7

Etiopathology of Type 1 Diabetes: Focus on the Vascular Endothelium

Petru Liuba and Emma Englund
Division of Paediatric Cardiology, Pediatric Heart Center, Lund University and Skåne University Hospital Lund Sweden

1. Introduction

Type 1, or insulin-dependent diabetes results from the destruction of insulin-producing β-cells in the pancreas. It typically occurs in previously healthy children, being one of the most common childhood diseases in modern time. Intriguingly, the diabetes morbidity continues to rise in most parts of the world, but the causes of this development remain elusive (the Diabetes Mondial (DIAMOND) Project Group, 2006).

Many of the patients with type 1 diabetes may develop particularly in adult life severe complications encompassing both the microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (myocardial infarction, stroke and peripheral artery disease) system. The main underlying mechanism in the large vessels is represented by accelerated atherosclerosis with subsequent narrowing of the vessels and potential risk for plaque rupture. In smaller, as in the large vessels, severely impaired function of the inner layer (so-called endothelium) has been detected, and correlated with the risk of developing vascular complications, suggesting it to play a major role in precipitating the vascular disease.

It is now well established that this widespread vasculopathy develop many years before the onset of vascular complications, perhaps even before the outbreak of diabetic hyperglycemia. What exactly drives this process remains speculative, but increasing evidence suggest that factors thought to trigger type 1 diabetes may as well be harmful for the vessels. Furthermore, as delineated below, the microvascular network surrounding the islets in the pancreas appears to have important contribution to the injury process that ultimately leads to type 1 diabetes. Further multidisciplinary efforts are warranted in order to better understand the mechanism of this disease and its complications.

2. Epidemiology and pathogenesis of type 1 diabetes

There is a widespread global variation in the incidence and prevalence of type 1 diabetes. In a report by Karvonen et al. from 2000, age-adjusted incidences ranged from a low of <1/100,000 per year in China and South America to a high of >20/100,000 per year in Sardinia, Finland, Sweden, Norway, Portugal, the United Kingdom, Canada, and New Zeeland. The incidence increased with age in most of the populations with the highest incidence observed in children 10-14 years of age. An updated report from 2006 (the

DIAMOND Project Group, 2006) showed trends of increased incidence annually across the world in the populations studied (4.0% in Asia, 3.2% in Europe, and 5.3% in North America) with the exception of Central America and the West Indies were the trend was a decrease of 3.6%. The rate of increase in incidence cannot be explained by genetic shift in such a short period of time. An increasing burden of environmental factors, probably along with increased immune-mediated sensitivity of pancreatic cells to gene-environment interaction, could account at least in part for the rising prevalence of type 1 diabetes.

Traditionally, interplay between genetic susceptibility and environmental factors is thought to provide the fundamental element for the disease. The major genetic susceptibility for developing type 1 diabetes is located on the human leukocyte antigen (HLA)-DQ region on chromosome 6. Two HLA-DQ haplotypes, DQA1*0301-DQB1*0302 (DQ8) and DQA1*0501-DQB1*0201 (DQ2) are associated with high risk for developing diabetes. Almost 90% of patients with type 1 diabetes have at least one of these two haplotypes, compared to 20% of the general population (Redondo et al., 2001). These susceptibility genes are important regulators of the immune response; the molecules they encode reside on the cell surface and have the ability to process and present antigens to autoreactive T-cells.

In genetically susceptible individuals there is a pathological presentation of autoantigens on the cell surface of the pancreatic islet cells. This, in combination with a failing negative selection of the T-cells in the thymus and decreased regulatory capacity of regulatory T-cells in peripheral blood (Lindley et al., 2005), leads to an inflammatory response within the pancreatic islets as well as to the production of antibodies against β-cell antigens. Islet cell antibodies were the first ones described, but we now also recognize autoantibodies to insulin, glutamic acid decarboxylase and protein tyrosine phosphatase. Up to 90% of the patients with new onset type 1 diabetes have autoantibodies directed against one or more of these autoantigens It is yet to prove if the autoantibodies have an active role in the pathogenesis of type 1 diabetes but the presence and persistency of autoantibodies appear to increase the likelihood of developing type 1 diabetes. The inflammatory response leads to destruction of the pancreatic β-cells and progressive loss of insulin secretion until reaching critically low levels or even complete insulin deficiency.

