

## Effect of glycemic control on markers of subclinical atherosclerosis in patients with type 2 diabetes mellitus: A review

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### Abstract

Cardiovascular disease is the predominant cause of death in type 2 diabetes mellitus (T2DM). Evidence suggests a strong association between duration and degree of hyperglycemia and vascular disease. However, large trials failed to show cardiovascular benefit after intensive glycemic control, especially in patients with longer diabetes duration. Atherosclerosis is a chronic and progressive disease, with a long asymptomatic phase. Subclinical atherosclerosis, which is impaired in T2DM, includes impaired vasodilation, increased coronary artery calcification (CAC), carotid intima media thickness, arterial stiffness, and reduced arterial elasticity. Each of these alterations is represented by a marker of subclinical atherosclerosis, offering a cost-effective alternative compared to classic cardiac imaging. Their additional use on top of traditional risk assessment strengthens the predictive risk for developing coronary artery disease (CAD). We, herein, review the existing literature on the effect of glycemic control on each of these markers separately. Effective glycemic control, especially in earlier stages of the disease, attenuates progression of structural markers like intima-media thickness and CAC. Functional markers are improved after use of newer anti-diabetic agents, such as incretin-based treatments or sodium-glucose co-transporter-2 inhibitors, especially in T2DM patients with shorter disease duration. Larger prospective trials are needed to enhance causal inferences of glycemic control on clinical endpoints of CAD.

**Key Words:** Glycemic control; Atherosclerosis; Type 2 diabetes mellitus; Cardiovascular disease; Carotid intima media thickness

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**Core Tip:** Progression or even regression of atherosclerosis is possible in type 2 diabetes mellitus, especially at an early stage of the disease, with better glycemic control and use of newer agents, such as dipeptidyl peptidase 4 inhibitors and sodium-glucose co-transporter-2 inhibitors. Despite considerable evidence, especially for structural markers like intima media thickness or coronary artery calcification, and pulse wave velocity, larger and longer trials are needed to establish their clinical utility and correlation with clinical end-points.

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## INTRODUCTION

Cardiovascular disease (CVD) is the predominant cause of death in type 2 diabetes mellitus (T2DM). Generalized vascular disease is found even in asymptomatic patients with T2DM, who appear to have worse cardiovascular prognosis compared to healthy individuals. Increased cardiovascular risk cannot fully be attributed to the presence of traditional risk factors, such as dyslipidemia, hypertension, smoking or hyperglycemia, in these patients. Although existing evidence suggests the presence of a strong association between duration and degree of hyperglycemia and vascular disease[1], large trials have failed to show cardiovascular benefit of strict glycemic control in T2DM, especially those with longer disease duration[2,3].

Endothelial dysfunction is an early event in the progression of atherosclerosis[4]. Subclinical atherosclerosis, which is increased in T2DM patients, includes impaired vasodilation, increased coronary artery calcification (CAC), carotid intima media thickness (cIMT), arterial stiffness (AS) and reduced arterial elasticity. Each of these alterations is represented by a marker of subclinical atherosclerosis, serving as a cost-effective alternative to classic complex cardiac testing.

This is of great importance, given that the current diagnostic strategy is based on targeting traditional risk factors or using scoring systems that might either be insufficient to identify high-risk patients or present limited value in asymptomatic populations who lack these risk factors and yet suffer from CVD complications[5,6]. Therefore, imaging-guided risk assessment for detection of subclinical atherosclerosis might not only improve the compliance of those at high risk but also help reclassify lower risk patients who might benefit from targeted or more aggressive treatment. The Framingham risk score, an established tool for asymptomatic patients, appears to be less predictive for diabetics as opposed to the general population[7]. Therefore, increasing interest has led to the development of other screening tests for this population. As a subclinical marker of CVD, CAC scoring is known to predict cardiac events and has been a valuable tool for coronary artery disease (CAD) stratification of low-intermediate-risk patients, such as asymptomatic diabetics, and was recommended according to American Heart Association/American College of Cardiology Foundation guidelines[8].

In this review, we searched PubMed and Google Scholar for potentially relevant articles published from January 1, 1990 to December 31, 2020 with the following search terms: "subclinical atherosclerosis," "endothelial dysfunction in diabetes mellitus type 2," "effect of glycemic control in type 2 diabetes mellitus," "effect of glycemic control on subclinical atherosclerosis" and "HbA1c and markers of endothelial dysfunction."

## STRUCTURAL MARKERS

### cIMT-Carotid atherosclerosis

The use of B-mode ultrasound for cIMT assessment is a noninvasive, sensitive and

reproducible technique, which can be used to identify and quantify subclinical vascular disease and detect carotid plaques. It is considered a strong predictor for cardiovascular morbidity and mortality in T2DM and is used in numerous studies to detect patients at high risk of developing these complications.

Normally, cIMT increases with age, while male sex is associated with higher values [9]. The Atherosclerosis Risk In Communities (ARIC) study found a 0.07 mm increase of mean cIMT in all age groups of diabetic patients compared to nondiabetics after adjustment for other cardiovascular risk factors [10].

Interestingly, HbA1c is independently associated with cIMT values even in persons without diagnosed diabetes, suggesting the significance of glycemic control in development and progression of atherosclerosis [11]. It has become clear that, even in the prediabetic state, the risk of CVD is modestly increased [12,13]. In this direction, Di Pino *et al* [14] reported that, even in patients with prediabetes or newly onset diabetes, cIMT is impaired and correlates significantly with HbA1c. Moreover, higher HbA1c values are associated with higher cIMT values in subjects with normal glucose tolerance (NGT). Therefore, HbA1c is better than fasting glycemia or oral glucose tolerance tests as a surrogate marker to identify patients at high CVD risk.

In T2DM patients with near-normal HbA1c levels (5.8%–6.4%), further improvement of glycemic control prevents cIMT progression [15]. Recently, it has been suggested that poor glycemic control (*i.e.* HbA1c > 7%) and longer diabetes duration (> 1 year) independently exert adverse effects on cIMT in a smaller population ( $n = 45$ ) of younger patients with diabetes (aged 10–25 years). The presence of hypertension and higher body mass index are predisposing factors as well [16].

