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Diabetes Complications in Childhood Diabetes—New Biomarkers and Technologies

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Abstract

A major challenge in preventing vascular complications in diabetes is the inability to identify high-risk patients at an early stage, emphasizing the importance of discovering new risk factors, technologies and therapeutic targets to reduce the development and progression of complications.

Promising biomarkers which may improve risk stratification and serve as therapeutic targets, include: uric acid, insulin sensitivity, copeptin, SGLT-2 and Klotho/FGF-23. Non-invasive measures of macrovasuclar disease in youth, include: 1) pulse wave velocity to examine arterial stiffness; 2) carotid intima-media thickness to evaluate arterial thickness; 3) cardiac MRI to investigate cardiac function and structure. Novel microvascular measures include: GFR by iohexol clearance using filter paper to directly measure GFR, retinal vascular geometry to predict early retinal changes and corneal confocal microscopy to improve detection of early nerve loss to better predict diabetic neuropathy.

Herein we will review technologies, novel biomarkers, and therapeutic targets in relation to vascular complications of diabetes.

Keywords

Type 1 diabetes; microvascular complications; macrovascular complications; continuous glucose monitor; artificial pancreas

Introduction

Cardiorenal complications are the leading cause of morbidity and mortality in type 1 diabetes [1]. While diabetic nephropathy remains the most common cause of end-stage renal

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Conflict of Interest

Petter Bjornstad declares that he has no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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disease (ESRD) in the Western world [2, 3], coronary artery disease is the single strongest determinant of mortality in type 1 diabetes [1, 4]. Diabetic sensorimotor polyneuropathy is also an important complication of diabetes that predisposes to neuropathic pain, sensory and autonomic dysfunction and limb amputation [5]. Diabetic retinopathy, another form of microvascular disease, represents the most common cause of new-onset blindness [6]. Major determinants of vascular complications in type 1 diabetes include glucose, blood pressure, and lipid control, but the literature suggests significant under-treatment of these risk factors in children and adolescents with diabetes [1, 7–11].

By the time macro- and microvascular complications manifest clinically, significant vascular injuries are well established and usually refractory to conventional therapeutic strategies [7, 12]. Current therapeutic strategies may slow but do not prevent the progression of vascular complications [9, 13, 14][15]. Identification of early phenotypes of vascular disease would potentially allow interventions to decrease the rate of progression and prolong the time to development of overt disease. The public health burden of type 1 diabetes is largely caused by the prevalence of vascular complications [1, 16], and for that reason there is a need for improved methods to identify people at risk for, and prevent the development and progression of, these complications. Accordingly, in this review, we examine the current evidence addressing novel mediators and therapeutic targets in type 1 diabetes.

Macrovascular disease

The mortality and morbidity of CVD are markedly increased in individuals with type 1 diabetes compared to the nondiabetic population [1, 7, 8]. Annually, up to 1–2% of young adults (28–38 years of age) with T1D develop CAD [4, 16, 17]. By their mid-forties, over 70% of men and 50% of women with T1D develop measureable coronary artery calcification (CAC) by CT scan [4, 16–18] - a marker of significant atherosclerotic plaque burden. It is increasingly recognized that atherosclerosis begins in early life [19, 20]. Long-term follow-up studies have demonstrated the importance of cardiovascular risk factors during childhood, with their presence increasing the likelihood of CVD in adulthood [21–23]. There is therefore a growing awareness of the importance of prevention of CVD risk factors early in the course of type 1 diabetes. Successful prevention strategies require accurate risk stratification of CVD in children and adolescents with type 1 diabetes. It is necessary to identify children with type 1 diabetes with the highest risk for CVD using objective and noninvasive studies. Advances in imaging techniques are needed to better identify early vascular changes through noninvasive imaging; including measures of arterial stiffness, impaired vasodilation and thickening of the artery wall.

Arterial stiffness has emerged as a useful marker of atherosclerosis in childhood and adolescence [24–26]. It is also increasingly recognized that youth with type 1 diabetes have increased arterial stiffness compared to healthy controls [27]. Measures of arterial stiffness including pulse wave velocity (PWV), augmentation index (AIx) and brachial distensibility (BrachD) have been shown to predict future CVD and all-cause mortality [24–26] (Table 1). In adolescents with type 1 diabetes, we recently reported an inverse relationship between achieving International Society of Pediatric and Adolescents Diabetes' targets for HbA1c, LDL-C, HDL-C, TG, BMI and BP and arterial stiffness (measured by PWV, AIx and

BracD) [28]. Furthermore, we have shown that apoB is strongly associated with arterial stiffness by PWV in adolescents with type 1 diabetes, and that measurement of apoB in addition to LDL-C may be helpful in stratifying CVD-risk in adolescents with type 1 diabetes and borderline LDL-C (100–129mg/dL) [29].

