

Comparative Subclinical Vascular Damage in Rheumatoid Arthritis and Type 2 Diabetes Mellitus: An Exploratory Propensity-Matched Cross-sectional Study with Vascular Phenotyping and Metabolomics

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Abstract

Purpose

Chronic inflammation in rheumatoid arthritis (RA) and metabolic dysregulation in type 2 diabetes mellitus (T2DM) confer increased atherosclerotic cardiovascular disease (ASCVD) risk. However, it remains unclear whether the vascular dysfunction arises from shared or distinct mechanisms. We compared vascular dysfunction and metabolomics between RA and T2DM, and examined disease-specific links between metabolites and vascular measures.

Methods

In this cross-sectional, propensity-matched study (1:1 by age, sex, body mass index, hypertension, hyperlipidemia) of 58 participants without ASCVD, vascular measurements including brachial artery flow-mediated dilation (FMD), carotid–femoral pulse wave velocity (cf-PWV) and ultrasonography of carotid and femoral arteries were compared between RA and T2DM. Untargeted metabolomics and lipoprotein profiling with multiple-testing control were performed and correlated with vascular measurements.

Results

Compared with RA, T2DM had higher arterial stiffness (cf-PWV, 12.8 vs 10.9 m/s; $P = 0.005$), endothelial dysfunction (FMD < 7%: 79.3% vs 69.0%; $P = 0.021$), and higher plaque burden (24.1% vs 3.4%; $P < 0.001$). Metabolomics profiling showed several differences in amino acids and ketone intermediates between RA and T2DM. Lipoprotein–vascular links were disease-specific with low-density lipoprotein (LDL) subclasses dominating the vascular associations in RA, and small dense high-density lipoprotein (HDL) in T2DM. In RA, 2-ketoisovalerate was inversely related to FMD ($r = -0.49$; $P = 0.007$), while alanine, glucose, glutamate, and 4-hydroxyphenylacetate were associated with higher cf-PWV or CIMT; in T2DM, alanine inversely correlated with CIMT ($r = -0.39$; $P = 0.035$).

Conclusions

In this contemporary cohort, T2DM showed greater vascular dysfunction than RA. Distinct metabolic profiles, with disease-specific vascular correlates, support tailored risk stratification and targeted cardiovascular prevention in RA versus T2DM.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of mortality globally [1]. Inflammation and metabolic dysregulation are critical factors driving its pathogenesis [2]. Type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA) are archetypes of metabolic and chronic

inflammatory disease, respectively. Individuals with T2DM are at 2-4-fold increased risk of ASCVD [3] and nearly half of deaths are ASCVD-related [4]. Similarly, ASCVD accounts for nearly 40% of deaths among RA patients [5]. A large Danish cohort study reported comparable ASCVD risks between RA and T2DM [6]. However, it remains unclear whether RA and T2DM differ in the phenotype of subclinical vascular dysfunction, and whether such differences reflect distinct mechanisms.

Multiple mechanisms contribute to vascular complications in T2DM. Metabolic perturbations including hyperglycemia, insulin resistance and dyslipidemia are key drivers. Hyperglycemia increases proinflammatory cytokines, endothelial adhesion molecules [7], and induces advanced glycation end products (AGEs) formation and binding with the receptors for AGEs (RAGE). AGE-RAGE signaling aggravates oxidative stress, promote inflammation and worsen endothelial dysfunction [7]. Endothelial insulin resistance impairs the phosphoinositide 3-kinase (PI3K) pathway responsible for nitric oxide synthesis, while activating the counteracting mitogen-activated protein kinase (MAPK) pathway to induce vasoconstrictor release [8, 9]. Diabetic dyslipidemia, is characterized by hypertriglyceridemia, increased circulating fatty acids and oxidized low-density lipoprotein cholesterol (LDL-C) [10]. These metabolites serve as danger-associated molecular patterns, which bind to pattern recognition receptors to trigger the release of proinflammatory cytokines and endothelial adhesion molecules [11].

The cause of ASCVD in RA is multifactorial. Besides traditional risk factors such as smoking, physical inactivity, and metabolic disorders, systemic inflammation is a central driver of vasculopathy in RA [12]. Proinflammatory cytokines, such as tumour necrosis factor alpha (TNF- α) and interleukin (IL)-6 upregulate endothelial adhesion molecules and enhance leukocyte recruitment, thereby initiating vascular dysfunction [13]. Moreover, RA is characterized by a 'lipid paradox', where lower concentrations of LDL-C are paradoxically associated with higher cardiovascular risk [14]. This may be due to inflammation-driven alterations in lipoprotein composition and function, including an increase in pro-atherogenic small dense LDL-C and oxidized LDL-C [15].

While overt ASCVD represents advanced disease, atherosclerosis is a continuous process that begins early in life and remains subclinical for several years before clinical manifestation [16]. These subclinical changes can be detected in asymptomatic individuals using non-invasive techniques, from functional endothelial dysfunction to structural abnormalities including arterial stiffening, carotid intima-media thickening (CIMT), and atherosclerotic plaque development. A comparative study evaluating subclinical vascular dysfunction and morphology demonstrated a similar degree of vasculopathy in RA and T2DM patients [17]. However, these findings have not been sufficiently validated in contemporary, geographically diverse populations. In addition, the specific metabolic pathways and mechanisms linking inflammation in RA and metabolic disturbances in T2DM to vasculopathy remain inadequately understood.

