Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Review Article

Atherosclerosis Early Detection in Type 1 Diabetes Mellitus

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ARTICLE INFO

Keywords:
Rype I diabetes mellitus;
Atherosclerosis;
Ankle–Brachial Index.

ABSTRACT

Cardiovascular disease caused by accelerated atherosclerosis is a major cause of disease and often premature death in T1DM patients. Risk management is very important. A sensitive and specific instrument is needed to assess atherosclerosis. Currently, methods for determining atherosclerosis involve risk calculations based on vascular risk factors, ankle-brachial index (ABI), intima-media artery thickness, coronary artery calcification (CAC), and angiography, as well as optical coherence tomography (OCT). and intravascular ultrasonography (IVUS) for more advanced lesions

1. Introduction

The incidence of ST-segment elevation myocardial infarction (STEMI) has increased in developing low-income countries, while it has declined in developed high-income countries in recent decades.[1] According to the American Heart Association, the prevalence is 3% in the United States.[2]

Acute myocardial infarction mortality has fallen from 20% in the late 1980s to 5–7% in normal practice in the United States and Europe, with considerable regional variability owing to differences in use and manner of reperfusion.[1] The average 30-day mortality following acute myocardial infarction was 13.6 percent in 2018, which included 2363 institutions. Rural hospitals had higher mortality.[3] Large infarct area, late hospitalization, and the lack of tissue-level reperfusion after revascularization remain etiology for mechanical complications, hemodynamic instability, and pump failure.[2]

2. T1DM Incidence and Prevalence

T1DM had an incidence of 15 per 100,000 individuals and a prevalence of 6.9 per 10,000 people in Asia, respectively. In Africa, the incidence of T1DM was 8 per 100,000 individuals, whereas the prevalence was 3.5 per 10,000 people. T1DM had an incidence of 15 per 100,000 people in Europe and a prevalence of 12.2 per 10,000 people. While in America, T1DM had an incidence of 20 per 100,000 people and a prevalence of 12.2 per 10,000. Globally, T1DM had an incidence of 15 per 100,000 individuals and a prevalence of 9.5 per 10,000 people.[1]

Table 1. Prevalence and incidence of type 1 diabetes in the world.[1]

	Prevalence per 10.000	Incidence per 100.000
World	9.5	15
Asia	6.9	15
Africa	3.5	8
Europe	12.2	15
America	12.2	20

According to data from the Indonesian Paediatric Society (IPS), 1220 children in Indonesia were diagnosed with T1DM in 2018. Between 2000 and 2010, the incidence of T1DM in children and adolescents increased about sevenfold, from 3.88 to 28.19 per 100 million population. According to data from 2003 to 2009, girls have a 60% greater prevalence of T1DM than boys in the age category 10-14 years. In 2017, an estimated 71% of children with T1DM were initially diagnosed with Diabetic Ketoacidosis (KAD), higher than 63% in 2015 and 2016. It is believed that there's still a significant number of T1DM patients who are either undiagnosed or misdiagnosed when they present to the hospital for the first time. The incidence of T1DM among children in Indonesia is unknown due to the difficulties of collecting national statistics.[2]

Along with classic T1DM, there is a slower-onset type of antibody-positive T1DM known as latent autoimmune diabetes in adults (LADA), typically diagnosed between the ages of 25 and 40. The majority of articles concern atherosclerosis in type 2 diabetes mellitus (T2DM), with a few focusing on T1DM and LADA. A recent cross-sectional investigation discovered that LADA patients had much more (subclinical) carotid plaque than age- and sex-matched individuals with classic T1DM or T2DM.[3]

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https://doi.org/10.21776/ub.hsj.2022.003.03.3
Received 9 March 2022; Received in revised form 30 April 2022; Accepted 15 June 2022
Available online 30 July 2022

