complications in the near future and will potentially lead to a personalized medicine for young patients with diabetes

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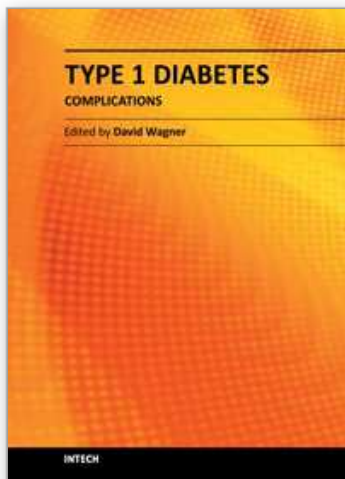
**Type 1 Diabetes Complications**

Edited by Prof. David Wagner

This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. The complications associated with T1D cover a range of clinical obstacles. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes.

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