In recent years, advances in high-throughput metabolomics profiling have created opportunities to understand the molecular underpinnings of disease pathophysiology. Simultaneous analysis of large numbers of metabolites can provide a snapshot of the biological pathways occurring in a systematic,

comprehensive manner [18]. Metabolomics profiling can help identify novel predictive markers of vascular dysfunction [19]. Comparing metabolite profiles between RA and T2DM could yield further insights into underlying mechanisms and identify targeted pathways to predict and potentially reverse vascular dysfunction. To our knowledge, no study has directly compared the metabolomic differences driving vascular dysfunction in RA and T2DM. In this study, we aimed to 1) compare the extent and pattern of subclinical vascular dysfunction in RA with T2DM, using measures of endothelial function, arterial stiffness, CIMT and plaque burden; 2) characterize and compare the lipoprotein and metabolomic profiles of RA and T2DM patients, and 3) investigate associations between differential lipoproteins, metabolites and vascular dysfunction parameters.

Methods

Study Design and Participants:

Participants were identified from the Personalized Cardiometabolic Risk Management Program (Predict-2-Prevent), a cohort study in Singapore recruiting 1500 adults aged 21–80 years with at least one cardiovascular risk factor to undergo deep vascular phenotyping, polygenic risk scoring, and lifestyle and dietary characterization. The study was approved by the National Healthcare Group Domain Specific Review Board (reference number: DSRB 2023/00960). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants prior to study enrolment.

All participants with RA fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism criteria [20]. Data collected included sociodemographic characteristics, comorbidities, the Disease Activity Score in 28 joints (DAS-28), pharmacologic treatments, and laboratory findings. Participants with T2DM were recruited based on the ICD-10-CM coding in electronic medical records, current use of diabetes medications or guidelines-defined biochemical diagnosis.

Participants were eligible for inclusion into this nested pilot cross-sectional study if they had complete baseline data and non-invasive vascular assessments, including flow-mediated dilation of brachial artery (FMD), carotid–femoral pulse wave velocity (cf-PWV), CIMT, and plaque evaluation. We excluded any individuals with missing data on key covariates or vascular measurements, a history of clinical cardiovascular disease, or concomitant RA and T2DM. To minimize confounding and improve comparability between groups, we performed 1:1 nearest-neighbor propensity score matching without replacement. The propensity score was derived from a logistic regression model incorporating age, sex, body mass index (BMI), systolic blood pressure, hypertension and hyperlipidemia. After applying eligibility criteria and matching, 29 propensity-matched RA–T2DM pairs (58 participants total) were included (Fig. 1).

Vascular measurements

FMD

FMD was performed using high-resolution ultrasound (Terason uSmart 3300). The ultrasound images were analyzed using an automated edge detection software (Bloodflow Analyzer, Reed Electronics). FMD was calculated as the percentage change in brachial artery diameter between baseline and maximum diameter during reactive hyperemia. According to the Japan Society for vascular failure diagnostic criteria, FMD < 7% was classified as abnormal [21].

Pulse wave velocity

Carotid-femoral pulse wave velocity (cf-PWV) was assessed using applanation tonometry (SphygmoCor XCEL system; Atcor Medical, Sydney, Australia). Two consecutive readings were taken and their average was used for analysis. All assessments were conducted in accordance with the Artery Society's consensus guidelines, and arterial stiffness was defined by a cf-PWV threshold of ≥ 10 m/s [22].

Carotid and femoral ultrasonography

CIMT and carotid plaque assessment were performed per the Mannheim consensus 2013[23] and the American Society of Echocardiography guidelines[24] using high-resolution ultrasound (Phillips EPIQ Elite 7). Average and maximum CIMT were measured at four distal carotid segments bilaterally: right lateral, left lateral, right posterior, and left posterior. An automatic sweep of both carotid bulbs was performed. Carotid plaque was defined as a focal protrusion > 0.5mm into the lumen or thickness > 50% of the surrounding intima [23]. Maximum average CIMT were compared against locally derived age, sex and ethnic specific population reference ranges for CIMT [25]. Abnormal CIMT was defined as either maximum or average CIMT exceeding 75th percentile for age, sex and ethnicity (Singapore-specific reference interval) [25]. For ultrasound of the femoral arteries, a 20mm segment of the common femoral arteries, proximal to the bifurcation of the deep femoral arteries, was assessed for the presence of femoral plaques bilaterally [26]. The ultrasound images were analyzed offline using the Vascular Plaque Quantification tool QLab version 10.2. Intra- and inter-operator coefficients of variability were < 5 %.

Lipoprotein and Metabolomics Measurement by Nuclear Magnetic Resonance (NMR) Spectroscopy

Sample Preparation. Plasma samples were prepared following the standard operating procedures (SOPs) of the Bruker In Vitro Diagnostics research (IVDr) platform (Bruker, Germany). Briefly, frozen samples were thawed at room temperature for 40 min and centrifuged at 4 °C, 12000 rpm for 10 min. 300 μ L of each sample was aliquoted out into 2ml Eppendorf tubes and mixed with 300 μ L of plasma phosphate buffer (75 mM Na₂HPO₄, 4.6 mM 3-(trimethylsilyl) propionic-2,2,3,3-d₄ acid sodium salt (TSP), 2 mM NaN₃ in 80% D₂O, pH 7.4 $\pm$ 0.1). The mixture was vortexed for 30 seconds, and 600 μ L of the resulting solution was transferred into 5 mm NMR tubes for analysis.

NMR Spectroscopy. NMR spectra were acquired using a Bruker® Avance III Ascend™ 600 MHz NMR spectrometer (Bruker, Germany), equipped with a high-order shimming system (BOSS III), a 5 mm BBI Z-Gradient high-resolution probe, and a SampleJet automatic sample changer with cooling and preheating capabilities (Bruker, Germany). Data acquisition and processing were carried out in accordance with the Bruker AVANCE™ IVDr platform protocols.

Automated measurement and processing were performed using ICONNMR and TopSpin 3.7.0 software (Bruker Biospin, Rheinstetten, Germany). A standard noesygppr1d pulse sequence was applied to capture an overall spectral profile of proton-containing compounds. Spectra were recorded over a 30 ppm spectral width using 4 dummy scans followed by 32 scans, with 96K data points.

