e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(6); 2625-2634

Original Research Article

Association of Postprandial Hypertriglyceridaemia with Carotid Intima-Media Thickness in Type 2 Diabetes Mellitus: A Hospital-Based Cross-Sectional Study

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Received: 01-04-2026 / Revised: 25-05-2026 / Accepted: 12-06-2026

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Conflict of interest: Nil

Abstract

Background: Type 2 diabetes mellitus accelerates atherosclerosis, and diabetic dyslipidaemia is characterised as much by disturbed postprandial lipid handling as by abnormal fasting values. Whether postprandial triglycerides outperform fasting triglycerides as a marker of early atherosclerosis in Indian patients is not well defined.

Objectives: To estimate fasting and postprandial triglyceride levels and carotid intima-media thickness (CIMT) in patients with type 2 diabetes, and to determine the strength of association of each triglyceride measure with CIMT.

Methods: One hundred adults with type 2 diabetes were studied cross-sectionally. Patients on lipid-lowering agents, thiazides or beta blockers, and those with established cardiovascular, renal or hepatic disease, were excluded. Lipids were measured fasting and 4 hours after a standardised mixed meal (9 kcal/kg; 20% fat, 60% carbohydrate, 20% protein). CIMT was measured by B-mode carotid Doppler. Patients were grouped as normo-normo (NN), normo-hyper (NH) and hyper-hyper (HH) using fasting and postprandial triglyceride thresholds of 150 and 200 mg/dL. Analysis of variance, the Student t-test and Pearson correlation were used.

Results: Mean CIMT was 0.96 ± 0.30 mm in the NN group, 1.85 ± 0.47 mm in the NH group and 1.80 ± 0.49 mm in the HH group. CIMT rose across postprandial triglyceride strata from 0.96 ± 0.30 mm below 200 mg/dL to 2.03 ± 0.18 mm at 400 mg/dL or above (p less than 0.001). CIMT correlated with fasting triglycerides ($r = 0.454$, $p = 0.004$) and more strongly with postprandial triglycerides ($r = 0.542$, $p = 0.001$). Body mass index, blood pressure, total cholesterol and LDL cholesterol showed no significant association with CIMT.

Conclusion: Patients with normal fasting but raised postprandial triglycerides had CIMT as high as those hypertriglyceridaemic in both states, indicating that postprandial triglycerides identify early atherosclerosis missed by fasting sampling alone.

Keywords: Type 2 diabetes mellitus; Postprandial hypertriglyceridaemia; Carotid intima-media thickness; Subclinical atherosclerosis; Diabetic dyslipidaemia; Mixed meal test.

DOI: 10.25258/ijcpr.18.6.406

Introduction

Type 2 diabetes mellitus is a group of metabolic disorders that share the phenotype of hyperglycaemia, and its global expansion over the past three decades has been of a scale that justifies the term epidemic. International Diabetes Federation estimates placed the number of adults living with diabetes at 366 million in 2011, with a projection to 552 million by 2030, and the largest absolute increases were forecast for low and middle income countries in South Asia.[1] India carries a disproportionate share of this burden, and Indian patients characteristically develop diabetes a decade earlier and at a lower body mass index than their Western counterparts, which extends the period of lifetime exposure to the vascular consequences of the disease. Cardiovascular disease is the principal cause of morbidity and mortality in this population. Diabetes accelerates atherogenesis to such a degree that it has historically been described as a coronary risk

equivalent, and it raises the risk of coronary events roughly two to three fold. The atherosclerotic process in diabetes is driven substantially by the characteristic dyslipidaemia of the insulin-resistant state rather than by elevated LDL cholesterol alone. Diabetic dyslipidaemia comprises elevated triglycerides, a preponderance of small dense LDL particles, reduced HDL cholesterol and, importantly, exaggerated and prolonged postprandial lipaemia. Each of these components is mechanistically linked to insulin resistance through overproduction of large triglyceride-rich VLDL1 particles, impaired lipoprotein lipase activity and delayed hepatic clearance of remnant particles.

For much of the past half century, triglycerides occupied an ambiguous position in cardiovascular risk assessment, since their univariate association with coronary disease weakened substantially on adjustment for HDL cholesterol. That position has now shifted decisively. Nordestgaard and Varbo, reviewing the epidemiological, genetic and mechanistic evidence, concluded that triglyceride-rich lipoproteins and their remnants are causally involved in atherosclerotic cardiovascular disease rather than merely correlated with it.[2] Borén and colleagues reached the same conclusion specifically for the postprandial state, arguing that postprandial hypertriglyceridaemia should be regarded as a coronary risk factor in its own right.[3] The mechanistic basis is the arterial retention of apolipoprotein B48-containing and apolipoprotein B100-containing remnant particles, which are small enough to cross the endothelium, are taken up by macrophages without prior oxidative modification, and are retained by intimal proteoglycans.[4]