3. Vascular endothelium in type 1 diabetes

In children with diabetes risk HLA, signs of systemic endothelial cell activation can be seen already before the clinical onset of diabetes (Toivonen et al, 2004), suggesting it to be an early event in the disease process. Postmortem studies near the onset of type 1 diabetes have shown that class II HLA molecules may be abundantly expressed on vascular endothelial cells lining the capillaries and capillary sinusoids in the islets (Itoh et al., 1993). The upregulation of HLA is paralleled by strong expression of adhesion molecules (i.e. ICAM-1) in the same endothelial areas (Hanninen et al., 1992). These events, seemingly induced by circulating proinflammatory mediators, facilitate homing and migration of inflammatory cells such as T cells across the dysfunctional endothelium . Interaction between antigen-specific T-cells and antigen/HLA complexes on the endothelial cells surface induced a rapid transmigration of the T-cells across the endothelial cell layer (Greening et al., 2003). Similar changes may be found on the surface of endothelial cells of other vascular beds (Greening et al., 2003).This fits well with the clinical observation that type 1 diabetes is often comorbid with chronic autoimmune diseases in other organs such as gut (celiac disease) and thyroid

gland (autoimmune thyroiditis). These disorders also share some of the HLA DQ diabetes risk alleles. An activated endothelium could be the link.

It is well known that long-term exposure to hyperglycemia, hyperlipidemia and inflammation, all of which being important features of type 1 diabetes, is harmful to the endothelial cells, causing further endothelial dysfunction, and in the long run, accelerated atherosclerosis. Lymphocyte accumulation within the arterial wall is an important mechanistic component in the atherosclerotic process and contributes to endothelial cell injury and dysfunction. The endothelial injury, in turn, promotes additional immune events, including release of different chemokines and cytokines resulting in further transmigration of immune cells, and synthesis of C-reactive protein via liver activation by interleukin-6.

Recent study, assessing the relationship of genetic susceptibility with endothelial dysfunction in young patients with type 1 diabetes, found significant correlation between HLA-DQ 2/8, which confers the highest risk for developing type 1 diabetes, and cutaneous microvascular dysfunction (Odermarsky et al., 2007). This could imply, although its does not prove, a role for HLA in the pathogenesis of type 1 diabetes. Further studies at our center are under way to investigate whether such changes could be present already before the clinical onset of type 1 diabetes.

4. Exogenous risk factors and type 1 diabetes: Is vascular endothelium a link?

Putative environmental triggers include viruses, environmental toxins and foods, but it has been difficult to demonstrate a reproducible correlation between them and the development of type 1 diabetes (The environmental determinants of diabetes in the young (TEDDY) Study Group, 2008). Although appealing, there is no evidence to date of a direct interplay between infections and genetics in the causation of type 1 diabetes. the risk of developing T1D seems to increase with the number of infections experienced by an individual during the year preceding the onset of T1D. Although we currently lack the knowledge of the precise underlying mechanisms, there are other reports on similar associations between infectious recurrence and chronic diseases such as multiple sclerosis or rheumatoid arthritis. In some animal studies, the development of atherosclerotic plaque was accelerated by repeated infection. One possible mechanistic link between these chronic inflammatory diseases (e.g. atherosclerosis and T1D) and infection might be endothelial injury. Infections cause vascular endothelial dysfunction, which may persist for up to 1 year after the infectious illness. Mild respiratory infections (“common cold”) seem to aggravate arterial endothelial dysfunction in young patients with T1D. Those with increased recurrence of infections of this type are more susceptible to decreased carotid artery elasticity. The latter was earlier shown to be in part dependent on the functional integrity of endothelial cells. In atherosclerosis-susceptible mice, the degree of endothelial vasomotor dysfunction in skin microcirculation correlates with the number of pathogen inoculations (Odermarsky M, Liuba P unpublished data).

It has been shown that even mild viral infection causes vascular endothelial dysfunction, which may persist for up to 1 year after the infectious illness (Charakida et al., 2005). Infections promote the inflammatory environment needed for endothelial cell activation and upregulation of HLA. These changes could, if genetic susceptibility is present, contribute to homing, transmigration, and accumulation of inflammatory cells in certain tissues. In the

pancreas these microcirculatory changes could perhaps have a role in the pathogenesis of type 1 diabetes, but this is still hypothetical.

5. Endothelial function and dysfunction

The endothelial cells line the inner surface of all blood vessels, providing a metabolically active interface between blood and tissue. These cells modulate blood flow, nutrient delivery, coagulation and thrombosis, and leukocyte diapedesis. The endothelium synthesizes important bioactive substances. Of these, nitric oxide is the most potent vasodilator and protector of vascular function, inhibiting platelet activation and aggregation, preventing leukocyte adhesion and migration through the vessel wall, diminishing smooth muscle cell proliferation and migration, and counteracting adhesion molecule expression (Beckman et al., 2002). Nitric oxide is synthezised by the endothelial isoform of nitric oxide synthase. The process involves enzymatic conversion of L-arginine into nitric oxide and L-citrulline. The release of nitric oxide can be up- or downregulated by different factors. The hormone estrogen, physical exercise, and certain dietary factors are examples of upregulators, whereas smoking and oxidized low-density lipoproteins, via oxidative stress, are examples of downregulators (Michel & Vanhoutte, 2010).

