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Review

Subclinical vascular disease in patients with diabetes is associated with insulin resistance

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ABSTRACT

Patients with diabetes experience increased cardiovascular risk that is not fully explained by deficient glycemic control or traditional cardiovascular risk factors such as smoking and hypercholesterolemia. Asymptomatic patients with diabetes show structural and functional vascular damage that includes impaired vasodilation, arterial stiffness, increased intima-media thickness and calcification of the arterial wall. Subclinical vascular injury associated with diabetes predicts subsequent manifestations of cardiovascular disease, such as ischemic heart disease, peripheral artery disease and stroke. Noninvasive detection of subclinical vascular disease is commonly used to estimate cardiovascular risk associated to diabetes. Longitudinal studies in normotensive subjects show that arterial stiffness at baseline is associated with a greater risk for future hypertension independently of established risk factors. In patients with type 2 diabetes, vascular disease begins to develop during the latent phase of insulin resistance, long before the clinical diagnosis of diabetes. In contrast, patients with type 1 diabetes do not manifest vascular injury when they are first diagnosed due to insulin deficiency, as they lack the preceding period of insulin resistance. These findings suggest that insulin resistance plays an important role in the development of early vascular disease associated with diabetes. Cross-sectional and prospective studies confirm that insulin resistance is associated with subclinical vascular injury in patients with diabetes, independently of standard cardiovascular risk factors. Asymptomatic vascular disease associated with diabetes begins to occur early in life having been documented in children and adolescents. Insulin resistance should be considered a therapeutic target in order to prevent the vascular complications associated with diabetes.

1. Introduction

Asymptomatic patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) suffer generalized vascular disease that is not fully explained by insufficient glycemic control or conventional cardiovascular risk factors, such as smoking and hypercholesterolemia.

Subclinical vascular damage present in patients with diabetes includes impaired vasodilation, reduced arterial elasticity, increased arterial intima-media thickness, and increased calcification of the arterial wall. Early vascular injury is not present in patients with T1D when they are first diagnosed whereas asymptomatic vascular lesions are apparent in patients with newly diagnosed T2D. These findings suggest that insulin resistance has a crucial effect on the development of early vascular disease in subjects with diabetes. Patients with T2D endure a lengthy phase of insulin resistance before the clinical onset of the disease and asymptomatic vascular injury develops long before the diagnosis of diabetes. In contrast, patients with T1D lack the preceding phase of insulin resistance, as they are first diagnosed based on insulin deficiency [1–8]. Numerous investigations confirm the association between insulin resistance and subclinical vascular injury in patients with diabetes beyond traditional cardiovascular risk factors. Asymptomatic vascular injury associated with insulin resistance predicts clinical manifestations of cardiovascular disease, such as ischemic heart disease, stroke, and peripheral artery disease.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CACT1, Coronary Artery Calcification in type 1 diabetes; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HDL-c, cholesterol associated with high-density lipoproteins; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-c, cholesterol associated with low-density lipoproteins; MESA, Multiethnic Study of Atherosclerosis; NAFLD, non-alcoholic fatty liver disease; PDHS, Penn Diabetes Heart Study; QUICKI, quantitative insulin sensitivity check index; SIRCA, Study of Inherited Risk of Coronary Atherosclerosis; T1D, type 1 diabetes; T2D, type 2 diabetes.

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Patients with diabetes and subclinical vascular damage sustain worse cardiovascular prognosis compared with healthy subjects [9–16].

2. Subclinical vascular disease in patients with type 2 diabetes

2.1. Impaired vascular reactivity in patients with type 2 diabetes

Nitric oxide is a gas synthesized by the endothelial cells that induces relaxation of smooth muscle cells and subsequent arterial vasodilation. Acetylcholine enhances the endogenous production of nitric oxide by the endothelium whereas glyceryltrinitrate (nitroglycerin) and sodium ntroprusside are exogenous sources of nitric oxide. An increase in arterial blood flow induces adaptive vasodilation that has been attributed to endogenous production of nitric oxide by endothelial cells [17].

