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REVIEW

Carotid intima-media thickness as a surrogate marker of cardiovascular disease in diabetes

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Background: Diabetes mellitus is associated with a high risk of cardiovascular disease. Carotid intima-media thickness (CIMT) is increasingly used as a surrogate marker for atherosclerosis. Its use relies on its ability to predict future clinical cardiovascular end points.

Methods: This review examines the evidence linking CIMT as a surrogate marker of vascular complications in people with type 1 and type 2 diabetes. We have also reviewed the various treatment strategies which have been shown to influence CIMT.

Conclusions: CIMT measurement is an effective, noninvasive tool which can assist in identifying people with diabetes who are at higher risk of developing microvascular and macrovascular complications. It may also help to evaluate the effectiveness of various treatment strategies used to treat people with diabetes.

Keywords: carotid, intima-media thickness, CIMT, diabetes

Cardiovascular disease in diabetes

Diabetes mellitus is associated with a high risk of cardiovascular disease (CVD) which is the most common cause of mortality in people with diabetes.[1,2] CVD accounts for more than 80% of deaths in people with diabetes.[3,4] A two- to fourfold increased risk of CVD in people with diabetes compared with the background population has been reported by various research groups.[5,6]

The risk of stroke is increased 150% to 400% in people with diabetes.[7–9] In the Multiple Risk Factor Intervention Trial (MRFIT), people taking medications for diabetes were three times as likely to develop cerebrovascular disease compared with those not receiving medications for diabetes.[5] In type 1 diabetes, the prevalence of cerebrovascular disease has varied from 4% to 21% depending on the duration of diabetes and the population studied[10–13] and was found to confer an increased risk of stroke (odds ratio 11.6; 95% confidence interval [CI]: 1.2–115.2) in a study of 201 people younger than 55 years who developed a stroke due to cerebral infarction.[14]

Diabetes is also associated with increased incidence and extent of peripheral arterial disease.[15] Thus, not only does atherosclerosis develop at a younger age in people with diabetes, it is also more diffuse and severe than that found in people without diabetes. People with diabetes have a two- to fourfold increased risk of peripheral arterial disease.[16]

Ultrasonographic assessment of endothelial function of brachial artery flow-mediated dilatation and evaluation of carotid intima-media thickness (CIMT) have been used as a surrogate marker of CVD in people with diabetes.

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Endothelial function and CVD

Endothelial dysfunction precedes the development of atherosclerosis and is believed to play a central role in its pathophysiology. Ludmer and colleagues first demonstrated impaired endothelial-dependent vasodilatation in the presence of atherosclerosis.[17] Endothelial dysfunction in the peripheral vessels are modestly correlated with the endothelial function in the coronary vessels.[18,19]

Flow-mediated dilatation in response to postocclusive reactive hyperemia has been used to noninvasively assess endothelial function in the peripheral vascular system.[20] Brachial flow-mediated dilation (FMD) has been found to be inversely associated with CIMT.[21–23] In the Cardiovascular Risk in Young Finns Study, FMD and CIMT were measured in 2109 healthy people aged 20 to 39 years.[21] Individuals were classified into subgroups as those with impaired, intermediate, and enhanced FMD if the FMD was <10th percentile, between 10th to 90th percentile, and >90th percentile, respectively. The number of cardiovascular risk factors was correlated with increased CIMT in those individuals with impaired or intermediate FMD, but not in those with enhanced FMD, which suggests a crucial link between CIMT and endothelial dysfunction, with the latter appearing to be essential for cardiovascular risk factors to be able to contribute to atherosclerosis in the arterial wall.

CIMT

CIMT is the area of tissue starting at the luminal edge of the artery and ending at the boundary between the media and the adventitia (Figure 1).[24] It is measured using B-mode ultrasound as the composite thickness of the intima and media. The 'double-line pattern' is thus the distance between the two echogenic lines that represent the lumen–intima interface and the media–adventitia interface. CIMT in healthy middle-aged adults measures 0.6 to 0.7 mm and greater than 1.20 mm is considered abnormal.[25] CIMT is age-dependent and increases at a rate of 0.005 to 0.010 mm/year.[26] Thus, in younger individuals, a CIMT of greater than 1.00 mm would be considered abnormal.[27]

Iglesias del Sol and colleagues measured the CIMT at the common carotid, bifurcation, internal carotid, and combined CIMT and found that the area under the receiver operator characteristic (ROC) curves, as a predictor of coronary artery disease, for these segments were 0.67 (95% CI: 0.61–0.73), 0.69 (0.63–0.75), 0.67 (0.61–0.73), and 0.67 (0.61–0.73), respectively.[28] Thus the authors concluded that all the measurement sites had the same ability to predict future cardiovascular events.