Atherosclerotic burden can also be assessed by artery intima-media thickness (IMT), which has been shown to predict CVD in adults [30]. Rodriguez et al. have shown that carotid IMT (cIMT) is significantly higher in adolescents with type 1 diabetes compared to non-diabetic controls (31). In adults, intensive therapy in the Diabetes Control and Complications Trial (DCCT), resulted in decreased progression of cIMT 6-years after the end of the trial [32].

Cardiac magnetic resonance imaging (CMR) is another novel method of non-invasively evaluating coronary artery disease, non-atherosclerotic myocardial damage (e.g. from microvascular disease), cardiac function and structure. A study with CMR in adults with type 1 diabetes with and without diabetic nephropathy, demonstrated a significant increase in right coronary artery mean and maximum thickness and plaque detection in type 1 diabetes with nephropathy compared to those without nephropathy [33, 34].

New biomarkers are revealing potential mechanisms responsible for the development of macrovascular disease in type 1 diabetes (Table 2). A greater understanding of these mechanisms may provide novel therapeutic targets to supplement the conventional therapies in preventing complications. Reduced insulin sensitivity is an increasingly recognized component of type 1 diabetes and is implicated in the pathogenesis of macrovascular disease [35]. We have previously demonstrated that reduced insulin sensitivity was associated with atherosclerosis in adults with type 1 diabetes [36]. The Metformin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) trial is a promising trial underway examining the benefits of metformin on vascular complications in type 1 diabetes (NCT01483560). The Effects of Metformin on Cardiovascular Function in Adolescents With Type 1 Diabetes (EMERALD, NCT01808690) is an ongoing double-blind randomized clinical trial with metformin to evaluate if metformin will improve tissue-specific insulin resistance in T1D adolescents using the hyperinsulinemic-euglycemic clamp technique, as well as improve vascular, cardiac, exercise and muscle mitochondrial function [37].

Increased neurohormonal activation is a key feature of macrovascular disease. Copeptin is a stable metabolite of vasopressin and the prognostic value of copeptin, as a marker of endogenous stress, has been reported for cardiovascular disease in several studies [38, 39]. Several studies have reported that plasma AVP levels are elevated in animals and patients with diabetes [40–42]. Recently, Riphagen et al. demonstrated that copeptin is associated with cardiovascular and all-cause mortality in adults with type 2 diabetes. Vasopressin is a particularly promising risk factor due to its modifiable nature [43]. Vasopressin activity can be suppressed by reducing salt intake and blocking AVP receptors by vaptans [43, 44]. Studies are needed to examine whether copeptin is an important risk factor for CVD in type 1 diabetes.

Microvascular disease

In addition to macrovascular disease, microvascular disease continues to cause morbidity and mortality; for example, diabetic nephropathy remains the leading cause of end-stage renal disease and dialysis in the United States [2, 14, 45], and diabetic retinopathy and diabetic sensorimotor polyneuropathy remain leading causes of new-onset blindness and limb amputations respectively [6, 46, 47].

Diabetic nephropathy

Early detection of diabetic nephropathy has a pivotal role in the prevention of end-stage renal failure in the prevention of end-stage renal failure in diabetes [48]. The appearance of microalbuminuria is often the earliest clinical sign of diabetic nephropathy, but the paradigm of early diabetic nephropathy has been further questioned over the past few years after the demonstration that microalbuminuria does not necessarily imply progressive nephropathy, and may in fact regress to normoalbuminuria (49, 50). Furthermore, markers of early DN prior to the renal function loss, such as renal hyperfiltration (glomerular filtration rate [GFR] ≥135mL/min/1.73m^2) and rapid GFR decline (annual GFR loss >3.3% or >3mL/min/1.73m^2) are thought to be stronger predictors of nephropathy progression in type 1 diabetes than albuminuria [3, 51–54]. For that reason, glomerular filtration rate (GFR) may be the most clinically relevant measure of kidney function in type 1 diabetes. The American Diabetes Association, National Kidney Foundation and International Society of Nephrology recommend annual measurement of estimated glomerular filtration rate (eGFR) to identify and monitor diabetic nephropathy [55–57]. The most state-of-the-art equations to estimate GFR for adults are the three recently published CKD-EPI equations: CKD-EPI Creatinine, CKD-EPI Cystatin C and CKD-EPI Creatinine and Cystatin C [58], and for children and adolescents are the combined Creatinine and Cystatin C equations (e.g. CKiD, Schwartz, Bouvet etc] [59]. The creatinine and cystatin-C based eGFR equations are associated with greater variability when eGFR >60 mL/min/1.73m^2 [58]. However, by the time eGFR is ≤60 mL/min/1.73m^2 almost half of renal function has already been lost [56]. For that reason, improved methods to easily and accurately measure GFR as well as changes in renal function in the normal and hyperfiltration range are needed [3, 60]. Gold-standard measures of GFR with iothalamate, iohexol or inulin clearance in type 1 diabetes are impractical and not routinely performed in clinical practice. Recently, a practical method of measuring GFR by iohexol clearance using dried capillary blood spots on filter paper was shown to accurately measure GFR in adults with type 1 diabetes and could be translated to screening for early kidney disease. This method is ideally suited for people with type 1 diabetes [61] in whom early detection of nephropathy is imperative to prevent early morbidity and mortality [62].