Resting forearm blood flow is comparable in patients with T2D and control subjects, but the normal increase in blood flow in response to acetylcholine or methacholine is attenuated in patients with T2D compared to control subjects [17–20]. Likewise, patients with T2D show impaired forearm flow-mediated vasodilation compared to healthy individuals. Further, flow-mediated vasodilation is impaired in normotensive and normoglycemic first-degree relatives of patients with T2D compared to control subjects [21–24]. In a cross-sectional study including 800 asymptomatic adults with no clinical evidence of vascular disease (102 patients with T2D), multivariate analyses show that diabetes is an independent predictor of reduced vasodilatation in response to nitroglycerin [25]. In patients with T2D, vasodilation in response to exogenous donors of nitric oxide (such as sodium nitroprusside and nitroglycerin) has been found blunted [17–19,23,25,26] or similar [18,21,27,28] to control subjects. In patients with T2D, intensive glycemic control did not improve forearm flow-mediated vasodilation compared to usual glycemic control in a randomized trial, suggesting that other factors than glycemia are important to explain the development of early vascular dysfunction associated with diabetes [29].

Reduced vascular reactivity in patients with T2D has been consistently associated with insulin resistance evaluated by different methods, independently of known cardiovascular risk factors, suggesting that insulin resistance has an important effect on diabetes-related subclinical vascular disease [18,22,23,27,30–32]. Insulin resistance, assessed by a modified steady state plasma glucose method using octreotide acetate, has been found to be the sole predictor of flow-mediated vasodilation in patients with T2D. High steady state plasma glucose levels (insulin resistance) were independently associated with defective flow-mediated vasodilation [28]. Likewise, insulin resistance evaluated by euglycemic hyperinsulinemic clamps is associated with impaired flow-mediated vasodilation in adolescents with T2D compared to control subjects [31]. Insulin resistance estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index is also independently associated with impaired flow-mediated vasodilation in patients with T2D free of insulin therapy [30]. Consistently, insulin resistance (estimated by 2-h plasma glucose level during an oral glucose tolerance) was associated with impaired flow-mediated dilatation of the brachial artery in patients with T2D. Linear regression analysis showed a negative correlation between flow-mediated vasodilation and insulin resistance [23]. Further, in normotensive normoglycemic first-degree relatives of patients with T2D, stepwise multiple regression analysis showed an association between insulin resistance, evaluated by hyperinsulinemic euglycemic clamps, and blunted flow-mediated vasodilation, independently of classic cardiovascular risk factors. Flow-mediated vasodilation was more attenuated in more insulin-resistant individuals. Patients with T2D and insulin-resistant relatives showed similar reduction of flow-mediated vasodilation [22]. Network meta-analyses confirm the association between insulin resistance and blunted vascular reactivity and reveal a progressive impairment in flow-mediated vasodilation from an overweight status through T2D [32]. Impaired arterial vasodilation in response to methacholine in patients with T2D has also been found independently associated with insulin resistance, evaluated by hyperinsulinemic euglycemic clamps. Regression analysis revealed an inverse correlation between insulin resistance and vasodilatation in response to methacholine [27]. Consistently, defective vasodilation in response to acetylcholine was independently correlated with higher triglyceride and lower cholesterol associated with high-density lipoprotein (HDL-c) level (reflecting insulin resistance) in patients with T2D [18]. The effect of metformin versus placebo on acetylcholine-mediated vasodilation has been investigated in patients with diet-treated T2D. Insulin resistance was assessed by the HOMA-IR index. Stepwise multivariate analysis revealed that insulin resistance was the sole predictor of acetylcholine-mediated blood flow. Metformin treatment improved both insulin resistance and acetylcholine-stimulated blood flow compared to placebo with a strong statistical link between these variables, suggesting a central role of insulin resistance in the pathogenesis of early vascular dysfunction in patients with T2D [33].

