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# Correlations between Body Compositions with Subclinical Atherosclerosis as Assessed by Carotid Artery Intima Media Thickness in Patients with Type 2 Diabetes Mellitus: A Single Centre Study in Southern Sri Lanka

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## ABSTRACT

**Background**: Type 2 diabetes mellitus (T2DM) is a risk factor for atherosclerosis. Subclinical atherosclerosis is identified by measuring carotid artery intima media thickness (CIMT) with ultrasound. This study describes selected factors associated with CAIMT and cardiovascular disease (CVD) risk in patients with T2DM.

**Materials and methods**: Data of 212 patients registered at a diabetes center in Southern Sri Lanka was analyzed. Details on demographic characteristics, anthropometry, fat mass, glycated haemoglobin ($HbA_{1c}$) level and CIMT of both common carotid arteries were collected. Association of these parameters with CIMT was elicited using appropriate statistical tests.

**Results:** There were 98 males and 114 females with the mean age of 58±10 years. Majority of them had overweight and obesity. Poor glycemic control (HbA1c>7%) was detected in 164 (73.3%) patients. There were 166 (78.3%) patients with increased CVD risk (≥ $75^{th}$ percentile CIMT) based on age and gender specific values. Significant positive correlations were observed between mean CIMT and mean age (r=0.308, p=0.001), age of initial detection of T2DM (r=0.180, p=0.008), duration of T2DM (r=0.228, p=0.001), mean $HbA_{1c}$ (r=0.206, p=0.003) and visceral adiposity (r=0.239, p=0.001). Males had significantly higher mean CIMT (0.736±0.16 vs. 0.678±0.011, p=0.003) and visceral fat (12.3±5.0 vs. 9.9±3.9, p=0.001) than females.

**Conclusions:** This study underscores that a majority of T2DM patients demonstrated both obesity and suboptimal glycemic control, thus elevating their CVD risk. Factors including age, duration of T2DM, late age of diagnosis, elevated levels of visceral fat, and poor glycemic control were substantively correlated with increased CIMT.

## INTRODUCTION

There is a rapid increase in the burden of type 2 diabetes mellitus (T2DM) globally and the incidence is projected to be alarmingly high in the future, leaving 552 million people with T2DM by the year 2030 (Guariguata et al., 2014; Whiting et al., 2011). The situation in Sri Lanka is similar and according to the Indoor Morbidity and Mortality Return in 2016, both T2DM and Cardiovascular diseases (CVD) are among the major causes of hospital deaths (Ministry of Health, Sri Lanka.,2016). An individual with T2DM has increased CVD risk which is about two to three times higher compared to the general population (Carson et al., 2014; Juutilainen et al., 2008). The incidence of CVD and cardio-metabolic risk factors are increasing among Sri Lankans (Arambewela et al., 2018; Wijesuriya et al., 2012; Rannan-Eliya, et al., 2023).

Visceral fat is a key component of metabolic syndrome and it has an independent association with atherosclerosis, incidence of coronary artery disease and related events (Bergman et al., 2007). Metabolic syndrome is a common health concern among Sri Lankans at present (Katulanda et al., 2012). Furthermore, metabolic syndrome is known to increase mortality and morbidity due to CVD in patients with T2DM (Randrianarisoa et al., 2019). Poor glycaemic control in patients with DM further increases the CVD risk (Paul et al., 2015).

Estimation of carotid artery intima-media thickness (CIMT) has been used as a method of identifying subclinical atherosclerosis in patients with T2DM (Bosevski & Stojanovska, 2015). It is reported that CIMT remains a forecaster of CVD events independent of conventional CVD risk factors (Polak et al., 2011). It has been hypothesized that the atherosclerotic process initiates simultaneously in carotid, cerebral, and coronary arteries as it is a systemic process (Nambi et al., 2010). This study describes the baseline characteristics and factors associated with CIMT and CVD risk in patients with T2DM from a developing country. Therefore, this study was designed to, evaluate and characterize Cardiovascular Risk in T2DM Patients using CIMT as a marker to estimate the prevalence of subclinical atherosclerosis and assess the overall CVD risk among patients with T2DM. The objective of the study was to identify the demographic, anthropometric, and clinical factors that correlate with CIMT and the cardiovascular disease (CVD) risk in T2DM patients.