Large prospective cohorts have made the clinical case. In the Copenhagen City Heart Study, Nordestgaard and colleagues followed approximately 14,000 men and women and found that the incidence of myocardial infarction, ischaemic heart disease and total mortality rose progressively across quintiles of non-fasting triglycerides, with excess risk appearing at concentrations as low as 89 to 176 mg/dL.[5] In the same issue, Bansal and colleagues reported from the Women's Health Study that non-fasting triglycerides predicted cardiovascular events independently of conventional risk factors, whereas fasting triglycerides showed little independent association after adjustment.[6]

The same group subsequently demonstrated an equivalent relationship between non-fasting triglycerides and ischaemic stroke.[7] Earlier work had pointed in the same direction: in the Baltimore Coronary Observational Long-Term Study, coronary events were more frequent among patients whose fasting triglyceride concentrations exceeded 100 mg/dL, a value well within the range then considered normal,[8] and in the Helsinki Heart Study cohort of patients with non-insulin-dependent diabetes, triglyceride concentration was among the determinants of coronary incidence.[9]

The rationale for measuring triglycerides in the postprandial rather than the fasting state is straightforward. Human beings spend the greater part of the day in a postprandial or absorptive condition, and each meal is superimposed on lipaemia that has not yet resolved from the preceding one. Triglyceride concentrations rise for three to six hours after a meal, and this excursion is both higher in amplitude and longer in duration in patients with diabetes because of impaired lipolysis of VLDL1 and defective clearance of remnants. The arterial wall is therefore exposed to atherogenic remnant particles for most of the twenty-four-hour cycle, and a single fasting measurement samples the one period of the day when triglyceride concentrations are at their lowest. A patient may consequently be classified as normolipidaemic on fasting criteria while carrying a substantial daily remnant burden.

Teno and colleagues tested this proposition directly in patients with type 2 diabetes. Measuring lipids fasting and four hours after a meal in 61 patients, they stratified subjects into a normo-normo group with normal fasting and normal postprandial triglycerides, a normo-hyper group with normal fasting but raised postprandial values above 2.27 mmol/L, and a hyper-hyper group elevated in both states. Carotid intima-media thickness was significantly greater in the normo-hyper group at 0.86 ± 0.13 mm and the hyper-hyper group at 0.85 ± 0.12 mm than in the normo-normo group at 0.73 ± 0.13 mm, and on multivariate analysis postprandial triglycerides showed the strongest independent association with intima-media thickness.[10] The finding that the normo-hyper group was indistinguishable from the hyper-hyper group is the crux of the argument, since those patients would have been reassured by a normal fasting lipid profile. Karpe and colleagues had reported a comparable relationship in non-diabetic middle-aged men, where postprandial triglycerides measured six hours after a test meal correlated with common carotid intima-media thickness with a correlation coefficient of 0.44, independently of both LDL cholesterol and fasting triglycerides.[11]

Detecting atherosclerosis before it becomes symptomatic requires a measurement that reflects the arterial wall rather than the lumen. This distinction matters because arteries undergoing atherosclerotic change initially enlarge outward to preserve luminal calibre, so that luminal narrowing does not begin until plaque occupies roughly forty per cent of the area bounded by the internal elastic lamina. Glagov and colleagues demonstrated this compensatory enlargement in human coronary

arteries and thereby explained why angiography, which images the lumen alone, is insensitive to early disease.[12] B-mode ultrasonographic measurement of carotid intima-media thickness addresses this limitation directly. It is non-invasive, quantitative, reproducible and repeatable, and it measures the wall itself. Wong and colleagues validated the measurement against histology, confirming that the distance between the lumen-intima interface and the media-adventitia interface on ultrasound corresponds to the combined intimal and medial thickness of the vessel wall.[13] The prognostic value of the measurement is well established. Lorenz and colleagues, in a systematic review and meta-analysis of prospective cohorts, showed that carotid intima-media thickness predicts future myocardial infarction and stroke, with risk rising in a graded fashion per increment of thickness.[14]

The measurement is also informative in Indian populations specifically. In the Chennai Urban Population Study, Mohan and colleagues found that carotid intima-media thickness was significantly greater in subjects with diabetes than in those without, at 0.95 ± 0.31 mm compared with 0.74 ± 0.14 mm.[15] That study established both that Indian patients with diabetes carry measurable subclinical carotid disease and that the technique is capable of detecting it in routine clinical settings.

What remains less well characterised, particularly in Indian cohorts, is the relative performance of fasting and postprandial triglycerides as correlates of that subclinical disease. If postprandial triglycerides prove the stronger correlate, and if patients with normal fasting values but exaggerated postprandial excursions carry a carotid burden comparable to those hypertriglyceridaemic throughout, then a fasting lipid profile alone misclassifies a clinically meaningful proportion of patients as being at low lipid-related risk. The corollary would be that a postprandial or non-fasting triglyceride measurement, which is cheap, requires no additional laboratory infrastructure and is arguably more convenient than a fasting sample, deserves a place in the routine assessment of patients with type 2 diabetes.

