

Inflammation in Pediatric Patients with Type 1 Diabetes— An Early Predictor of Complications?

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Abstract

Type 1 diabetes is an autoimmune disease caused by the destruction of the pancreatic beta cells, and common complications include both microvascular (kidney disease, retinopathy, neuropathy) and macrovascular (peripheral arterial disease, coronary artery disease, stroke) disease. Hyperglycemia is a well-known risk factor for microvascular as well as macrovascular complications. However, even when glycemic control is improved, complications are not completely avoided, which has resulted in a theory of a 'metabolic memory.' Systemic inflammation is a common finding in patients with type 1 diabetes, and increased inflammatory markers appear even among children who have been recently diagnosed. Increased inflammatory cytokines have been found to be associated with later development of cardiovascular disease, diabetic nephropathy, retinopathy, and diabetic neuropathy, and may therefore act as a 'second hit' to hyperglycemia in the development of complications. Here we review the evidence for associations between inflammation and complications among children and youth with type 1 diabetes.

Keywords

Type 1 diabetes, coronary artery disease, atherosclerosis, diabetic nephropathy, retinopathy, diabetic neuropathy, inflammation, fibrinolysis

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Type 1 diabetes is characterized by the loss of beta-cell function in the pancreas due to an autoimmune reaction. The incidence of type 1 diabetes peaks during childhood (six to nine years of age) and adolescence (12–15 years of age).^{1,2} Over the past few decades, an increase in the incidence of type 1 diabetes has been noted worldwide,^{3–7} and there is some evidence that the age at diagnosis has been decreasing. Complications of type 1 diabetes include microvascular (kidney disease, retinopathy, and neuropathy) and macrovascular (peripheral arterial disease, coronary artery disease [CAD], and stroke) disease.

The majority of deaths among patients with type 1 diabetes are attributed to cardiovascular disease,^{8,9} which occurs at younger ages⁹ and is more often fatal in adults with type 1 diabetes than in the general population.¹⁰ While clinical events typically do not occur until the third decade of life, evidence that the process of atherosclerosis begins in childhood has been established by several large studies, including the Bogalusa Heart Study¹¹ and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study.¹² As a result, the identification of risk markers during childhood is critical for primary prevention of cardiovascular complications of type 1 diabetes.

Microvascular complications also contribute to increased mortality and morbidity in patients with type 1 diabetes, as diabetic nephropathy is

responsible for 25% of cases of end-stage renal disease in the US,¹³ and diabetic retinopathy is the leading cause of blindness.¹⁴ Microvascular complications do not usually develop until after puberty in pediatric patients with type 1 diabetes,¹⁵ but the development of these complications may likely be predicted by factors that occur earlier in the course of the disease.

Role of Hyperglycemia in Microvascular and Macrovascular Complications

The Diabetes Control and Complications Trial (DCCT) established the importance of glycemic control in reducing the microvascular complications of type 1 diabetes.¹⁶ The follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that improved glycated hemoglobin (HbA_{1c}) during the period of the DCCT study contributed to lower complication rates years later, even when glycemic control in the intensively treated and control groups converged following the DCCT.^{17,18} As a result, it appears that there is a 'metabolic memory' of prior glycemic control that continues to affect the rate of development of complications. It has been hypothesized that the accumulation of advanced glycation end-products (AGEs) during periods of chronic hyperglycemia may continue to contribute to tissue damage and complications even after improvement of hyperglycemia, as the degradation of AGEs occurs slowly.¹⁷

Table 1: Association Between Inflammatory Markers and Complications of Type 1 Diabetes

	CVD	Renal Disease	Retinopathy	Neuropathy
IL-6	X ^{21,22,48}	X ^{21,48}	X ^{21,31,48}	X ²²
TNF- α	X ^{21,48}	X ^{21,30,48}	X ^{21,29-31,63}	X ^{22,70}
CRP	X ^{21,24,47-50}	X ^{21,48}	X ^{21,31,48}	X ⁷⁰
TNF- α RI + II				X ^{22,33}
sICAM-1	X ²¹	X ²¹	X ²¹	X ⁷⁰
sVCAM-1	X ²¹	X ²¹	X ²¹	X ⁷⁰
E-selectin	X ²¹	X ²¹	X ²¹	
VEGF		X ^{58,71}	X ³¹	
IL-12			X ⁶⁶	
IL-1 β	X ⁵⁰			
Uric acid	X ⁶³	X ^{60,61}		
Fibrinogen				X ⁷⁰
PAI-1, t-PA	X ³⁵	X ^{35,72}	X ^{34,35}	X ³⁵