There are also several promising biomarkers and therapeutic targets worth mentioning (Table 2). Multiple studies have linked serum uric acid (SUA) levels to diabetic nephropathy development and accumulating data have suggested that lowering SUA prevents renal function loss in animal models of diabetes and in patients with type 2 diabetes [63, 64]. To determine the role of SUA lowering in patients with T1D, the multi-center double-blind randomized clinical trial “Preventing Early Renal Function Loss - PERL”, will test the

hypothesis that lowering SUA with allopurinol will prevent GFR decline measured by iohexol [65]. An additional study design innovation in PERL is the use of GFR (measured by iohexol) as the study end point allowing for assessment of therapy earlier in the pathophysiologic pathway.

Reduced insulin sensitivity is also implicated in the pathogenesis of diabetic nephropathy. We have previously demonstrated that insulin sensitivity predicts development of microalbuminuria and rapid eGFR decline by cystatin C over 6 years in patients with T1D [66], similar to data in the Epidemiology of Diabetes Complications study [67]. Despite the findings from the BARI-2D study [68] which showed no benefit of insulin sensitizing strategy on DN in subjects with type 2 diabetes, modification of insulin sensitivity is being investigated as a therapeutic target to reduce vascular complications in T1D, since both life style changes (diet and exercise) and drugs such as metformin can improve insulin sensitivity.

Sodium glucose co-transporter 2 (SGLT2) inhibitors are being investigated as a therapy to prevent progression of diabetic nephropathy in type 1 diabetes. SGLT2 inhibition with empagliflozin reduced HbA1c, but also significantly attenuated renal hyperfiltration to near normal GFR levels in patients with uncomplicated type 1 diabetes and did not lower GFR in those with normal baseline GFR [69]. Patients with type 1 diabetes also exhibited significant weight loss, HbA1c reductions and a decline in blood pressure [70–72]. Concern has been raised that the mechanism of action (glycosuria) may mask the typical hyperglycemia seen with insulin insufficiency and reduce awareness of developing ketonemia and impending diabetic ketoacidosis [73]; further study is required on this class of medications in people with type 1 diabetes.

Arginine vasopressin (AVP) may also play a role in the development of diabetic nephropathy. AVP modulates tubular cell growth thereby causing vasoconstriction of the renal microcirculation and in particular in the efferent arteriole [74, 75]. Furthermore, AVP infusion induces hypertension, glomerular hyperfiltration and albuminuria [42–44] and lowering the AVP concentration may provide renal protection [43, 44, 76], but requires study in humans. There is also evidence linking increased fluid intake with decreased risk for developing CKD [77]. Copeptin is a more stable peptide derived from the same precursor molecule as AVP, and appears to be a useful surrogate marker for AVP in the assessment of fluid and osmosis status in various diseases. Recently Boertien et al demonstrated copeptin predicts the estimated glomerular filtration rate decline in subjects with type 2 diabetes; however, there is little if any data on its ability to predict DN in subjects with T1D [78]. With the availability of AVP receptor antagonists (e.g. vaptans), AVP might also become a promising therapeutic target for diabetic nephropathy in the future.