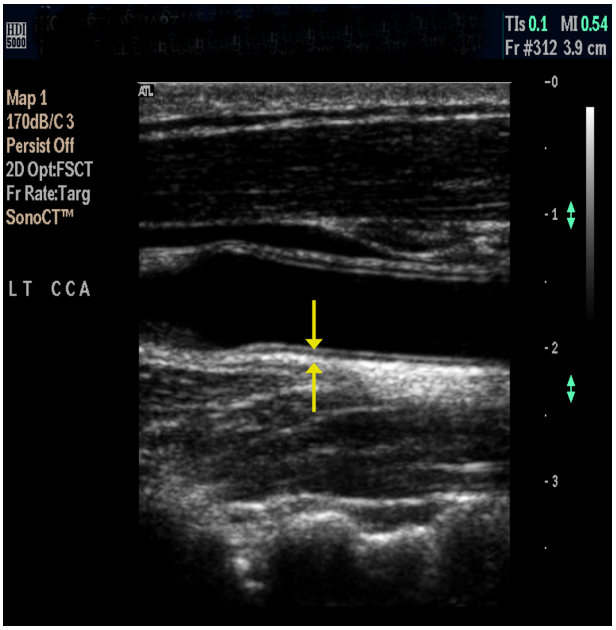

Figure 1 Carotid intima-media thickness measured at the far wall of the common carotid artery using the double-line pattern.

Limitations of CIMT measurement

There is no standardized protocol for measurement of CIMT. This can result in inaccurate measurements of the progression or regression of CIMT during the follow up studies or in the assessment of any therapeutic interevention on the measured CIMT. Since the implementation of the edge detection software there has been improved reproducibility and reduced interobserever variation.[29]

Different portions of the carotid artery have been used to measure the CIMT, common carotid, bifurcation, internal carotid, and combined CIMT which may influence the value of the measured CIMT. However in the study by Iglesias del Sol and colleagues CIMT was measured at the common carotid, bifurcation, internal carotid, and combined CIMT and they found that all the measurement sites had the same ability to predict future cardiovascular events.[28]

Measurement of CIMT involves a combined measure of the intimal and medial layer of the arterial wall, whereas the atherosclerotic process is restricted in the intimal layer, particularly in its early phase of atherosclerosis. Furthermore, CIMT is only an indirect assessment of the possible atherosclerotic burden in the coronary artereries which is the commonest cause of cardiovascular death. In a systematic review, Bots and colleagues reviewed 34 studies on the relationship of CIMT to coronary atherosclerosis. Thirty of these studies showed a modest positive relationship, the magnitude of which was similar to that found in autopsy studies. The modest relationship between CIMT and coronary

atherosclerosis most likely reflects variability in atherosclerosis development between the vascular beds rather than limitations of CIMT measurements.[30]

Lastly, measured CIMT is not only a reflection of the atherosclerotic burden in the carotid arteies but also reflects age-related changes, and it is imperative that the age of an individual is taken into account when CIMT is measured.

CIMT – ultrasound vs histology

Ultrasonographic measurements of CIMT compared with histological measurements at the far-wall have been found to provide an accurate estimation of the IMT.[31–33] Pignoli and colleagues compared pathological findings in vitro or in situ at autopsy with ultrasonographic measurement of intima-media thickness (IMT) of the aorta and the common carotid arteries.[34] The authors found an error of less than 20% for measurements in three-quarters of normal and pathological aortic walls. In addition, no significant difference was found between the ultrasonographic measurement in the common carotid arteries evaluated in vitro and that determined by this method in vivo in young subjects indicating that ultrasonography represents a useful approach for the measurement of IMT in human arteries in vivo.