Interestingly, Di Flaviani *et al* [17] investigated the effect of glucose variability and overall glucose load on CVD risk by monitoring blood glucose and pressure continuously for 24 h in patients with optimal glycemic control. Glucose fluctuations appear to activate the oxidative stress pathway, but cIMT is affected by chronic and postprandial hyperglycemia rather than glucose variability. The prognostic information of postprandial glucose in CVD was previously suggested by the DECODE Study group [18].

In theory, metabolic control could potentially attenuate or reduce cIMT. Twelve to fourteen weeks after treatment with the peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) agonist, pioglitazone, cIMT was found to be significantly reduced. This effect was independent of improved glycemic control [19]. Pioglitazone is superior to glimepiride in terms of insulin resistance (IR) improvement and cIMT reduction [19]. PPAR- $\gamma$  activation has both antiatherogenic and proatherogenic properties.

The effect of sitagliptin on cIMT has been reported from several studies. In the PROLOGUE study, sitagliptin was not superior to conventional treatment in terms of cIMT progression, despite significant improvement of glycemic control [20]. Alogliptin, a dipeptidyl peptidase-4 inhibitor (DDP-4i), was also found to attenuate cIMT progression [21]. It must be noted, though, that in the PROLOGUE trial, insulin-treated patients were excluded, and the HbA1c changes were lower compared to that in other studies.

Last but not least, cIMT progression is inhibited after metformin use. Metformin has several metabolic effects. It modulates hepatic glucose, improves IR and has recently been found to decrease the plasma DDP-4 activity with subsequent increase in glucagon-like peptide-1 (GLP-1) concentrations [22]. In T2DM without former CVD, the combination of liraglutide, a GLP-1 analogue, with metformin decreased cIMT after 8 mo. These changes could not be attributed entirely to the HbA1c improvement or lipid changes, suggesting a possible beneficial role in reducing plaque formation and inflammation, as previously reported [23]. Interestingly, the addition of metformin to insulin treatment, aiming at achievement of HbA1c < 7%, did not reduce cIMT in the Copenhagen Insulin and Metformin Therapy (CIMT) trial, a fact attributed partially to the smaller-than-expected final study size [24].

Table 1 summarizes the interventional and observational studies on cIMT outcomes after glycemic control in T2DM patients.

### CAC score

The CAC score (CACS) is a well-established marker for the assessment of CVD risk in the general population.

Several researchers have reported CAC progression in T2DM. In a subanalysis of the Multiethnic Study of Atherosclerosis involving 5662 patients with T2DM or metabolic syndrome (MetS) without evident CVD, both categories were found to have greater incidence and accelerated progression of CAC compared to healthy individuals, which in turn can predict future CVD events [25].

**Table 1** Interventional and observational studies on glycemic control in type 2 diabetes mellitus patients and carotid intima media thickness outcomes

Ref.	Year	HbA1c (%), mean ± SD	Type of study	Intervention	Sample size	Main findings
Nambi <i>et al</i> [10]	2010	Glucose levels 105 ± 30.7 mg/dL	Population-based cohort	Risk prediction model: Whether cIMT and plaque improves CHD risk prediction when added to traditional risk factors	13145	0.07 mm greater cIMT in the presence of DM
Kawasumi <i>et al</i> [15]	2006	5.8-6.4	Cohort	Insulin, sulfonylureas, nateglinide, metformin, pioglitazone, α-GI for 3 yr	100	HbA1c improvement > 0.2% prevents cIMT increase
Di Pino <i>et al</i> [14]	2014	5.7-6.4 or > 6.5	Cohort	Subjects without a previous history of diabetes were stratified into three groups according to HbA1c levels	274	Impaired cIMT even in pre-diabetes
Sharma and Pandita[16]	2017	> 7 or < 7	Cohort	T2DM duration > 1 yr or newly diagnosed, age 10-25 yr	45	HbA1c and longer diabetes duration affect cIMT
Di Flaviani <i>et al</i> [17]	2011	6.7 ± 1.3	Cohort	Continuous glucose monitoring; Diet and/or metformin	26	No association was observed between cIMT any glucose variability or overall glycemic load
Langenfeld <i>et al</i> [19]	2005	7.5 ± 0.9	RCT	Pioglitazone 45 mg/d vs glimepiride 2.7 ± 1.6 mg/d for 12-24 wk	173	Pioglitazone reduces cIMT independently of improvement in glycemic control
Oyama <i>et al</i> [20]	2016	6.2 < HbA1c < 9.4%	Multicenter PROBE	Sitagliptin 25 to 100 mg/d vs conventional treatment over 2 yr	442	Sitagliptin had no additional effect on cIMT progression
Rizzo <i>et al</i> [23]	2014	8.4 ± 0.8	Prospective pilot	Liraglutide added on metformin over 8 mo	64	Beneficial role in plaque formation and inflammation

α-GI: Alpha-glucosidase inhibitors; CHD: Coronary heart disease; cIMT: Carotid intima media thickness; CVD: Cardiovascular disease; DM: Diabetes mellitus; LDL: Low-density lipoprotein; RCT: Randomized controlled trial; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

The link between CAC and HbA1c or plasma glucose levels is well established. Anand *et al*[26] showed that suboptimal HbA1c levels (> 7%) are associated with increased risk for CAC progression. In an asymptomatic Korean population without T2DM, higher HbA1c levels predicted CAC, with the association being more prevalent in women[27]. The ARIC study showed higher relative risk for coronary heart disease for the highest quantile of HbA1c[28].

Although data for prediabetes are inconsistent, it is suggested that even without glycemic transition from impaired fasting glucose to T2DM, in the presence of IR, higher CAC prevalence is observed[29].

Moreover, symptomatic CAD patients (angina) with T2DM and poor glycemic control appear to have higher plaque volume[30]. The presence of noncalcified plaques and higher plaque burden are confirmed in asymptomatic T2DM patients as well[31, 32]. This underlies the importance of extended screening, even at the onset of diabetes.

