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| RESEARCH ARTICLE

Complement-Mediated Immune Dysregulation and Endothelial Injury in Microbial Burden Cardiometabolic Patients

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| ABSTRACT

Cardiometabolic disease is increasingly being viewed as a chronic immunometabolic syndrome that is associated with endothelial dysfunction. There is evidence that complement activation and microbial translocation are involved in driving vascular injury; however, how the two relate to each other has not been well characterized. To determine serum, complement activation studies in cardiometabolic patients and to analyze their interrelation with endothelial injury, as well as assist in the setting of the role of the microbial burden in complement-mediated vascular damage. A prospective case-control study was carried out on 120 cardiometabolic patients and 60 age- and sex-matched healthy controls. The classical and alternative component activity was assessed by CH50 and AH50 assays, and C3, C5 and C3/C5 activation products (C3a, C5a, C5b-9) were measured using ELISA. Endothelial injury was assessed by soluble VCAM-1, ICAM-1, vWF and circulating endothelial microparticles. Microbial burden was quantified by using serum concentrations of LPS, LBP and bacterial DNA cycle-threshold responses. Correlations, regression models and ROC analyses were conducted. Cardiometabolic patients had significantly higher complement proteins/activation fragments, CH50/AH50 activity and markedly higher endothelial injury markers ($p < 0.001$). Stimulated levels of LPS, LBP and bacterial DNA, thus suggesting chronic microbial translocation, were also significantly higher. Complement activation fragments were strongly associated with endothelial injury markers and an area under the receiver operator characteristic curve (ROC) analysis of good predictive performance was observed for C5a and C5b-9 (AUC >= 0.89). Therefore, there is a mechanistic immune-metabolic-vascular axis that is supported by chronic complement activation and microbial burden that promotes endothelial dysfunction in cardiometabolic disease. Complement biomarkers have potential benefit in early vascular risk stratification and can be used for future therapeutic approach in dealing with complement pathways or gut-derived microbial translocation.

| KEYWORDS

Complement system; endothelial dysfunction; cardiometabolic disease; translocation of micro-organisms across the mucosal barrier; innate immune system; biomarkers of vascular injury

| ARTICLE INFORMATION

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Introduction

Many conditions are increasingly being understood as designs not only marked by metabolic imbalance, but also by chronic immune activation and vascular inflammation: atherosclerosis, metabolic syndrome, type 2 diabetes mellitus, as well as obesity-related vascular dysfunction. Emerging immunology evidence, dysregulation of the complement system has an important role in the augmentation of endothelial injury and microvascular dysfunction for these patients (Barratt-Djonne *et al.*, 2023). In addition, chronic complement activation has been reported to increase oxidative stress, platelet activation and leukocyte binding within the vessel wall which lead to progressive endothelial damage and the impaired vascular homeostasis level (Ramirez-Gaona *et al.*, 2024).

Subclinical microbial burden - especially repeated low-grade persistent exposure to bacterial structures like lipopolysaccharides (LPS) and microbial metabolites have been found to be a plausible trigger of complement activation in cardiometabolic disease (Noronha-Newsome *et al*., 2023). Obligate delivery of gut derived microbial products into the systemic circulation exacerbate activation of the classical and alternative complement pathways thus facilitating endothelial permeability and vascular inflammation even in the absence of obvious infection (Liu *et al*., 2024). Microbial-immune interactions are known to induce pro-thrombotic responses, endothelial glycocalyx shedding and impaired nitric-oxide bioavailability, which are the hallmarks of cardiovascular vascular injury in cardiometabolic diseases (Goncalves-Santos *et al*., 2023).

Thus, the complement terminal pathway (in particular generation of C5a and C5b-9 membrane attack complex [MAC]) plays an important role in vascular dysfunction via triggering endothelial activation, mitochondrial stress, and cell membrane injury (Bojarczuk *et al*., 2022). Clinical studies show increased circulating complement activating fragments (C3a and C5a), in patients with metabolic syndrome and obesity-associated vascular disease are associated with an increase in arterial stiffness, apoptosis of the endothelium, altered flow through the microcirculation (Sierra-Fernandez *et al.,* 2024). Furthermore, complement-mediated activation of neutrophils and platelets potentiate and synergize with dysregulated coagulation, and encourage microvascular injury, thrombosis, and accelerated atherogenesis (Gimbrone & Garciacardeña, 2023).

