



Emerging Evidence

Observational Cross-Sectional Study of Inflammatory Markers After Transient Ischemic Attacks, Acute Coronary Syndromes, and Vascular Stroke Events

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ABSTRACT

We identified the prevalence of elevated high-sensitivity C-reactive protein and interleukin-6 in patients with recent cardiovascular (CV) events with or without prediabetes/diabetes, and in a control group of patients with remote CV events. Interleukin-6 was elevated in patients with prediabetes/diabetes and recent CV events (median, 4.84 pg/mL; interquartile range, 3.27–7.45) compared with patients with remote events (2.36 pg/mL; interquartile range, 1.09–4.00). There was a trend for elevated high-sensitivity C-reactive protein in patients with acute events and prediabetes/diabetes ($P = 0.147$). This supports the notion that patients with prediabetes/diabetes and recent CV events have higher inflammatory burdens than patients without recent CV events or dysglycemia.

RÉSUMÉ

Nous avons défini la prévalence de l'augmentation du taux de protéine C réactive à haute sensibilité et d'interleukine-6 chez des patients ayant récemment subi des événements cardiovasculaires (CV), atteints ou non de prédiabète ou de diabète, et dans un groupe témoin de patients ayant subi des événements CV antérieurement. Le taux d'interleukine-6 était élevé chez les patients atteints de prédiabète ou de diabète ayant récemment subi des événements CV (médiane de 4,84 pg/ml; écart interquartile de 3,27 à 7,45) par rapport aux patients ayant subi des événements antérieurement (2,36 pg/ml; écart interquartile de 1,09 à 4,00). Le taux de protéine C réactive à haute sensibilité avait tendance à être élevé chez les patients atteints de prédiabète ou de diabète ayant subi des événements aigus ($p = 0,147$). Ces données appuient la notion selon laquelle les patients atteints de prédiabète ou de diabète qui ont récemment subi des événements CV présentent des fardeaux inflammatoires supérieurs à ceux des patients qui n'ont pas récemment subi d'événements CV ou présenté de dysglycémie.

Patients with diabetes are at increased risk of suffering premature atherosclerotic disease-related cardiovascular (CV) events (eg, acute coronary syndrome [ACS], stroke, transient ischemic attacks [TIAs]), and have a higher recurrent event rate than the general population.¹ Systemic and vascular inflammation has been extensively investigated as a promoter of atherosclerosis development and destabilization.²

Furthermore, several recent trials have shown that therapies focused at blocking the inflammatory cascade directly reduced vascular events.^{3–6} The results from these trials raise an intriguing question of how to identify the patients who might benefit the most from these innovative therapies. By examining biomarkers of inflammation, we might be able to identify patients who are at particularly high risk of vascular events, and might benefit the most from inflammation-targeted therapies to reduce subsequent CV events.

Currently the prevalence of elevated serum high-sensitivity (hs-) C-reactive protein (CRP) levels after a vascular event has not been widely studied. Identification of the prevalence of patients with elevated inflammatory markers post event might enable the prospective evaluation of inflammation-targeted therapies and the identification of patients at high risk for CV events.

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Ethics Statement: This study was approved by University of Ottawa Heart Institute's Research Ethics Board. All participants gave written informed consent.

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See page 678 for disclosure information.

We hypothesized that because of the link between inflammation and CV events, as well as the higher prevalence of CV events in patients with diabetes, these diabetic or prediabetic patients might have a higher burden of inflammation than a general population of patients with CV disease. We posited that the prevalence of increased hs-CRP and interleukin (IL)-6 as markers of vascular inflammation in patients with diabetes or prediabetes after recent CV events (ACS, TIA, stroke), would be greater than in a control group of patients without recent acute CV events.

Methods

We conducted an observational cross-sectional study in 2 cohorts of patients: (1) those with a recent CV event (ACS, TIA, or stroke) within 30-60 days; and (2) those with remote previous CV events (> 1 year). Patients were divided into 3 groups. Group 1 comprised patients with a recent CV event with prediabetes/diabetes (as defined by the Canadian Diabetes Association Guidelines)⁷; group 2, those with a recent CV event without prediabetes/diabetes, and group 3, patients who suffered a remote CV event (> 1 year).