CRP = C-reactive protein; CVD = cardiovascular disease; IL = interleukin; PAI-1 = plasminogen activator inhibitor type 1; sICAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = soluble vascular cell adhesion molecule-1; TNF = tumor necrosis factor; t-PA = tissue plasminogen activator; VEGF = vascular endothelial growth factor.

Therefore, while hyperglycemia is a well-recognized risk factor for the development of microvascular complications of type 1 diabetes, and has also been associated with the development of macrovascular disease,^{16,19} improved glycemic control alone does not completely remove the risk of complications in patients with type 1 diabetes.²⁰ Furthermore, most adults and children with type 1 diabetes are unable to achieve the optimal glycemic control that would be needed to reduce complications further. As a result, investigators have searched for additional biomarkers that might provide a common thread between renal disease, retinopathy, neuropathy, and cardiovascular disease (see Table 1).

Low-grade Systemic Inflammation and Fibrinolysis

Tissue damage in type 1 diabetes has been linked to abnormalities in the inflammatory cytokine system as well as altered fibrinolysis and coagulation.²¹ Increased pro-inflammatory cytokines and acute-phase proteins have been reported to be associated with cardiovascular disease,²²⁻²⁴ and have also been implicated in the development of diabetic nephropathy,²⁵⁻²⁸ diabetic retinopathy,²⁹⁻³² and neuropathy.³³ Increased fibrinolytic capacity and coagulation factors have been associated with peripheral arterial disease, microalbuminuria, retinopathy,³⁴ and neuropathy.³⁵ Therefore, in addition to the established role of chronic hyperglycemia in the development of multiple complications of type 1 diabetes, increased inflammation and altered fibrinolysis may provide additional common threads in the development of diabetes complications. If this is the case, the detection of excess inflammation and altered fibrinolysis may allow for the earlier prediction of diabetes complications, particularly among children with type 1 diabetes, before complications typically become clinically apparent.

Inflammation in Pediatric Patients with Type 1 Diabetes

Type 1 diabetes is an autoimmune disease characterized by a shift towards a T helper 1 (Th1) subset of T-cells. Th1 cytokine products

(interleukin-2 [IL-2], interferon- γ [INF- γ], and tumor necrosis factor- α [TNF- α]) may induce the production of pro-inflammatory cytokines in the pancreatic islet cells, leading to beta-cell apoptosis and eventual insulin deficiency, as suggested by animal studies.³⁶

In a study involving 35 children with poorly controlled type 1 diabetes and 30 age- and sex-matched controls, levels of pro-inflammatory cytokines IL-6 and TNF- α were significantly increased only among children with less than a year's duration of type 1 diabetes, while levels of the chemokine IL-8 were significantly increased among all children with type 1 diabetes compared with controls.³⁷ C-reactive protein (CRP), an acute-phase protein that indicates systemic inflammation, was also reported to be increased among children with type 1 diabetes relative to controls in this study, although the difference was not significant.³⁷

Among a group of 27 children with type 1 diabetes of varying duration and 25 healthy controls studied by Dogan et al. in Turkey, higher levels of pro-inflammatory cytokines IL-1 β and TNF- α , but lower levels of IL-2 and IL-6, were reported among children with long-standing diabetes, as well as among those who were newly diagnosed, both before and after treatment was initiated.³⁸ Increased levels of inflammation (IL-1 β , IL-4, and IL-6) were reported among 22 children with hyperglycemia, but short-term improvement in glycemic control using intravenous insulin infusion did not reduce levels of these cytokines.³⁹ These study results suggest that improved glycemic control may not be sufficient to treat the increased inflammation in pediatric patients with type 1 diabetes.