To analyze low-molecular-weight metabolites, a Carr–Purcell–Meiboom–Gill (CPMG) spin-echo experiment was performed with a 20 ppm spectral width, 32 scans, and 72K data points.

Quantification of 112 lipoprotein subfractions, along with small-molecule metabolites, was performed using the Bruker IVDr platform’s automated analysis pipeline.

Statistical Analysis:

With 29 matched pairs, this exploratory pilot study has an estimated 74% power to detect a moderate within-pair effect size (Cohen’s $d = 0.5$) using a two-sided paired t-test at an alpha level of 0.05 (calculated with G*Power software version 3.1.9.7). Given the propensity score–matched study design, all analyses accounted for the paired nature of the data. Continuous variables with a normal or approximately normal distribution were summarized as mean and standard deviation (SD) and compared using the paired t-test. Variables with skewed distributions were reported as median (1st quartile, 3rd quartile) and analyzed using the Wilcoxon signed-rank test. Categorical variables were expressed as frequency (percentage), and comparisons between matched pairs were conducted using the McNemar test with continuity correction. The metabolites data from NMR were log-transformed and z-scaled. The lipoprotein data were only z-scaled. Multidimensional analysis, including Principal Component Analysis (PCA), Partial Least Square- Discriminant Analysis and Orthogonal Partial Least Square-Discriminant Analysis were performed. FDR adjusted $p < 0.05$ were considered significant given the exploratory nature of this study. Network analysis was performed to identify distinct signatures of lipoproteins species and metabolites (modules) between RA and T2DM. Spearman correlation was used to assess the correlation between lipoproteins, metabolites and vascular measurements in RA and T2DM. All statistical tests were two-tailed, with a significance level set at $p < 0.05$. The same statistical approach was applied to analyze both baseline demographic and clinical characteristics as well as vascular outcome parameters. R version 4.4.1 was used for analysis. All the codes for data analysis in this study can be accessed at GitHub: https://github.com/jaspershen-lab/chuanhui_project.

Results

Characteristics of the study participants

Of 556 individuals in the Predict-2-Prevent cohort, 179 were eligible after excluding those with concomitant RA and T2DM, incomplete baseline or vascular data, or a history of cardiovascular disease. From these, 29 RA and 29 T2DM participants were propensity-matched and included in the final analysis. (Figure 1) The baseline demographics, cardiometabolic profiles and medications of propensity-matched RA and T2DM groups are presented in Table 1. The RA and T2DM groups were similar in age (mean 63.8 vs. 63.3 years) and sex distribution (86.2% vs. 75.9% female). RA patients had well-controlled disease activity, with a median DAS-28 of 1.93 (IQR 1.51–2.64). Ethnicity and smoking status differed significantly, with more non-Chinese in T2DM than RA (27.6% vs. 17.2%, $p=0.008$) and one current smoker in the T2DM group ($p < 0.001$). Participants with RA had longer disease duration on average than T2DM (19.8 ± 11.2 vs. 11.8 ± 7.5 years, $p=0.002$). Regarding cardiometabolic profiles, HDL-cholesterol was significantly different between both groups (RA: 1.7 ± 0.5 mmol/L versus T2DM: 1.5 ± 0.3 mmol/L, $p=0.031$), while LDL-C was similar.

Comparison of vascular function and structure between RA and T2DM

Endothelial function, measured as brachial artery FMD, was numerically lower in T2DM ($5.3\% \pm 2.67$) than in RA ($6.33\% \pm 2.02$), although the difference was not statistically significant ($p=0.141$) (Table 2). However, the proportion of individuals with endothelial dysfunction (FMD < 7%) was significantly higher in T2DM (79.3%) than in RA (69%, $p=0.021$) (Table 2).

Individuals with T2DM have significantly higher cf-PWV than those with RA (12.8m/s vs 10.9m/s, $p=0.005$) (Table 2). Arterial stiffness was more prevalent in T2DM than in RA (86.2% vs 51.7%, $p=0.109$) (Table 2).

The average CIMT, maximum CIMT or proportion of individuals with CIMT exceeding 75th percentile of the population threshold were similar between RA and T2DM. In contrast, plaque burden differed between groups. There was a higher proportion of plaque present at either carotid or femoral in the T2DM group compared to the RA group (62.1% vs 31%) but the difference didn't reach statistical significance ($p=0.871$) (Table 2). When plaque presence was further stratified based on site, the carotid plaque burden was significantly higher in T2DM (24.1% vs 3.4%, $p < 0.001$), while femoral plaque prevalence was similar between both groups. The presence of plaque at both sites was significantly higher in T2DM (17.2%) compared to RA (3.4%, $p < 0.001$) (Table 2).

Differential Expression of Lipoproteins and Metabolites Between RA and T2DM Groups

To characterize the distinct metabolic profiles associated with RA and T2DM, we first identified differentially expressed lipoproteins and metabolites between the two groups. A total of 34 lipoproteins were significantly altered (Student's t-test, FDR-adjusted $p < 0.05$), with 23 lipoproteins upregulated in the RA group and 11 downregulated (Figure 2a). Notably, the majority of lipoproteins elevated in RA belonged to the LDL subclasses, whereas those decreased in RA (*i.e.*, higher in T2DM) were predominantly HDL (Figure 2b), reflecting disease-specific shifts in lipoprotein subclass composition.

Principal component analysis (PCA) of the 34 differentially expressed lipoproteins revealed a clear separation between the RA and T2DM groups, further supporting distinct lipoprotein profiles between the two disease states (Figure 2c).