The present study was therefore designed to estimate fasting and postprandial triglyceride concentrations and carotid intima-media thickness in patients with type 2 diabetes attending a tertiary care teaching hospital, to compare these measures across groups defined by fasting and postprandial triglyceride status after the manner of Teno and colleagues, and to determine which of the two triglyceride measures is more closely associated with carotid intima-media thickness.

Patients receiving lipid-lowering therapy and those with established cardiovascular or renal disease were deliberately excluded so that the relationship observed would reflect untreated lipid physiology in patients without clinically manifest vascular disease, that is, precisely the group in whom early detection would alter management.

Aims and Objectives

Aim: To determine the association between postprandial triglyceride levels and carotid intima-media thickness in patients with type 2 diabetes mellitus.

Objectives

1. To estimate fasting and postprandial triglyceride levels in patients with type 2 diabetes mellitus.
2. To estimate carotid intima-media thickness by Doppler ultrasonography in the same patients.
3. To investigate the extent of association between fasting triglyceride levels and carotid intima-media thickness, between postprandial triglyceride levels and carotid intima-media thickness, and to determine which of the two shows the stronger association.

Materials and Methods

Study design and setting: This was a hospital-based, observational, cross-sectional study conducted in the Department of General Medicine at hospitals attached to a tertiary care teaching institute.

Study Period: Patients were recruited between February 2021 and June 2022.

Ethical Considerations: The study protocol was reviewed and approved by the Institutional Ethics Committee before recruitment commenced. Written informed consent was obtained from every participant after the purpose, procedures, potential risks and benefits of the study had been explained in a language the participant understood. Participation was voluntary and withdrawal at any stage was permitted without prejudice to clinical care. All data were anonymised and used solely for the stated scientific purpose. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion Criteria

1. Age greater than 18 years.
2. Diagnosis of type 2 diabetes mellitus established using American Diabetes Association criteria.
3. Provision of written informed consent.

Exclusion Criteria

1. Refusal or inability to provide informed consent.
2. Age less than 18 years.

3. Current treatment with lipid-lowering agents, thiazide diuretics or beta blockers, since each alters triglyceride handling.
4. Chronic complications of diabetes, specifically nephropathy, together with hepatic disease, current alcohol use and current smoking.
5. Established ischaemic heart disease or any cardiovascular disease determined by history and clinical examination.
6. History or clinical findings suggestive of familial hyperlipidaemia.

Sample Size Estimation: The sample size was calculated using the formula for estimation of a mean, $n = Z\alpha^2\sigma^2/d^2$, where $Z\alpha$ was 1.96 for a 95% confidence level. Taking the standard deviation of fasting triglyceride values in the normo-normo and normo-hyper groups reported by Teno and colleagues,[10] a pooled standard deviation of 0.345 was derived, and precision was set at 0.1. Substitution yielded n = 91.45, which was rounded upward to a final sample size of 100.

Baseline Assessment: All patients underwent a structured history and clinical examination recorded on a case record form, with measurement of height, weight, body mass index and blood pressure. Baseline investigations performed before entry comprised haemoglobin, total and differential leucocyte counts, erythrocyte sedimentation rate, random, fasting and postprandial blood glucose, glycatedhaemoglobin, blood urea, serum creatinine, urine microscopy with sugar and albumin, 24-hour urine protein and electrocardiography. These investigations served to confirm the diagnosis and to exclude the nephropathy and cardiac disease specified in the exclusion criteria.

Standardised Mixed Meal Test: Subjects underwent a standardised mixed meal test after an overnight fast. The total energy content of the meal was 9 kcal/kg body weight, with 20% of energy derived from fat, 60% from carbohydrate and 20% from protein. Blood samples for the lipid profile were drawn immediately before the meal and 4 hours afterwards.

Total cholesterol, fasting and postprandial triglycerides and HDL cholesterol were measured by standard automated laboratory methods. LDL cholesterol was calculated using the Friedewald formula, LDL cholesterol = total cholesterol minus HDL cholesterol minus triglycerides divided by five.

Measurement of Carotid Intima-media Thickness: Carotid intima-media thickness was measured by B-mode Doppler ultrasonography. The patient lay supine with the neck slightly extended, and both carotid arteries were scanned in anteroposterior projection. Intima-media thickness was defined as the linear distance between the lumen-intima interface and the media-adventitia interface of the far wall. Three measurements were obtained on each side, one at the carotid bifurcation and one each 1 cm proximal and 1 cm distal to it, and the mean of the three values was recorded as the carotid intima-media thickness for that patient.

Group Definitions: Patients were classified into three groups following the scheme of Teno and colleagues.[10] The normo-normo (NN) group comprised patients with normal fasting triglycerides and normal postprandial triglycerides. The normo-hyper (NH) group comprised patients with normal fasting triglycerides but raised postprandial triglycerides.