Participants were enrolled from either the University of Ottawa Heart Institute or the Stroke Prevention Clinic at the Ottawa Hospital. Enrolled participants for group 1 and 2 had to: have suffered a recent CV event (ACS, TIA, or stroke) within 30-60 days, be 18 years of age or older, and be symptomatically and hemodynamically stable. Group 1 patients had prediabetes/diabetes, group 3 (control group) patients had a remote CV event (> 1 year earlier) and met the other inclusion criteria. All patients provided written informed consent. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board and the study was conducted in accordance with the Declaration of Helsinki.

For patients in group 1 and 2, IL-6 and hs-CRP were measured within 30-60 days after their CV event. For those in group 3, IL-6 and hs-CRP were measured > 1 year after their CV event. hs-CRP was measured with a commercially available kit available on a high-throughput diagnostic platform (ROCHE sro, Diagnostics Division, Praha, Czech Republic). IL-6 was assayed using a commercially available enzyme-linked immunosorbent assay kit (R&D Systems Inc, Minneapolis, MN).

Demographic data including age, sex, ethnicity, height, weight, waist circumference, and blood pressure were recorded as well as data on current medications, medical history, smoking status, and family history of CV disease. IL-6 and hs-CRP were measured within 30-60 days after their vascular event in those in groups 1 and 2 and at time of enrollment for those in group 3.

Demographic characteristics are presented as median (interquartile range [IQR]). Differences between patient groups were evaluated using the Fisher exact test for discrete clinical variables and the Mann-Whitney *U* test for continuous variables. Follow-up data were collected as scheduled. All tests were 2-sided, and a *P* value of < 0.05 was considered statistically significant. For comparisons of hs-CRP and IL-6 values between groups, Kruskal-Wallis tests were conducted to compare the medians between groups. Missing data were considered missing completely at random and pairwise

deletion was used to handle the missingness. Statistical analyses were done using MedCalc Statistical Software version 19.5.3 (MedCalc Software Ltd, Ostend, Belgium).

Results

Participant characteristics are described in Table 1. In summary, 24% of participants were women, with a median age of 64.0 (IQR, 57.0-71.0) years—these were similar between the 3 groups. Median body mass index was 28.6 (IQR, 25.0-33.0) and participants in the 3 groups had a similar proportion of cardiac risk factors except for diabetes (as expected).

IL-6 median values for groups 1, 2, and 3 were 4.84 (IQR, 3.27-7.45) pg/mL, 2.47 (IQR, 1.65-5.61) pg/mL, and 2.36 (IQR, 1.09-4.00) pg/mL, respectively, with a significant difference between IL-6 levels across the 3 groups (*P* = 0.034). A post hoc Mann-Whitney test revealed the median between group 1 and 3 was significantly different (*P* = 0.009). hs-CRP median values were 2.20 (IQR, 1.20-7.98) mg/mL, 1.00 (IQR, 0.48-2.50) mg/mL, and 1.20 (IQR, 0.78-2.10) mg/mL, respectively, and showed a trend toward significant differences across the 3 groups (*P* = 0.147). Results shown in Figure 1.

The subset of patients with prediabetes/diabetes and a recent CV event (group 1) had a numerical, but nonsignificant trend toward higher median IL-6 values (4.84; IQR, 3.27-7.45 pg/mL) compared with the subset of patients with prediabetes/diabetes who experienced remote events (2.77; IQR, 1.50-4.00 pg/mL). hs-CRP levels were also numerically higher in patients with prediabetes/diabetes who suffered a recent CV event (1.95; IQR, 1.09-7.80 mg/mL) compared with those with prediabetes/diabetes with remote events (1.75; IQR, 1.20-2.70 mg/mL; *P* = 0.815).