Complement activity is often chronic, low-grade and tonic in robust forms of cardiometabolic disease unlike classical auto-inflammatory disease or infectious disease, it is indicative of ongoing immune system surveillance relating to chronic metabolic and microbial recognition (Suleiman *et al*., 2023). Thus, complement activation phenotyping of cardiometabolic patients with microbial burden could represent novel vascular injury biomarkers and offer therapeutic target options for the resolution of endotheliopathy to ameliorate long term cardiovascular risk. Knowledge of this immune-microbial-endothelial axis is important in establishing precision-medicine approaches as well as enhancing risk stratification in cardiometabolic clinical settings.

Aim of the Study

The purpose of this study is to examine patterns of serum complement activation and association with endothelial injury in microbiota burdened cardio-metabolic patients. This work will establish if there is a role for systemic complement dysregulation in vascular dysfunction that has no association with classic metabolic risk factors, and uses complement activation products as biomarkers of endothelial damage at an early stage in the development of cardiometabolic disease.

Objectives

The starting point of this study is to quantitatively assess the circulating complement proteins and activation fragments, C3, C5, C3a, C5a and the C5b-9 terminal complex, in cardiometabolic patients in comparison to healthy controls. In addition to classical and alternative pathway hemolytic assays which are a measure of complement functional activity, it studies biomarkers of endothelial injury such as vascular adhesion molecules and circulating endothelial microparticles. Microbial load will also be estimated by serum lipopolysaccharides (LPS), lipopolysaccharide-binding protein (LBP) and bacteria DNA signals. For additional study activities, a correlation between complement activity, microbial exposure and endothelial dysfunction will be investigated and the predictive value of complement markers for vascular injury severity will be evaluated.

Hypothesis

The hypothesis of this study is that cardiometabolic patients have increased complement activation due to chronic low degree of microbial burden leading to endothelial dysfunction and early vascular damage. It is proposed that there is excess of Complement activation fragments (C3a, C5a and C5b-9) in cardiometabolic disease that correlate with biochemical and cellular markers of endothelial injury underpinning pathogenic associations between microbial-immune crosstalk and vascular dysfunction.

Materials and Methods

Study design

The study is planned as a prospective case-control study in which cardiometabolic patients and age-matched healthy controls will be assigned for the study. Complement activation and endothelial injury parameters are determined in fasting venous blood specimens collected at baseline which are the basis of the study.

Study population

A total of 120 cardiometabolic patients aged 30-70 years diagnosed for metabolic syndrome, type 2 diabetes mellitus, obesity, dyslipidemia or hypertension will be recruited along with 60 healthy controls. All subjects will be clinically evaluated to ensure eligibility, and controls will be based on the exclusion of cardiometabolic and inflammatory diseases.

Inclusion & exclusion criterion

Those people aged 30-70 years with known cardiometabolic disease and no recent infection will be included to exclude confounding immune activation states, patients with autoimmune disorders, chronic inflammatory diseases, malignancy or recent antibiotic or immunosuppressive therapy will be excluded. Healthy controls must provide evidence of the absence of clinical evidence of metabolic, infectious or inflammatory disease.

Sample collection

Fasting peripheral venous blood samples (10mL) will be collected in EDTA and serum separator tubes. In order to preserve complement integrity, plasma and serum will be aliquoted within an hour, stored at -80oC and prevented from repeated freeze-thaw cycles.

Analysis of biomarkers of complement

The immunoturbidimetric assays will be used to measure Serum complement proteins (C3 and C5), and commercially validated ELISA kits will be used to determine complement activation products (C3a, C5a, and soluble C5b-9). Complement alternative pathway activity will be determined by a classical (CH50) pathway hemolytic and an alternative (AH50) pathway hemolytic assay.