The hyper-hyper (HH) group comprised patients with raised triglycerides in both states. The thresholds applied were a fasting triglyceride concentration of 150 mg/dL and a postprandial triglyceride concentration of 200 mg/dL, the latter corresponding to the 2.27 mmol/L cut-off used in the index study.

Statistical Analysis: Data were entered in a Microsoft Excel spreadsheet and analysed using SPSS version 20. Frequency tables were generated and measures of central tendency and dispersion, namely mean and standard deviation, were obtained. Analysis of variance was used to compare means across the three groups and F values with the appropriate degrees of freedom were derived.

The Student t-test was used to compare means between two groups. The strength of association between triglyceride concentrations and carotid intima-media thickness was assessed using the Pearson correlation coefficient. The level of significance was set at 5%, and a two-tailed p value below 0.05 was regarded as statistically significant.

Results

One hundred patients with type 2 diabetes mellitus were studied. Forty-eight were allocated to the normo-normo group, 21 to the normo-hyper group and 31 to the hyper-hyper group.

Baseline Demographic and Clinical Characteristics: The three groups were closely comparable at baseline (Table 1). Mean age was 51.98 ± 7.52 years in the NN group, 47.76 ± 7.53 years in the NH group and 51.77 ± 7.04 years in the HH group, with an F value of 1.265 and a p value of 0.234. Mean systolic blood pressure was 122.38 ± 9.89, 124.76 ± 12.60 and 124.65 ± 9.32 mmHg respectively (F = 0.627, p = 0.685), and mean diastolic blood pressure was 76.29 ± 6.82, 76.86 ± 8.93 and 76.94 ± 7.40 mmHg (F = 0.455, p = 0.495).

Mean body mass index was 23.38 ± 4.17, 24.19 ± 4.24 and 24.45 ± 3.92 kg/m² (F = 0.718, p = 0.490). The absence of significant differences in any of these variables is important to the interpretation of

the carotid findings, since it indicates that the groups did not differ in the conventional determinants of arterial wall thickness.

Table 1: Baseline demographic and clinical characteristics across the three study groups (n = 100)

Variable	NN (n = 48)	NH (n = 21)	HH (n = 31)	F value	p value
Age (years)	51.98 ± 7.52	47.76 ± 7.53	51.77 ± 7.04	1.265	0.234
Age range (years)	36 to 65	36 to 64	36 to 65	-	-
Systolic BP (mmHg)	122.38 ± 9.89	124.76 ± 12.60	124.65 ± 9.32	0.627	0.685
Diastolic BP (mmHg)	76.29 ± 6.82	76.86 ± 8.93	76.94 ± 7.40	0.455	0.495
Body mass index (kg/m²)	23.38 ± 4.17	24.19 ± 4.24	24.45 ± 3.92	0.718	0.490

Values are mean ± standard deviation. NN, normo-normo; NH, normo-hyper; HH, hyper-hyper; BP, blood pressure.

Sex, Treatment and Comorbidity: Of the 100 patients, 52 were male and 48 female, and the sex distribution was broadly balanced within each group (Table 2). Sixty-five patients were managed on oral hypoglycaemic agents alone, 22 on insulin alone and 13 on a combination of the two, with a similar pattern across the three groups.

Twenty-six patients were hypertensive, comprising 10 of 48 in the NN group, 7 of 21 in the NH group and 9 of 31 in the HH group.

Table 2: Distribution of sex, antidiabetic treatment and hypertension across the three study groups (n = 100)

Variable	NN (n = 48)	NH (n = 21)	HH (n = 31)	Total (n = 100)
Male	22 (46)	14 (67)	16 (52)	52 (52)
Female	26 (54)	7 (33)	15 (48)	48 (48)
Oral hypoglycaemic agents	32 (67)	15 (71)	18 (58)	65 (65)
Insulin	9 (19)	4 (19)	9 (29)	22 (22)
Oral agents plus insulin	7 (15)	2 (10)	4 (13)	13 (13)
Hypertension present	10 (21)	7 (33)	9 (29)	26 (26)
Hypertension absent	38 (79)	14 (67)	22 (71)	74 (74)

Values are n (%). Percentages are calculated within each group column.

Lipid Profile: A graded rise in atherogenic lipid indices was evident across the three groups (Table 3). Mean total cholesterol rose from 140.19 ± 18.00 mg/dL in the NN group to 164.67 ± 26.46 mg/dL in the NH group and 178.42 ± 24.69 mg/dL in the HH group.Mean HDL cholesterol fell in the same sequence, from 40.57 ± 5.23 to 35.43 ± 6.33 and 32.87 ± 6.30 mg/dL. Mean LDL cholesterol was 85.98 ± 19.12, 100.14 ± 26.98 and 97.84 ± 31.32 mg/dL respectively, and was therefore not appreciably different between the NH and HH groups.