2.2. Increased arterial stiffness in patients with type 2 diabetes

Increased arterial stiffness involving aorta, femoral, carotid, and brachial arteries has been consistently documented in asymptomatic patients with T2D compared to healthy subjects [6,8,11,26,34–39]. Reduced arterial elasticity in patients with T2D has been confirmed across ethnic groups in a biracial African American and Caucasian study population, the Atherosclerosis Risk in Communities (ARIC) study [8]. Increased arterial stiffness has been detected in children and adolescents with T2D without clinical manifestations of cardiovascular disease [40]. In population groups including patients with T2D and subjects with normal glucose tolerance, T2D has been associated with increased carotid, femoral, and brachial arteries stiffness, compared to normal glucose tolerance, after adjustment for conventional cardiovascular risk factors [6,37]. Prospective studies in normotensive subjects have shown that increased arterial stiffness precedes the development of hypertension and predicts future cardiovascular events [41–45].

Insulin resistance (or its clinical expression, the metabolic syndrome) has been repeatedly associated with increased arterial stiffness in patients with T2D [26,46]. In 1995, results from the ARIC study suggested for the first time that insulin resistance was associated with arterial stiffness in a biracial sample of African American and Caucasian participants with and without T2D. Fasting hyperinsulinemia was a strong predictor of several arterial stiffness indexes in multivariate analyses. In addition, serum insulin showed a synergistic association with triglycerides to predict arterial stiffness [8]. The independent association between insulin resistance and increased arterial stiffness has been confirmed in adults and adolescents with T2D in studies that quantify insulin resistance with hyperinsulinemic euglycemic clamps [31,38,46]. Likewise, a profound effect of insulin resistance evaluated by the HOMA-IR index on vascular compliance has been observed in adolescents with T2D. Patients with insulin resistance show increased arterial stiffness compared to control subjects, independently of confounding factors [40].

Clinical manifestations of insulin resistance have been associated with increased arterial stiffness in patients with T2D as well. Indigenous Australians (a population group with high frequency of T2D) experience higher arterial stiffness compared to European

Australians. Metabolic syndrome components (reflecting insulin resistance) cluster with Indigenous participants and contribute to explain increased arterial stiffness in this population group [47]. In Indigenous Australians with and without T2D, obesity, defined either by fat mass, waist circumference, weight, or body mass index (BMI), is associated with increased arterial stiffness, suggesting that insulin resistance plays a role reducing arterial elasticity [48]. In patients with T2D, microalbuminuria (an expression of insulin resistance) is also associated with increased arterial stiffness independently of conventional cardiovascular risk factors. Asymptomatic T2D patients with microalbuminuria show higher arterial stiffness compared to T2D patients with normal urinary excretion of albumin. Microalbuminuria is an independent determinant of arterial stiffness in multiple linear regression analysis, after adjustment for conventional cardiovascular risk factors [49]. Likewise, T2D patients with increased albumin/creatinine ratio (≥3 mg/mmol) had higher arterial stiffness compared to those with normal urinary excretion of albumin. Multiple linear step-down regression analysis showed that the albumin/creatinine ratio was an independent predictor of arterial stiffness [50]. Arterial stiffness is higher in T2D patients with hypertension (reflecting a greater degree of insulin resistance) compared to normotensive T2D patients with similar glycemic control [51]. In patients with T2D and control subjects, systolic blood pressure and post-prandial glucose are positively correlated with arterial stiffness while plasma adiponectin level is negative correlated, suggesting that insulin resistance is associated with arterial stiffness [52].

Several studies have revealed that arterial stiffness deteriorates progressively across the spectrum of glucose intolerance, from normal glucose tolerance to T2D. Arterial elasticity declines with worsening insulin resistance independently of traditional cardiovascular risk factors [6,40,53,54]. The Hoorn study is a population-based cohort that investigated the association between impaired glucose tolerance and arterial stiffness in patients with and without T2D. Arterial stiffness occurs in patients with insulin resistance before the diagnosis of T2D, independently of conventional cardiovascular risk factors and glycemic control [6]. In a study that examined the association between insulin resistance and arterial stiffness in normal-weight, obese and T2D adolescents, arterial stiffness was highest in the T2D patients, followed by the obese and lowest in the normal-weight adolescents [40]. Similarly, arterial stiffness increased across groups from lean to obese to T2D young subjects (10–24 years) in a cross-sectional study. In multivariate models, status as obese or obesity-associated T2D was an independent predictor of arterial stiffness after adjusting for cardiovascular risk factors [53]. In patients with hypertension and different degree of insulin resistance estimated by the HOMA-IR index, arterial stiffness showed a progressive increment from normal glucose tolerance to T2D after adjustment for confounding factors [54].