## MATERIALS AND METHODS

### Study setting

The study was conducted at a Diabetes Centre, Co-operative Hospital, Galle, Sri Lanka where the patients are referred to by physicians for regular follow-up.

### Study design and data collection

A cross-sectional extraction of data from the medical records of the patients registered at the center from 2014 to 2017 were done. This includes demographic information and anthropometric measurements, glycated haemoglobin (HbA1c) percentage, body fat and carotid arterial intima-media thickness (CIMT) in both common carotid arteries. Poor glycemic control was defined (when HbA1c was > 7%) using the American Diabetes Association guidelines (American Diabetes Association., 2018).

### Anthropometric and body fat measurements

Weight, height and waist circumference (WC) were measured following the standard protocols. Height (HT) was measured using a portable stadiometer with a precision of ± 0.1 cm and readability up to 200 cm. Weight (WT) was measured using a portable beam balance with a precision of ± 0.1 kg and readability up to 100 kg. Waist circumference (WC) was measured to the nearest 0.1 cm using a non-stretchable measuring tape. WC was measured at the midway between the iliac crest and the lower rib margin keeping the tape horizontal but not compressing the skin. All the anthropometric parameters were measured by a single person to minimize the inter-personal variability.

Body mass index (BMI) and central obesity were interpreted using the cut-off values defined for Asia-Pacific region by the World Health Organization (WHO) (WHO.,2000), accordingly, BMI ranged from ≥23 to 24.9 was considered as overweight and BMI ≥ 25 $kg/m^2$ as obese. Central obesity was defined when WC exceeds ≥ 90 cm in men and ≥ 80 in women. Body composition was estimated by Bioelectrical Impedance Analysis (BIA) machine (Omron-HBF/516B) by a single trained operator and the percentage of total body fat and visceral fat was estimated as per the protocol (Khaled et al., 1988). Western Pacific Regional Office (WPRO) of WHO reference standards for BF% was used to define obesity based on fat mass if BF% is ≥ 25% and ≥35% in men and women respectively are considered as obese (WHO., 1995).

**Carotid intima-media thickness (CIMT)**

B mode ultrasound scans of carotid arteries were performed by an experienced radiologist who was blind to clinical information and other investigation findings of the study participants. The same radiologist performed the ultrasound scans to minimize the interpersonal variability of data. “GE” ultrasound unit with standard 2D grey scale imaging with 7.5 MHz linear array transducer was used in the measurements. Greyscale amplification and time-gain compensation curve were adjusted to acquire the best quality images. A single focus point was adjusted at the level of the posterior wall of the carotid artery and the measurements were obtained from the posterior wall in optimum magnification. Both common carotid arteries were scanned up to the carotid bifurcation to identify plaques. Carotid-wall intima-media thickness was determined as the distance between the lumen-intima interface to the media-adventitia interface of the artery wall as described earlier (Yanase et al., 2006). In a longitudinal scan, the anterior and posterior walls of the carotid artery were displayed as two bright lines separated by a linear hypoechoeic zone. Carotid-wall intima-media thickness was defined as the distance between two echogenic lines, including both into the measurement and was measured in both common carotid arteries in a plaque free segment. Cardiovascular risk was ascertained based on age and gender-specific percentile cut-off values for CIMT, as outlined in prior literature (Simova, 2015).

**Data analysis**

Data were examined for normality using histogram plots and normality tests, before the analysis. Continuous variables were expressed as mean (±SD). The categorical variables were presented as frequencies and percentages. The correlation was analyzed using Pearson correlation coefficient. A comparison of the continuous variables was done using the two-sample t-test. The relationship between categorical variables was analyzed by a sample proportion test. The significance level was defined as a probability of less than 0.05.

## RESULTS

There were a total of 238 patients registered at the clinic during the period, but 212 were considered in the final analysis excluding the patients with missing data, patients with plaques in carotid arteries, and patients with history of CVD events. Table 1 shows basic characteristics. They were in the age range of 33-83 years.