A recent study from Germany showed that in established T2DM, poor glycemic control is associated with CAC progression. This progression is inevitable and rather unaffected by the burden of risk factors[33]. The question of whether tight glycemic control exerts beneficial effects on CAC, either regression or attenuation, remains unanswered because, even now, very few data are available. A small study from Schindler *et al*[34] showed that, after 1 year of treatment, effective glycemic control defined as fasting plasma glucose ≤ 126 mg/dL resulted in lower progression of both cIMT and CACS in treatment-naive, relatively newly-diagnosed T2DM patients (*i.e.* mean DM duration of 25 mo) without known CVD.

In the Veterans Affairs Diabetes (VADT) trial, after a 7.5-year follow-up period, intensive glucose lowering reduced cardiovascular events in patients with less extensive calcified coronary atherosclerosis, implying that aggressive glycemic control may be less effective in more advanced atherosclerosis. This was the case in other major trials such as the ACCORD study, which showed that patients without CVD and HbA1c < 8% are the ones who benefit the most from intensive treatment[35]. However, the extended follow-up to the VADT trial revealed that intensive glycemic control in patients with T2DM of > 5 years duration with previous cardiovascular events resulted in 8.6-fold fewer major cardiovascular events *per* 1000 person-years than those assigned to standard therapy[36]. This might suggest that a longer observation period is needed so that the beneficial effect becomes clinically apparent.

Yang *et al*[37] showed that long-term HbA1c variability plays an important role because metabolic stabilization for longer periods and at earlier stages of the disease might prevent subclinical coronary atherosclerosis. This is in agreement with the presence of the so-called legacy effect, a hypothesis that supports that early metabolic control has beneficial effects in terms of CVD prevention[37,38]. Recently, it has been shown that in asymptomatic CAD patients with known T2DM, optimal glycemic control attenuates CAC progression, whereas those patients with more calcified coronary lesions (defined as CAC > 400) appear to benefit the most.

At the tissue level, advanced end-glycation products were found to accelerate calcification in microvascular pericytes[39]. Other experimental data suggest a positive feedback loop of calcification and inflammation that plays an important role in disease progression, induced by the very same atherosclerotic lesions[40]. It is possible, though, that intensive treatment might be able to stop this vicious cycle triggered by baseline calcification.

Funck *et al*[41] showed higher burden and a greater number of atherosclerotic plaques in asymptomatic T2DM patients compared to healthy controls, despite optimal control of classical risk factors (hyperglycemia, BP, hyperlipidemia). They hypothesized that intensive risk factor control could not adequately control atherosclerosis progression, probably due to higher burden at baseline, in accordance with data supporting higher CVD risk in T2DM patients with known macrovascular complications.

Malik *et al*[42] found that CAC score could improve long-term risk stratification to prevent CVD in T2DM and MetS. Importantly, CACS of 0 is associated with lower CVD risk independent of T2DM duration, glycemic control or insulin treatment. Even in T2DM patients with disease duration of more than 10 years, the absence of CACS was associated with low risk for future events, as in those with shorter disease duration. Finally, a recent study by Razavi *et al*[43] found that long-term absence of CAC during a follow-up period of 10 years in patients with T2DM and MetS was associated with baseline CAC of 0. Optimal multifactorial control is needed for healthy arterial aging. These data suggest that although T2DM is a CVD risk equivalent, it demonstrates considerable heterogeneity[44].

Table 2 summarizes the effect of glycemic control on CAC in T2DM patients.

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## FUNCTIONAL MARKERS

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### *Flow-mediated dilatation*

Originally described in 1992, Flow-mediated dilatation (FMD) is a noninvasive functional marker of subclinical atherosclerosis that utilizes ultrasound to record the reaction of brachial artery to an ischemic stimulus. It describes the vascular response to elevated blood flow, which is mediated by the produced vasoactive nitric oxide. FMD has been found to correlate with the severity and extent of coronary atherosclerosis [45].

In T2DM, postprandial hyperglycemia occurs early in the course of the disease and is thought to be a better marker of glycemic burden regarding associated complications[46].

In a study with 30 T2DM patients, the investigators measured FMD and circulating endothelial cells (CECs), a marker of vascular damage. Patients were found to have impaired endothelial function compared to healthy controls, while HbA1c > 7% was associated with higher levels of CECs and lower FMD, suggesting the crucial role of glycemic control in diabetes management[47]. Some data suggest that glycemic control may result in improved vasodilatory responses and that certain glucose-lowering agents can improve FMD.

Watanabe *et al*[48] hypothesized that improvement of IR, a major metabolic cause of atherosclerosis, following treatment with troglitazone for 4 wk would improve endothelial dysfunction as well. At the end of the study, improvements in fasting glucose, insulin levels and FMD were documented. Similar results were confirmed in recent-onset diabetes without macrovascular complications, meaning that improvement of fasting insulin concentrations might be the underlying mechanism [49].

It seems that PPAR- $\gamma$  agonists exert their antiatherogenic effect independently of their glucose-lowering effects, given that pioglitazone improves FMD irrespective of significant changes in insulin, C-reactive protein (CRP), free fatty acids, and adiponectin levels[50]. In nondiabetic patients with IR and recent history of stroke or transient ischemic attack, pioglitazone appears to reduce the risk for future CVD

**Table 2** Interventional and observational studies on glycemic control in type 2 diabetes mellitus patients and coronary artery calcification outcomes