2.3. Increased intima-media thickness of the arterial wall in patients with type 2 diabetes

Numerous investigations have consistently documented that asymptomatic patients with T2D show increased carotid intima-media thickness compared to healthy subjects and that this early atherosclerotic lesion is associated with insulin resistance independently of classic cardiovascular risk factors [1,2,4,21,24,55–62]. Similarly, increased intima-media thickness of the aortic wall has been observed in patients with T2D compared to healthy controls [61]. Increased carotid intima-media thickness is already observable in newly diagnosed T2D patients, indicating that vascular disease begins to develop before the clinical onset of T2D, during the preceding phase of insulin resistance [1,2,4]. In subjects with and without T2D, increased carotid intima-media thickness is associated with carotid plaques and arterial stenosis [57] and inversely associated with the ankle brachial index [60], after adjustment for cardiovascular risk factors. Prospective cohort studies show that increased carotid intima-media thickness at baseline predicts independently coronary artery calcification [59] and cardiovascular events [62] in asymptomatic patients with T2D. Similarly, in patients with T2D free of cardiovascular disease, increased brachial artery intima-media thickness is associated with coronary artery calcification, after adjusting for traditional cardiovascular risk factors. The coronary artery calcification score is higher in patients with thicker brachial artery intima-media [24].

Multiple investigations have established that age is an independent predictor of carotid intima-media thickness in patients with T2D and healthy subjects. Carotid intima-media thickness increases with age, independently of traditional cardiovascular risk factors. Age-related insulin resistance probably contributes to widen the arterial wall [1,49,55,57,63].

In South Indian subjects with and without T2D, selected from the Chennai Urban Population Study, multivariate linear regression analysis showed that age and diabetes were the major risk factors for carotid intima-media thickness in the whole population [4]. In patients with T2D, no correlation between serum cholesterol and carotid intima-media thickness has been observed [2].

In patients with T2D, a number of studies indicate that insulin resistance evaluated by different approaches is associated with increased arterial intima-media thickness independently of conventional cardiovascular risk factors. In 1997, the association between insulin resistance and carotid intima-media thickness in patients with T2D and healthy controls was first evaluated. Insulin resistance was assessed by computing the rate of glucose disappearance from plasma after intravenous insulin injection. Multiple regression analysis showed that insulin resistance was associated with carotid intima-media thickness independently of established cardiovascular risk factors [58]. Consistently, insulin resistance was an independent predictor of carotid intima-media thickness in patients with T2D when insulin sensitivity was assessed with a frequently sampled intravenous glucose tolerance test [63]. The association between common carotid intima-media thickness and insulin resistance was evaluated in patients with recently diagnosed T2D and control subjects selected from a population-based study. Insulin sensitivity was measured by the quantitative insulin sensitivity check index (QUICKI) and the HOMA-IR index. Multiple regression analyses show that insulin resistance was a major determinant of carotid intima-media thickness. Patients with insulin resistance had a 5-fold risk for severe carotid atherosclerosis compared with more insulin-sensitive individuals (those in the highest QUICKI tertile) [64].

A variety of components of the metabolic syndrome (the clinical expression of insulin resistance) have been associated with increased intima-media thickness of the arterial wall in patients with T2D, including hypertension, obesity, hypertriglyceridemia, and reduced HDL-c level [49,55,57,63–65]. In addition, multiple regression analyses show that microalbuminuria (reflecting insulin resistance) is independently associated with carotid intima-media thickness in patients with T2D free of vascular disease. Carotid intima-media thickness is higher in T2D patients with microalbuminuria compared with T2D patients with normal urinary excretion of albumin, after adjustment for conventional cardiovascular risk factors [49]. The association between non-alcoholic fatty liver disease (NAFLD) and carotid intima-media thickness has been investigated in patients with diet-controlled T2D. Insulin resistance was evaluated by the HOMA-IR index. T2D patients with NAFLD had a markedly greater carotid intima-media thickness than T2D patients without NAFLD, after adjusting for potential

confounders (ANCOVA analysis). However, additional adjustment for the HOMA-IR score abolished any significance. Consistently, in fully adjusted multivariate linear regression models, HOMA-IR score was independently associated with carotid intima-media thickness, whereas NAFLD was not. HOMA-IR score was the strongest predictor of carotid intima-media thickness. In patients with diet-controlled T2D, insulin resistance explains the increased carotid intima-media thickness in the presence of NAFLD [66].