**Table 1.** Basic characteristics of patients

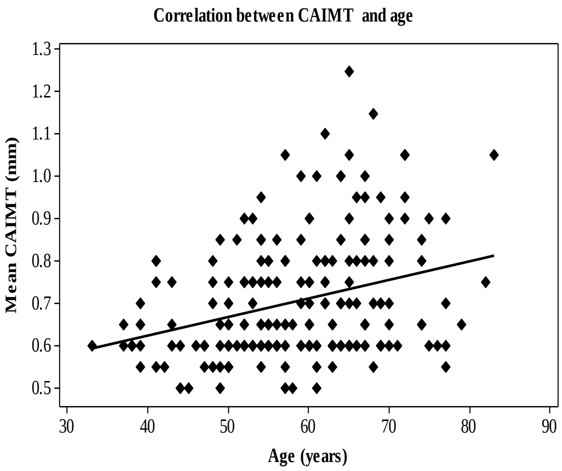
| **Characteristic** | **Patient (n=212)**<br>Mean (±SD |
|---|---|
| Age (years) | 58 ± 10 |
| Age of onset of DM (years) | 46 ± 9 |
| Duration of DM (years) | 12 ± 6 |
| BMI ($kg/m^2$) | 25.2 ± 3.7 |
| WC (cm) | 95.3 ± 11.5 |
| Total fat % | 34.0 ± 6.0 |
| Visceral fat % | 11.0 ± 4.6 |
| Glycated hemoglobin ($HbA_{1c}$) | 8.0 ± 1.4 |
| CIMT (±SD) (mm) | 0.704 ± 0.14 |
| Current smokers (n) | 17 (8.2%) |
| Current alcohol users (n) | 56 (26.4%) |

*BMI = Body mass index, WC = Waist circumference, CIMT = Common carotid artery intima media thickness. n = Number of patients. The latest values of the variables are presented. Data are presented as mean (±SD), frequencies and percentages.*

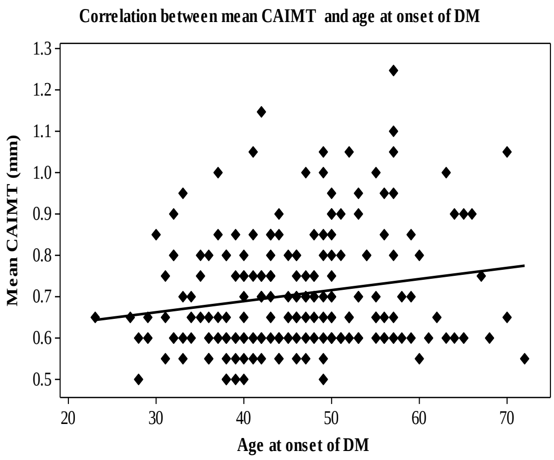
Mean right and left CIMT showed a significant positive correlation with mean age (r=0.286, p=0.001; r=0.280, p=0.001), age of initial detection of diabetes mellitus (r=0.176, p=0.010; r=0.156, p=0.023), duration of DM (r=0.202, p=0.003; r=0.215, p=0.002), mean $HbA_{1c}$ level (r=0.172, p=0.012; r=0.203, p=0.003) and percentage of visceral adiposity (r=0.219 , p=0.001) (Figures 1 A - E). However, waist circumference, BMI, and body total fat did not show significant correlation with the CIMT.

There were 146 (68.9%) patients with overweight and obesity, 62 (29.2%) with normal BMI and 4(1.9%) with underweight defined by BMI. There were 176 (83.0%) patients with obesity defined by the total body fat percentage. There were 184 (86.8 %) patients with central obesity defined according to the waist circumference. The majority of the patients had poor glycemic control 164 (73.3%) according to $HbA_{1c}$ levels. However, most of them had attended a dietician 169 (79.7%).

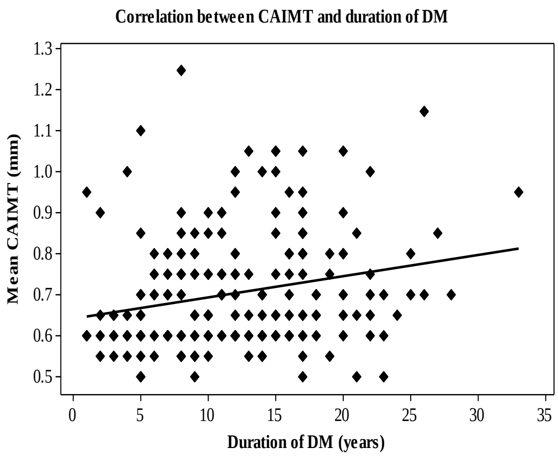
There were 166 (78.3%) patients with a high risk of CVD (≥ $75^{th}$ percentile CIMT), 37 (17.4%) with average risk, and 9 (4.2%) with low risk according to the age and gender-specific CIMT values of the right common carotid artery. According to CIMT of left common carotid artery, there were 178 (83.9%) patients with high, 28 (13.2 %) with average and 6 (2.8 %) with low CVD risk. The mean left CIMT was significantly higher than the right CIMT (0.722±0.164 VS 0.688 ± 0.143, p=0.024). Table 2 shows the comparison between males and females.