CIMT and CVD

CIMT is a surrogate marker of atherosclerosis and provides a noninvasive method for the risk assessment of CVD.[35–38] It is a strong predictor of future cardiovascular events and is associated with conventional markers of cardiovascular risk such as age, diabetes and serum cholesterol.[39,40]

CIMT is a well-established index of atherosclerosis that correlates with prevalent and incident coronary artery disease[41,42] and stroke.[43,44] Studies have shown a relationship between atherosclerosis in the carotid and coronary arteries.[45,46] Furthermore, statistically significant correlations (range 0.3–0.5) between CIMT and coronary atherosclerosis, the latter based on a coronary angiogram, coronary calcium studies, or intravascular ultrasound, have been noted.[30,47,48]

CIMT is associated with cardiovascular risk factors[49] and both prevalent and incident coronary artery disease and stroke.[41,44,50,51] Furthermore, the progression of CIMT is influenced by cardiovascular risk factors and is directly related to the risk of future cardiovascular events.[48,52] CIMT has therefore become a valuable research tool in clinical trials in the assessment of therapeutic agents directed against atherosclerosis. Thus, on account of these characteristics, CIMT has been used as an intermediate end point to assess the therapeutic efficacy of various interventions in a number of clinical studies.[53]

In a meta-analysis of 37197 individuals followed-up for a mean duration of 5.5 years, Lorenz and colleagues found that a 0.1 mm absolute difference in CIMT was associated with a relative risk of myocardial infarction of 1.15 (95% CI: 1.12–1.17) and a relative risk of stroke of 1.18 (95% CI: 1.16–1.21).[54]

Studies have also demonstrated association between cardiovascular risk and increased CIMT in people with type 1 diabetes.[55–57]

In the recent Multi-Ethnic Study of Atherosclerosis (MESA), coronary artery calcium (CAC) scoring was compared to CIMT in predicting CVD incidence in 6698 individuals aged 45 to 84 years who were asymptomatic and free of CVD at baseline. The study found that compared with CIMT, CAC was more strongly associated with incident CVD in the overall population. In contrast, CIMT was found to be a modestly better predictor of stroke than CAC scoring, which could be perhaps the result of the difference between vascular territories targeted by the two measures.[58] Although the CAC estimation was a better predictor of incident CVD in this study, measurement of CAC has a major disadvantage of exposing people to ionizing radiation.

CIMT and cardiovascular risk factors

A number of risk factors have been associated with the development of atherosclerosis in the carotid arteries. The findings that the risk factors that predict CIMT are those that also predict coronary artery disease is concordant with the evidence that atherosclerosis is a diffuse disease.[59] These risk factors include increasing age,[60–62] male sex,[63] smoking,[61–64] blood pressure,[61–64] measures of adiposity such as body mass index,[60,65] waist-to-hip ratio,[66] sedentary lifestyle,[66] family history,[67] ethnicity,[68] and the presence of diabetes or glucose intolerance.[63,64,66] CIMT has also been reported to be associated with serum cholesterol,[60–64] triglyceride levels,[60] high-density lipoprotein (HDL) cholesterol,[60–64] low-density lipoprotein LDL cholesterol,[65] high-sensitivity C-reactive protein,[69] and asymmetric dimethylarginine.[70]

A number of studies have evaluated the determinants of change in CIMT over time.[71] The Atherosclerosis Risk in Communities (ARIC) study among 15,792 individuals aged 45 to 64 years reported statistically significant associations of change in CIMT with baseline diabetes, current smoking, HDL cholesterol, pulse pressure, white blood cell count, and fibrinogen during the follow-up from 1987 to 1998.[72] Furthermore, significant associations were found between change in CIMT and change in LDL cholesterol, and serum triglyceride

and with onset of diabetes and hypertension, during the follow-up. Data from the Rotterdam study among 3409 men and women aged ≥55 years, in which CIMT was measured twice 6.5 years apart, indicated that moderate to severe progression of CIMT (above the 60th and 90th percentile of CIMT, respectively) was related to age, body mass index, male sex, current smoking, systolic blood pressure, and the presence of hypertension.[73] Lipid levels, however, were not related to increased progression of CIMT. Recently, the Carotid Atherosclerosis Progression Study among 3383 men and women found that age, male sex, hypertension, presence of diabetes, and smoking were related to increased progression of internal CIMT over 3 years, whereas no relation was found for common CIMT.[74]

These studies suggest that CIMT is increased in the presence of risk factors associated with CVD and furthermore, the progression of CIMT is associated with cardiovascular risk factors.