Mean fasting triglycerides were 107.29 ± 20.69, 132.57 ± 7.52 and 230.13 ± 48.96 mg/dL, and mean postprandial triglycerides were 146.35 ± 27.75, 276.10 ± 72.84 and 333.29 ± 87.38 mg/dL. The essential observation is that the NH group, whose fasting triglycerides averaged 132.57 mg/dL and were normal in every patient by conventional criteria, showed a postprandial mean of 276.10 mg/dL, a more than twofold excursion.

Table 3: Lipid profile across the three study groups (n = 100)

Parameter (mg/dL)	NN (n = 48)	NH (n = 21)	HH (n = 31)
Total cholesterol	**140.19 ± 18.00**	**164.67 ± 26.46**	**178.42 ± 24.69**
LDL cholesterol	85.98 ± 19.12	100.14 ± 26.98	97.84 ± 31.32
HDL cholesterol	40.57 ± 5.23	35.43 ± 6.33	32.87 ± 6.30
Fasting triglycerides	107.29 ± 20.69	132.57 ± 7.52	230.13 ± 48.96
Fasting TG range	60 to 145	120 to 145	158 to 327
Postprandial triglycerides	146.35 ± 27.75	276.10 ± 72.84	333.29 ± 87.38
Postprandial TG range	93 to 198	210 to 501	202 to 522

Values are mean ± standard deviation unless stated. TG, triglycerides.

Distribution of Fasting and Postprandial Triglycerides: All 48 patients in the NN group and all 21 in the NH group had fasting triglycerides below 150 mg/dL, so that 69 of 100 patients (69%) would have been classified as normotriglyceridaemic on a fasting sample alone (Table 4). In the HH group, 16 patients had fasting values between 150 and 249 mg/dL and 15 between 250 and 349 mg/dL, and no patient in the cohort had a fasting value of 350 mg/dL or above.

On postprandial sampling the picture changed materially: 52 of 100 patients (52%) recorded values of 200 mg/dL or more, comprising all 21 patients of the NH group and all 31 of the HH group. Twenty-eight patients fell in the 200 to 299

mg/dL band, 17 in the 300 to 399 mg/dL band and 7 at 400 mg/dL or above.

Table 4: Distribution of fasting and postprandial triglyceride concentrations (n = 100)

Triglyceride band (mg/dL)	NN (n = 48)	NH (n = 21)	HH (n = 31)	Total (n = 100)
Fasting, less than 150	48 (100)	21 (100)	0 (0)	69 (69)
Fasting, 150 to 249	0 (0)	0 (0)	16 (52)	16 (16)
Fasting, 250 to 349	0 (0)	0 (0)	15 (48)	15 (15)
Fasting, 350 or above	0 (0)	0 (0)	0 (0)	0 (0)
Postprandial, less than 200	48 (100)	0 (0)	0 (0)	48 (48)
Postprandial, 200 to 299	0 (0)	-	-	28 (28)
Postprandial, 300 to 399	0 (0)	-	-	17 (17)
Postprandial, 400 or above	0 (0)	-	-	7 (7)

Values are n (%). Postprandial band counts for the NH and HH groups separately were not recoverable from the source data and are shown for the combined cohort only.

Carotid Intima-media Thickness: Mean carotid intima-media thickness was 0.96 ± 0.30 mm in the NN group, 1.85 ± 0.47 mm in the NH group and 1.80 ± 0.49 mm in the HH group (Table 5). The values recorded in the NH and HH groups were closely similar to one another and both were substantially higher than in the NN group. Thirty of the 48 NN patients (63%) had a thickness in the 0.5 to 1.0 mm band and none exceeded 2.0 mm. By contrast, no patient in the NH group had a value in the lowest band, and 7 of 20 NH patients with evaluable measurements (35%) recorded a thickness above 2.0 mm. In the HH group, 16 of 31 patients (52%) fell in the 1.6 to 2.0 mm band and 6 patients (19%) exceeded 2.0 mm, including one patient above 3.0 mm.

Table 5: Distribution and mean value of carotid intima-media thickness across the three study groups

CIMT (mm)	NN (n = 48)	NH (n = 20)	HH (n = 31)	Total (n = 99)
0.5 to 1.0	30 (63)	0 (0)	1 (3)	31 (31)
1.1 to 1.5	12 (25)	7 (35)	8 (26)	27 (27)
1.6 to 2.0	6 (13)	6 (30)	16 (52)	28 (28)
2.1 to 2.5	0 (0)	5 (25)	3 (10)	8 (8)
2.6 to 3.0	0 (0)	2 (10)	2 (6)	4 (4)
Above 3.0	0 (0)	0 (0)	1 (3)	1 (1)
Mean ± SD	0.96 ± 0.30	1.85 ± 0.47	1.80 ± 0.49	-
Range	0.60 to 1.60	0.99 to 2.71	0.88 to 3.13	-

Values are n (%) unless stated. CIMT, carotid intima-media thickness; SD, standard deviation. Distribution data were available for 99 of 100 patients; group means are those reported for all patients in each group.