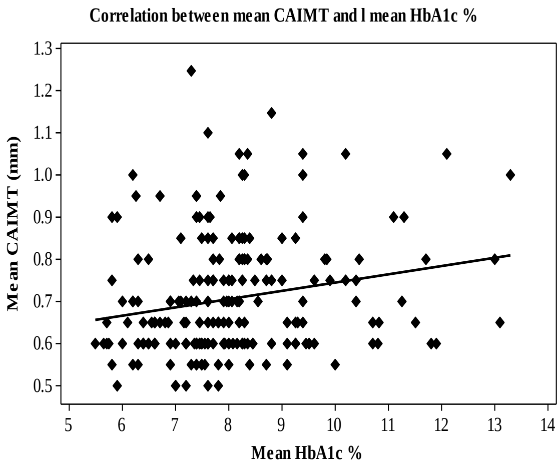

**(A)**



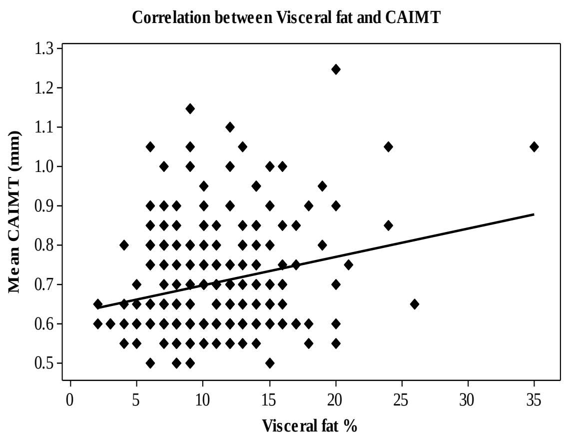

**(B)**




**(C)**




**(D)**




**(E)**

**Figure 1.** Correlation between mean CIMT and (A). Age, (B). Age at onset (initial detection) of diabetes mellitus, (C). Duration of diabetes mellitus, (D). Mean $HbA_{1c}$ level, (E). Mean visceral fat percentage

**Table 2.** Comparison of characteristics between males and females

| Characteristics | Male (n=98) Mean ± SD | Female (n=114) Mean ± SD | P |
|---|---|---|---|
| Age (years) | 59 ± 10 | 58 ± 10 | 0.374 |
| CIMT (mm) | 0.736 ± 0.16 | 0.678 ± 0.11 | 0.003 |
| Right CIMT(mm) | 0.718 ± 0.16 | 0.661± 0.11 | 0.004 |
| Left CIMT(mm) | 0.753 ± 0.19 | 0.695 ± 0.13 | 0.011 |
| Visceral fat % | 12.3 ± 5.0 | 9.9 ± 3.9 | 0.001 |
| Total fat % | 29.0 ± 4.0 | 38.2 ± 4.2 | 0.001 |
| Obesity by total fat mass (n) | 83 (84.7%) | 93 (81.6%) | 0.544 |
| BMI ($kg/m^2$) | 26.0 ± 3.9 | 24.5 ± 3.6 | 0.003 |
| Obesity and overweight by BMI (n) | 74 (75.5%) | 72 (63.1%) | 0.049 |
| Waist circumference (cm) | 95.7 ± 12.0 | 95.0 ± 11.2 | 0.679 |
| Central obesity by WC (n) | 73 (74.5%) | 111(97.4%) | 0.001 |
| $HbA_{1c}$ % | 7.83 ± 1.30 | 8.17 ± 1.58 | 0.087 |
| Poor glycemic control (n) | 73 (74.5%) | 91 (79.8%) | 0.357 |

*CIMT = Carotid artery intima media thickness, BMI = Body mass index, WC = Waist circumference, $HbA_{1c}$ = Glycated hemoglobin, n = Number of patients*