Ref.	Year	HbA1c (%), mean $\pm$ SD	Type of study	Intervention	Sample size	Main findings
Razavi <i>et al</i> [43]	2021	Fasting glucose > 126 mg/dL	Multiethnic cohort	Two CAC scans with a 10-yr interval	574	More than 40% of adults with MetS or T2DM and baseline CAC = 0 had long-term absence of CAC
Schindler <i>et al</i> [34]	2009	9.8 $\pm$ 2.7	Prospective	Glyburide 10-20 mg/d $\pm$ metformin 500-1000 mg/d; Observation for 14 $\pm$ 2 mo	39	Lower progression of cIMT and CAC with glucose-lowering treatment
Won <i>et al</i> [38]	2018	7.5 $\pm$ 1.2 and 6.4 $\pm$ 0.9	Retrospective, single-ethnicity, multicenter observational	Data on the impact of optimal glycemic control on CAC progression	1637	Attenuation of CAC progression, especially if CAC > 400
Funck <i>et al</i> [41]	2017	6.5 $\pm$ 0.7	Prospective cohort	Observational, 5-yr follow-up	106	CAC progression in DM compared to healthy. Independently associated with PWV
Malik <i>et al</i> [42]	2017	HbA1c measurements were not available at baseline	Prospective cohort	Observational	6814	Baseline CAC values most important progression determinant

CAC: Coronary artery calcification; cIMT: Carotid intima media thickness; DM: Diabetes mellitus; MetS: Metabolic syndrome; PWV: Pulse wave velocity; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

events[51]. The important role of reduction in IR is more apparent after comparison with insulinotropic sulfonylureas that achieve similar HbA1c effects without improvement of FMD[52,53]. The PROactive study did not shed light on the mechanism by which pioglitazone exerts its vascular benefit; it did, however, show a reduction in primary cardiovascular outcomes by almost 16% [54]. The reported improvement in fat cell metabolism is another argument toward the positive effects of thiazolidinediones beyond glycemic control[55]. Interestingly, gliclazide, unlike glimepiride, is reported to improve IR, CECs and FMD in a small group of T2DM patients[56,57].

FMD, glucose, and insulin levels were recorded prior to and after a dietary tolerance test in 30 newly diagnosed T2DM patients after treatment with acarbose (300 mg/d), nateglinide (270 mg/d), or placebo for 12 wk. Fasting FMD responses remained similar at follow-up in all groups. Despite comparable improvement in glycemic control, treatment with acarbose, unlike insulinotropic nateglinide, was associated with higher postprandial FMD responses. Major-Pedersen *et al*[58] reported that single administration of nateglinide initially improves postprandial endothelial dysfunction, but the effect disappears after 12 wk. This might imply that insulin secretion in the long term obviates the beneficial effects of controlled postprandial hyperglycemia on endothelial dysfunction.

Naka *et al*[59] compared the effect of two insulin sensitizers, metformin and pioglitazone, on poorly controlled T2DM already treated with sulfonylureas. Despite similar improvements in glycemic control, homeostatic model assessment insulin resistance index (HOMA-IR) and changes in FMD, only in the pioglitazone group did FMD and IR improve significantly. The authors concluded that treatment-induced changes in FMD are not associated with the effects on glycemic control or IR. Nevertheless, the reduction in IR achieved in this study was smaller compared to others, while the additional role of longer diabetes duration cannot be ignored.

Alpha-glucosidase inhibitors are also superior to nateglinide in terms of FMD improvement, IR index and markers of atherogenic dyslipidemia, despite similar HbA1c reduction[60].

Incretin-based treatments have been available for over a decade, and there is now evidence of important effects on cardiovascular outcomes beyond their glucose-lowering effects, such as antiatherogenic properties, modulation of arterial inflammation and endothelial function[61].

Improvement of both HbA1c and FMD in T2DM with stable CAD is reported after infusion of recombinant GLP-1. Interestingly, IR, as assessed by the hyperinsulinemic isoglycemic clamp technique, was not improved. Therefore, it is rather unlikely that GLP-1 exerts its beneficial effects on endothelium through improvement of insulin sensitivity index[62].

The beneficial effects of GLP-1 analogue treatment are possibly the result of improved insulin secretion and effect on postprandial glycemic control[63]. Based on this observation, Irace *et al*[64] tested the differences between intensification of metformin treatment with exenatide *vs* glimepiride and found that this combination ameliorates FMD through improvements of glycemic control and glycemic variability. The role of glucose variability and its possible deleterious effects on vascular endothelium were suggested earlier because glucose swings appeared to be more damaging for the endothelium than constantly high glucose levels[65]. Further large-scale trials are needed to establish the validity of this notion.

A randomized controlled trial comparing the effects of insulin glargine and of the GLP-1 analogue liraglutide failed to show an improvement in FMD after 14 wk, although liraglutide appeared to protect  $\beta$ -cell function and reduce oxidative stress. Low plasma concentration of liraglutide, the last dose of which was given 1 d prior to FMD measurement, might explain the negative results[66]. A similar conclusion regarding FMD is drawn after comparison of sitagliptin with glimepiride[67], which resulted in similar HbA1c improvements. That said, in a study from Egypt, sitagliptin improved endothelial dysfunction, insulin sensitivity, BP and hyperlipidemia in newly diagnosed T2DM patients[68]. A beneficial effect on FMD after sitagliptin is suggested by other authors without superiority against the  $\alpha$ -glucosidase inhibitor voglibose[69].

More recently, Lambadiari *et al*[70] showed that in patients with poorly controlled T2DM, treatment intensification with incretin-based treatment improves not only FMD but other markers of subclinical atherosclerosis and cardiac function as well. This improvement is more profound in patients who achieve optimal glycemic control.

Linagliptin (at a dose of 5 mg daily) does not improve large-vessel endothelial function despite decreasing inflammation in patients with longer T2DM duration after 12 wk of treatment. Mitochondrial function and muscle oxygenation were not increased either[71]. This suggests that diabetes duration might play an additional, important role. Surprisingly, Ayaori *et al*[72] showed a deterioration of FMD after both alogliptin and sitagliptin. This was rather unexpected because positive effects had been reported, as mentioned earlier. A possible explanation for this phenomenon is that DPP-4 enzyme physiologically degrades GLP-1 (7-36) into the non-insulinotropic GLP-1 (9-36), which might be inactive but possibly exerts nitric oxide-mediated vasodilatory effects translated into worse FMD values.

In summary, studies with incretin-based agents are mostly relatively small, nonrandomized trials, and therefore observed differences on vascular function with the various agents are difficult to interpret.