2.4. Increased arterial calcification in patients with type 2 diabetes

T2D is independently associated with increased coronary artery calcification [67]. Asymptomatic patients with T2D experience increased coronary artery [68] and carotid artery [69] calcification compared to nondiabetic subjects, after adjustment for conventional cardiovascular risk factors. In addition, T2D is associated with increased carotid plaque burden compared with controls [69]. In patients with T2D free of cardiovascular disease, the coronary artery calcification score is inversely related to forearm flow-mediated vasodilation. Coronary calcification is greater in T2D patients with lower brachial flow-mediated vasodilation [24]. In patients with T2D, age is independently associated with coronary artery calcification scores [59,70]. Prospective studies show that subclinical arterial calcification predicts cardiovascular events and mortality in patients with T2D, independently of established cardiovascular risk factors. The independent association between coronary artery calcification and cardiovascular events is similar across ethnic groups, including African American, Asian, Hispanic and Caucasian [71–75].

Insulin resistance is associated with increased arterial calcification in patients with T2D, independently of standard cardiovascular risk factors. The Penn Diabetes Heart Study (PDHS) and the Study of Inherited Risk of Coronary Atherosclerosis (SIRCA) are cross-sectional community-based investigations on Caucasian subjects without clinical evidence of cardiovascular disease. PDHS participants were T2D patients while SIRCA recruited nondiabetic participants with a family history of premature cardiovascular disease. HOMA-IR was calculated in patients with T2D excluding those (15%) on insulin therapy. In patients with T2D, insulin resistance was associated with coronary artery calcification scores after adjusting for traditional cardiovascular risk factors. Insulin resistance evaluated by HOMA-IR values was associated with coronary artery calcification beyond standard cardiovascular risk factors in patients with T2D [76]. The risk of incident coronary artery calcification associated with insulin resistance was investigated in nondiabetic subjects at study entry in a longitudinal study analyzed retrospectively. Coronary artery calcification was measured at baseline and four years later. Insulin resistance was assessed by HOMA-IR index. Over 4 years, subjects who progressed to T2D showed the highest incidence of coronary artery calcification. More insulin-resistant subjects showed increased risk for incident coronary artery calcification after adjustment for standard cardiovascular risk factors. In contrast, subjects with lower HOMA-IR showed no increased risk for incident coronary artery calcification even in subjects who developed T2D [7]. The DIACART ("Diabète et Calcification Arterielle") study is a cross-sectional trial that investigated the association between metformin use and lower limb arterial calcification in patients with T2D. Metformin-treated T2D patients had reduced arterial calcification score compared to metformin-free T2D patients, after adjusting for confounding variables [77].

The prospective relationship between the metabolic syndrome and coronary artery calcification was investigated in the Multi-ethnic Study of Atherosclerosis (MESA) that included African American, Asian, Caucasian, and Hispanic adults free of cardiovascular disease at baseline. Patients with metabolic syndrome showed greater incidence and progression of coronary artery calcification compared with control subjects without the metabolic syndrome [68]. In participants of the PDHS and the SIRCA, the presence of metabolic syndrome was associated with coronary artery calcification score in patients with T2D, after adjustment for cardiovascular risk factors, suggesting an association between insulin resistance and coronary artery calcification [76]. In large cross-sectional studies of subjects with and without T2D, the presence of the metabolic syndrome increased the risk of coronary artery calcification, independently of standard cardiovascular risk factors. The prevalence and extent of coronary artery calcification was higher in subjects with metabolic syndrome compared to those without this condition [78,79]. In a cross-sectional study of patients with T2D free of coronary heart disease, multivariate models show a strong independent association between coronary artery calcification and waist-to-hip ratio and systolic blood pressure, suggesting that coronary artery calcification is particularly linked to insulin resistance in patients with T2D [80]. Likewise, obesity ($BMI \geq 30\ kg/m^2$) was associated with increased carotid calcification in patients with T2D and control subjects, compared with $BMI < 25\ kg/m^2$ [69].