In parallel, analysis of the plasma metabolomics data identified thirteen significantly altered metabolites, including two metabolite elevated in RA and eleven decreased (Figure 2d, supplementary Table S1). Among them, glucose was markedly higher in the T2DM group as expected. Interestingly, most of the metabolites downregulated in RA were amino acids, particularly branched-chain amino acids (BCAAs) (Figure 2e). PCA based on these thirteen metabolites also successfully distinguished RA from T2DM patients (Figure 2f).

Functional Module Identification Reveals Distinct Lipoprotein-Metabolite Signatures in RA and T2DM

To further explore the coordinated metabolic alterations between RA and T2DM, we constructed a correlation network using all differentially expressed lipoproteins and metabolites identified (Figure 2). Although certain lipoproteins and metabolites were dysregulated in the same direction, their patterns varied substantially across subclasses (Figure 2b,e), suggesting underlying modular structures.

Using correlation-based community detection, we identified five distinct functional modules from the integrated lipoprotein-metabolite network (Figure 2g). These modules represent biologically coherent clusters of molecules that covary across samples and may reflect shared regulatory or functional pathways. The relative activity of each module across RA and T2DM participants was visualized via fold change ($\log_2$ transformed) distribution (Figure 2h). Among the five modules, Module 1, Module 2, and Module 4 were significantly upregulated in the T2DM group, while Module 2_2 and Module 3 were upregulated in RA (Figure 2h).

Module 1: Small HDL Enrichment in T2DM: Module 1, which was upregulated in T2DM, was composed predominantly of small HDL subclasses and their apolipoprotein components, including HDL-4-Phospholipids, HDL-4-Cholesterol, HDL-4-Apo A1, HDL-3-Apo A2, HDL-Apo A2, HDL-3-Apo A1, and Apo A2.

Module 2: Atherogenic Lipoprotein Profile in T2DM: Module 2 was also upregulated in T2DM participants and included a spectrum of lipid-rich lipoprotein particles from VLDL, IDL, LDL, and HDL subclasses. Key components included VLDL-1/4-Free Cholesterol, VLDL-1-Triglyceride, VLDL-1-Cholesterol, IDL-Free Cholesterol, IDL Particle Number, IDL-Apo B100, LDL-5-Cholesterol, LDL-5-Apo B100, and HDL-3/4-Triglycerides.

Module 2_2: HDL-1 Enrichment in RA: In contrast, Module 2_2 was elevated in RA and consisted of components of large HDL particles, including HDL-1-Free Cholesterol, HDL-1-Apo A1, HDL-1-Apo A2, HDL-1-Phospholipids, and HDL-1-Cholesterol.

Module 3: Broad LDL Subclass Enrichment in RA: Module 3, also enriched in RA, was composed primarily of multiple LDL subclasses, including LDL-1, LDL-2, and LDL-3, along with their associated features:

cholesterol, free cholesterol, phospholipids, triglycerides, Apo B100, and particle numbers.

Module 4: NMR-based metabolomic profiling revealed distinct differences in amino acid and energy metabolism between RA and T2DM (Supplementary Table S1). Several amino acids were significantly lower in RA, including alanine, glutamate, valine, isoleucine, histidine, and asparagine. In contrast, phenylalanine was higher in RA compared with T2DM. Among amino acid-derived metabolites, 4-hydroxyphenylacetate was elevated in RA, whereas 2-ketoisovalerate and 3-hydroxyisobutyrate were reduced. Glucose levels were lower in RA, consistent with the hyperglycemic state in T2DM. In the carbohydrate and energy metabolism pathway, acetoacetate, a ketone body, was also lower in RA.

Lipoprotein Correlates of Subclinical Vascular Damage

Correlation analyses were performed using the lipoprotein particles that were upregulated in T2DM and RA respectively with the vascular markers. Distinct patterns in lipoprotein subclasses and vascular markers were observed between the T2DM and RA cohorts (supplementary Table S2 and S3).

In T2DM (supplementary Table S2), the lipoprotein subclasses comprising small dense HDL particles and small dense LDL particles, were inversely correlated with PWV, CIMT and FMD. In terms of specific lipoprotein subclass composition, the small dense HDL-4-triglyceride was inversely correlated with PWV ($R = -0.57$, $p=0.001$), average CIMT ($R = -0.45$, $p=0.014$), maximum CIMT ($R = -0.43$; $p=0.019$) and plaque burden ($R = -0.40$, $p=0.034$).

In RA (supplementary Table S3), a spectrum of lipoprotein subclasses was correlated with vascular function and structure. In terms of lipoprotein subclasses, small dense LDL particles (LDL-4 and LDL-5) were positively correlated with PWV and CIMT. Medium to small dense HDL particles (HDL-2 and HDL-3) and large LDL particles were inversely correlated with FMD.

Metabolite Correlates of Subclinical Vascular Damage

Disease-specific patterns were observed when metabolite-vascular associations were grouped by metabolic category (supplementary Table S4 and S5).

In T2DM (supplementary Table S4), significant associations were fewer: phenylalanine was positively associated with plaque ($R = 0.51$, $p=0.005$), alanine was inversely associated with CIMT ($R = -0.39$, $p=0.035$), and methanol was inversely correlated with PWV ($R = -0.42$, $p=0.022$).

In RA (supplementary Table S5), the BCAA catabolism intermediate 2-ketoisovalerate was inversely associated with FMD ($R = -0.49$, $p=0.007$), while the tyrosine-derived metabolite 4-hydroxyphenylacetate correlated positively with CIMT ($R = 0.41$, $p=0.029$). Carbohydrate-related metabolites showed multiple positive associations: β -glucose with CIMT ($R = 0.37$, $p=0.049$), α -glucose with PWV ($R = 0.38$, $p=0.043$), and alanine with both CIMT ($R = 0.38$, $p=0.044$) and PWV ($R = 0.38$, $p=0.044$). Glutamate was also positively associated with PWV ($R = 0.38$, $p=0.042$). Methanol correlated inversely with both FMD ($R = -0.37$, $p=0.048$) and PWV ($R = -0.37$, $p=0.048$).