Similarly, the subset with no prediabetes/diabetes and a recent CV event had a trend toward higher IL-6 values (2.47; IQR, 1.65-5.61 pg/mL) compared with the subset of patients with prediabetes/diabetes who had remote events (IL-6: 1.57; IQR, 0.84-4.26 pg/mL; *P* = 152). hs-CRP did not differ significantly between the groups with median levels of 1.00 (IQR, 0.48-2.50) mg/mL in the subset with no prediabetes/diabetes and a recent CV event compared with levels of 1.00 (IQR, 0.70-2.45) mg/mL in patients without prediabetes/diabetes and remote events (*P* = 0.815).

In investigating the group of patients with remote events, IL-6 levels were numerically (but not statistically) higher in patients with prediabetes/diabetes (2.77; IQR, 1.50-4.00 pg/mL) compared with those without (1.57; IQR, 0.84-4.26 pg/mL; *P* = 0.347). Similarly, hs-CRP levels were numerically (but not statistically) higher in patients with prediabetes/diabetes (1.75; IQR, 1.20-2.70 mg/mL) compared with those without (1.00; IQR, 0.70-2.45 mg/mL; *P* = 0.271). Data are available upon request.

Discussion

In this observational cohort study, we compared IL-6 values in patients with prediabetes/diabetes who had experienced recent CV events, with those in patients with remote CV events, and there was a numerical but not statistically significant trend of higher median values of hs-CRP in

Table 1. Baseline characteristics of the participants

Variable	Acute events with (pre-)DM (n = 18)	Acute events without (pre-)DM (n = 17)	Remote events (n = 24)
Age, years	60.5 (57.0-71.0)	64.0 (55.5-70.25)	67.0 (60.5-71.0)
Male sex	13 (72)	13 (76)	19 (79)
BMI	28.8 (25.0-33.3)	26.6 (24.6-28.8)	29.1 (25.8-34.2)
Hypertension	13 (72)	8 (47)	15 (62)
Dyslipidemia	13 (72)	8 (47)	23 (96)
Smoking	10 (56)	6 (32)	14 (58)
Diabetes/pre-diabetes	18 (100)*	0 (0)*	12 (50)*
Baseline medical therapy			
ECASA	18 (95)	16 (94)	21 (88)
P2Y12 inhibitors	18 (95)*	15 (88)*	12 (50)*
Anticoagulant	1 (5)	1 (6)	4 (17)
β-Blocker	15 (79)	14 (82)	18 (75)
ACEi	16 (84)	15 (88)	15 (63)
CCB	2 (11)	2 (12)	0 (0)
Statin	19 (100)	15 (88)	23 (96)
Metformin	6 (32)	0 (0)	3 (13)
Insulin	3 (16)	0 (0)	2 (8)
Steroids	0 (0)	0 (0)	2 (8)
Any other anti-inflammatory medication	0 (0)	0 (0)	1 (4)
Cell count and differential			
Leukocytes × 10 ⁹ /L	8.3 (6.9-9.6)	6.9 (5.2-8.1)	8.0 (7.0-9.3)
Platelets × 10 ⁹ /L	234.5 (177.0-271.0)	220.2 (170.3-271.3)	220.0 (181.5-254.0)
Neutrophils × 10 ⁹ /L	5.2 (4.5-6.0)	3.9 (2.9-5.3)	4.8 (4.1-5.8)
Lymphocytes × 10 ⁹ /L	2.0 (1.7-2.3)	1.7 (1.2-2.1)	2.1 (1.6-2.4)
Monocytes × 10 ⁹ /L	0.6 (0.6-0.7)	0.6 (0.4-0.7)	0.6 (0.5-0.7)
Eosinophils × 10 ⁹ /L	0.3 (0.2-0.4)	0.2 (0.1-0.3)	0.2 (0.1-0.3)
Biomarkers/biochemistry			
IL-6, pg/mL	4.83 (3.27-7.45) [†]	2.47 (1.65-5.61) [†]	2.36 (1.09-4.00) [†]
hs-CRP, mg/mL	2.20 (1.20-7.98) (n = 17)	1.00 (0.48-2.50) (n = 17)	1.20 (0.78-2.10) (n = 13)
Random glucose level, mmol/L	6.10 (5.38-7.53)	5.30 (5.03-5.53)	5.50 (4.88-7.18)
Creatinine, μmol/L	82.0 (73.0-97.0)	79.0 (73.0-92.5)	81.50 (73.0-93.5)
HbA1c, %	6.25 (5.90-7.20)	5.50 (5.40-5.70)	5.95 (5.50-6.65)

Data are median (IQR) or n (%).