3. Subclinical vascular disease in patients with type 1 diabetes

Like T2D patients, asymptomatic subjects with T1D suffer subclinical vascular dysfunction that includes impaired vasodilation, increased arterial stiffness, increased arterial intima-media thickness, and arterial calcification. Early vascular injury in patients with T1D predicts future cardiovascular events. Traditional cardiovascular risk factors or poor glycemic control do not fully explain the structural and functional damage to the arterial wall, but insulin resistance has been independently associated with subclinical vascular disease in patients with T1D. Unlike patients with T2D who develop vascular disease long before the clinical diagnosis of diabetes, early vascular dysfunction in patients with T1D appears after the clinical onset of T1D [13].

3.1. Defective vascular reactivity in patients with type 1 diabetes

Resting blood flow measured at the brachial artery is comparable in patients with T1D and control subjects, but patients with T1D experience impaired vascular reactivity in response to stimuli such as increased blood flow, methacholine, or nitroglycerin [21,81,82].

Forearm flow-mediated vasodilation has been consistently found reduced in patients with T1D compared with control subjects [16,82–90]. Reduced vascular reactivity at the brachial artery occurs at an early age, having been documented in children and adolescents with T1D within the first decade of diabetes onset [16,82,84,88,89]. A longitudinal study reveals that flow-mediated vasodilation impairs overtime. At baseline, 43.6% of children and adolescents with T1D presented impaired flow-mediated vasodilation. After a follow-up period of at least 1 year, altered values were observed in 61.5% of patients and initial values worsened in 74.3% of them [89]. Intravenous infusion of L-arginine (the substrate for endothelial nitric oxide synthase) did not improve brachial artery reactivity in patients with T1D [85]. The forearm vasodilative response to methacholine [81] and nitroglycerin [83–86] is also defective in patients with T1D compared to healthy subjects. Impaired vascular reactivity in asymptomatic patients with T1D is not accounted for by glycemic control or traditional cardiovascular risk factors, including smoking, total cholesterol, and cholesterol associated with low-density lipoproteins (LDL-c) levels [81,83,84,87].

3.2. Increased arterial stiffness in patients with type 1 diabetes

Numerous studies have consistently documented increased arterial stiffness in patients with T1D compared with nondiabetic controls. Reduced arterial elasticity in patients with T1D has been observed early in life, in children with average disease duration of 4.3 years. Increased arterial stiffness in patients with T1D has been documented in brachial artery, aorta, femoral artery, carotid artery and radial artery [13,16,88,91–98]. Several studies show that the presence of T1D is an independent predictor of increased arterial stiffness, after adjusting for traditional cardiovascular risk factors [13,93,95,98,99]. A beneficial effect of intensive versus conventional glycemic control on arterial stiffness has not been documented in patients with T1D. The Diabetes Control and Complications Trial (DCCT) is a prospective study that examined whether intensive insulin therapy with the goal of maintaining glycemia close to the normal range could decrease vascular complications in patients with T1D. The mean follow-up period was 6.5 years. At the close of DCCT in 1993, most patients continued to participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term observational study of the original DCCT cohort. In T1D patients from the DCCT/EDIC cohort, there was no differential effect of intensive versus conventional insulin therapy on aortic distensilility [99].

Increased arterial stiffness in patients with T1D is associated with insulin resistance independently of standard cardiovascular risk factors. The SEARCH CVD study is a prospective cohort trial that investigated the association of insulin sensitivity with progression of arterial stiffness in young patients with T1D. Insulin sensitivity was assessed at baseline by the estimated glucose disposal rate, an index calculated by an equation that has been validated using direct measurement of glucose disposal rate from euglycemic hyperinsulinemic clamps. The estimated glucose disposal rate assesses insulin sensitivity in patients with T1D. Measurement of pulse wave velocity was performed at baseline and at 5-year follow-up to quantify changes in arterial stiffness. Linear mixed models adjusted for risk factors showed that baseline insulin resistance was associated with increased progression of arterial stiffness, after adjustment for cardiovascular risk factors, indicating that insulin resistance is an important risk factor for increased arterial stiffness over time in youth with T1D [100]. A number of investigations have documented that microalbuminuria and components of the metabolic syndrome, such as BMI, waist-to-hip ratio, blood pressure, and HDL-c level (reflecting insulin resistance) are independently associated with increased arterial stiffness in patients with T1D [13,15,95,98].