In a study of 553 children with type 1 diabetes and 215 non-diabetic control children who participated in the SEARCH for Diabetes in Youth case-control study, levels of IL-6 and fibrinogen were significantly higher in youths with type 1 diabetes than in non-diabetic youths, independent of levels of hyperglycemia and body mass index (BMI).⁴⁰ In addition, levels of CRP were significantly higher among youths with type 1 diabetes who were normal weight compared with non-diabetic youths who were normal weight. Increased levels of inflammatory markers were associated with adverse lipid levels, suggesting that increased inflammation may influence cardiovascular risk through promoting an atherogenic lipid profile.

Macrovascular Disease

CAD remains the most common cause of death for patients with type 1 diabetes. Young adults with type 1 diabetes are at dramatically increased risk for CAD death, which is generally rare among individuals less than 40 years of age in the non-diabetic population.⁹ Annually, up to 2% of young adults with type 1 diabetes develop CAD.^{41,42} By their mid-40s, over 70% of men and 50% of women with type 1 diabetes develop coronary artery calcification⁴³—a marker of significant atherosclerotic plaque burden. Autopsy studies have demonstrated that fatty streaks are present even among children,^{11,12} and the extent of coronary artery plaque during childhood and adolescence correlates with risk factors such as cholesterol and obesity.⁴⁴ Risk factors for CAD track from childhood to adulthood, and so the identification of children with increased CAD risk factors presents an opportunity for primary prevention.

While cardiovascular events typically do not occur until at least the third decade of life even among patients with type 1 diabetes,⁹ vascular

changes and cardiometabolic abnormalities have been detected in childhood. A German study of over 27,000 children and young adults with type 1 diabetes found high rates of cardiovascular risk factors, and inadequate treatment.⁴⁵ Endothelial function, a marker for vascular changes associated with atherosclerosis, is impaired in children with type 1 diabetes.⁴⁶ Carotid intima-media thickness (CIMT), a marker for the development of plaque and atherosclerosis, is also increased among children and youths with type 1 diabetes.⁴⁷

Chronic low-grade inflammation has been shown to precede the development of atherosclerosis, and is a likely initiator of atherosclerotic plaque development. In a study examining CIMT in 148 youths and young adults with type 1 diabetes compared with obese (n=86) and normal-weight (n=142) controls, both CRP and CIMT were increased in patients with type 1 diabetes, and there was a significant association between higher levels of CRP and increased CIMT, indicating that systemic inflammation may be responsible for the increased macrovascular disease in young patients with type 1 diabetes.²⁴

A cross-sectional report from the European Diabetes (EURODIAB) Prospective Complications Study Group examined whether inflammatory markers were associated with cardiovascular disease, defined as a cardiovascular event (myocardial infarction, coronary artery bypass graft, stroke), angina, or ischemic changes on electrocardiogram (ECG). A combined risk score using CRP, IL-6, and TNF- α was associated with cardiovascular disease even when adjusted for age, sex, glycemic control, diabetes duration, and blood pressure.⁴⁸

Similarly, among 55 young adults (mean age 22.1 \pm 3.6 years) with type 1 diabetes evaluated in Osaka, Japan, elevated CRP and fibrinogen levels and greater CIMT were reported compared with 75 healthy controls.⁴⁹ CRP levels were significantly correlated with both mean and maximum CIMT in univariate correlation analysis and multivariate regression modeling.

An association has been reported between higher levels of inflammation and higher levels of lipids, suggesting that the effect of inflammation on cardiovascular risk may be at least partially mediated through dyslipidemia. In a study of 69 children with type 1 diabetes and 74 age-matched healthy controls under 22 years of age, children with type 1 diabetes were reported to have higher levels of CRP, and IL-1 β was higher among newly diagnosed children with type 1 diabetes.⁵⁰ A negative correlation was reported between IL-1 β levels and lipids, including total and low-density lipoprotein (LDL) cholesterol and triglycerides.

Potential mechanisms through which increased inflammation may mediate the development of atherosclerosis include the build-up of AGEs due to chronic hyperglycemia, which may activate macrophages. Furthermore, hyperglycemia may induce oxidative stress. Stressed vascular endothelial cells may release chemokines, increasing factors such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. Pro-inflammatory genes may then be activated, leading to increased secretion of IL-6, TNF- α , IL-18, IFN- γ , and other cytokines. In addition, macrophages and endothelial cells may increase plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (t-PA) expression, leading to higher levels of fibrinogen and factor VIII and a procoagulant state.