CIMT in people with type 1 diabetes

Several research groups have found an association between type 1 diabetes and CIMT.[55,57,75–79] Yamasaki and colleagues evaluated CIMT to assess the carotid arteries in 105 young patients with type 1 diabetes, 529 patients with type 2 diabetes, and 104 nondiabetic healthy people subjects. People with type 1 diabetes had significantly higher CIMT than healthy controls, whereas people with noninsulin-dependent diabetes showed CIMT values equivalent to those in normal adults. They reported that on multiple regression analysis CIMT in insulin-dependent diabetes patients was positively related to the duration of diabetes as well as to age. No other possible risk factors, such as serum total cholesterol level, serum HDL cholesterol level, LDL cholesterol, serum triglycerides, serum lipoprotein(a) level, or systolic or diastolic blood pressure showed any significant correlations. However, non-HDL cholesterol, smoking, and systolic hypertension were independently responsible for increases in CIMT values of type 2 diabetes patients as well as age and duration of diabetes.[55] Larsen and colleagues reported higher CIMT values in people with type 1 diabetes. They also reported a significant association between the glycosylated hemoglobin (HbA_{1c}) levels and CIMT ($r^2 = 0.77$; $P < 0.0001$ when adjusted for age) in women with type 1 diabetes, though no such correlation was seen in men. Among women, a significant association was also found between CIMT and the percentage of coronary vessel area stenosis, measured by intravascular ultrasound.[57] The Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group found that traditional cardiovascular risk factors including increasing age, smoking, and LDL cholesterol were related to CIMT.[80] In a further study, 40 people aged 11 to 30 years with duration of type 1 diabetes of 3 to 25 years compared with 40 healthy controls confirmed a higher CIMT in the cohort with diabetes (0.6 ± 0.1 vs 0.4 ± 0.1 mm; $P < 0.001$). CIMT was found to correlate with age ($r = 0.76$; $P < 0.001$), body mass index ($r = 0.82$; $P < 0.001$), duration of diabetes ($r = 0.66$; $P < 0.001$), systolic blood pressure ($r = 0.82$; $P < 0.001$), diastolic blood pressure ($r = 0.83$; $P < 0.001$), HbA_{1c} ($r = 0.40$; $P = 0.004$) and HDL ($r = -0.88$; $P < 0.001$).[81]

In an observational longitudinal study over a period of 2.5 years of 102 people with type 1 diabetes, CIMT increased by a mean of 0.033 mm per year.[82] Furthermore, CIMT was found to correlate with age ($r = 0.34$; $P < 0.01$), diabetes duration ($r = 0.25$; $P < 0.05$) and systolic blood pressure ($r = 0.28$; $P < 0.05$) at baseline. In addition, the maximum change in CIMT was observed in people who had hypertension and nephropathy. CIMT has been reported to be increased in children with type 1 diabetes compared with healthy controls.[83,84] Atherogenic risk factors such as systolic blood pressure, duration of diabetes, and body weight were positively correlated with CIMT in children and adolescents with type 1 diabetes.[84]

In type 1 diabetes, the increase in CIMT has been shown to start in childhood and adolescence by some[55,75] but not all studies.[85,86] In a recent study of young children with type 1 diabetes with modest glycemic control, Margeirsdottir and colleagues reported increased CIMT despite intensive insulin treatment.[86] In another study, Schwab and colleagues reported increased CIMT in the pediatric population (body mass index), markers of sustained inflammation, endothelial dysfunction, and fibrinolytic activity were increased in diabetic versus nondiabetic children, none of these measures being significant correlates of CIMT. The authors reported that that in well-controlled type 1 diabetes, systolic blood pressure may be of greater importance than dyslipidemia in early atherogenesis.[84]

In a study of young people with type 1 diabetes without known macrovascular disease or microalbuminuria, CIMT was found to be increased by 25% ($P < 0.001$) in type 1 diabetes compared with healthy controls.[22]

CIMT in people with impaired glucose tolerance and type 2 diabetes

People with impaired glucose tolerance (IGT) have been shown to have endothelial dysfunction and are at increased risk of CVD. CIMT has been observed to be increased in people

who would subsequently develop diabetes.[87] Yamasaki and colleagues have reported that people with IGT had increased CIMT and there was no difference in CIMT among the people with IGT and age- and sex-matched people with type 2 diabetes.[88] In another study postchallenge glucose levels were strongly associated with CIMT in people at risk of diabetes or who were at the early stages of type 2 diabetes.[89] These studies suggest that people with IGT or at the early stages of type 2 diabetes are already at increased risk of CVD.