Discussion

In this study, we found that individuals with T2DM exhibited greater arterial stiffness, endothelial dysfunction, and higher carotid plaque burden than RA despite similar CIMT, and that the two conditions displayed distinct metabolic and lipoprotein signatures with disease-specific metabolite–vascular links. These results support our a priori hypothesis that inflammatory and metabolic vasculopathies are phenotypically and biochemically distinct for these two diseases in the modern treatment era.

Contrary to the studies demonstrating comparable arterial stiffness and carotid plaque prevalence in RA and T2DM cohorts [17, 27], we observed less vascular dysfunction and lower carotid plaque burden in RA compared with T2DM. This is likely due to differences in the study population. In our modern era cohort, the majority of RA patients achieved remission (69%) or low disease activity (17%), with a median DAS28-CRP of 1.93 mg/L (IQR 1.51–2.64). By contrast, Stamatelopoulos et al. (2009) reported that only ~ 50% of RA patients were in remission[17]. Our cohort in the contemporary treat to target era, and higher remission rate likely contribute to the lower endothelial dysfunction, arterial stiffness and carotid plaque burden observed in our study. Our findings align with longitudinal data showing markedly slower CIMT progression in RA versus diabetes [28]. The underlying pathophysiology is fundamentally different: chronic hyperglycemia in T2DM causes permanent arterial stiffening through AGE-mediated collagen cross-linking and vascular calcification, resulting in persistently elevated PWV and a greater plaque burden despite glycemic control, whereas RA-associated stiffness is primarily driven by inflammation and often improves with potent anti-inflammatory therapy.

Through detailed characterization of HDL particle composition, emerging evidence suggests that triglyceride-enriched small HDL particles (HDL-triglyceride) are associated with cardiovascular risk. In a Spanish cohort of 502 individuals with T2DM or metabolic syndrome, HDL-triglyceride was associated with carotid plaques [29]. In the UK Biobank cohort of over 20,000 individuals with coronary artery disease (10.8% with DM),, each standard deviation increase in HDL-triglyceride was associated with a 6.7% higher risk of incident CAD [30]. In our cohort, we observed an inverse association between HDL-triglyceride and subclinical vascular alterations. While contrary to existing literature, this finding has several important implications. First, our Southeast Asian cohort represents distinct genetic, cultural and environmental backgrounds, highlighting the need for population-specific studies to delineate potential ethnic differences in HDL-triglyceride and ASCVD associations. Second, our findings raise the possibility that cholesterol efflux may be preserved in T2DM despite an increase in HDL-triglyceride. Third, NMR-based approach has limited sensitivity in detecting other HDL subclass particles that could contribute to HDL function. Emerging mass spectrometry integrated with proteomics characterizes HDL particles at higher resolutions [31]. Further in-vitro and in-vivo studies are required to elucidate the molecular underpinnings linking the HDL proteome, function and cardiovascular disease pathogenesis.

In our T2DM cohort, the smallest and most dense LDL subclass particles (LDL-6) was significantly correlated with endothelial dysfunction. The atherogenicity of small dense LDL is attributed to the increased retention within the the arterial intimal layer, higher affinity for LDL receptors [32] oxidation

[33], thereby induce endothelial activation and upregulate the synthesis of endothelial adhesion molecules [34].

In RA, small dense LDL particles were increased and correlated with vascular dysfunction. The proinflammatory milieu in RA, enriched with TNF- α , IL-6 and IFN- α , upregulates scavenger receptor A, lectin-like oxidized LDL receptor-1 (LOX-1), promotes vascular uptake of small dense LDL particles and activates the LOX-1/NF κ B/Arginine pathway, collectively impairing nitric oxide synthesis [35, 36]. Additionally, increased myeloperoxidase activity in RA, enhances the formation of oxidized lipoproteins, which accumulate in foam cells and promote atherogenesis [37, 38].

Normal or elevated HDL subfractions have been observed in RA patients [39], correlating with systemic inflammation [40]. The increased large HDL particles in our RA cohort may reflect reduced CETP activity, promoting cholesteryl ester accumulation in HDL particles [40]. In addition, lecithin-cholesterol acyltransferase activity is reduced, impairing cholesterol efflux and HDL maturation [41]. HDL antioxidant function is also attenuated in RA [42], potentially induced by oxidation of fatty acids such as arachidonic acid, linoleic acid, reduced PON-1 activity, and increased serum amyloid A in HDL [41]. Moreover, post-translational lipoprotein modifications may further accelerate atherogenesis in RA [15]. Our findings suggest that RA-associated vascular dysfunction involves a broader spectrum of lipoprotein alterations than previously recognized and that RA-specific pathways contributing to atherogenesis warrant further investigation.

Our metabolomics data reveal a metabolically distinct signature between the two diseases, underscoring divergent immune–metabolic pathways despite overlapping cardiometabolic risk. RA was characterized by consistently lower BCAAs (valine, leucine, isoleucine), alanine, and glutamate, together with lower glucose and reduced ketone-related intermediates (e.g., acetoacetate, 2-ketoisovalerate, 3-hydroxyisobutyrate); phenylalanine and 4-hydroxyphenylacetate were higher. This pattern supports a catabolic metabolic state consistent with inflammation-driven muscle wasting (rheumatoid cachexia) [43]. In contrast, T2DM typically showed higher BCAAs and glucose, aligning with insulin resistance and substrate excess [10].