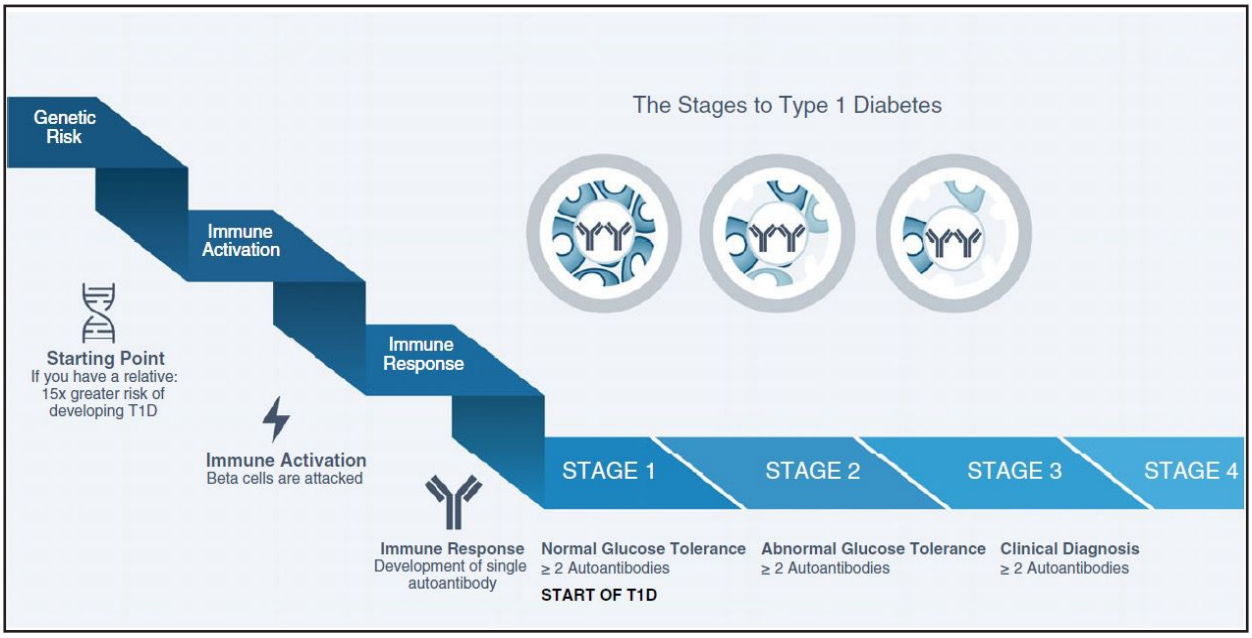

Figure 1. The stages of T1DM (DiabetesTrialNet.org). A proportion of individuals with increased genetic risk of T1DM progress at variable rates to immune activation and the development of islet autoimmunity. The development of two or more islet antibodies (stage 1) ultimately progresses to dysglycemia (stage 2) and then to symptomatic T1DM (stage 3).[4]

3. T1DM Stages and Chronic Complications

Type 1 diabetes is classified into four stages, as illustrated in Figure 1.
Stage 1: Multiple islet antibodies, normal blood glucose levels, and no symptoms.
Stage 2. Antibodies to many islets, elevated blood glucose, and presymptomatic.
Stage 3: Islet autoimmunity, hyperglycemia, and symptomatology.
Stage 4: Prolonged type 1 diabetes.[4]

Diabetes has chronic consequences that affect the vascular and nerves. Atherosclerosis results in peripheral arterial disease (PAD), cerebrovascular disease (CVD), and coronary artery disease (CAD), with CVD being the leading cause of death among people with diabetes.[5] Atherosclerosis is the build-up process of lipid-rich plaque in arteries. At the same time, arteriosclerosis is the process of stiffness of arteries caused by aging, which may develop concurrently with or without atherosclerosis.

Individuals with T1DM microvascular problems are at an increased risk of developing CVD. Numerous guidelines and experts suggest active risk factor management for those with T1DM. The latter have clinical manifestations of macrovascular or microvascular illness, including those with intermediate or high CVD risk without apparent problems. The latter category includes individuals with T1DM who are at least 40 years old, even if they do not have vascular abnormalities, or who are at least 30 years old and have had T1DM for more than 15 years (without vascular complications).[6,7]

The phases of atherosclerosis are summarized in Figure 2. Individuals may also have CVD risk factors well before developing T1DM. Once T1DM is established, the milieu generates and/or aggravates risk factors, causing vascular damage. Atherosclerosis does not often manifest clinically until a thrombosis, embolus, or plaque rupture occurs.[8]