A review of 21 studies including 24,111 people with type 2 diabetes (n = 4019) and IGT (n = 1110) found that CIMT was higher in individuals with diabetes compared to the healthy controls. Compared with healthy controls, CIMT was increased in individuals with type 2 diabetes by 0.13 (95% CI: 0.12–0.14) mm and by 0.04 (95% CI: 0.01–0.07) mm in individuals with IGT.[90] Other research groups have found CIMT to be increased in type 2 diabetes.[91–93] Furthermore, CIMT has been demonstrated to be higher in people with diabetes and macrovascular disease.[94] In a prospective study, Bernard and colleagues reported that CIMT provides a similar predictive value for coronary events compared with the Framingham score, and suggested that the combination of these two indexes would significantly improve risk prediction in these patients.[95]

A study was conducted in 98 people with type 2 diabetes with no known CVD to ascertain the clinical usefulness of CIMT in identifying those individuals in whom the single-photon emission computed tomography myocardial perfusion imaging is abnormal.[96] An increased CIMT was found to be significantly related to the presence and extent of abnormal myocardial perfusion. In another study, the usefulness of CIMT in predicting the presence of coronary artery disease, as detected by noninvasive computed tomographic coronary angiography, in asymptomatic people with diabetes was investigated (n = 150, aged 50 ± 13 years, 83 men).[97] Mean CIMT increased from 0.58 ± 0.08 mm in those with normal coronary arteries (n = 59, 39%), to 0.67 ± 0.12 mm in those with nonobstructive atherosclerosis (n = 54, 36%) and 0.75 ± 0.12 mm in those with obstructive stenosis defined as a ≥50% narrowing of the luminal diameter (n = 36, 25%; $P < 0.01$). Furthermore, a cut-off value of 0.67 mm for CIMT predicted obstructive coronary atherosclerosis with a sensitivity of 85% and specificity of 72%.

CIMT has been shown to be a predictor of incidence and recurrence of stroke.[44,98] Similarily, increased CIMT has been found to be associated with increased risk of ischemic stroke in people with type 2 diabetes.[99,100] Increased CIMT and plaque score have been demonstrated to correlate with acute ischemic stroke in patients with type 2 diabetes.[99]

Along with hyperglycemia, other metabolic factors associated with diabetes that are known to increase cardiovascular risk including obesity, insulin resistance, hypertension, hyperlipidemia, and increased inflammatory state have all been shown to contribute to progression of CIMT in people with diabetes.[98,99,101,102] The Relationship between Insulin Sensitivity and Cardiovascular disease (RISC) study conducted in 1326 European nondiabetic healthy individuals aged 30 to 60 years measured CIMT and its associations with fasting insulin and insulin resistance by performing standard oral glucose tolerance tests and hyperinsulinemic euglycemic clamps.[103] CIMT was statistically significantly associated with fasting insulin in healthy people. In contrast, Kong and colleagues studied normotensive individuals with type 2 diabetes and found no association between CIMT and fasting insulin or insulin sensitivity as assessed with an insulin-modified frequently sampled intravenous glucose tolerance test.[104]

Thus CIMT is increased in people with diabetes from a young age. The progression of CIMT is associated with the traditional risk factors of CVD such as hypertension and dyslipidemia.

CIMT and microvascular complications

CIMT has been shown to be increased in people with type 1 diabetes and retinopathy.[105,106] In a cross-sectional study, the severity of retinopathy was found to be associated with CIMT (odds ratio per 0.1 mm CIMT 1.09 [95% CI: 1.01–1.17; $P = 0.01$]),[107] consistent with studies in people with type 2 diabetes.[108,109] In a recent study, Vigili de Kreutzenberg and colleagues studied the association between diabetic retinopathy and CIMT in people with type 2 diabetes. The authors reported that retinopathy either alone or in combination with nephropathy, is independently associated with CIMT in people with type 2 diabetes, and the severity of microangiopathy correlates with severity of carotid atherosclerosis.[110] In another study of people with type 1 diabetes, the association between CIMT and microangiopathic complications including retinopathy or nephropathy was reported.[111]

Effect of therapeutic interventions on CIMT in people with diabetes

Blood glucose lowering in type 1 and type 2 diabetes and CIMT

A 16-week intensive lifestyle modification program and subsequent monthly meetings during the 6-month study period in 58 people with type 2 diabetes was found to be associated