Endothelial dysfunction is considered to be the first step in a long-lasting and complex development that leads to atherosclerosis. The dysfunction is a result of an imbalance in the redox-equilibrium towards oxidative stress leading to impaired nitric oxide bioavailability, either caused by its reduced synthesis or by increased breakdown via reactive oxygen species. (Versari et al., 2009). The dysfunctioning endothelium may produce other substances and mediators such as endothelin 1, thromboxane A_2, prostaglandin H and reactive oxygen species, with vasoconstricting, pro-inflammatory, and proatherosclerotic effects (Virdis et al., 2010).

Given the excess of inflammatory and oxidative stress in type 1 diabetes, the endothelium in individuals with type 1 diabetes is continually exposed to factors promoting the development of endothelial dysfunction. The hyperglycemia, excess free fatty acid release, and insulin resistance leads to adverse events within the endothelial cell (Beckman et al., 2002). Recent findings support the concept that genetically susceptible individuals, i.e. diabetes high-risk HLA, are more prone to develop endothelial dysfunction (Odermarsky et al., 2007) and ongoing studies are investigating whether this dysfunction in fact may precede the clinical onset of type 1 diabetes.

The generalized microvascular dysfunction in type 1 diabetes is an important mechanism in the development of these microvascular complications. Nephropathy, retinopathy and neuropathy are all related to damage to the small vessels of the kidney, retina and nerves. Significant associations have been reported between the different microvascular complications of type 1 diabetes; patients with one complication often develops a second one, suggesting common risk factors and pathogenetic mechanisms (Girach & Vignati, 2006).

Overt microvascular disease is however rare during childhood and adolescence. Early signs, such as increases in albumin excretion rates and glomerular filtration rates, renal hypertrophy, changes in retinal microvasculature and impaired autonomic nervous system function may be detectable in kids with type 1 diabetes and often progress during puberty. Microalbuminuria is the earliest stage of clinical nephropathy and is predictive of progression to overt diabetes nephropathy and, notably, of cardiovascular disease (Rossing et al., 1996).

6. Methods for evaluating endothelial function

The ability to detect endothelial dysfunction, before it progresses to overt vasculopathy, could facilitate the early diagnosis and management of high-risk individuals in childhood. There are several techniques that can be used, though they are not in clinical use to any higher extent. Here we will present two methods; flow-mediated dilatation and laser doppler flowmetry with iontophoresis, which are the ones used in our research.

6.1 Assessment of arterial dysfunction via flow-mediated dilatation of the brachial artery

Blood vessels respond to an increase in blood flow, or more precisely shear stress, by dilating. This phenomenon is called flow-mediated dilatation. The principal mediator for this is endothelium-derived nitric oxide. Assessment of flow-mediated dilatation of the brachial artery safely and non-invasively provides a measure of the systemic endothelial function. The brachial artery response to increased shear stress has been shown to correlate significantly with invasive testing of brachial (Irace et al., 2001) and coronary endothelial function (Andersson et al., 1995), as well as with the extent and severity of coronary atherosclerosis (Neunteufl et al., 1997), and carotid artery intima-media thickness (Gaeta et al., 2000).

Several factors affect the response to the increase in shear stress, including temperature, food, drugs and sympathetic stimuli, female hormonal status, among others, and when conducting a study using this technique you must take these confounding factors into consideration. Ultra sound systems used must be equipped with software for two-dimensional imaging, colour and spectral Doppler, an internal electrocardiogram monitor and a high-frequency vascular transducer. A straight segment of the brachial artery above the antecubital fossa is imaged in the longitudinal plane with the ultrasound probe securely fixed using a stereotactic clamp. A blood pressure cuff is then placed on the forearm and inflated to supra-systolic pressure. After cuff release, reactive hyperaemia results and is quantified using Doppler. The arterial diameter is recorded at end diastole using electrocardiographic gating to determine the response of the brachial artery to increase in flow. The flow-mediated dilatation is expressed as a percentage change of the arterial diameter from the baseline vessel size (Corretti et al., 2002; Thijssen et al., 2011). To control the smooth muscle cells ability to dilate the vessel, independently of the endothelium, and to determine maximum obtainable vasodilatation a dose of nitro-glycerine is administrated via spray or sublingual tablet.

