Synergistic relationship between hyperglycaemia and inflammation with respect to clinical outcomes in non-ST-elevation acute coronary syndromes: analyses from OPUS-TIMI 16 and TACTICS-TIMI 18

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Aims To investigate the relationship between diabetes and inflammation and the potentially synergistic relationship between hyperglycaemia and inflammation on clinical outcomes in non ST-elevation ACS.

Methods and results The principal analysis was conducted in 2200 patients in OPUS-TIMI 16 with C-reactive protein data available and then validated in the invasive arm of TACTICS-TIMI 18 (n = 929). In addition, two further inflammatory markers [monocyte chemoattractant protein-1 (MCP-1) and von Willebrand factor (vWF)] were assessed in OPUS-TIMI 16. Diabetic patients had higher C-reactive protein and MCP-1 levels vs. non-diabetic patients in OPUS-TIMI 16 (9 vs. 7.8 mg/L, P = 0.002, and 190.6 vs. 170.8 pg/mL, P = 0.04, respectively), higher C-reactive protein levels in TACTICS-TIMI 18 (6.6 vs. 5.2 mg/L, P = 0.0005), and as expected higher glucose levels in both trials. Stratifying by the median C-reactive protein and diabetes in OPUS-TIMI 16, diabetic patients with C-reactive protein greater than or equal to the median were the highest risk group vs. non-diabetic patients with C-reactive protein less than the median (adjusted HR 1.63, 95% CI 1.20–2.23, P = 0.002). Directionally, similar findings were observed for MCP-1 and vWF in OPUS-TIMI 16 and for C-reactive protein in TACTICS-TIMI 18. After adjustment for diabetes, the risk associated with a 1 mmol/L increase in glucose was greater among those with a C-reactive protein greater than or equal to the median (adjusted HR 1.63, 95% CI 1.20–2.23, P = 0.002). Directionally, similar findings were observed for MCP-1 and vWF in OPUS-TIMI 16 and for C-reactive protein in TACTICS-TIMI 18. After adjustment for diabetes, the risk associated with a 1 mmol/L increase in glucose was greater among those with a C-reactive protein greater than or equal to the median (HR 1.07, 95% CI 1.03–1.11) vs. those with a C-reactive protein less than the median (HR 1.02, 95% CI 0.97–1.06). After multivariable adjustment, the synergistic relationship between glucose and C-reactive protein and clinical outcomes remained statistically significant (P = 0.01). A similar pattern was observed in TACTICS-TIMI 18. Conclusion Among ACS patients, diabetes was associated with both greater inflammation and higher glucose levels and patients with both hyperglycaemia and inflammation had worse outcomes. Better control of both inflammation and hyperglycaemia should be assessed in future ACS trials as a means to reduce the cardiovascular risk among diabetics.

Introduction

Diabetes mellitus (DM) is associated with an increased risk of recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes (ACS).1 This hazard could in part be related to greater pre-existing co-morbidities or more extensive coronary artery disease (CAD) among diabetic patients. Recent data from patients with stable CAD also show that hyperglycaemia is associated with greater systemic inflammation,2,3 and systemic inflammation is independently associated with recurrent cardiovascular events in ACS patients.4–6 In addition, hyperglycaemia in patients with ACS is associated with increased cardiovascular risk among both diabetic and non-diabetic patients although the mechanisms behind this association are not clearly understood.7,8 In vitro hyperglycaemia appears to enhance the deleterious effects of C-reactive protein on the endothelium.9,10 These observations raise the possibility that a synergistic relationship between inflammation and hyperglycaemia contribute to the increased cardiovascular risk observed among diabetics with ACS.

Our group has previously reported the relationship between serum glucose levels and death or myocardial infarction (MI) in ST-elevation myocardial infarction (STEMI) patients from the TIMI database at 30 days,11 and

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a prior analysis from the OPUS-TIMI 16 dataset has evaluated the relationship between glucose and long-term outcomes in the entire OPUS-TIMI 16 cohort, which included STEMI. The present analysis was carried out to assess the potentially synergistic relationship between inflammation and both diabetes and serum glucose in non-STEMI, and limited to those patients in whom inflammatory biomarker data [C-reactive protein, MCP-1, and van Willebrand factor (vWF)] and glucose were available. Similar analyses were performed in a second data set of non-ST-elevation ACS patients (TACTICS-TIMI 18). We assessed whether the previous observations in stable subjects that diabetes was associated with increased inflammation, extended to the ACS setting and hypothesized that subjects with both hyperglycaemia and inflammation would have worse outcomes.