The newest class of glucose-lowering agents, sodium-glucose co-transporter-2 (SGLT2) inhibitors, have been shown to reduce cardiovascular mortality in patients with T2DM. Several scholars have investigated whether glycemic control with these agents has any beneficial effects on the progression of atherosclerosis. In poorly controlled T2DM with CAD, administration of 100 mg canagliflozin for 4 wk improved HbA1c [from 9.2 (mean  $\pm$  SD)  $\pm$  1.4 to 8.6  $\pm$  1.1%,  $P < 0.01$ ] and FMD[73]. In this study, none of the patients were treated with insulin.

Improvement of HbA1c and FMD was found in two recent studies after treatment with dapagliflozin. The first study included newly diagnosed metformin-treated T2DM patients with HbA1c of  $< 8\%$ [74], whereas the second included T2DM patients with established ischemic heart disease. In the latter, surrogate markers of endothelial dysfunction and inflammation, such as adhesion molecule 1, endothelial nitric oxide synthase and high-sensitivity CRP, decreased with dapagliflozin therapy, and FMD correlated negatively with HbA1c[75]. Assessment of the Dapagliflozin Effect on Diabetic Endothelial Dysfunction of the Brachial Artery (ADDENDABHS2) trial, in which patients with poor glycemic control were randomized to receive either dapagliflozin or glibenclamide, shed more light on the effect of this agent[76].

A Mediterranean diet, except for reducing acute hyperglycemia and increasing antioxidant defenses and the protective action of GLP-1, improves FMD as well. Similarly, insulin sensitivity and FMD improves in T2DM patients with training, especially interval aerobic exercise[77].

Glycemic variability is believed to have unfavorable effects on macro- and microvascular events as well as all-cause mortality in T2DM. Wei *et al*[78] showed that glycemic visit-to-visit variability correlates with impairment of renal and endothelial dysfunction, as assessed by FMD.

In an attempt to elucidate the underlying mechanism, Costantino *et al*[79] examined the role of glycemic variability and mitochondrial oxidative stress in endothelial dysfunction. The investigators showed that glucose fluctuations rather than HbA1c cause epigenetic changes. This chromatin remodeling favors a proatherosclerotic phenotype. Owing to overexpression of stress molecules, FMD impairment and

oxidative stress persist even after improvement of HbA1c.

**Table 3** summarizes interventional and observational studies on FMD outcomes after glycemic control in T2DM patients.

### **Pulse wave velocity**

Pulse wave velocity (PWV) is a marker of AS, which in turn expresses the reduced flexibility and elasticity of blood vessels. It is assessed noninvasively and predicts future cardiovascular events and all-cause mortality[80]. Reduced elasticity occurs naturally with increasing age or under the rather destructive effect of metabolic disorders, such as T2DM or hypertension. T2DM and hypertension seem to have a synergistic effect on the progression of AS. PWV is a useful marker in the investigation of hypertension[81].

The prognostic value of PWV in T2DM is the subject of several studies. It has been estimated that for every 1 m/s increase in PWV, there is a 14.5% increase in the risk of CVD in patients with T2DM[82]. The association of glycemic control with PWV was earlier supported by Yokoyama *et al*[83], who showed that along with conventional risk factors, such as hyperlipidemia, hypertension and age, microalbuminuria is a determinant of cIMT and PWV and should, therefore, be taken into account for the detection of subclinical atherosclerosis and treatment stratification.

Control of hyperglycemia, even in the short term, appears to improve AS[83]. De Pascale *et al*[84] showed that good glycemic control is associated with lower AS and increased number of endothelial progenitor cells, which reflects the endothelium's regenerating capacity after damage.

Another study with 1675 participants in rural Brazil showed that increase of HbA1c by 1% was associated with increase of 54% in the odds of increased AS in the diabetic group. Both HbA1c and fasting blood glucose (FBG) had higher discriminatory power in the risk assessment for increased AS in nondiabetics compared to diabetics. Therefore, HbA1c elevation, even within the normal range, might cause endothelial dysfunction[85]. Similarly, Lee *et al*[86] concluded that even in the nondiabetic population, higher HbA1c levels were associated with increased brachial-ankle PWV. Therefore, early detection and management are essential to avoid atherosclerosis progression. There are additional studies that support the prognostic value of PWV in both diabetes and IGT[87].

In an older study, Webb *et al*[88] aimed to investigate the impact of glucose metabolism and IR on PWV. For this purpose, they enrolled 570 participants in the large ADDITION-Leicester program, who were divided into the three groups after a standard 75-g oral glucose tolerance test, namely NGT, IGT and T2DM. HbA1c as well as PWV gradually worsened from NGT to IGT and T2DM (all  $P < 0.01$ ). Multivariate models demonstrated a strong relationship among PWV, fasting and 2-h postprandial glucose levels as well as HOMA-IR. Moreover, although all three indices contribute to PWV increase of about 3%–6%, postprandial glucose appears to be the most significant determinant. The effect of postprandial glucose on PWV was later supported by Li *et al* [89], who found that AS was increased in patients with IGT and newly diagnosed T2DM but not in those with impaired fasting glucose tolerance. Again, the hypothesis was that glycemic control, especially by targeting postprandial hyperglycemia, might reverse this phenomenon or even improve PWV.

Improvement of glycemic control after glimepiride, unlike glibenclamide, is associated with improved brachial ankle PWV and Augmentation Index (AIx). Notably, glimepiride decreases proinflammatory markers such as tumor necrosis factor- $\alpha$ , interleukin and CRP, with improvement of IR[90]. In that study, insulin-treated T2DM patients were used as the control group.

Beneficial effects on PWV through normalization of IR, as well as reduction of inflammation, are reported after glycemic control with rosiglitazone even in patients with established CAD[91].

The effect of hyperinsulinemia on other markers of subclinical atherosclerosis has already been discussed. In patients without evident macrovascular disease, higher insulin levels remain a significant predictor of PWV, even after adjustment for other well-established risk factors, concerning AS[92]. Interestingly, in this study, only 2% of the participants had a history of diabetes[92].