with a significantly reduced mean CIMT progression after 6 months (–0.040 ± 0.136 vs +0.083 ± 0.167 mm; $P = 0.007$).[112] Furthermore, changes in HbA_{1c} ($r = 0.34$; $P = 0.028$), fasting plasma glucose ($r = 0.31$; $P = 0.045$), and 2-hour postprandial plasma glucose ($r = 0.37$; $P = 0.015$) correlated with the mean CIMT change after adjustment for age and sex. Thus, in addition to improved blood glucose control, lifestyle measures have decreased progression of CIMT. Data analyses from 11 studies (n = 1578) in people with type 2 diabetes and IGT evaluated the effect of interventions on change in CIMT. The annual increase of CIMT was 0.034 mm/y (95% CI: 0.029–0.039) in people with type 2 diabetes without any specific interventions in which mean HbA_{1c} was 7.86%. A significant close correlation of HbA_{1c} with rate of CIMT change was found ($r = 0.35$; $P = 0.01$). Agents for lowering of blood glucose, platelet activation, or blood pressure significantly reduced the CIMT increase, independent of blood glucose control.[113]

As part of the EDIC study, the long-term follow-up of the Diabetes Control and Complications Trial (DCCT), 1229 people with type 1 diabetes (intensive blood glucose lowering arm n = 618; conventional blood glucose lowering arm n = 611) underwent internal and common CIMT measurements in 1994 to 1996 and again in 1998 to 2000.[56] Although CIMT was not statistically significantly different between the people with diabetes and the healthy controls after 1 year of follow-up in the EDIC study,[114] CIMT was significantly greater in people with type 1 diabetes compared with the healthy controls after a follow-up of 6 years in the EDIC study.[56] Furthermore, the progression of CIMT in the common carotid artery was significantly less in the group that received intensive therapy than in the group that received conventional therapy during the DCCT (0.032 vs 0.046 mm; $P = 0.01$) after adjustment for other risk factors. Factors that were associated with progression of CIMT were age, the EDIC base-line systolic blood pressure, smoking, ratio of LDL to HDL cholesterol, urinary albumin excretion rate, and the mean HbA_{1c} during the DCCT.

A Japanese study randomized individuals with type 2 diabetes without known macrovascular disease to pioglitazone with or without other oral glucose-lowering agents (n = 89) or other oral glucose-lowering agents excluding thiazolidenediones (n = 97), with treatment goal of $HbA_{1c} < 6.5\%$. The authors found that pioglitazone induced regression of mean CIMT from 0.839 ± 0.1873 to 0.780 ± 0.1571 mm; $P = 0.002$), although the between-group difference did not reach statistical significance.[115]

The Pioglitazone in the Prevention of Diabetes (PIPOD) study assessed the effects of pioglitazone in Hispanic women with prior gestational diabetes mellitus who had previously completed the troglitazone in the Prevention of Diabetes (TRIPOD) study.[116–118] Thirty-one women came to PIPOD from the troglitazone arm while 30 came from the placebo arm of TRIPOD. During the 3-year follow-up, the 31 women who came to PIPOD from the troglitazone arm of TRIPOD were found to have a lower progression of CIMT of 38% during pioglitazone treatment than during troglitazone treatment, although this was not statistically significant (0.0037 vs 0.0060 mm/year; $P = 0.260$). The progression of CIMT was 69% lower during pioglitazone treatment than it had been during placebo in the 30 women who came to PIPOD from the placebo arm of TRIPOD (0.0031 vs 0.0100 mm/year; $P = 0.006$). The authors concluded that pioglitazone slows progression of CIMT in women who had been on placebo in the TRIPOD study and maintained a low rate of progression in those who had previously been treated with troglitazone. The low CIMT progression during treatment with the thiazolidendiones was speculated to be due to PPAR-γ activation in the vasculature and change in proinflammatory and prothrombotic markers.[119,120]

A greater reduction in CIMT independent of improved glycemic control, after 12 and 24 weeks of pioglitazone treatment, compared to glimeperide in 173 people with type 2 diabetes has been reported.[121] These data were later confirmed by Mazzone and colleagues in 462 people with type 2 diabetes (mean age 60 years) during a 72-week study. The authors found that the mean change in CIMT was less with pioglitazone than with glimepiride (–0.001 mm vs +0.012 mm, respectively; difference –0.013 mm; $P = 0.020$).[122]

In another study, pioglitazone, but not glibenclamide or voglibose, was found to reduce CIMT in people with type 2 diabetes and diabetic nephropathy at 6- and 12-month follow-up.[123]

In the randomized, placebo-controlled, Study of Atherosclerosis with Ramipril and Rosiglitazone (STARR), the effect of ramipril and of rosiglitazone on CIMT in people with IGT or impaired fasting glucose (IFG) was investigated.[124] People with IGT and/or IFG but without CVD or diabetes (n = 1425) were randomized to ramipril 15 mg/day or its placebo and to rosiglitazone 8 mg/day or its placebo with a 2 × 2 factorial design. The annual change of the maximum CIMT and the mean common CIMT were measured after a median follow-up of 3 years. Rosiglitazone significantly reduced the mean CIMT (difference 0.0043 ± 0.0017 mm/y,

$P = 0.010$) but not the maximum CIMT. In contrast, there was no statistically significant difference between the ramipril and placebo groups.