ACEi, angiotensin converting enzyme inhibitor; BMI, body mass index; CCB, calcium channel blocker; DM, diabetes mellitus; ECASA, ; HbA1c, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IQR, interquartile range; P2Y12, purinergic signalling receptor Y₁₂.

* Distribution of variables differed significantly across groups on Fisher exact testing ($P < 0.05$).

[†] Median values differed across groups during Kruskal-Wallis testing.

patients with prediabetes/diabetes with recent CV events compared with patients with remote CV events. There was a trend for higher IL-6 and hs-CRP levels in patients with prediabetes/diabetes and recent CV events compared with those without dysglycemia who also experienced recent CV events. There was also a trend for higher IL-6 and hs-CRP levels in patients with prediabetes/diabetes and a recent CV event compared with the subgroup of patients with prediabetes/diabetes and a remote CV, although this did not reach statistical significance. Finally, there was also a numerical, but not significant trend for higher IL-6 and hs-CRP levels in patients without prediabetes/diabetes and a recent CV event compared with the subgroup of patients with no prediabetes/diabetes and a remote CV.

There is a large body of evidence that supports the notion that atherosclerosis is an inflammatory process.⁸⁻¹⁰ CV events occur more frequently in persons with higher burdens of circulating inflammatory markers, and treating patients on the basis of these inflammatory markers has been shown to reduce adverse outcomes.^{3,4} Inflammation promotes atherosclerotic CV disease through multiple mechanisms. It might play a role in the evolution of plaque biology and contribute to acute plaque rupture.¹¹ It has an overall negative effect on vessel anatomy and function after the acute CV insults.¹² The

inflammatory activity is also the highest immediately after a CV event, indicating tissue repair pathways being coordinated by inflammatory activation.

The results of our study also support the notion that patients with diabetes or prediabetes and who have had recent CV events¹³ have a higher inflammatory burden than patients without recent CV events. There was also a trend to suggest that in patients who have suffered a recent CV event, there is a higher inflammatory burden in patients with dysglycemia than in those without. This is congruent with other literature that supports the notion that diabetes is linked to inflammation.¹⁴⁻¹⁶ There is a growing body of literature that suggests that diabetes is a chronic inflammatory condition.¹⁷ Numerous epidemiologic studies have shown associations between plasma markers of inflammation and diabetes.¹⁸⁻²¹ In a nested case-control study of > 32,826 women, baseline levels of the inflammatory markers, tumour necrosis factor-α receptor 2, IL-6, and CRP were all predictive of the future development of diabetes. In a cohort study of 75 patients who underwent coronary stenting, it was reported that patients with diabetes had higher preprocedural levels of IL-6, IL-1 receptor antagonist, and soluble CD40 ligand than those without diabetes, thereby suggesting a higher inflammatory burden in these patients.²² There are many proposed