6.2 Assessment of microvascular dysfunction via laser doppler flowmetry with iontophoresis in the skin

Iontophoresis is a non-invasive method of introducing charged substances across the surface of the skin by means of a small electric charge. The basic principle is that molecules of drugs in a solution that are positively or negatively charged will migrate across the skin under influence of an applied current according to the rule that like charges repel each other. The amount of drug delivered is dependent on the magnitude and duration of the current applied. The response in the skin vasculature is measured via a laser doppler device (Morris & Shore, 1996). The coherent light directed at the skin changes when it comes in contact with moving tissues (red blood cells) and the emerged light, i.e. skin perfusion, is measured by a photodiode.

Acetylcholine is the standard test drug for the assessment of endothelial function. The response to acetylcholine, using iontophoresis, correlates with diabetes duration and level of glycosylated haemoglobin (Khan et al., 2000). The mechanisms of acetylcholine-induced vasodilatation via ionphoresis remain debatable. In humans, nitric oxide appears to be the main mediator, but other endothelium-dependent vasodilators may contribute as well (Turner et al., 2008).
Sodium nitroprusside is a nitric oxide donor and acts directly, i.e. endothelium-independent, as a control on the smooth muscle cells causing vasodilatation. Cathodal current is used for delivering sodium nitroprusside.
The current for both substances is set to 100 μA for 20 seconds. For each of the substances to be tested five consecutive and equal doses are applied to generate dose-response curves. Baseline perfusion and changes in response to the substance are expressed as area under the curve.

7. The ”common soil” hypothesis-is this applicable in type 1 diabetes?

In 1995, Michael Stern put forward the “common soil” hypothesis, which suggests a shared genetic and environmental origin for type 2 diabetes and atherosclerosis (Stern, 1995). According to this hypothesis, infections leading to chronic inflammation could pertain to the group of environmental etiological factors. Indeed, the risk of developing type 1 diabetes – a condition associated with significant morbidity in cardiovascular diseases in adult life – could rise during viral infections (Blom et al., 1991). Moreover, the risk for childhood diabetes seems to increase in accordance with a higher number of infections during the year preceding diagnosis. Studies in rodent models of atherosclerosis suggest similar dose-dependent association between infection and vascular changes (Liuba et al., 2000; Tormakangas et al., 2005). Furthermore, diabetic patients are more vulnerable to viral infections due to defective lymphocyte-related immunity. In a previous cross-sectional study on diabetic children, we found that recurrent viral infections in the upper airways (“common cold”) during the past year had cumulative adverse effects on the elastic properties (i.e. compliance) of carotid arteries. In a multivariate analysis, the number of viral infections, along with age and plasma levels of glycosylated hemoglobin, significantly and independently predicted the decrease in carotid artery compliance (Odermarsky et al., 2008a). Although impaired carotid elasticity is generally regarded as a marker of early atherosclerosis, these findings do not necessarily imply causality to accelerated atherosclerosis. Prospective studies in children are currently in progress.

8. Prevention strategies in type 1 diabetes via vascular pathways?

Should vascular endothelial dysfunction prove to play a pivotal role in the pathogenesis of both type 1 diabetes and its associated vascular disease, it is then conceivable that combined endothelium-targeting and immunoregulatory strategies already in diabetes-risk individuals without overt type 1 diabetes (i.e. diabetes high-risk HLA individuals) might reduce not only the cardiovascular burden but also the prevalence of type 1 diabetes later in life. Dietary supplementation with L-arginine (substrate for nitric oxide synthesis via nitric oxide synthase), or antioxidants, in order to improve nitric oxide bioactivity, could for instance be relatively simple, risk-free strategy with potential benefit on endothelial dysfunction. Further studies are needed to provide additional mechanistic insights into the

gene-environment interaction on vascular endothelium and the timing and role of endothelial dysfunction in the development of type 1 diabetes and associated cardiovascular disease.

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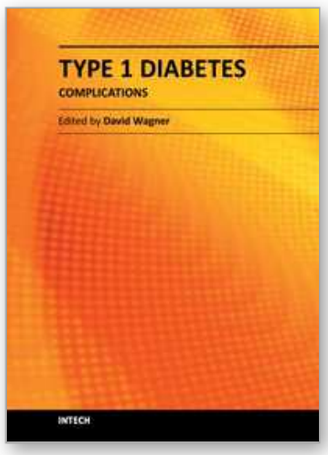

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This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology 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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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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