Carotid Intima-media Thickness in Relation to Triglyceride Strata: Carotid intima-media thickness increased across ascending strata of both fasting and postprandial triglycerides, but the gradient was steeper and more orderly for the postprandial measure (Table 6).

Among patients with fasting triglycerides below 150 mg/dL, mean thickness was 1.23 ± 0.54 mm, rising to 1.78 ± 0.51 mm in the 150 to 249 mg/dL band and 1.83 ± 0.59 mm in the 250 to 349 mg/dL band, with an F value of 2.418 and a p value of 0.004. For postprandial triglycerides, mean thickness was 0.96 ± 0.30 mm below 200 mg/dL, 1.74 ± 0.39 mm in the 200 to 299 mg/dL band, 1.86 ± 0.65 mm in the 300 to 399 mg/dL band and 2.03 ± 0.18 mm at 400 mg/dL or above, with an F value of 3.313 and a p value below 0.001. The lowest fasting stratum, which contained 69 patients, had a mean thickness of 1.23 mm and a wide standard deviation of 0.54, reflecting the fact that this apparently homogeneous group in fact contained both the NN patients with thin carotid walls and the NH patients with thick ones. The lowest postprandial stratum, containing 48 patients, had a mean of 0.96 mm with a much narrower dispersion of 0.30. Postprandial stratification therefore separated the low-risk patients more cleanly than fasting stratification did.

Table 6: Carotid intima-media thickness by fasting and postprandial triglyceride stratum (n = 100)

Triglyceride stratum (mg/dL)	Number	CIMT (mm), mean ± SD	F value	p value
Fasting, less than 150	69	1.23 ± 0.54	2.418	0.004
Fasting, 150 to 249	18	1.78 ± 0.51		
Fasting, 250 to 349	13	1.83 ± 0.59		
Postprandial, less than 200	48	0.96 ± 0.30	3.313	Less than 0.001
Postprandial, 200 to 299	28	1.74 ± 0.39		
Postprandial, 300 to 399	17	1.86 ± 0.65		
Postprandial, 400 or above	7	2.03 ± 0.18		

CIMT, carotid intima-media thickness; SD, standard deviation.

Correlation Analysis: Pearson correlation confirmed the primary hypothesis (Table 7). Carotid intima-media thickness correlated positively with fasting triglycerides, with a coefficient of 0.454 and a p value of 0.004, and more strongly with postprandial triglycerides, with a coefficient of 0.542 and a p value of 0.001. Fasting and postprandial triglycerides were themselves correlated with a coefficient of 0.545 and a p value of 0.001, which indicates that the two measures share substantial variance but are far from interchangeable. None of body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol or LDL cholesterol showed a significant relationship with carotid intima-media thickness, with p values of 0.567, 0.521, 0.517, 0.797 and 0.640 respectively.

Mean thickness by body mass index category was 1.28 ± 0.57 mm below 25 kg/m², 1.51 ± 0.65 mm at 25 to 29.9 kg/m², 1.36 ± 0.61 mm at 30 to 35 kg/m² and 1.40 ± 0.01 mm at 35 kg/m² or above, a pattern without discernible gradient.

Table 7: Correlation of triglyceride measures with carotid intima-media thickness, and association of other variables with carotid intima-media thickness

Analysis	n	Pearson correlation coefficient	p value
CIMT versus fasting triglycerides	100	0.454	0.004
CIMT versus postprandial triglycerides	100	0.542	0.001
Postprandial versus fasting triglycerides	100	0.545	0.001
CIMT versus body mass index	100	Not applicable	0.567
CIMT versus systolic blood pressure	100	Not applicable	0.521
CIMT versus diastolic blood pressure	100	Not applicable	0.517
CIMT versus total cholesterol	100	Not applicable	0.797
CIMT versus LDL cholesterol	100	Not applicable	0.640

CIMT, carotid intima-media thickness. Analyses marked not applicable were tested by analysis of variance across categories rather than by correlation.

Discussion

The principal finding of this study is that patients with type 2 diabetes who had entirely normal fasting triglyceride concentrations but exaggerated postprandial excursions carried a carotid intima-media thickness indistinguishable from, and numerically slightly greater than, that of patients who were hypertriglyceridaemic in both the fasting and the postprandial state.

Since these patients would be reassured by a conventional fasting lipid profile, the finding has direct implications for how lipids are measured in diabetes clinics.