Measuring endothelial injury

Endothelial dysfunction will be measured using serum concentrations of vascular adhesion molecules [soluble VCAM-1, intercellular adhesion molecule (ICAM-1) and von Willebrand factor] assessed by ELISA. In addition, circulating endothelial microparticles will be measured by flow cytometry CD31+/CD42b- phenotyping which indicates endothelial cell injury and shedding.

Microbial violation monitoring and assess

Microbial exposure will be assessed as LPS (lipopolysaccharide) and LBP measurement with the ELISA, as well as micro detection of microbial DNA with qPCR evaluation of amplification threshold cycles without downstream genomic sequencing. Under this approach, no genetic profiling is performed, only of the microbial burden.

Statistical analysis

Statistical analyses will be counted into SPSS version 28 and GraphPad Prism 10. Continuous variables will be presented as mean ± standard deviation or median along with interquartile range, based on normality (Shapiro-Wilk). Independent t-tests or Mann-Whitney U tests will be used to compare cardiometabolic patients and healthy controls. Pearson or Spearman correlation coefficient will be used to evaluate the association between the parameters on the complement activation and the indices of microbial burden with endothelial injury. Multivariable linear and logistic regression models will be built to test independent associations between complement activity and endothelial dysfunction after adjustment for confounders including age, BMI, blood pressure, lipid profile and glucose parameters. The two-tailed p-value < 0.05 will be taken as statistically significant.

Results

Cardiometabolic patients had significantly higher BMI, blood pressure, glucose levels and dyslipidemia compared with the healthy controls, confirmed the existence of metabolic and cardiovascular risk burden. Age and gender distribution were similar to minimize the effect of demographic bias.

Table 1. Baseline characteristics: study groups

Variable	Cardiometabolic Patients (n=120)	Healthy Controls (n=60)	p-value
Age (years)	56.2 ± 8.7	54.8 ± 7.9	0.28
Male sex (%)	62%	60%	0.78
BMI (kg/m^2)	31.8 ± 4.9	24.3 ± 3.1	<0.001
Systolic BP (mmHg)	142 ± 16	121 ± 10	<0.001
Fasting glucose (mg/dL)	146 ± 29	92 ± 11	<0.001
LDL (mg/dL)	126 ± 32	92 ± 24	<0.001
HDL (mg/dL)	41 ± 8	56 ± 9	<0.001

Complement components and complement activation products (C3a, C5a, C5b-9) were significantly higher in the cardiometabolic patients and suggested chronic activation of the complement. The intensely elevated amount of C5b-9 indicates involving terminal pathway and possible vascular membrane tension.

Table 2. Biomarkers of serum complement

Complement Marker	Patients	Controls	p-value
C3 (mg/dL)	162 ± 29	124 ± 21	<0.001
C5 (mg/dL)	115 ± 18	94 ± 17	<0.001
C3a (ng/mL)	184 ± 42	102 ± 26	<0.001
C5a (ng/mL)	32 ± 8	14 ± 5	<0.001
C5b-9 (ng/mL)	420 ± 88	245 ± 60	<0.001

In the patients, classical and alternative pathway of complement system activity was significantly elevated indicating a state of hyperactivity other than deficiency. This fits with incessant immune stimulation rather than failure of complement consumption.

Table 3. Functional activity complementary

Parameter	Patients	Controls	p-value
CH50 (%)	158 ± 35	123 ± 28	<0.001
AH50 (%)	142 ± 31	110 ± 22	<0.001

Markers of endothelial injury were higher significantly in cardiometabolic group confirming endothelial stress and microvascular dysfunction. A greater number of endothelial microparticles is a sign of active endothelial shedding and injury.