As previously mentioned, part of the connection between diabetic nephropathy and macrovascular disease may be explained by dysregulation of Klotho and FGF-23 (Table 2). Klotho, a protein that is predominantly expressed in the distal tubule of the kidney, serves as a co-receptor for fibroblast growth factor 23 (FGF-23) [79]. It is thought that Klotho and FGF-23 work together to increase urinary phosphorus and calcium reabsorption, thereby in

health ensuring optimal concentration of calcium and phosphorus in bone and blood. Klotho and FGF receptor 1 and 3 are expressed in human arteries with downregulation in response to phosphorus and TNFα [79]. Klotho and FGF-23 signaling inhibits vascular calcification [79–81]. In contrast, decreased Klotho or Klotho resistance leads to increased vascular calcification [81]. Kidney disease is associated with decreased Klotho and/or Klotho resistance which leads to increased FGF23 concentrations and subsequent transformation of vascular smooth muscle cells to osteo- and chondrocytic cells with vascular calcification. Moreover, it is hypothesized that inflammatory states are also associated with Klotho deficiency and increased FGF23 levels [79], and that serum uric acid is a possible determinant of FGF23 metabolism [82]. Several published studies identified FGF23 as a risk factor for CKD progression [83]. In 177 patients with non-diabetic CKD, higher levels of cFGF23 and iFGF23 were independently associated with incident ESRD [84]. It is unknown whether this holds true for humans with type 1 diabetes, but recently a genetic deficiency of Klotho exacerbated early nephropathy in STZ-induced diabetes in mice [85]. Klotho and FGF-23 are not only promising biomarkers to risk stratify vascular disease in type 1 diabetes, but also a potential therapeutic agent, as Klotho administration has been shown to protect the kidney from ischemia-reperfusion injury [79, 86, 87]

Diabetic retinopathy

Diabetic retinopathy remains one of the most common microvascular complications in type 1 diabetes and is also a risk factor for other complications, with retinopathy being associated with several fold increases in the risk of cerebrovascular accidents (CVA) and CVD independent of other risk factors [3]. Data from Sydney, Australia show a decline in retinopathy in adolescents with type 1 diabetes from 1990 to 2009, which was associated with improved achievement of recommended lower glycemic targets and use of multiple daily injections and continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes [88]. Since diabetic retinopathy tends to be asymptomatic, regular screening in youth with type 1 diabetes is advised. The ADA recommends annual retinopathy screening once a child is 10 years old and has had type 1 diabetes for 3–5 years [89]. ISPAD recommends screening for retinopathy from 10 years of age, or at onset of puberty if this is earlier, with 2–5 years of diabetes duration [7]. The techniques used by general ophthalmologists and optometrists in the clinical setting may not have the resolution to detect early retinal changes in youth with type 1 diabetes. There is therefore a need for better methods to predict early DR. Improved imaging techniques and advances in computer-based retinal image analysis have allowed earlier identification of retinal changes in type 1 diabetes, and may also improve our understanding of retinal vascular parameters and diabetic retinopathy [90]. Benitez-Aguirre et al. demonstrated that retinal vascular geometry predicted incident retinopathy in young people with type 1 diabetes [91–93] (Table 1). These vascular geometry measures may serve as risk markers for diabetic retinopathy and provide insight into the early structural changes in diabetic microvascular complications [91–93]. The retina offers a unique opportunity to noninvasively and repeatedly examine the microvasculature in vivo.

Diabetic neuropathy

Diabetic sensorimotor polyneuropathy (DSP) is the most common complication of type 1 diabetes with important clinical sequelae including neuropathic pain, sensory and autonomic dysfunction and limb amputation [94, 95]. In fact, the lifetime risk of DSP and ulceration is respectively 50% and 25% [5, 94–96]. In adolescents with type 2 diabetes in the SEARCH for Diabetes in Youth study prevalence of diabetic peripheral neuropathy approached the rates reported in adults with type 2 diabetes. The prevalence of DPN was significantly higher in youth with type 2 compared with those with type 1 diabetes (25.7 vs. 8.2%, $p<0.0001$) [97]. Identification of DSP at an early stage of disease will aid in risk stratification and facilitate the selection of subjects for targeted interventions [46, 47, 98].

Routinely performed clinical techniques such as neurological examination, assessment of vibration perception or insensitivity to the 10 g monofilament only evaluate advanced neuropathy. Unfortunately non-invasive techniques that examine early neuropathy including neurophysiology and quantitative sensory testing are highly subjective while more objective techniques, such as skin biopsies to quantify nerve fiber density, are invasive and not widely available. For that reason, there is a need for non-invasive and accurate methods to identify early disease. Corneal confocal microscopy is an emerging ophthalmic technique which allows quantification of corneal nerve morphology and diagnosis of peripheral neuropathy (Table 1). Ding et al. showed that individuals with diabetes and early retinal arteriolar abnormalities are more likely to have DPN independent of other major vascular risk factors, supporting the hypothesis that early microvascular dysfunction, evident in the retina, is an independent risk factor for DPN [99]. Sivaskandarajah et al. demonstrated that small nerve fiber structural morphology assessed by *in vivo* corneal confocal microscopy correlated well with functional measures of small nerve fiber injury [100]. Petropoulos et al reported that corneal confocal microscopy noninvasively demonstrates corneal nerve loss, which predicts neuropathy [101]. Sellers et al. performed a pilot study in children to evaluate the acceptability and feasibility of corneal confocal microscopy to detect early diabetic neuropathy in children. They demonstrated that corneal confocal microscopy is a rapid, non-invasive and well-tolerated technique that may prove to be useful for the assessment of early neuropathy in children. Detection of diabetic neuropathy at its earliest stages is important as improvement in risk factors may slow or prevents its progression and/or promote nerve regeneration [102].