3.3. Increased intima-media thickness of the arterial wall in patients with type 1 diabetes

Increased carotid intima-media thickness is a very consistent finding in asymptomatic patients with T1D compared to healthy individuals. After adjustment for potential confounders, patients with T1D show higher carotid intima-media thickness for any age group. Increased carotid intima-media thickness has been identified in children and adolescents with T1D as early as 5 years after the diagnosis of diabetes, suggesting that asymptomatic youth with T1D endure early vascular disease. T1D is an independent risk factor for increased arterial intima-media thickness [3,5,14,21,55,90,95–97,101–106]. No association between increased carotid intima-media thickness and glycemic control (HbA_{1c}) has been found in patients with T1D [14,101,107–109]. Participants in the DCCT/EDIC cohort had carotid intima-media thickness measurements at EDIC years 1, 6, and 12. Differences in carotid intima-media thickness progression between DCCT intensive and conventional treatment groups were examined. At the internal carotid artery, there were no differences between treatment groups in the progression of the carotid intima-media thickness. At the common carotid artery, progression of the intima-media thickness from EDIC years 1–6 was 0.013 mm less in the intensive group than in the conventional group, but change from years 6–12 was not different. The difference between groups in the change of common carotid intima-media thickness from years 1–12 was not significant after adjustment. Therefore, intensive glycemic treatment slowed common intima-media thickness progression by 0.013 mm for 6 years after the end of DCCT but did not affect common carotid intima-media thickness progression thereafter (6–12 years) [107]. Consistently, no beneficial effect on carotid intima-media thickness following intensive glycemic control was found in a group of children and adolescents with T1D [14]. Increased carotid intima-media thickness in patients with T1D is not associated with plasma level of total cholesterol or LDL-c [14,101–103,105,109]. Similarly to healthy individuals and T2D patients, multiple regression analyses in a number of investigations show that carotid intima-media thickness is independently associated with age in patients with T1D [3,102,108–110]. In addition, an independent linear regression of carotid intima-media thickness and age has been observed in a group of subjects with and without diabetes, suggesting that age is an important factor that determines intima-media thickness of the arterial wall [55].

Several cross-sectional and prospective studies have consistently documented that insulin resistance, assessed by the estimated glucose disposal rate or its clinical manifestations, is an independent predictor of increased carotid intima-media thickness in patients with T1D, after adjustment for standard cardiovascular risk factors. Prospective studies show that carotid intima-media thickness is independently associated with hypertriglyceridemia, low HDL-c concentration, and microalbuminuria [3,5]. Prospective and cross-sectional investigations reveal that obesity estimates such as BMI, waist circumference, and waist-to-hip ratio are independently associated with increased carotid intima-media thickness in multivariate analyses [95,105,107–110]. Similarly, increased carotid intima-media thickness is associated with arterial hypertension (reflecting insulin resistance) in patients with T1D, after adjustment for cardiovascular risk factors [5,14,95,101,103,108,109,111]. A cross-sectional study reveals that NAFLD (reflecting insulin resistance) is associated with increased carotid intima-media thickness in patients with T1D independently of conventional cardiovascular risk factors. T1D patients with NAFLD have markedly greater carotid intima-media thickness (and frequency of carotid plaques) compared to T1D patients without NAFLD, after adjusting for potential confounders [108]. Elevated daily insulin dosage (reflecting insulin resistance) increases the risk of developing carotid intima-media thickness in patients with T1D, compared to low insulin doses, after adjustment for confounders. Insulin resistance increases insulin requirement to achieve metabolic control and promotes carotid intima-media thickness in patients with T1D [111,112]. A cross-sectional study reveals that insulin resistance, assessed by the estimated glucose disposal rate, is an independent predictor for increased carotid intima-media thickness and presence of carotid plaques in asymptomatic women with T1D. More insulin-resistant T1D patients have increased carotid intima-media thickness and carotid plaques, after adjusting for cardiovascular risk factors [109].