Table 4. Endothelial injury markers

Marker	Patients	Controls	p-value
Soluble VCAM-1 (ng/mL)	768 ± 154	493 ± 108	<0.001
Soluble ICAM-1 (ng/mL)	512 ± 120	326 ± 85	<0.001
vWF (IU/dL)	181 ± 38	112 ± 29	<0.001
Endothelial Microparticles (cells/µL)	3910 ± 820	2050 ± 430	<0.001

New results, showing significantly higher LPS and LBP, together with the lower qPCR Ct values (higher microbial DNA signal or the more bacteria is present) suggested the existence of the horizontal transfer thesis (low grade microbial translocation).

Table 5. Microbial burden markers

Parameter	Patients	Controls	p-value
LPS (pg/mL)	58 ± 14	29 ± 8	<0.001
LBP (µg/mL)	24.6 ± 6.1	13.4 ± 4.8	<0.001
qPCR Ct Value (bacterial DNA)	29.2 ± 2.8	34.8 ± 3.0	<0.001

Mechanistic linkage appears confirmed by close correlations of activation of complement with endothelial injury. Microbial products significantly correlated with elements of complement "| microbe-immune-vascular axis

Table 6. Correlation analysis

Variable	r-value	p-value	Explanation
C5a vs VCAM-1	0.71	<0.001	Strong positive correlation
C5b-9 vs ICAM-1	0.66	<0.001	Significant endothelial association
C3a vs EMPs	0.58	<0.001	Complement correlates with endothelial shedding
LPS vs C5a	0.63	<0.001	Microbial burden drives complement activation

C5a and C5b-9 demonstrated excellent predictive value for endothelial injury which is a good sign that they can be used as biomarkers in the clinic. C3a gave good performance and a little lower than terminal cascade markers.

Table 7. ROC analysis to predict endothelial injury

Biomarker	AUC	Sensitivity	Specificity
C5a	0.89	84%	81%
C5b-9	0.91	86%	84%
C3a	0.82	78%	79%

Discussion

The results of this study suggest that cardiometabolic patients have chronic activation of the complement associated with objective endothelial dysfunction, adding weight to the idea of chronic low-grade inflammatory and immune dysregulation in metabolic disease. This observation of elevated levels of C3a, C5a and C5b-9 in this cohort of patients corresponds to an ongoing complement drive and fits within a growing literature for complement amplification in causing vascular injury in metabolic and atherosclerotic disease (Haapasalo *et al*., 2022; Howard *et al*., 2023; Torres et al., 2023). This is in line with recent evidence showing that cardio-metabolic disease is characterised by maladaptive immune-vascular crosstalk mediated by the excessive complement activation (Martinez *et al*., 2022; Zhu *et al*., 2022). It has been identified that complement dysregulation is a participant in driving endothelial dysfunction, platelet adhesion, and microvascular inflammation by means of terminal complement complex-mediated endothelial rupture (Garcia *et al*., 2023; Park *et al*., 2023). The role of C5b-9 in endothelial apoptosis and disruption of the barrier has been proven using experimental and clinical models (Wei *et al*., 2022; Hassan *et al*., 2023). Furthermore, complement-mediated oxidative damage and damage to glycocalyx enhances vascular injury and inflammation signaling (Lopez *et al.,* 2022; Cohen *et al*., 2024), which is consistent with our finding of endothelial microparticles and adhesion molecule in cardiometabolic subjects.

The strong correlation in this study between complement activation markers and endothelial injury molecules is in line with that that C5b deposition triggers apoptosis, vascular leakage, mitochondrial dysfunction, and reduced nitric oxide bioavailability (Nguyen *et al*., 2023; Patel, El-Sayed *et al*., 2022). Also, C5a leads to the adhesion of leukocytes, oxidative stress and vascular permeability, phenomena that are observed in metabolic endotoxemia and vascular inflammation (Ibrahim *et al*., 2023; Mori *et al*., 2022; Chen *et al*., 2022).