Another argument toward this hypothesis is that the use of insulin-sensitizer metformin in patients with nonalcoholic fatty liver disease (NAFLD)—a condition associated with IR—was associated with a significant reduction of both PWV and AIx in this population, with marginal improvements in fasting glucose, triglycerides, alkaline phosphatase and high-density lipoprotein cholesterol. These favorable effects of metformin were also observed in NAFLD patients without T2DM[93].



**Table 3** Interventional and observational studies on glycemic control in type 2 diabetes mellitus patients and flow-mediated dilatation outcomes

Ref.	Year	HbA1c (%), mean $\pm$ SD	Type of study	Intervention	Sample size	Main findings
Watanabe <i>et al</i> [48]	2000	Fasting glucose 4.9 $\pm$ 0.3 mmol/L	Prospective cohort	Troglitazone 400 mg/d for 4 wk in non-DM	13	Improvement on fasting glucose, insulin and FMD
Caballero <i>et al</i> [49]	2003	7.5 $\pm$ 1.2 to 7.9 $\pm$ 1.5	Prospective randomized double-blinded	Troglitazone 600 mg/d for 12 wk	87	Improvement of FMD in newly diagnosed without CAD
Martens <i>et al</i> [50]	2005	7.1 $\pm$ 0.3	Prospective, randomized, crossover, placebo-controlled, double-blinded	Pioglitazone 30 mg/d for 4 wk	20	Improvement of FMD and adiponectin levels
Asnani <i>et al</i> [52]	2006	10 $\pm$ 2.3	Prospective randomized double-blinded	Pioglitazone 30 mg/d for 16 wk	20	Improvement of FMD
Chen <i>et al</i> [56]	2011	7.4 $\pm$ 1.3	Prospective controlled	Gliclazide 30-90 mg/d for 12 wk	58	Improvement of FMD, ECs and insulin resistance
Naka <i>et al</i> [59]	2012	7.8 $\pm$ 0.9 and 8.1 $\pm$ 1.3	Open-label randomized	Pioglitazone 30 mg/d or metformin 850 mg/d added to sulfonylureas for 6 mo	36	Improvement of FMD and insulin resistance
Sawada <i>et al</i> [60]	2014	6.9 $\pm$ 0.7 vs 7.0 $\pm$ 0.4	Randomized prospective	Miglitol 150 mg/d or nateglinide 270 mg/d for 16 wk	104	Improvement of FMD, insulin resistance index and markers of atherogenic dyslipidemia in the $\alpha$ -GI miglitol group
Irace <i>et al</i> [64]	2013	8.9 $\pm$ 1.2 and 8.2 $\pm$ 1.2	Observational	Exenatide 10-20 $\mu$ g/d plus metformin vs glimepiride 2-4 mg/d plus metformin for 16 wk	20	Improvement of FMD; Better control on glycemic variability
Nomoto <i>et al</i> [66]	2015	8.6 $\pm$ 0.8 and 8.7 $\pm$ 0.8	Multicenter, prospective randomized parallel-group comparison	Liraglutide 0.3-0.9 mg/d vs glargine added on metformin and/or sulfonylurea for 14 wk	31	Similar FMD changes and $\beta$ -cell function protection
Amira <i>et al</i> [68]	2017	Median (range): 8.7 (8.03 - 9.15)	Prospective controlled	Sitagliptin 100 mg/d for 24 wk	80	Improvement of FMD, insulin sensitivity blood pressure and hyperlipidemia
Kubota <i>et al</i> [69]	2012	7.3 $\pm$ 0.8	Open-labeled prospective observational single-arm	Sitagliptin 50 mg/d for 12 wk	40	Improvement of FMD and plasma adiponectin increase
Lambadiari <i>et al</i> [70]	2019	8.9 $\pm$ 1.8	Prospective cohort	Incretin-based treatment	100	Improvement of FMD and subclinical atherosclerosis after optimal glycemic control
Baltzis <i>et al</i> [71]	2016	7.1 $\pm$ 0.8	Randomized, double-blind, placebo-controlled	Linagliptin 5 mg/d vs placebo for 12 wk	40	No improvement in large vessel endothelial function
Takase <i>et al</i> [73]	2018	9.2 $\pm$ 1.4	Retrospective preliminary cross-sectional single-center pilot	Canagliflozin 100 mg/d for 4 wk	11	FMD improvement
Shigiyama <i>et al</i> [74]	2017	6.8 $\pm$ 0.5 and 6.9 $\pm$ 0.5	Prospective, randomized, open-label, blinded endpoint, parallel-group, comparative	Dapagliflozin 5 mg/d added on metformin 1500 mg/d for 16 wk	80	Improvement of FMD in newly diagnosed T2DM
Zainordin <i>et al</i> [75]	2020	9.7 $\pm$ 1.9	Prospective, randomized, crossover, placebo-controlled, double-blind	Dapagliflozin 10 mg/d vs placebo added on metformin and insulin over 12 wk	81	No difference in FMD between the two groups observed; Significant reduction in surrogate marker of the endothelial function ICAM-1

$\alpha$ -GI: Alpha-glucosidase inhibitor; CAD: Coronary artery disease; DM: Diabetes mellitus; EC: Endothelial cell; FMD: flow-mediated dilatation; SD: Standard deviation; T2DM: Type 2 diabetes mellitus; IL: Interleukin.

In obese patients, treatment with metformin, rosiglitane or a combination of both with lifestyle modification improved not only glycemic control but PWV as well. In this study, however, only femoral PWV, known to assess peripheral stiffness rather than central AS, was associated with HbA1c[94]. On the contrary, reduction in the body fat mass of obese T2DM patients after exenatide improved lipid profile and aortic PWV, whereas PWV of the extremities did not change. The authors concluded that visceral fat reduction affecting the measurements could explain these findings

[95]. Using a different method, weight loss was found to strongly and independently reduce AS[96]. Because several classes of glucose-lowering agents are associated with weight gain, this should be considered prior to treatment stratification. Nevertheless, the beneficial effects of exenatide on PWV do not rely solely on weight reduction because improvements were shown after HbA1c reduction in T2DM patients without evident CAD, treated with metformin (sulfonylurea was prescribed in 5 patients only) [97].