We found that metabolically distinct signatures correlated with vascular damage in RA and T2DM, again implying divergent immune–metabolic-vascular pathways. In RA, elevated α -ketoisovalerate, a valine catabolite, was linked to reduced FMD, indicating greater endothelial dysfunction. Mechanistically, α -ketoisovalerate may act as a pro-inflammatory signal, promoting macrophage M1 polarization and cytokine release [44], while its precursor BCAAs can induce endothelial stress via mTORC1 activation [45]. The association of 4-hydroxyphenylacetate, potentially originating from gut dysbiosis, with increased CIMT implicates aromatic amino acid and gut microbial phenolic pathways—possibly through aryl-hydrocarbon receptor and oxidative stress signaling—in vascular remodeling [46]. The divergent alanine–CIMT correlations in RA and T2DM align with inconsistent associations between alanine and ASCVD in the literature [47, 48], suggesting alanine is a context-dependent biomarker rather than a direct driver of atherosclerosis, reflecting systemic inflammation in RA versus dysregulated gluconeogenesis in

T2DM. The positive association between phenylalanine and plaque is consistent with findings in T2DM [49]. Associations of α - and β -glucose with arterial stiffness and CIMT in RA highlight the potential for even modest dysglycemia to exacerbate macrovascular changes in an inflammatory milieu. These disease-specific metabolic–vascular associations highlight the different pathophysiological processes in RA and T2DM, suggesting the need for tailored biomarker strategies and targeted interventions in different diseases.

Strengths of our study include a contemporary RA–T2DM cohort matched for age, sex, BMI, hypertension, and hyperlipidemia, and excluding overt cardiovascular disease. Comprehensive vascular phenotyping were performed using standardized methods for FMD, cf-PWV, CIMT, and plaque assessments. Untargeted NMR metabolomics added mechanistic depth and reflected modern treat-to-target RA care. However, several limitations warrant mention. The cross-sectional design cannot support causal inference. Potential confounding from medications, disease duration, and body composition cannot be ruled out. As a single-center cohort from Southeast Asia, generalizability may be limited. Additionally, microvascular endpoints were not assessed. The sample size of 29 matched pairs limited statistical power and precluded multivariable regression analyses for confounder adjustment.

In conclusion, T2DM exhibits greater endothelial dysfunction, arterial stiffness and carotid plaque than RA despite similar CIMT. The two diseases also showed distinct metabolic and lipoprotein profiles and different associations with vascular dysfunction. Given the small sample size and cross-sectional design, these results should be interpreted as exploratory and hypothesis-generating. Nonetheless, these pilot findings lay the groundwork for larger longitudinal and mechanistic studies and may inform biomarker-guided risk stratification and targeted cardiovascular prevention strategies tailored to RA and T2DM.

Declarations

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Conflicts of Interest

We have no conflicts of interest.

Ethics approval

The study was approved by the National Healthcare Group Domain Specific Review Board (reference number: DSRB 2023/00960).

Consent to Participate

Written informed consent was obtained from all participants before study enrolment.

Consent to Publish

Not applicable. This manuscript does not contain any identifiable individual participant data.

Availability of data and material

The data and study materials are available from the corresponding author upon reasonable request, subject to institutional and ethical requirements.

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Disclaimer

Grammarly was used to assist with grammar checking and readability improvements. The authors take full responsibility for the content and accuracy of the manuscript.

Author Contribution

Chuanhui Xu: Conceptualization; methodology; investigation (clinical phenotyping/data acquisition); data curation; formal analysis; writing—original draft; funding acquisition; writing—review & editing. Ying Jie Chee: Conceptualization; methodology; investigation (clinical phenotyping/data acquisition); data curation; writing—original draft; writing—review & editing. Sanchalika Acharyya: Methodology; formal analysis (including statistical approach); data curation; writing—review & editing. Ai Ying Teh: Investigation (data acquisition); data curation; writing—review & editing. Claire Min-Li Teo: Investigation (data acquisition); data curation; writing—review & editing. Justina Wei Lyn Tan: Investigation (data acquisition); data curation; writing—review & editing. Ee Tzun Koh: Investigation (data acquisition); data curation; writing—review & editing. Khai Pang Leong: Investigation (data acquisition); data curation; writing—review & editing. Yuanyuan Du: Metabolomics/lipoprotein profiling: methodology and data acquisition; formal analysis; writing—review & editing. Xiaotao Shen: Metabolomics/lipoprotein profiling: methodology and supervision of analysis; formal analysis; visualization; writing—review & editing. Rinkoo Dalan: Conceptualization; supervision; project administration; funding acquisition; writing—review & editing. All authors critically revised the manuscript for important intellectual content, approved the final version for publication, and agree to be accountable for all aspects of the work.

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Tables

Table 1: Distribution of baseline characteristics of propensity-matched participants with RA and T2DM

Variables	RA (n=29)	T2DM (n=29)	p-value
Demographics			
Age in years, mean (SD)	63.8 (9.9)	63.3 (8.9)	0.827
Female sex, n (%)	25 (86.2)	22 (75.9)	0.504
Ethnicity, n (%)			0.008
Chinese	24 (82.8)	21 (72.4)	
Non-Chinese	5 (17.2)	8 (27.6)	
Smoking, n (%)			
Never	29 (100.0)	28 (96.6)	<0.001
Current	0	1 (3.4)	
Disease duration in years, mean (SD)	19.8 (11.2)	11.8 (7.5)	0.002
Cardiovascular risk factors			
BMI (kg/m ²), mean (SD)	24.1 (5.1)	24.6 (4.4)	0.643
SBP (mmHg), mean (SD)	135.4 (17.8)	136.5 (14.4)	0.795
DBP (mmHg), mean (SD)	74.9 (10.5)	78 (10.4)	0.287
Total cholesterol (mmol/L), mean (SD)	4.9 (0.9)	4.6 (0.9)	0.334
HDL (mmol/L), mean (SD)	1.7 (0.5)	1.5 (0.3)	0.031
nonHDL (mmol/L), mean (SD)	3.2 (0.7)	3.1 (0.9)	0.969
LDL (mmol/L), mean (SD)	2.6 (0.6)	2.4 (0.9)	0.349
HbA1c (%), median [IQR]	5.6 [5.5-5.9]	6.9 [6.6-8.1]	<0.001
CRP (mg/L), median [IQR]	3.4 [1.9-6.2]	1.2 [0.7-1.7]	0.001
RA-specific parameters			
DAS-28 score, median [IQR]	1.93 [1.51–2.64]	-	-
Positive rheumatoid factor, n (%)	19 (65.5)	-	
Positive anti-CCP, n (%)	19 (65.5)	-	
Medications, n (%)			
SGLT2-inhibitor	-	9 (31)	
GLP-1 RA	-	2 (6.9)	
Insulin	-	8 (27.6)	