Comparison With the Index Study: The design followed that of Teno and colleagues, who studied 61 Japanese patients with type 2 diabetes and reported carotid intima-media thickness of 0.73 ± 0.13 mm in the normo-normo group, 0.86 ± 0.13 mm in the normo-hyper group and 0.85 ± 0.12 mm in the hyper-hyper group, with a p value below 0.01.[10] The pattern in our cohort was identical in structure: 0.96 ± 0.30, 1.85 ± 0.47 and 1.80 ± 0.49 mm respectively, with the normo-hyper value again equalling or marginally exceeding the hyper-hyper value. The absolute values in our patients were substantially higher throughout. Several factors plausibly contribute. Our patients had lower HDL cholesterol across all three groups, at 40.57, 35.43 and 32.87 mg/dL compared with 53, 59.6 and 49.9 mg/dL in the Japanese cohort, consistent with the low-HDL phenotype well described in South Asians. Postprandial triglycerides in our normo-hyper group averaged 276.10 mg/dL against 263.1 mg/dL in theirs, a close match, whereas the corresponding carotid thickness differed by nearly a millimetre. Measurement protocol is the more likely explanation, since our measurements were taken at the carotid bifurcation and 1 cm on either side, and the bifurcation is the segment with the greatest local thickness and the site where plaque forms preferentially, whereas many reference cohorts report far-wall common carotid values distal to the bifurcation. Values should therefore be compared within, not across, measurement protocols.

Comparison with Other Cohorts: Karpe and colleagues reported that postprandial triglycerides measured six hours after a test meal correlated with common carotid intima-media thickness with a coefficient of 0.44, and that this relationship was independent of both LDL cholesterol and fasting triglyceride concentration.[11] Our coefficient of 0.542 for postprandial triglycerides is of the same order and slightly stronger, which is unsurprising given that our cohort comprised patients with diabetes in whom postprandial lipid handling is by definition more disturbed. Chen and colleagues examined the same question in Chinese patients with type 2 diabetes and likewise reported an association between postprandial triglycerides and carotid intima-media thickness.[16] In Indian patients, Mohan and colleagues established in the Chennai Urban Population Study that carotid intima-media thickness was significantly greater in subjects with diabetes than in those without, at 0.95 ± 0.31 mm against 0.74 ± 0.14 mm.[15] Notably,

the mean value in our normo-normo group, 0.96 ± 0.30 mm, is almost exactly the Chennai diabetic figure, which suggests that our normo-normo patients represent the expected baseline for Indian patients with diabetes and that the elevation seen in the other two groups is genuinely attributable to postprandial lipaemia rather than to diabetes alone.

The absence of any relationship between carotid intima-media thickness and total cholesterol ($p = 0.797$) or LDL cholesterol ($p = 0.640$) in our cohort deserves comment, since it appears to contradict a large literature. The explanation lies in the exclusion criteria. Patients receiving lipid-lowering therapy were excluded, and the resulting cohort had a mean LDL cholesterol of only 85.98 to 100.14 mg/dL, with 65 of 100 patients below 100 mg/dL and only 5 above 130 mg/dL. There was therefore too little variance in LDL cholesterol for an association to emerge. This restriction of range is a feature of the sampling frame, not evidence that LDL cholesterol is unimportant. It also has an interpretive advantage: in a cohort in which LDL cholesterol was uniformly at or near target, postprandial triglycerides still explained a substantial part of the variation in carotid thickness, which is precisely the residual risk that concerns clinicians managing statin-treated patients. The similar absence of association with body mass index ($p = 0.567$) and with systolic and diastolic blood pressure ($p = 0.521$ and 0.517) reflects the same phenomenon, since the three groups were closely matched on all of these variables by chance rather than by design.

Mechanistic Interpretation: The mechanistic case for postprandial triglycerides as the more informative measure is well developed. Insulin resistance drives hepatic overproduction of large triglyceride-rich VLDL1 particles, which in health are secreted only in the fasting state and are suppressed after a meal. In the insulin-resistant patient this suppression fails, so that the intestinal chylomicron flux is superimposed on continuing VLDL1 secretion. Lipoprotein lipase, itself insulin-dependent and less active in type 2 diabetes, cannot clear the combined load, and remnant particles accumulate. Borén and colleagues set out this pathway in detail and argued that the resulting postprandial hypertriglyceridaemia constitutes a coronary risk factor in its own right.[3] The atherogenicity of the remnants derives from their size and their apolipoprotein content: apolipoprotein B48-containing and B100-containing remnants penetrate the endothelium, are retained by intimal proteoglycans and are taken up by macrophages without requiring prior oxidative modification, as reviewed by Proctor and colleagues.[4] Grønholdt and colleagues added a plaque-stability dimension by showing that echolucent carotid plaques, the morphology associated with clinical events, were linked to elevated fasting and postprandial triglyceride-rich lipoproteins.[17]

Postprandial lipaemia also acts through more immediate vascular mechanisms. Ferreira and colleagues demonstrated that postprandial hypertriglyceridaemia raises circulating endothelial cell microparticles, a marker of acute endothelial injury,[18] and Ceriello and Motz proposed oxidative stress as the unifying mechanism linking postprandial dysmetabolism to endothelial dysfunction in insulin resistance and diabetes.[19] Ginsberg and colleagues had earlier linked postprandial triglyceride and retinylpalmitate responses to exercise-induced myocardial ischaemia in middle-aged subjects, indicating that the association extends to functional as well as structural endpoints.[20] Taken together, these observations describe a cycle in which each meal produces a transient burst of endothelial injury and remnant deposition, repeated three or more times daily over years.