Based on the evidence of associations between chronic inflammation and cardiovascular disease in adults as well as vascular abnormalities in youths with type 1 diabetes, it is possible that elevated inflammatory markers in childhood could predict the development of cardiovascular disease later in life.

Renal Function and Diabetic Nephropathy

Nearly 25% of type 1 diabetes patients develop end-stage renal disease (ESRD),⁵¹ and renal disease increases the risk of cardiovascular disease and premature mortality.^{52,53} The conventional theory is that the sequence of events leading to diabetic nephropathy (DN) begins from microalbuminuria, progressing to overt proteinuria and eventual reduction of glomerular filtration rate (GFR) and ESRD. Primary prevention of renal disease with angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) treatment usually begins when persistent microalbuminuria is found. However, recent prospective studies using serial measurements of GFR estimated from serum cystatin C (cysGFR) have changed this paradigm by demonstrating that the decline in GFR may begin in the absence of microalbuminuria or continue despite remission of microalbuminuria.^{54,55} Furthermore, by the time patients with type 1 diabetes have developed microalbuminuria, there are already structural changes in the kidney,⁵⁶ suggesting that subclinical renal damage occurs for a period of time prior to the development of microalbuminuria, and could potentially be detected using novel biomarkers, leading to earlier intervention.

In an investigation of CRP levels and microalbuminuria in the Oxford Regional Prospective Study, 49 youths (mean age 15.3 years) with type 1 diabetes who developed microalbuminuria were compared with 49 normoalbuminuric subjects; CRP levels increased among subjects who developed microalbuminuria.⁵⁷ In the EURODIAB Prospective Complications Study, systemic inflammation, as evidenced by a combined risk score using CRP, IL-6, and TNF- α levels, was associated with albuminuria, as well as other complications of type 1 diabetes (CAD and retinopathy).⁴⁸ Inflammatory cytokines are cleared through the kidney, so reduced glomerular filtration may lead to higher plasma levels of these factors. As a result, it is unclear whether the increased inflammation observed in association with renal disease simply represents a marker of decreased glomerular filtration.

Vascular endothelial growth factor (VEGF) is a cytokine that promotes angiogenesis and also regulates vascular permeability. Increased VEGF has been reported to predict the development of persistent microalbuminuria.⁵⁸ Higher levels of VEGF have been reported in a group of 196 children with type 1 diabetes compared with 223 age- and sex-matched controls without diabetes, and VEGF concentrations were correlated with HbA_{1c} and severity of microvascular complications.⁵⁹

Uric acid is increased in renal disease, but more recently variation in uric acid even in the normal range has been reported to be associated with reduced glomerular filtration rate.⁶⁰ A prospective study of uric acid levels found that high normal uric acid levels predict the development of microalbuminuria in patients with type 1 diabetes.⁶¹ Uric acid may induce endothelial dysfunction^{62,63} and can be considered a pro-inflammatory agent, and therefore may induce renal complications through inflammatory pathways.

Type 1 Diabetes

Diabetic Retinopathy

Retinopathy is a progressive disease that begins with non-reversible microaneurysms and can lead to proliferative retinopathy. Diabetic retinopathy is the leading cause of blindness, and leads to substantial healthcare costs. The Wisconsin Epidemiologic Study of Diabetic Retinopathy followed 995 patients with insulin-dependent diabetes for 25 years, and found a cumulative rate of retinopathy progression of 83%.⁶⁴

Hyperglycemia has been established as a risk factor for retinopathy, and intensive treatment in the DCCT reduced the incidence of retinopathy by 76% among those without any evidence of retinopathy at randomization.⁶⁵ After a decade of follow-up in the EDIC study, those patients who received intensive insulin therapy during the DCCT experienced more than a 50% reduction in retinopathy progression, despite the convergence of HbA_{1c} in the DCCT treatment groups during the follow-up.¹⁸ The results of the DCCT and EDIC studies have clearly shown that hyperglycemia is a strong predictor of retinopathy incidence and progression, with an apparent 'metabolic memory' that continues to reduce the risk for up to a decade after a return to moderate glycemic control (mean HbA_{1c} 8%).