Regarding the effects of DDP-4i on PWV, data are variable. When added to metformin, in T2DM with suboptimal HbA1c (> 7%), neither sitagliptin nor glibenclamide demonstrated any PWV benefits. Neither drug significantly influenced oxidative stress[98]. Zografou *et al*[99] showed no increase of PWV in drug-naive patients with T2DM, despite changes in HbA1c after treatment with vildagliptin. These patients had suboptimal HbA1c (7%–9%) at baseline and, moreover, a significant improvement in 24-h BP or waist circumference, all of which are important in terms of endothelial dysfunction.

Conversely, Duvnjak and Blaslov[100] studied 51 T2DM patients with good glycemic control, assigned to receive either sitagliptin or vildagliptin (100 mg/d). Both drugs were associated with improved PWV and AIx despite insignificant HbA1c changes. The authors concluded that the positive effects on AS are beyond glucose control. Favorable effects of linagliptin treatment for 26 wk with minimal yet significant HbA1c reduction (-0.4%,  $P < 0.001$ ) were recently reported in newly diagnosed T2DM patients. Interestingly, after a 4-wk washout period, PWV returned to pre-intervention levels[101].

Large trials on DDP4-is support a neutral effect on CVD outcomes, although data show an important positive effect on PWV[102]. It is, therefore, possible that not all agents of this class share the same beneficial effects. Additionally, these studies differ in terms of baseline HbA1c as well as diabetes duration.

It has been proposed that a HbA1c of > 7% and diabetes duration of > 5 years are important cutoffs, above which stiffening of the arteries accelerates, especially in the presence of hypertension[103]. A recent observational study from Chang *et al*[104] rather confirms this observation. In hypertensive, poorly controlled T2DM (HbA1c<sup>3</sup> 9%), reduction of HbA1c was not accompanied by significant differences in PWV or AIx in the short term. In a subanalysis based on cutoff HbA1c level of 7%, those with better HbA1c values had lower PWV, yet not significantly, and shorter T2DM duration. Even in high-risk middle-aged to elderly patients, PWV can be attenuated after improvements of glycemic control, BP, and heart rate. Furthermore, the rate of HbA1c reduction is associated with reduced risk for increased PWV[105].

Based on the aforementioned facts, it would be reasonable to hypothesize that improvement of glycemic and systemic BP control would attenuate or even improve PWV in T2DM. Amongst the various antidiabetic agents, SGLT2 inhibitors may efficiently lower both HbA1c and BP. Available data suggest that the reduction in CVD mortality is beyond their glycemic and antihypertensive effects, both factors being important for AS. Animal models show improvement in AS after the use of empagliflozin by promoting glycosuria and reducing systemic and renal AS based on improvements of periarterial and tubulointerstitial fibrosis[106]. Given that numerous studies support the relationship among AS, albuminuria and kidney injury[107], this could be a possible additional mechanism beyond glycemic control. In animal models, dapagliflozin improves hyperglycemia, AS and smooth muscle cell function, meaning that the positive effects on CVD mortality in diabetes are possibly owing to improvements in generalized vascular function[86]. The newest agent in this category, tofogliflozin, attenuated PWV in T2DM without history of CVD[108]. A recent meta-analysis on newer agents showed that both GLP-1 analogues as well as DDP-4i effectively reduce PWV[109].

An association between HbA1c and PWV has been previously reported from some cross-sectional studies[110]. The implication that hyperglycemia alters material within the arterial wall and contributes to atherosclerosis was reinforced by other similar data. As Ferreira *et al*[105] reported, early intervention aiming to improve glycemic control might at least partially affect PWV, probably before the structural alterations occur.

Table 4 summarizes interventional and observational studies on PWV outcomes after glycemic control in T2DM patients.

### **Large and small artery elasticity**

Arterial elasticity is also a noninvasive measure for the assessment of cardiovascular risk. It reflects the extent of vascular injury owing to cardiovascular risk factors and allows risk stratification with considerable prognostic value[111].

**Table 4** Interventional and observational studies on glycemic control in type 2 diabetes mellitus patients and pulse wave velocity outcomes

Ref.	Year	HbA1c (%), mean $\pm$ SD	Type of study	Intervention	Sample size	Main findings
Koshiha <i>et al</i> [90]	2006	7.8 $\pm$ 2.0 and 7.7 $\pm$ 1.9	Prospective, randomized	Glibenclamide followed by glimepiride for 28 wk <i>vs</i> continuous administration of glibenclamide <i>vs</i> insulin therapy	34	Improvement of PWV, AIx, IR in the glimepiride group
de Oliveira <i>et al</i> [85]	2015	5.6 $\pm$ 0.7 and 6.3 $\pm$ 1.1	Prospective cohort	Observational	1675	Higher HbA1c levels are associated with higher PWV
Yu <i>et al</i> [91]	2007	6.5 $\pm$ 0.2	Prospective, randomized	Rosiglitazone 4 mg/d for 12 wk in diabetic patients with CAD	123	Decrease in PWV
Sofer <i>et al</i> [93]	2011	Fasting glucose: 132 $\pm$ 51 mg/dL	Prospective, randomized, placebo-controlled, double-blind	Metformin in patients with NAFLD with or without T2DM/IFG for 4 mo	63	Decrease in PWV and AIx
Shah <i>et al</i> [94]	2018	7.7 $\pm$ 2.0	Subanalysis of an RCT	Obese patients with metformin <i>vs</i> metformin plus intensive lifestyle intervention <i>vs</i> metformin plus rosiglitazone for 7.6 yr post-randomization	453	PWV increased; Attenuation possible
Scalzo <i>et al</i> [97]	2017	7.3 $\pm$ 1.1	Prospective, randomized, placebo-controlled, double-blind	Exenatide 20 $\mu$ g/d subcutaneously, 30-60 min prior to meals, for 3 mo	23	Decrease in PWV
Koren <i>et al</i> [98]	2012	Fasting glucose: 169 $\pm$ 12 mg/dL	Prospective, controlled, open labeled, crossover	Sitagliptin 100 mg/d or glibenclamide 5 mg/d for 3 mo, cross-over switch for an additional 3 mo	34	No PWV benefits; Beneficial BMI effects of sitagliptin
Zografou <i>et al</i> [99]	2015	8.1 $\pm$ 0.8	Prospective randomized open-label	Vildagliptin 100 mg/d plus metformin 1700 mg/d <i>vs</i> metformin monotherapy 1700 mg/d	64	No effect on arterial stiffness in drug-naive patients with T2DM
Duvnjak and Blaslov [100]	2016	6.9 $\pm$ 1.1	Prospective, uncontrolled, open label, parallel-arm, randomized	Sitagliptin 100 mg/d or vildagliptin 100 mg/d for 3 mo	51	Decrease in PWV and Aix; No HbA1c reduction
De Boer <i>et al</i> [101]	2017	6.3 $\pm$ 0.4	Prospective, randomized, placebo-controlled, double-blind	Linagliptin 5 mg/d <i>vs</i> placebo for 26 wk	45	PWV improvement disappears after 4-wk washout period in newly diagnosed T2DM
Chen <i>et al</i> [103]	2009	6.9 $\pm$ 1.3	Prospective cohort	Observational	1000	PWV correlates with HbA1c and diabetes duration in patients with T2DM and hypertension
Chang <i>et al</i> [104]	2018	11.7 $\pm$ 1.9	Prospective cohort	Insulin or oral hypoglycemic agents (metformin, sulfonylurea, $\alpha$ -GI, DDP-4i) or combined insulin and oral agents for 12 wk	64	No PWV improvement
Ferreira <i>et al</i> [105]	2015	7.6 $\pm$ 1.4	Prospective cohort	Metformin, sulfonylureas or insulin for 4.2 yr	417	Attenuation of PWV progression