In another study, glibenclamide in combination with metformin was associated with reduced progression of CIMT (0.003 ± 0.048 mm) compared with glibenclamide alone (0.064 ± 0.045 mm) and gliclazide group (0.032 ± 0.036 mm) ($P < 0.0001$ and $P = 0.043$ respectively).[125] The annual progression of maximum CIMT in the gliclazide group (0.044 ± 0.106 mm) and the glibenclamide plus metformin group (0.041 ± 0.105 mm) was smaller than that of the glibenclamide group (0.114 ± 0.131 mm). Attenuation of the CIMT progression by metformin in people with type 2 diabetes has been confirmed by others.[126] Metformin has antithrombotic effects, modulates the generation of reactive oxygen species, and reduces systemic methylglyoxal concentration, all of which might contribute to the beneficial effect on CIMT.[127,128]

The Copenhagen Insulin and Metformin Therapy trial aims to assess the effect of an 18-month treatment with metformin versus placebo in combination with one of three insulin analog regimens, with CIMT being the primary outcome measured in 950 individuals with type 2 diabetes. The three insulin regimens compared are 1) insulin detemir before bedtime (n ~ 315 patients), 2) biphasic insulin aspart 30 before dinner with the possibility to increase to 2 or 4 injections daily (n ~ 315 patients), and 3) insulin aspart before the main meals (three times daily) and insulin detemir before bedtime (n ~ 315 patients).[129]

In the prospective, randomized, placebo-controlled, Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial, an α-glucosidase inhibitor, acarbose, delayed progression from IGT to overt type 2 diabetes and reduced cardiovascular events.[130] A subgroup analysis of the STOP-NIDDM study examined the efficacy of acarbose on progression of CIMT in people with IGT.[131] One hundred thirty-two individuals with IGT were randomized to placebo (n = 66) or acarbose (n = 66). After a mean follow-up of 3.9 years, significant reduction in the progression of CIMT was observed in the acarbose group versus placebo. CIMT increased by 0.02 ± 0.07 mm in the acarbose group versus 0.05 ± 0.06 mm in the placebo group ($P = 0.027$). The annual increase of CIMT was reduced by approximately 50% in the acarbose group versus placebo. CIMT progression was significantly related to acarbose intake on multiple linear regression analyses. As the primary effect of acarbose is on meal-time hyperglycemia, these data supported the importance of postprandial hyperglycemia.

A substudy was performed in 175 of 401 individuals with type 2 diabetes who had participated in an epidemiological study to assess the relationship between postprandial hyperglycemia and surrogate markers of atherosclerosis.[132] The effects of repaglinide (n = 88) and glyburide (n = 87) on CIMT were compared after 12 months. Although, HbA_{1c} improved to a comparable extent in both groups (–0.9%), the postprandial glucose peak was lower in the repaglinide group ($P < 0.010$). CIMT regression, defined as a decrease of >0.020 mm, was noted in a greater proportion of people on repaglinide (52%) than on glyburide 18% ($P < 0.010$). Furthermore, the reduction in CIMT was associated with changes in postprandial but not fasting hyperglycemia. These data add to recent research, which suggests that postprandial hyperglycemic excursions may be more important than basal hyperglycemia in triggering atherosclerosis.

Antihypertensive agents and CIMT in people with diabetes

Post-hoc analyses of the association between antihypertensive treatment and CIMT in the Troglitazone Atherosclerosis Regression Trial (TART), which assessed CIMT progression in adults with insulin-treated type 2 diabetes, found that higher systolic blood pressure was associated with a higher CIMT progression rate ($P = 0.03$). Furthermore, anti-hypertensive treatment reduced this association in a duration-dependent manner (interaction $P = 0.035$).[133]