Current management has resulted in a decrease in the number of fatalities and admissions associated with atherosclerosis-related conditions. Between 1998 and 2013, a Swedish registry survey (includes 36.869 T1DM patients and 184.110 non-diabetic healthy subjects) found that all-cause mortality rates in T1DM decreased by 29% (vs. 23% in healthy subjects), CVD death rates decreased by 42% (vs. 38% in healthy subjects), and CVD admissions decreased by 36% in T1DM. Hospital admissions for heart failure have not reduced in T1DM. T1DM death rates remain between two and eightfold compared to the overall population, with CVD becoming a significant contributing factor.(9) Additionally, another piece of information from Swedish studies with a median follow-up 8.3year period from 1998 to 2011 revealed that the relative acute myocardial infarction (AMI) and coronary heart disease (CHD) rates of death in T1DM ranged from 5 to 33 fold in females and 2 to 15 fold in males. The excess was reduced in males with adequate blood glucose control and good kidney function but persisted in females with normal glycemia and no renal impairment.[10]

4. Atherosclerosis Characteristics in T1DM Patients

Arteriosclerosis refers to the stiffening (related to aging) of arterial walls, while atherosclerosis results in the narrowing of arteries due to plaque development. Atherosclerosis, primarily manifested as fatty streaks, appears to develop in adolescence, notably in Westernized societies. Atherosclerosis develops earlier, advances more rapidly, and reaches farther distally in people with diabetes than in non-diabetics. This, along with a decreased production of artery collaterals, may render bypass surgeries challenging, though not unfeasible. In T1DM, plaques are much more located centrally, have more fibrous content, more lipid-rich content, are softer and inflamed (with macrophage and T-cell infiltration); contain more apoptotic cells surrounding a necrotic core, exhibit increased thrombosis, and immunostain for AGE-products; and are far more fragile and susceptible to rupture. The last one frequently results in a catastrophic episode.[11]

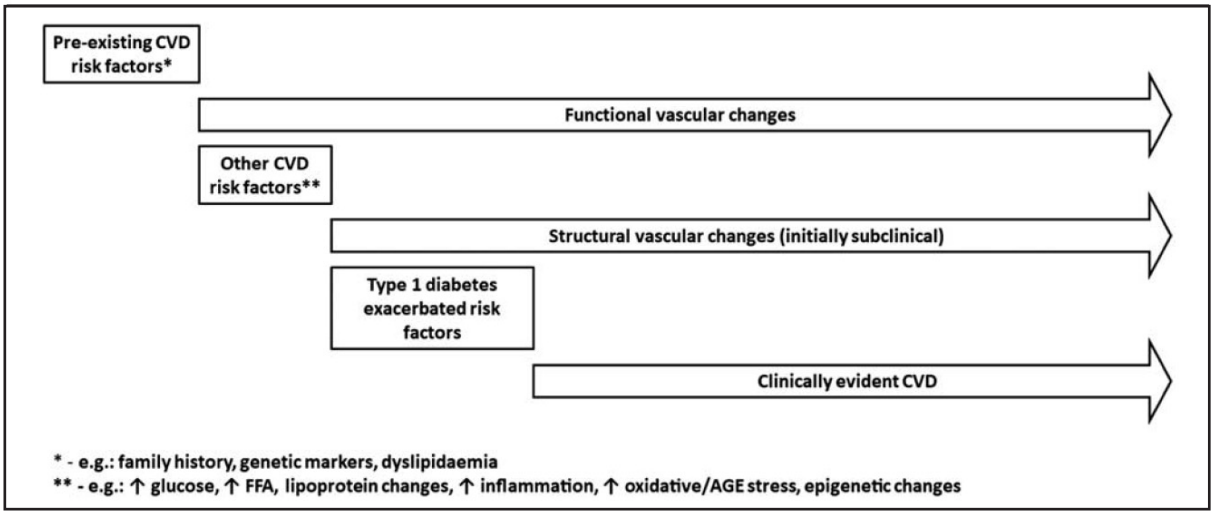

Figure 2. Stages in the development of atherosclerosis in type 1 diabetes. AGE, advanced glycoxidation end product; CVD, cardiovascular disease; FFA, free fatty acid.[8]