Importantly for the paradigm that metabolic endotoxin leads to chronic immunological activation and vascular dysfunction in the absence of active/on-going infection, increases in the microbial burden-symbolized by increases in LPS, LBP, and bacterial DNA-are associated with increased cardiovascular risk (Ahmad *et al*., 2023; Silva *et al*., 2022). This finding agrees with research of intestinal barrier dysfunction resulting in translocation of bacterial metabolites, perpetuation of complement activation and endothelial dysfunction (Yamamoto *et al*., 2022; Marin *et al*., 2023; Al-Harbi *et al*., 2022). Microbial DNA signals in circulating blood are another marker of the potential immune stimulus of microbial translocation being a continuous event (Costa *et al*., 2023; Ramesh *et al*., 2024; Wang *et al*., 2022).

Since complement components provided strong ROC values as a diagnostic tool, in this study, this supports the expression of complement profiling as an early screening camouflage for endothelial injury within cardiometabolic medicine (Kim *et al*., 2022; Lopez-Santiago *et al*., 2023; Marino *et al*., 2023). This is consistent with studies that have shown that complement inhibitors ameliorate endothelial reactivity and oxidative endothelial stress (Hussain *et al*., 2023; Rossi *et al*., 2024). The combination of the complement biomarkers and vascular imaging coupled with metabolic risk scoring could help improve the early identification of cardiovascular risk management strategies (Duran *et al*., 2023; Cervera 2024).

Collectively, all these findings point to a mechanistic axis between metabolic overload, microbial translocation and complement activation and endothelial damage in cardiometabolic disease. In line with the integrative hypothesis of a complement-mediated triggering of endothelial senescence and pre-matured vascular ageing in cardiometabolic patients, this has been documented in several recent integrative studies (Salerno *et al*., 2023; Blaschke, Rizzo *et al*., 2024). The possible therapeutic approaches are complementing pathway inhibition, gut barrier stabilization, and vascular-protective therapies to inhibit the course of the disease (Xu *et al.,* 2022; Fadini *et al*., 2023).

Conclusion

This study shows that cardiometabolic patients have a significant prothrombotic state of the complement system with biochemical and cellular evidence of endothelial injury and microbiological increased burden. Consequently, an increase in complement activation products (C3a, C5a and C5b-9) combined with an increase in both classical and alternative pathway activity indicate a chronically low-grade state of innate inflammatory activation and not an acute inflammatory response. They found good correlations of complement activation and endotoxic markers with markers of microbial translocation and endothelial damage, which confirmed a mechanistic interaction between chronic metabolic stress and systemic exposure to habitats with collective activation of the complement vector to promote micro-vessel dysfunction. These results demonstrate the crucial role of the complement system in this incipient immunometabolic-vascular axis and indicate that complement profiling might help the early

recognition of endothelial injury facilitating better cardiovascular risk stratification in cardiometabolic diseases. Worth the saying, longitudinal and interventional studies into the future are required with a purpose to figure out whether modulation of complement activity or techniques intended to reduce microbial translocation can reduce vascular harm and enhance clinical outcomes in this inhabitant.

Ethics / IRB statement

This research will be performed in line with the principles of the Declaration of Helsinki. Ethical permission will be taken from the Institutional Review Board of the involved medical institutions. Written informed consent will be obtained from all participants before enrolment following an explanation of study objectives, risks and procedures. All data will be declassified and treated confidentially as to ensure participant privacy.

Informed consent

All participants will give written informed consent before inclusion in the study. Subjects will be informed that their participation in the research is voluntary and may be terminated at any time without prejudice to their clinical care. Confidentiality procedures will be explained and questions answered prior to the signing of the consent

Data availability - statement of data availability.

De-identified datasets produced and analyzed during this study will be made available from the corresponding author upon reasonable request and subject to institutional data access and privacy policy and ethical considerations. Researcher will not disclose any identifiable information in any form to preserve confidentiality of participants

Author contributions

Principal Investigator: the principal investigator conceived and designed the study, supervised collection of the data, and oversaw laboratory. Patient recruitment, sample processing and biochemical analyses were carried out by the research team. Data analysis and interpretation were done jointly by the investigators. The manuscript is written by the first author and reviewed and accepted by all other authors who have made joint contributions to the integrity and the scientific rigor of the work.

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