In the EURODIAB Prospective Complications Study, a combined risk score using CRP, IL-6, and TNF- α levels was associated with the development of multiple complications of type 1 diabetes, including retinopathy.⁴⁸ An additional cross-sectional study found that levels of TNF- α , IL-6, and VEGF were higher in 39 children with early evidence of retinopathy than in 163 children without retinopathy.³¹ In addition to higher levels of TNF- α ,²⁹ the relative levels of TNF- α and IL-12, a T-cell stimulator and anti-angiogenesis cytokine, respectively, have been associated with the presence of retinopathy in children with type 1 diabetes.⁶⁶

Neuropathy

Diabetic neuropathy may develop in the peripheral and autonomic nervous system, leading to significant morbidity and increased mortality. One of the more serious manifestations of neuropathy in patients with type 1 diabetes is cardiac autonomic neuropathy (CAN). While symptoms of neuropathy are uncommon in childhood, the prevalence of asymptomatic neuropathy in adolescents was 57% in a study that carefully assessed patients using a series of electrophysiological evaluations⁶⁷ and 59% in a study of 80 youths between seven and 22 years of age with at least three years of diabetes duration.⁶⁸ In the DCCT study, diabetic neuropathy prevalence was 46% in conventionally treated participants and 26% in intensively treated participants.⁶⁹ In addition, neuropathy tends to occur in patients with other microvascular complications, including retinopathy and microalbuminuria. It is therefore likely that common mechanisms underlie the development of subclinical neuropathy, atherosclerosis, early renal disease, and retinopathy.

The etiology of diabetic neuropathy is poorly understood, and is likely complex. Hyperglycemia is implicated in the development of autonomic dysfunction and defects in peripheral nerve conduction, and improved glycemic control reduces the risk of developing neuropathy.⁶⁹ However, subclinical neuropathy is common even among youths with good glycemic control from the time of their diabetes diagnosis.⁶⁸ Among potential biological mechanisms that have been proposed to cause neuropathy independently of hyperglycemia are excess sorbitol and

fructose deposition in nerve cells, and increased inflammatory cytokines leading to nerve degeneration.

One of the earliest signs of CAN is reduced response of the heart rate to respiration, referred to as low heart rate variability (HRV). Among 120 patients with type 1 diabetes of 14 years' duration on average, lower HRV was associated with higher levels of serum IL-6.²² Additional inflammatory markers, including CRP, TNF- α , fibrinogen, leptin, osteoprotegerin, soluble E-selectin, soluble VCAM (sVCAM), and soluble ICAM (sICAM), have been reported to be associated with both symptomatic and asymptomatic neuropathy,⁷⁰ and higher levels of TNF- α receptors have been reported in patients with type 1 diabetes and neuropathy compared with patients with type 1 diabetes who are free from neuropathy.³³ Therefore, while hyperglycemia is a significant risk factor for diabetic neuropathy, systemic inflammation also plays a role in both central and peripheral neuropathy. Inflammation may influence neuropathy through mediating the effect of elevated glucose levels and through independent mechanisms leading to nerve damage.

Inflammation—The Common Thread of Multiple Diabetic Complications?

Over the past few decades, our understanding of the role of hyperglycemia has expanded, and improved treatment has led to impressive strides in the control of blood glucose levels. Improved glycemic control has been definitely shown to reduce the complications of type 1 diabetes, including retinopathy, nephropathy, and neuropathy, with more modest evidence for decreased macrovascular disease. Despite these improvements, however, a significant risk of complications remains.

Increased systemic inflammation and altered fibrinolysis and coagulation are commonly reported in patients with type 1 diabetes, and often precede the development of complications. Cross-sectional associations between inflammatory cytokines and markers of fibrinolysis with both microvascular and macrovascular complications have been found, and there is clustering of complications among patients with type 1 diabetes, suggesting common threads. Limited prospective data are available linking inflammation with the development of early complications in the pediatric population, so this remains an important area of investigation for new biomarkers and predictors. ■



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