Diabetics might experience clinical events with a lower detectable atherosclerotic load, probably due to increased plaque instabilities and the limits of existing detection methods. In diabetes, arterial walls are thicker, as measured by increasing IMT, and plaque and arterial media are frequently more calcified.[12]

4. Atherosclerosiss Risk Factors in TIDM

4.1 Genetics

Nowadays, neither genetic variable is being used therapeutically to estimate atherosclerosis risks in T1DM, despite high relationships with specific genotypes, such as haptoglobin 2/2 (hp 2-2). Hp 2-2 was not linked to incident CAD or myocardial infarction (MI) in the complete Diabetes Control and Complications Trial (DCCT) group. However, in pre-specified analytical subgroup analyses, it was observed those with Hp 2-2 had a higher risk of MI in the second cohort.[13]

4.2 Sex

Women having T1DM lost their relative cardioprotective ability. A long-term (with a median follow-up of 12.9 years) FinnDiane research showed associations between CAD and stroke occurrences and sex and nephropathy state. Men and women experienced equal rates of events for every stage of nephropathy, with increased rates linked with deteriorating kidney function. Compared to non-diabetics, the standardized incidence rate (SIR) for CAD was 5.3 in men and 17.2 in women with T1DM. SIR ratio of women to men rose as kidney function deteriorated. The SIR for stroke was 5.0, which was comparable between men and women. Women to men ratios of SIR for stroke were 0.8, 1.3, 1.6, and 1.7, respectively, as kidney function deteriorated. The SIR for CAD was 3.5 in persons with normal kidney function and 1.6 for stroke; thus, individuals with normal kidney function are at elevated risk of vascular events.[14]

4.3 Age of Onset of T1DM

Individuals that developed T1DM before the age of 10 seemed to have the highest HRs for all-cause and CVD mortality of 4.1 and 7.4, successively, 30 for CAD, 31 for AMI, and 6.4 for stroke, in a study of 27.195 T1DM and 135.178 non - diabetic individuals monitored between 1998 to 2012 for a median of ten years. For individuals diagnosed with T1DM before the age of ten, the average loss of life years was 17.7 for women and 14.2 for men. HRs were significantly decreased in T1DM patients when first diagnosed between 26–30 years of age.[15]

Microvascular problems are recognized as risk factors for atherosclerosis by clinical guidelines. It may be because numerous risk conditions, including dyslipidemia, inflammation, and hypertension, are exacerbated by renal impairment. Cardiac Autonomic Neuropathy (CAN) also has been linked to cIMT and hypertension in patients with T1DM.[16]

4.4 Lipoproteins

In T1DM patients, elevated total and LDL cholesterol rates and low high-density lipoprotein cholesterol (HDL-C) rates are related to and predictive of CVD and microvascular consequences. While normal or increased HDL-C levels frequently accompany T1DM, HDL could be defective in terms of cholesterol metabolism, anti-inflammatory, anti-clotting, and vasodilatory activities. Qualitative alterations in lipoproteins, such as oxidation, glycation, advanced-glycation-end products, and immunological complex formation contribute to lipoprotein pathogenicity in diabetes.[17] Lipoprotein sub-classes assessed by nuclear magnetic resonance (NMR) were also linked with and predictive of carotid intima-media thickness (cIMT) and CAC in T1DM.[18]

4.5 Glycaemia

The Diabetes Control And Complications Trial And The Epidemiology Of Diabetes Interventions And Complications (DCCT/EDIC) trial established a correlation between lower HbA1c levels and improved IMT (especially in teenagers), CAC, and later macrovascular outcomes. Hypoglycemia is related to a higher risk of atherosclerosis, with possible reasons including enhanced oxidative stressor, inflammatory response, endothelial dysfunction, and thrombogenic tendencies.[8] Glucose variability (GV) is a risk factor for microvascular and macrovascular problems. In T1DM and T2DM, long-term GV is a significant risk factor for chronic outcomes.