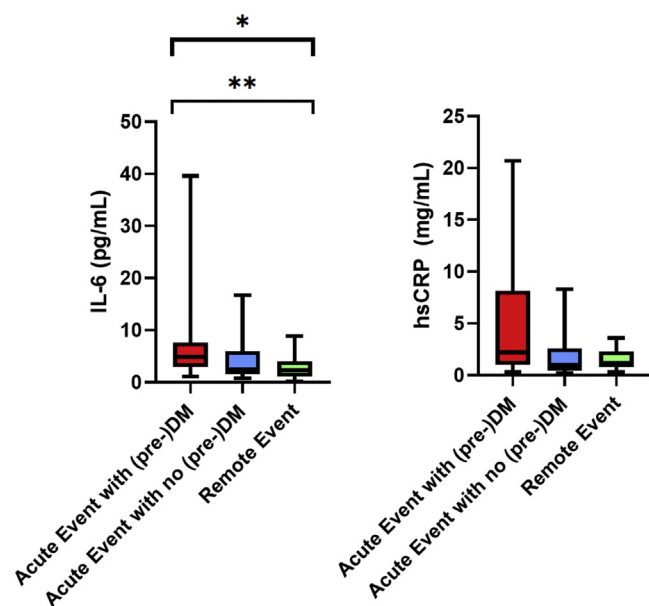


Figure 1. High-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 values in patients with cardiovascular events. DM, diabetes mellitus. * Kruskal-Wallis testing revealed IL-6 levels differed significantly across the 3 groups ($P < 0.05$). ** $P = 0.009$ with post hoc Mann-Whitney testing between group 1 (acute event with (pre-)DM) and group 3 (remote event).

mechanisms linking inflammation to diabetes, including pancreatic β -cell inflammation,²³ inflammation generated by adipocytes,¹⁷ and even contributions related to the gut microbiome.²⁴ Although we used IL-6 and hs-CRP to monitor inflammation in our patient population, recent literature has suggested that other markers such as platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio might also accurately reflect inflammatory levels and have prognostic value in other inflammatory conditions.^{25,26} Although our study was not powered to answer these questions in a CV disease population, more research in this area will certainly be needed to further elucidate the role that these biomarkers could potentially play in coronary artery disease prognostication and management in the future.

Using anti-inflammatory therapies for secondary CV prevention is a concept that has gained much traction in recent years. In the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial, canakinumab treatment was particularly effective in patients who achieved a significant hs-CRP reduction, but was associated with a significant increase in fatal sepsis, with no effect on de novo diabetes mellitus or worsening of diabetes control.³ This is important because approximately 40% of the patients enrolled in the CANTOS trial were patients with diabetes. This notion suggests the importance of identifying among patients with diabetes or prediabetes, those with the most potential for benefit, as opposed to universal treatment with the risk of potential harm. Further support for the concept of anti-inflammatory therapies for reduction of CV events was noted in the Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease (LoDoCo) study, in which colchicine led to a 67% reduction in the composite of ACS, arrest, and ischemic stroke, double the reduction that occurs with

statins.⁵ LoDoCo prompted the larger randomized trial of colchicine in 4500 patients, Colchicine Cardiovascular Outcomes Trial (COLCOT), which showed that low-dose colchicine (0.5 mg orally daily), reduces the rates of ischemic CV events in patients who recently (within 30 days) had myocardial infarction.⁶ Finally, the recent LoDoCo 2 study showed outcome benefit in 5522 patients with chronic coronary disease who were treated with colchicine (0.5 mg orally daily).²⁷

There are important limitations to note in our study. This was an observational, cross-sectional study. Thus, although we observed associations between inflammatory markers and diabetes and CV events, care should be taken in the interpretation of these relationships, because we cannot rule out underlying confounding as the explanation for these associations. Thus, these observed associations are merely hypothesis-generating, and should not be taken as causal. Additionally, our sample size was quite small, which limits the power of our study. However, even with these limitations, the observed numerical trends across groups were consistent, lending strength to our observations.

Inflammation is a key component in the progression of atherosclerosis and its sequelae, such as myocardial infarction, stroke, and CV death.^{3,28} As such, it represents a potentially transformative therapeutic target. Because patients with prediabetes/diabetes have a higher inflammatory burden, and are already at high risk for recurrent vascular events, this specific population might be an ideal group to target with therapies aimed at the reduction of inflammatory burden. These results set the stage for the evaluation and potential use of inflammation biomarkers to help define specific populations (such as those with diabetes or prediabetes) or even patients within such populations that will most benefit from anti-inflammatory therapies and thereby allow the personalization of therapies for patients at increased risk of subsequent CV events.

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