Clinical Implications: Three implications follow. First, in this cohort 69 of 100 patients had normal fasting triglycerides, yet 21 of those 69 had marked postprandial hypertriglyceridaemia and carotid thickening equivalent to the frankly hypertriglyceridaemic group. A fasting lipid profile alone would have classified almost a third of the fasting-normal patients as being at low lipid-related risk when they were not. Second, the practical barrier to adopting postprandial measurement is low. Nordestgaard, Bansal and their respective colleagues established that non-fasting triglycerides carry at least as much prognostic information as fasting values in general populations,[5,6] and Freiberg and colleagues extended this to ischaemic stroke.[7] Keirns and colleagues have reviewed the practical case for fasting, non-fasting and postprandial triglyceride measurement in cardiometabolic screening and note that a non-fasting sample is more convenient for the patient and better reflects habitual metabolic state.[21] Third, where postprandial hypertriglyceridaemia is identified, the response is not primarily pharmacological but centres on meal composition, meal timing, weight reduction, physical activity and tightening of glycaemic control, all of which reduce the postprandial excursion. Where drug therapy is indicated, the relevant target is the triglyceride-rich lipoprotein remnant, not the fasting triglyceride value alone, as argued by Nordestgaard and Varbo.[2]

The role of carotid intima-media thickness as the measurement endpoint also merits brief defence. The technique is validated against histology,[13] has established standards for reproducible acquisition,[22] and predicts incident myocardial infarction and stroke in prospective cohorts.[14] Its value in this context is that it detects wall change at

a stage when the lumen is still preserved by compensatory outward remodelling,[12] which is exactly the window in which lipid and lifestyle intervention has the most to offer.

Limitations: Several limitations qualify these findings. The design was cross-sectional, so temporal sequence and causality cannot be established; a longitudinal study measuring change in carotid thickness against postprandial triglyceride exposure would be required for that. The sample of 100 patients, unevenly distributed across three groups with only 21 patients in the normo-hyper group, limited the power of subgroup comparisons and precluded meaningful multivariate modelling, so the reported associations are unadjusted. Lipids were sampled at a single time point four hours after the meal rather than as a full postprandial curve with area under the curve, and the peak response may have been missed in some patients. No non-diabetic control group was studied, so the contribution of diabetes itself cannot be separated from that of postprandial lipaemia. Glycaemic control, measured as glycatedhaemoglobin at screening, was not analysed against carotid thickness despite being a plausible confounder, and neither were duration of diabetes, waist circumference, apolipoprotein B or remnant cholesterol. The exclusion of patients on lipid-lowering therapy, while methodologically necessary, produced a cohort with restricted LDL variance that is not representative of the treated diabetic population. Carotid measurements were made at the bifurcation and adjacent segments by a single technique, and reproducibility statistics were not reported. Finally, the study was conducted at a single centre, which limits generalisability.

Conclusion

This study demonstrates that postprandial triglyceride concentration is more closely associated with carotid intima-media thickness than fasting triglyceride concentration in patients with type 2 diabetes mellitus. Carotid intima-media thickness correlated with postprandial triglycerides with a coefficient of 0.542 ($p = 0.001$) and with fasting triglycerides with a coefficient of 0.454 ($p = 0.004$) and rose in a graded fashion across ascending postprandial strata from 0.96 ± 0.30 mm below 200 mg/dL to 2.03 ± 0.18 mm at 400 mg/dL or above.

The clinically decisive observation is that patients with normal fasting triglycerides but raised postprandial values had a mean carotid intima-media thickness of 1.85 ± 0.47 mm, marginally greater than the 1.80 ± 0.49 mm recorded in patients hypertriglyceridaemic in both states and nearly twice the 0.96 ± 0.30 mm of patients normal in both. Postprandial hypertriglyceridaemia therefore identifies accelerated subclinical atherosclerosis in patients who would be classified as normolipidaemic on fasting testing, and it does so independently of body mass index, blood pressure, total cholesterol and LDL cholesterol, none of which was associated with carotid thickness in this cohort. It follows that in patients with type 2 diabetes, postprandial triglycerides should be assessed in addition to, and not merely instead of, fasting triglycerides, and that a normal fasting triglyceride value should not be taken as evidence of absent lipid-related vascular risk.

Larger prospective studies incorporating full postprandial triglyceride curves, remnant cholesterol and apolipoprotein B measurement, a non-diabetic comparison group and longitudinal carotid follow-up are needed to establish whether postprandial triglyceride concentration predicts progression of carotid thickening and incident cardiovascular events, and whether interventions that flatten the postprandial excursion translate into measurable arterial benefit.

Declarations

Ethics approval and consent to participate: Approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: None.

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