Metformin	-	25 (86.2)	
Steroid	13 (44.8)	-	
Hydroxychloroquine	8 (27.6)	-	
Methotrexate	21 (72.4)	-	
Sulfasalazine	5 (17.2)	-	
Leflunomide	7 (24.1)	-	
Statin	14 (48.3)	22 (75.9)	0.324
Ezetimibe	1 (3.4)	2 (6.9)	<0.001

Values are presented as mean (SD), median [IQR], or n (%).

Abbreviations: RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; nonHDL, non-high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; CRP, C-reactive protein; DAS-28, Disease Activity Score in 28 joints; CCP, cyclic citrullinated peptide; SGLT2, sodium-glucose cotransporter 2; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Table 2: Comparison of vascular function and structure in RA and T2DM subjects

	RA (n=29)	T2DM (n=29)	p-value
Endothelial function			
Mean FMD (%)	6.33 (2.02)	5.3 (2.67)	0.141
FMD < 7% (n,%)	20 (69)	23 (79.3)	0.021
Arterial stiffness			
cf-PWV (m/s)	10.9 (2.57)	12.8 (2.56)	0.005
cf-PWV > 10 m/s (n,%)	15 (51.7)	25 (86.2)	0.109
Carotid IMT (mm)			
Average IMT	0.66 (0.10)	0.67 (0.16)	0.802
Maximum IMT	0.74 (0.14)	0.73 (0.20)	0.743
CIMT > 75 th percentile	21 (72.4)	17 (58.6)	0.109
Plaque			
Carotid plaque (n,%)	1 (3.4)	7 (24.1)	<0.001
Femoral plaque (n,%)	9 (31)	16 (55.2)	0.617
Both sites (n,%)	1 (3.4)	5 (17.2)	<0.001
Any site (carotid / femoral) (n,%)	9 (31)	18 (62.1)	0.871

Values are presented as mean (standard deviation) or n (%).

RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus; FMD, flow-mediated dilation; cf-PWV, carotid–femoral pulse wave velocity; IMT, intima–media thickness; CIMT, carotid intima–media thickness. Endothelial dysfunction was defined as FMD < 7%. Arterial stiffness was defined as cf-PWV > 10 m/s. CIMT > 75th percentile refers to population-based age- and sex-specific threshold.