3.4. Increased coronary artery calcification in patients with type 1 diabetes

Coronary artery calcification scores are higher in patients with T1D compared to control subjects, although their prevalence varies

in different studies. Coronary artery calcification scores ≥300 Agatston units have been found to occur in 68% of patients with T1D versus 14% in controls [113]. In patients with T1D from the DCCT/EDIC cohort, the prevalence of coronary artery calcification >0 and > 200 Agatston units is 31.0 and 8.5% respectively [114]. The prevalence of coronary artery calcification increases with age in patients with T1D from 11% before age 30 years to 88% in individuals aged 50–55 years [115]. Concurrent arterial calcification of both carotid and coronary arteries has been found in 53% of patients with long-term T1D (range 29–48 years) [116]. Longitudinal studies show that subclinical coronary artery calcification is an independent predictor of subsequent cardiovascular events in patients with T1D [115,117,118]. Intensive versus conventional glycemic control does not substantially improve the extent or progression of coronary artery calcification in patients with T1D [114,118].

Insulin resistance is a risk factor for coronary artery calcification in patients with T1D, independently of cardiovascular risk factors. The association between insulin resistance and coronary artery calcification in patients with T1D was first documented by the Coronary Artery Calcification in type 1 diabetes (CACT1) study, a prospective cohort trial that followed patients with T1D and nondiabetic control subjects free of cardiovascular disease at study entry. Insulin resistance was assessed by the estimated glucose disposal rate, calculated by a formula previously validated in hyperinsulinemic euglycemic clamps. Multivariate regression analysis showed that insulin resistance was associated with the extent of coronary artery calcification both in patients with T1D and in nondiabetic control individuals, independently of cardiovascular risk factors [119]. In a subsample of CACT1 study participants, insulin resistance assessed by hyperinsulinemic euglycemic clamps predicted the extent of coronary artery calcification in patients with T1D as well as nondiabetic subjects, independently of cardiovascular risk factors [120]. The longitudinal association between insulin resistance and coronary artery calcification was investigated by the CACT1 study in patients with T1D and control subjects without cardiovascular disease at baseline, followed for 6 years. Baseline insulin resistance assessed by the estimated glucose disposal rate was associated to both the extent and progression of coronary artery calcification in subjects with and without T1D, independently of cardiovascular risk factors. Greater insulin sensitivity at baseline conferred protection from the development of coronary artery calcification over 6-years follow-up, suggesting that insulin resistance is an important factor in the development of coronary artery calcification [121].

Similar results are obtained when insulin resistance is assessed by indirect estimates [114,122]. In patients with T1D free of coronary artery disease at baseline, multiple logistic regression analyses show that higher insulin dose and higher BMI (reflecting insulin resistance) are associated with progression of coronary artery calcification, after adjustment for cardiovascular risk factors. Higher insulin dose independently increased the risk of progression of coronary artery calcification, so that an increment in daily insulin dose of 0.2 units raised the risk of progression of coronary artery calcification more than sevenfold [122]. In the DCCT/EDIC cohort, triglyceride level, waist-to-hip ratio, and hypertension (reflecting insulin resistance) are independently associated with prevalence of coronary calcification. Neither total cholesterol nor LDL-c levels correlated with coronary artery calcification whereas a negative correlation with HDL-c was observed [114].

4. Summary

Asymptomatic patients with T1D and T2D endure extensive vascular disease that is not accounted for by traditional cardiovascular risk factors or inadequate glycemic control. Subclinical vascular disease in patients with diabetes predicts cardiovascular morbidity and mortality and includes impaired vascular reactivity, reduced arterial distensibility, increased arterial intima-media thickness, and calcification of the arterial wall that involves aorta, carotid, femoral, and coronary arteries. Similarly to nondiabetic subjects, insulin resistance is independently associated with subclinical vascular disease in patients with diabetes.

Consistently, ageing is associated with arterial stiffness, increased arterial intima-media thickness and increased arterial calcification, probably due to age-related insulin resistance.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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