Increased GV has been linked to decreased flow-mediated vasodilation, CAN, increased oxidative stress, and a worse classical vascular risk profile in T1DM.[19]

4.6 Hypertension

Ambulatory (24-hour) blood pressure measurement has been shown to improve the assessment and treatment of hypertension and therefore is advocated by several national organizations. The initial sign of aberrant blood pressure in T1DM patients is a phenomenon called 'non-dipping,' or the absence of a typical nighttime drop in blood pressure compared to daylight. In a cross-sectional investigation of 140 T1DM patients, hypertension was frequently diagnosed (25%) with ambulatory blood pressure monitoring and was linked to increased arterial stiffness.[20]

4.7 Inflammation

In 277 T1DM patients, rates of intracellular adhesion molecule (ICAM) and vascular cell adhesion molecule-1 (VCAM-1) predict the incidence of hypertension and arterial stiffness up to 20 years afterward.[21] Inflammation at the systemic level, as measured by high-sensitivity C-reactive protein and plasma matrix metalloproteinase-8 levels, was associated with the development of flow-mediated vasodilation (FMD), carotid IMT (cIMT), and carotid compliance in children with T1DM over two years of follow-up.[22]

5. Assessment Methods For Atherosclerosis

5.1 Arterial Intimal-Medial Thickness

cIMT is typically aided by software that detects the edges. Of the arterial wall. Ultrasound measurements of arterial distensibility and wall shear stress are also attainable. IMT measurements are non-invasive, without pain, and require no radiation or anesthesia. They are also relatively inexpensive. Its quantification can help guide decisions about additional examinations, surgery, or risk factor management. Both cIMT and plaque are higher in T1DM compared to seemingly healthy non-diabetic subjects. There are some observed sex disparities, even among T1DM adolescents. In 314 T1DM adolescents of 13.7 years mean age, T1DM duration of 5.5 years, HbA1c 8.4%, and 97% on intensive diabetic care, 19.5% had an increased mean cIMT. Males with diabetes had a greater mean cIMT than non-diabetic males, but not females. There were no plaques on any individual.[23]

Blood pressure, diabetes duration, smoking habits, age, increased body mass index (BMI), total cholesterol and LDL-C, and albumin excretion level have all been linked to or predict cIMT and plaque in T1DM subjects. Even though it is a frequently utilized research instrument, there are certain drawbacks. There are some concerns about whether cIMT would not function consistently well in the overall population to enhance risk classification on an individual basis but may be examined for intermediate-risk asymptomatic patients. The major diabetes guidelines organizations do not suggest regular screening for asymptomatic individuals with type 1 diabetes.[8]

The aorta, rather than the carotid, could be a better target for adolescent research, as it is frequently the first area of atherosclerosis. The carotid artery, aorta, brachial artery, and femoral artery were examined using ultrasonography in 38 adolescents with T1DM, with 13 years mean age, and 38 healthy subjects. In T1DM, the aortic and femoral artery IMTs were significantly increased, but the carotid and brachial IMTs remained unchanged.[24]

5.2 Flow-Mediated Dilatation (FMD)

Research suggests that altered brachial artery FMD responses are a typical vascular presentation in young children with T1DM, predisposing them to have more significant carotid artery IMT. This finding supports the concept that endothelial dysfunction is indeed a risk factor for atherosclerosis and contributes to the etiology of pre-diabetic macrovascular disease. Wiltshire et al. investigated FMD in 36 T1DM children with 14 years mean age and an average duration of diabetes of fewer than 6 years, as well as in 20 healthy control subjects. Compared to control subjects, these diabetic children without diabetes sequelae had impaired endothelial function. Donaghue et al. previously revealed in a study of twenty teenagers with T1DM that juvenile diabetics with clinical presentation have impaired endothelium and smooth muscle function compared to healthy controls. Only one previous research assessed both FMD response and carotid IMT in teenagers with T1DM concurrently. Singh et al. discovered no difference in carotid IMT across diabetes and healthy teenagers, while the T1DM group had a reduced FMD. Jarvissalo et al. observed that, while the endothelial function is damaged within the first decade of T1DM, a rise in carotid IMT occurs only after a significantly more extended exposure period to the diabetic milieu.[25]