## DISCUSSION

In this study we have found in the majority, the age of onset (initial detection) of T2DM was in the fourth decade. Most of them had an increased prevalence of global obesity and central obesity, elevated fat mass and poor glycemic control. Most of the patients are at high risk for cardiovascular disease (CVD) according to common carotid arterial intima-media thickness (CIMT). According to previous studies, obesity is highly prevalent among patients with DM and increases the CVD risk. A prospective follow-up study on adult females showed that obesity or weight gain before the development of diabetes mellitus is strongly associated with coronary heart disease (Cho et al., 2002). A retrospective study done on patients undergoing coronary computed tomography angiography revealed that there was an increased burden of coronary artery disease (CAD) for BMI > 25 $kg/m^2$ compared to patients with normal BMI (Hulten et al., 2017). In Sri Lanka, the prevalence of obesity among the general population is 34.4 % defined by the Asian cut-off values according to Katulanda et al. (Katulanda et al., 2010). We have found it very high (68.9%), almost doubled in this group of patients with T2DM. They have found the prevalence of central obesity as 26.2 % while we found central obesity as 86.8% in patients with T2DM which is nearly four times. The mean age of initial detection of T2DM in adults is lower in Asians than Caucasians. It is about 53.7 and 53.8 years for Americans in 1997 and 2011 respectively (National Center for Health Statistics., 2013). Asians such as Chinese have found the onset of T2DM as 3 years earlier than Caucasians (Chiu et al., 2011). Moreover, there is a higher prevalence of young diabetes (age of onset ≤ 40 years) among Asians than Caucasians (International Diabetes Federation., 2014). We have found the initial detection of T2DM at 46 years.

Weight gain causes an unfavorable metabolic profile and is a powerful risk factor for CVD. After 2 years of follow-up of newly diagnosed patients with T2DM in

Korea, the group who had gained weight (≥ 10%) indicates a high risk for stroke while weight loss (≥ 10%) causes increased all-cause mortality (Kim et al., 2019). Weight control has been identified as a keystone in the management of diabetes mellitus (Cho et al., 2002). Weight loss has shown an association with improved glycemic control and slow progression of complications related DM. A review article by Ross et al. suggested that prevention of weight gain or weight reduction is an important strategy to maintain glycemic control and to reduce morbidity and mortality in patients with DM (Ross et al., 2011). Retrospective analysis of 3-year weight trajectories of newly diagnosed patients with T2DM demonstrated that those with higher stable weight, lower stable weight, or weight-gain patterns were more likely than those who lost weight to have above-goal $HbA_{1C}$ (Feldstein et al., 2008). A review article based on randomized-controlled trials has shown that with maximal metformin therapy, all non-insulin anti-diabetes drugs were associated with similar $HbA_{1c}$ reductions (Phung et al., 2010). Sometimes weight gain occurs as an adverse effect of drug treatment such as insulin. A retrospective study on treatment chart review for two years of patients on insulin has shown weight gain (Boldo & Comi, 2012). Further, weight is linked to increased morbidity and mortality among DM patients. In the USA a long-term follow-up study (median of 9.6 years) to assess the effect of intensive physical activities on DM patients showed that weight loss did not reduce the rate of cardiovascular events in overweight or obese adults (Wing et al., 2013). A survey conducted on the US population displayed that better medication adherence is associated with weight loss in patients with DM (Grandy et al., 2013). However, there are studies that have found a positive association between weight loss and cardiovascular morbidity and mortality in DM (Doehner et al., 2012). A study conducted among community-dwelling elderly revealed that weight change might be detrimental for the elderly and therefore stabilization of weight is recommended (Beleigoli et al., 2017).

We found that visceral fat measured by BIA is significantly associated with subclinical atherosclerosis indicated by CIMT, but the two commonly measured anthropometric measurements of obesity, BMI and WC have no significant association with CIMT. This finding highlights the lack of sensitivity of both routinely measured anthropometric measurements in assessing visceral fat content or predicting the subclinical atherosclerosis and the need for a better clinical indicator of visceral fat to screen patients in routine clinical setting. However, there are mixed findings on this. Some studies had made known that waist circumference as a determinant of subclinical atherosclerosis in community-dwelling individuals (Alizargar & Bai, 2018). Study done on a group of patients with T2DM in the USA revealed the presence of an inverse association between BMI, WC, and severity of the calcified plaque in the aorta (Yuan et al., 2016) while suggesting increased waist circumference and longer DM duration as independent predictors of CVD only in women (Hong et al., 2015). Measurements of abdominal obesity (reflected by waist-to-hip ratio and WC) correlate better than BMI with arterial stiffness and with subclinical atherosclerosis evaluated by CIMT, independently of the presence of diabetes or hypertension (Recio-Rodriguez et al., 2012). In a group of patients without T2DM or cardiovascular disease, visceral fat is a better predictor of subclinical atherosclerosis than waist circumference (Rallidis et al., 2014).