Other promising techniques to evaluate early retinopathy include ultrasound assessment of posterior tibial nerve. Riazi et al. performed a cross-sectional study evaluating the association between size of the posterial tibial nerve on ultrasound and the presence and severity of diabetic sensorimotor polyneuropathy, and demonstrated a strong association, which may support the role of ultrasound as a point-of-care screening tool for DSP [103]. Point-of-care nerve conduction evaluation is being developed. Lee et al demonstrated excellent reliability and acceptable accuracy with point-of-care sural nerve conduction device for identification of diabetic neuropathy [104]. More recently, cooling detection threshold accurately detected early neuropathy [105].

Technologies and diabetic complications

Improved glucose control is the best proven method to prevent complications of type 1 diabetes [106–108]. Intensive blood glucose control in the DCCT reduced the risk of retinopathy by 76%, nephropathy by 50% and neuropathy by 60% [108–111]. For that reason, continuous glucose monitors and an artificial pancreas are logical efforts to optimize glycemia and prevent vascular complications related to hyperglycemia.

Fear of hypoglycemia is recognized as the most important obstacle in the path to achieve good glycemic control in the clinical setting. Continuous blood glucose monitoring system is an important aid in the management of type 1 diabetes and an essential prerequisite for closed loop systems. The superiority of continuous glucose monitors (CGMs) over self-monitoring of glucose in reducing the time spent in hypoglycemia has been demonstrated [13]. Although CGM use is currently low, it is associated with lower HbA1c in some age-groups, especially when used more frequently [112]. Significant progress has been made on artificial pancreas technology recently [113]. For example, low glucose suspend is currently available [114] and predicted low glucose suspend is in development [115]. Additionally, in two random-order, crossover studies glycemic control was superior with a bi-hormonal closed loop artificial pancreas compared to an insulin pump for 5 days in 20 adults and 32 adolescents with type 1 diabetes [116]. Patients with type 1 diabetes at a diabetes camp who were treated with an artificial-pancreas system also had less nocturnal hypoglycemia and tighter glucose control than when they were treated with insulin pumps [117].

Conclusion

A major challenge in preventing vascular complications in type 1 diabetes relates to the accurate identification of high risk patients at an early stage when injuries may be susceptible to intervention. By the time macro- and microvascular complications manifest clinically, significant vascular injuries are well established and usually refractory to conventional therapeutic strategies. For that reason, identifying risk factors and biomarkers associated with vascular complications will help us understand the mechanisms underlying the development and progression of micro- and macrovascular complications.

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** Of high importance

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Table 1

Measures of early micro- and macrovascular disease in type 1 diabetes

Outcome:	Surrogate:
Atherosclerosis/macrovascular disease	Arterial stiffness • Pulse wave velocity • Brachial distensibility • Augmentation index Arterial thickness • Intima-media thickness Arterial stenosis • Cardiac MRI
Diabetic nephropathy	Glomerular filtration rate • Measured by iohexol-clearance using dried blood spots • Estimated by creatinine and cystatin C based equations (CKiD and Bouvet)
Diabetic retinopathy	Retinal vascular geometry
Diabetic neuropathy	Corneal confocal microscopy Point-of-care nerve conduction Nerve ultrasound Cooling detection threshold

Table 2

Emerging markers and therapeutic targets of vascular complications of type 1 diabetes

Biomarker:	Randomized control trials:
Serum uric acid	The preventing early renal function loss (PERL) allopurinol study (NCT01575379)
Insulin sensitivity	Metformin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) trial (NCT01483560)
	Effects of Metformin On Cardiovascular Function In Adolescents with Type 1 Diabetes (EMERALD) study (NCT01808690)
	Metformin Therapy for Overweight Adolescents With Type 1 Diabetes (NCT01881828)
Sodium glucose co-transporter 2	Safety and Efficacy of Empagliflozin (BI 10773) in Type 1 Diabetes Mellitus Patients With or Without Renal Hyperfiltration (NCT01392560)
Copeptin	--
Klotho/FGF-23	The COMBINE Study: The CKD Optimal Management With BInders and NicotinamidE (NCT02258074)