5.3 Coronary Artery Calcification

An individual with T1DM has a 2 to 7-fold more significant chance of cardiovascular disease, which is not entirely explained by conventional risk factors. Additionally, glycemic fluctuation and obesity play a substantial role. Additionally, as demonstrated in many long-term trials, a considerable percentage of this elevated risk is linked to hyperglycemia. However, less than five years of research may not be sufficient to justify this impact.[26] For instance, the Diabetes Control and Complications Trial (DCCT), which established the critical role of glycemic control in avoiding microvascular complications of T1DM, was initially unable to demonstrate an apparent decrement in macrovascular or cardiovascular episodes between patients receiving intensive diabetes treatment. This failure to attain statistically significant results was most likely attributable to the research cohort's young age and the study's minimal incident rate. Nevertheless, a considerable benefit of intensive treatments was subsequently proven, with individuals receiving intensive treatment experiencing a 42% decrease in cardiovascular episodes over a median of 17 years. The EDIC study, a follow-up analysis to the DCCT study, established that the group receiving intensive treatment for a median of 6.5 years during DCCT saw a 45% decrease in any cardiovascular episodes during the subsequent 10.5 years of follow-up.[27] Table 2 summarizes the rationale pros and cons of routine CAC testing for screening asymptomatic patients for subclinical atherosclerosis. The reasoning cons simply because of the additional expenditure, exposure to radiation, and discomfort associated with CAC testing against other data collected. The most reasonable explanation for statin medication is that its efficacy has been thoroughly demonstrated for most individuals using only conventional risk factors. The most persuasive justification of CAC scan screening in asymptomatic subjects with T1DM is that this testing can precisely identify those who might profit from specific anti-atherosclerotic medication or those who may not. A list of frequently asked questions regarding CAC scanning is provided in Table 3.[26]

5.4 Pulse Wave Velocity (PWV)

In a T1DM trial cohort, 633 patients with T1DM with a median follow-up of 6.2 years. The purpose of this investigation is to establish a link between arterial stiffness,

Table 2. Pros and Cons of Screening for Subclinical Atherosclerosis Using Coronary Artery Calcium Scanning.[26]

Pros: factors in favor of CAC scanning	Cons: factors against routine CAC scans
Elevated CAC scores (>100) predict those with the highest likelihood of a cardiovascular event.	Prospective, double-blind, placebo-controlled clinical trial data are lacking on the utility of using CAC score alone as the indication for statin therapy.
CAC scanning offers superior discrimination and reclassification of individuals at risk for cardiovascular disease beyond the information provided by traditional risk factors, providing an indication of who should and who should not receive treatment.	CAC scanning exposes patients to ionizing radiation, although in very low doses (similar to mammography).
A negative CAC scan (0 score) provides a reliable indication that individuals are at a very low risk for a cardiovascular event over the next 5 years and therefore may not require treatment.	CAC scanning requires utilization of medical resources and may be more inconvenient to the patient than a simple laboratory draw.
CAC score predicts future ASCVD events more accurately than coronary artery angiography in asymptomatic patients.	CAC scanning is currently not covered by most medical insurance.

Table 3. Summary of Questions Addressed in the Text.[26]

Issue for asymptomatic type 1 diabetes	Recommendation in text
Are diabetic patients at greater risk with the same calcium score?	Yes, but increased events do not become evident for at least 5 years
At what age should CAC scan be first ordered in type 1 diabetes?	Between 30 and 40 years of age depending on risk factors (bp, lipids, A1C, fam. Hx, obesity)
Should CAC scan be ordered before starting statins?	Yes, to provide a baseline to assess progression and to withhold Rx if 0
How low an LDL should be the goal to reverse ASCVD?	Less than 50 mg/dL to include all individuals
Is an LDL-c below 50 mg/dL safe?	Yes–no, untoward effects have been observed in multiple studies
Do statins increase CAC?	Yes, but this change does not obscure unfavorable progression of the CAC score after starting statins
At what progression rate of CAC score is ASCVD inhibited?	Less than 15%/year
When should a CAC scan be repeated?	3–5 years to assess progression, depends on score
Does a CAC scan improve ASCVD risk behaviors?	Yes, knowledge of (+) coronary score motivates individuals
What does a CAC scan cost?	Usually between $0 and $200 in most U.S. cities
Is the CAC scan cost-effective?	Yes, for intermediate-risk individu