$\alpha$ -GI: Alpha-glucosidase inhibitor; AIx: Augmentation Index; BMI: Body mass index; CAD: Coronary artery disease; cIMT: Carotid intima media thickness; DDP-4i: dipeptidyl peptidase-4 inhibitor; HCT: Hydrochlorothiazide; IFG: Impaired fasting glucose; IR: Insulin resistance; NAFLD: Nonalcoholic fatty liver disease; PWV: Pulse wave velocity; RCT: Randomized controlled trial; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

It is suggested that small arteries compared to large ones—that is, the aorta—contain a more repairable component regarding arterial elasticity, where fixed fibrotic tissue is more prominent and requires a longer repair period [112]. Interestingly, in a group of nondiabetic patients with CAD, only small (C2) and FMD appeared to be impaired compared to healthy controls, suggesting that C2 is a surrogate marker for the clinical evaluation of endothelial function [113].

Shargorodsky *et al* [114] showed that 6 mo of treatment with rosiglitazone in 52 patients with moderate CVD risk and poor glycemic control (longer disease duration of 5–28 years, 24% on insulin) resulted in impressive improvement of C2, which was attributed to improvements in IR and hyperinsulinemia. Though there was a tendency toward improvement for large (C1), it did not reach statistical significance. The authors mentioned that a longer follow-up period was probably needed. After an

extended follow-up period of 2 years, improvements in both C1 and C2 after rosiglitazone treatment were confirmed, and the beneficial effect deteriorated after treatment discontinuation. Moreover, this was independent of glycemic control, implying the central role of hyperinsulinemia in AS. Last but not least, with data supporting that rosiglitazone inhibits cIMT progression in nondiabetic individuals, the antiatherogenic effect of PPAR- $\gamma$  activators is independent of glycemic control[115].

Prisant *et al*[116] aimed to investigate the relationship of HbA1c and arterial elasticity by performing measurements of both C1 and C2 in 111 subjects with longer diabetes duration (12 years) and poor glycemic control (HbA1c 8.9%). Increasing age and HbA1c were found to be associated with small, but not large, artery elasticity, whereas women with T2DM had lower C2 compared to men. In this study, 26% of participants were type 1 DM patients.

That said, McVeigh *et al*[117], in an older study analyzing intra-arterial brachial artery pulse waves in T2DM, suggested reduced C2 in T2DM but no correlations with fasting glucose or HbA1c, whereas C1 was not reduced. They used mostly diet intervention and/or sulfonylurea and metformin to achieve glycemic control.

Several data support that C2 can be raised by means of improvement of HbA1c such as through fish oil supplements[118] or telmisartan[119]. Mourot *et al*[120] investigated the effect of a cardiovascular rehabilitation program on arterial compliance in patients with T2DM and CAD. These patients had suboptimal or poor glycemic control at the time of admission. After 6 wk, improvement of arterial compliance was observed, probably thanks to regular exercise, optimal glucose-lowering, and hypolipidemic treatment. Because arterial compliance was improved in the subpopulation with no change in antihypertensive treatment as well, the observed increase extended beyond antihypertensive treatment. Moreover, decrease of IR through training and amelioration of glycemic control, which was achieved by insulin, oral agents, or a combination of both, appear to have contributed to this improvement as well.

## CONCLUSION

The additional use of these noninvasive markers of atherosclerosis strengthens the predictive risk for developing CAD beyond traditional risk assessment and enables the monitoring of selected treatment in T2DM. Progression or even regression of atherosclerosis is possible in T2DM, especially in patients with newly diagnosed diabetes, with relatively good glycemic control and use of newer agents, such as DDP4-is and SGLT2 inhibitors. This is best reflected in the updated guidelines, which support their use after metformin treatment, which also has beneficial effects. A multifactorial intervention with improvement of classical risk factors, such as hypertension and BP, should always be considered. Both structural and functional markers are easily accessible and could be an additional tool for clinicians to screen high-risk patients, with CAC, cIMT and PWV showing less intra-observer variability compared to FMD and small artery elasticity index. Despite considerable evidence for predictive value especially for cIMT, CAC and PWV, larger studies and studies over longer periods are needed to correlate clinical outcomes with improvement of subclinical atherosclerosis.

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