According to the present study the higher visceral fat, older age, later onset (initial detection) DM, longer duration of DM, and poor glycemic control are associated with increased CIMT which is a surrogate marker of atherosclerosis. The inclusion of CIMT makes the screening superior to detecting coronary artery diseases in asymptomatic patients with T2DM (Akazawa et al., 2016). A prospective analysis done on members of the Framingham Offspring study cohort has shown that mean common carotid arterial thickness predicts the cardiovascular outcome and it improves the classification of risk of CVD when added to the Framingham risk score (Polak et al., 2011). Further, a longitudinal study among a Finish cohort has discovered a close relationship between carotid arterial structural change (reflected in ultrasonography) with ischemic heart disease (Salonen & Salonen, 1991). A nested case-control study using the participants of the Rotterdam study demonstrated that CIMT is associated with cerebrovascular and cardiovascular events (Bots et al., 1997). A Japanese study has revealed endothelial dysfunction with excess visceral adipose tissue in patients with T2DM (Kurozumi et al., 2016). A cross-sectional study on Japanese exhibits high visceral fat with low subcutaneous fat accumulation as an important determinant of carotid atherosclerosis in patients T2DM (Bouchi et al., 2015). A Romanian study demonstrated that age, $HbA_{1c}$ and visceral fat area are independent predictors of CIMT and therefore controlling abdominal obesity and hyperglycemia (Silaghi et al., 2015). A follow-up study done on patients undergoing coronary angiography showed that duration of T2DM was strongly and positively correlated with all-cause and cardiovascular mortality (Silbernagel et al., 2012).

In this group, male patients had higher mean CIMT, BMI, visceral fat percentage, and a higher proportion of overweight and global obesity (based on BMI) compared to females. In contrast, females had a higher total fat percentage and a higher proportion of patients with abdominal obesity defined by waist circumference compared to males. However, there was no significant difference of mean age, waist circumference, $HbA_{1c}$ percentage and proportion of patients with poor glycemic control between males and females. Existing literature suggests that CIMT would increase with conventional CVD risk factors such as age and male gender (Davis et al., 2001; Silaghi et al., 2015), presence of DM, hypertension and its duration (Rynkowska-Kidawa et al., 2018; Sharma et al., 2009), metabolic syndrome and abdominal obesity (Kerimkulova et al., 2018). A higher proportion of visceral adiposity may alter adipokine profile predisposing the patients to develop CAD (Konishi et al., 2009) and is identified as an independent predictor of diabetes mellitus according to a follow up study among Koreans (E. H. Kim et al., 2018).

The present study is confined to a single center, which inherently restricts the generalizability of the findings across diverse healthcare settings. Future multi-center studies are recommended to validate and extend the observed results.

## CONCLUSIONS

In conclusion the present study elucidates that a significant proportion of patients with T2DM were burdened with obesity and suboptimal glycemic control, consequently elevating their risk for cardiovascular disease as evidenced by elevated CIMT. Moreover, the study found that the initial diagnosis of diabetes occurred at a relatively early age. Factors such as later age at the time of diagnosis, advanced age, an extended duration of diabetes management, elevated percentage of visceral adiposity, and poor glycemic control were positively associated with increased CIMT among T2DM patients. Intriguingly, males presented with statistically higher CIMT and levels of visceral fat compared to females. Given these findings, we advocate for targeted interventions aimed at controlling visceral adiposity and glycemic levels as viable strategies to mitigate the progression of atherosclerosis and, by extension, reduce the overall risk of cardiovascular diseases among patients with T2DM.

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## DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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The majority of investigations conducted were part of routine clinical evaluations at the center. Any additional expenses incurred in the course of the research were covered by the authors themselves.

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