Hosomi and colleagues did a prospective randomized clinical trial of 98 patients with type 2 diabetes who were randomized to either enalapril 10 mg/d (n = 48) or to a control group (n = 50) for 2 years.[134] The enalapril-treated group was found to have reduced annual thickening of the common carotid arteries by 0.01 ± 0.004 mm/y relative to the control group over the course of this study. These data concur with other data which showed that angiotensin-converting enzyme (ACE) inhibitors led to a reduction in myocardial infarction, stroke, cardiovascular death, total mortality, revascularization, and overt nephropathy.[135] Importantly, the D allele of the *ACE* gene has been shown to be an independent risk factor for coronary artery disease and with CIMT in individuals with type 2 diabetes.[136,137]

Lipid-lowering treatment and CIMT in people with diabetes

People with type 2 diabetes without prior cardiovascular events participated in the Stop Atherosclerosis in Native Diabetics Study (SANDS) trial and were randomized to a standard

group (target LDL cholesterol ≤2.6 mmol/L; non-HDL cholesterol ≤3.4 mmol/L; systolic blood pressure ≤130 mmHg) and an aggressive group with tighter targets (target LDL cholesterol ≤1.8 mmol/L; non-HDL cholesterol ≤2.6 mmol/L; systolic blood pressure ≤115 mmHg), and were treated with statins alone or statins plus ezetimibe.[138] The CIMT changes in both aggressive subgroups were compared with changes in the standard subgroups (target LDL cholesterol ≤2.6 mmolL; non-HDL cholesterol ≤3.4 mmol/L; systolic blood pressure ≤130 mmHg). Within the aggressive group, mean CIMT at 36 months regressed from baseline similarly in the ezetimibe (−0.025 mm, range −0.05 to 0.003 mm) and nonezetimibe subgroups (−0.012 mm, range −0.03 to 0.008 mm) but progressed in the standard treatment arm (0.039 mm, range 0.02–0.06 mm; intergroup; $P < 0.0001$). The authors concluded that reducing LDL cholesterol to aggressive targets resulted in similar regression of CIMT in patients who attained equivalent LDL cholesterol reductions from a statin alone or statin plus ezetimibe. CIMT increased in those achieving standard targets.

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) study found that niacin resulted in a significant regression of mean and maximal CIMT whereas there was no significant change in CIMT in the ezetimibe-treated subgroup.[139] Although not powered for clinical outcomes, there were more major cardiovascular events in the ezetimibe arm than in the niacin arm (9 events vs 2 events, respectively; $P = 0.040$).

Anti-platelet therapy and CIMT in people with diabetes

Kodama and colleagues followed up 150 people aged 52 to 76 years with type 2 diabetes and without known CVD whose baseline CIMT was >1.1 mm.[140] Antiplatelet agents (aspirin 81 mg/day, n = 40; ticlopidine 200 mg/day, n = 36; no drugs n = 74) were administered. Individuals without anti-platelet agents had an annual progression of CIMT of 0.067 mm/y. In contrast, low-dose aspirin or ticlopidine attenuated the progression of CIMT by 50% (0.033 mm and 0.034 mm/year, respectively).

More recently, the prospective, randomized, open-label, blinded Diabetic Atherosclerosis Prevention by Cilostazol (DAPC) study showed that in people with type 2 diabetes suspected of peripheral artery disease, a phosphodiesterase inhibitor, cilostazol (100–200 mg/day) caused greater regression in the maximum and mean CIMT compared with aspirin (81–100 mg/day) during a 2-year observation period (mean left CIMT −0.043 ± 0.182 vs 0.028 ± 0.202 mm; $P = 0.004$; mean right CIMT −0.024 ± 0.182 vs 0.048 ± 0.169 mm; $P < 0.001$).[141]

Conclusions

Diabetes is associated with increased cardiovascular and cerebrovascular disease-related mortality. Early identification of people at higher risk can influence the treatment strategies to reduce the morbidity and mortality. CIMT measurement is a relatively easy, noninvasive technique to identify atherosclerosis. People with diabetes have higher CIMT than the healthy population. CIMT increases in the presence of micro- and macrovascular complications of diabetes. Several treatment strategies in diabetes which have been shown to reduce diabetic complications also cause regression of CIMT. Thus, routine measurement of CIMT may add value to risk stratification and facilitate better use of various treatment strategies in people with diabetes.

Assessment of CIMT provides an excellent opportunity to evaluate the atherosclerotic risk in people with diabetes and can further be used to facilitate better use of various treatment strategies in people with diabetes. Further randomized studies would be required to assess the role of CIMT in predicting the development of various complications and how various available treatment strategies could be incorporated to influence the outcome.

Disclosure

The authors report no conflicts of interest in this work.

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