as determined by carotid-femoral pulse wave velocity (cf-PWV), and the progression of adverse events, such as advancement of albuminuria, decrease in estimated glomerular filtration rate (eGFR), a composite renal endpoint, cardiovascular episodes, and mortality. Elevated cf-PWF was related to an increased chance of advancements of albuminuria, reduction in eGFR, and the composite renal outcome. Cf-PWV was also associated with cardiovascular events and mortality from any cause but not independently of prior cardiovascular disease. cf-PWV measurement may well have a potential function in T1D risk classification.[29]

5.5 Peripheral Arterial Disease

An investigation includes T1DM patients of a total of 289 without symptoms, and normal leg arterial pulses identified aberrant ABI values <0.9 or >1.2 in 6% and 26% successively. Toe brachial index and ultrasonography were used to analyze those with aberrant ABI for subclinical PAD and/or carotid plaques, with a prevalence of 12.8% silent PAD. Among those with PAD, 4.8% had the carotid disease; thus, using the ABI test, when screening 3 T1DM patients without symptoms, the odds will be 1 patient with subclinical PAD. When screening, 7 T1DM patients will detect 1 patient with carotid disease.[28]

6. Atherosclerosis Screening Recommendation In T1DM Patients

Screening for chronic complications can be divided into microvascular complications and macrovascular. Microvascular complications include nephropathy, retinopathy, and neuropathy. Complications regarding the great vessels are coronary heart disease, cerebrovascular disease, and peripheral vascular disease (claudication, infection/gangrene, amputation). Screening recommendations are listed in Table 4.[30]

7. Conclusion

Cardiovascular disease, caused by accelerated atherosclerosis, is the leading cause of illness and premature death in T1DM patients. At the moment, risk equations based on vascular risk factors, arterial IMT, ABI, CAC, and PWV are used for assessing atherosclerosis. Risk calculations, including novel clinical, biochemical, and molecular testing, as well as vascular MRI and molecular imaging, are all evolving research tools. There is currently insufficient data to evaluate early atherosclerosis. More epidemiological and medical research are warranted to enable the translation into medical practice of reliable methods to detect, monitor, and treat T1DM patients with early atherosclerosis.

Table 4. Screening recommendations and risk factors for vascular complications in children with T1DM (ISPAD 2018).[30]

	When to commence screening?	Screening methods	Risk Factors
Nephropathy	11 years with 2-5 years of diabetes duration	Urinary albumin/creatinine ratio	Hyperglycaemia, high BP, Lipid abnormalities, smoking
Retinopathy	11 years with 2-5 years of diabetes duration	Fundal photography or mydriatic ophthalmoscopy	Hyperglycaemia, high BP, lipid abnormalities, Higher BMI
Neuropathy	11 years with 2-5 years of diabetes duration	History, Physical examination Clinical tests	Hyperglycaemia, Higher BMI, age, diabetes duration, genetics
Macrovascular disease	11 years with 2-5 years of diabetes duration	Lipid profile every 2 years, BP annually	Hyperglycaemia, High BP, Lipid abnormalities, Higher BMI, Smoking

8. Declarations

8.1. Ethics Approval and Consent to participate
Not applicable.

8.2. Consent for publication
Not applicable.

8.3. Availability of data and materials
Data used in our study were presented in the main text.

8.4. Competing interests
Not applicable.

8.5. Funding source
Not applicable.

8.6. Authors contributions
Idea/concept: SW. Design: SW. Control/supervision: NK, MSR, AF. Data collection/processing: SW. Analysis/interpretation: NK, MSR, AF. Literature review: NK, MSR, AF. Writing the article: SW. Critical review: NK, MSR, AF. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

8.7 *Acknowledgements*
We thank to Brawijaya Cardiovascular Research Center.

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