Figures

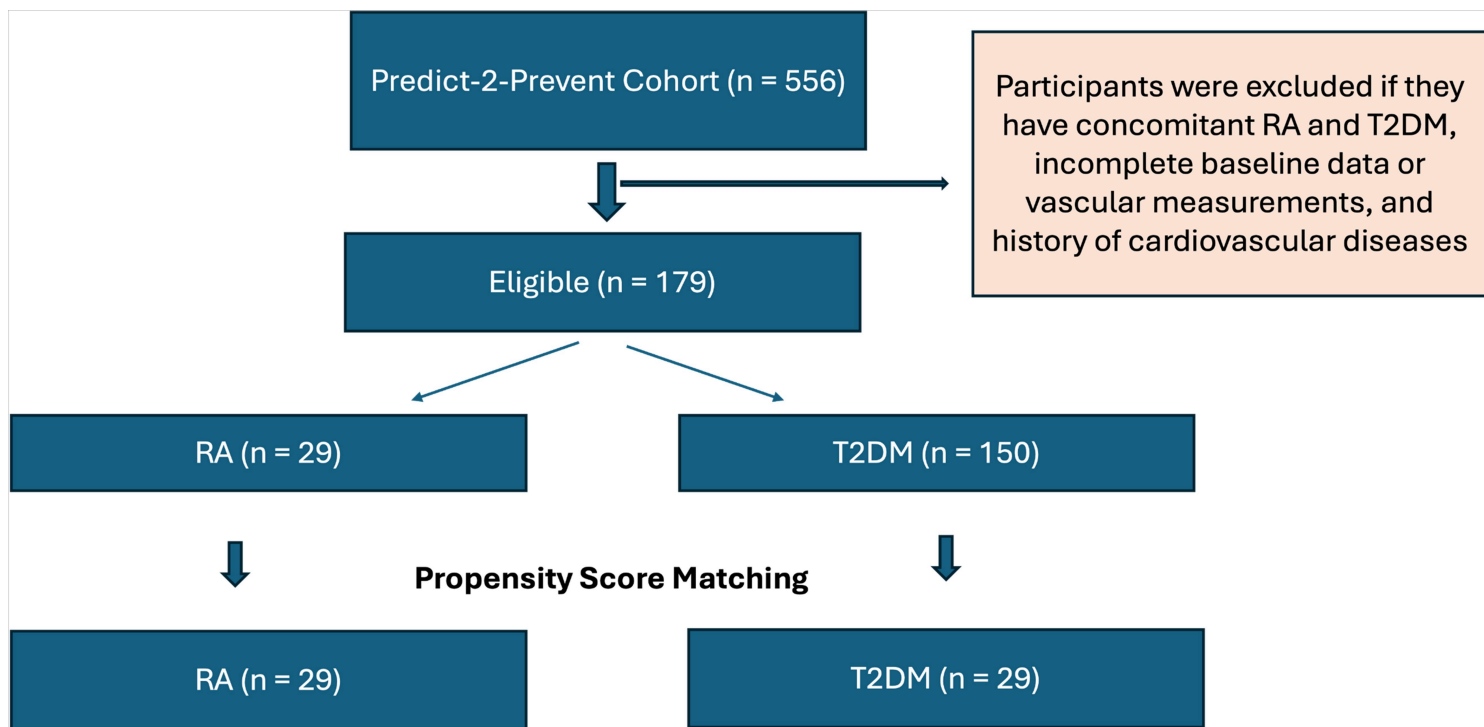


Figure 1

Study recruitment and propensity score matching

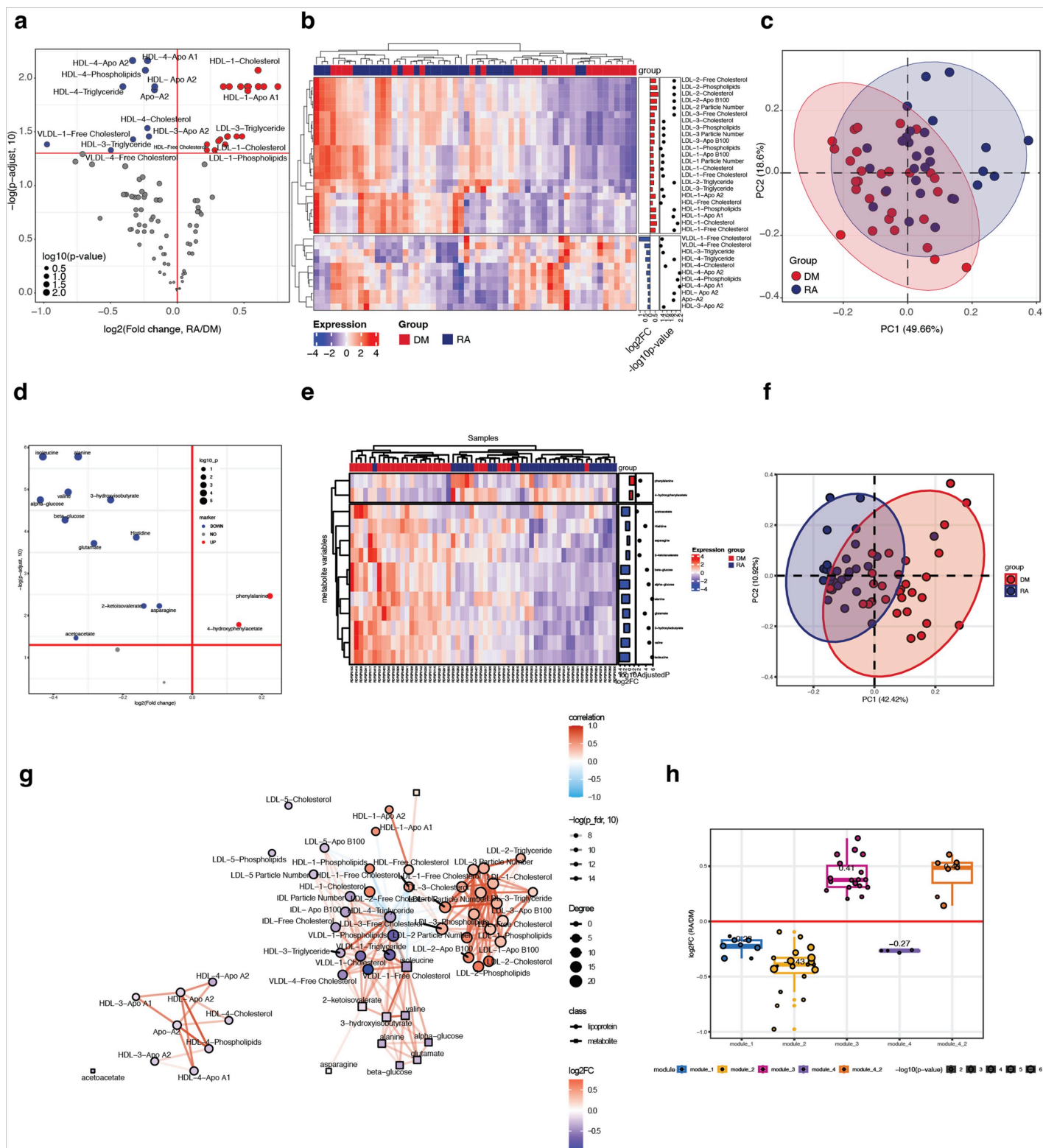


Figure 2

Differentially expressed lipoproteins and metabolites between T2DM and RA, and identification of functional modules via correlation network analysis. (a) Volcano plot highlighting lipoproteins differentially expressed between T2DM and RA. (b) Heatmap showing the expression patterns of these lipoproteins across all participants. (c) Principal component analysis (PCA) based on the differentially expressed lipoproteins reveals separation between T2DM and RA groups. (d) Volcano plot highlighting

metabolites differentially expressed between T2DM and RA. (e) Heatmap showing the expression patterns of these metabolites across all participants. (f) PCA based on the differentially expressed metabolites also separates the T2DM and RA groups. (g) A correlation network constructed from the differentially expressed lipoproteins and metabolites; five distinct functional modules were identified. (h) Distribution of log₂ fold changes for lipoproteins and metabolites within each module.

Supplementary Files

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- [SupplementaryTables.docx](#)