Methods
Study population
The primary analysis was performed using data from the Oral Glycoprotein Ilb/IIia Inhibition with Orbofiban in Patients with Unstable Coronary syndromes (OPUS TIMI-16) Trial, the details of which have been published. Briefly, 10,288 patients with ACS were enrolled into the trial within 72 h from the onset of symptoms. Patients were randomly assigned to one of the following three treatment arms oral glycoprotein Ilb/IIia inhibitor orbofiban: 50 mg orbofiban twice daily (50/50 mg group), 50 mg orbofiban twice daily for 1 month, followed by 50 mg orbofiban twice daily (50/30 mg group), or placebo. Measurement of C-reactive protein levels at study entry was part of a pre-specified analysis from OPUS-TIMI 16. This was carried out as follows: C-reactive protein levels were measured in the 1592 patients (including STEMI) who experienced the primary 10-month composite end point of death, recurrent MI, recurrent ischaemia at rest leading to rehospitalization or urgent revascularization, or stroke. C-reactive protein levels were also measured in 1633 patients who did not experience the primary endpoint and were chosen to be a representative sample of the remainder of the OPUS cohort with similar proportions of baseline characteristics, index diagnosis, and treatment allocation. Thus, there were 3225 patients across the spectrum of ACS with C-reactive protein data available. This analysis was restricted to the 2200 patients with non-ST-elevation ACS who had C-reactive protein data available. The potential role of inflammation was further explored using two other inflammatory biomarkers in OPUS-TIMI 16; monocyte chemotactant protein-1 (MCP-1) and vWF which were available in 1532 and 1367 patients, respectively.

Similar analyses were performed in all patients from the early invasive arm of TACTICS-TIMI 18 who provided a blood sample for biomarker measurement. In TACTICS-TIMI 18, a blood sample was to be obtained in all patients enrolled as part of the study protocol for biomarker analysis. C-reactive protein was therefore available in nearly all patients; thus, C-reactive protein data was available in a total of 929 patients out of 1114. In view of the treatment benefit of the early invasive strategy particularly among diabetics, we confined the present analysis to only the invasive arm to reduce the potential confounding of randomization. The patients in whom C-reactive protein was not available in TACTICS were demographically identical to those included in the study. The TACTICS-TIMI 18 trial has been previously described, but briefly patients with non-ST-elevation ACS were treated with intravenous tirofiban and randomized to an early invasive or conservative revascularization strategy. In both OPUS-TIMI 16 and TACTICS-TIMI 18, diabetes was assessed by the investigator at study entry using a clinical history.

Blood sampling and measurement of biomarkers
Non-fasting blood samples for biomarker and glucose were taken at study enrolment an average 41 h after onset of ACS in OPUS-TIMI 16. In OPUS-TIMI 16, high sensitivity C-reactive protein was measured using the nephelometric technique (Dade Behring, Illinois, USA), as previously described. MCP-1 was measured using an immunoassay (Biosite, San Diego, USA) and the principal findings of the relationship between MCP-1 and clinical events in patients (STEMI and non-ST-elevation ACS) in OPUS-TIMI 16 have been previously described. vWF was measured as vWF antigen and reported as mg/mL using a sandwich ELISA technique (Biosite). The inter-assay coefficient of variation for the vWF assay was 8.9%. Serum glucose was measured in a central laboratory and is reported as mmol/L. In TACTICS-TIMI 18 blood samples were taken at the time of randomization which was within the first 24 h after ACS. hs-C-reactive protein was measured as described above.

Clinical endpoints
All cause death and non-fatal MI were evaluated through the end of the follow-up period in OPUS-TIMI 16, with an average follow-up of 6 months. In TACTICS-TIMI 18, all patients had 6 months follow-up. Death and non-fatal MI were adjudicated by a clinical events committee in both trials using previously defined criteria.

Statistical analysis
Continuous variables were assessed for normality and are reported as medians with interquartile range or mean ± standard deviation (SD) as appropriate. The Wilcoxon rank-sum (for two-way comparisons) or Kruskal–Wallis test was used for the analysis of continuous variables and the χ² test was used for the analysis of categorical variables. Outcome data are presented as hazard ratios; these were determined using Cox proportional hazards regression models. Scaled and unscaled Schoenfield residuals were used to test for proportionality of hazards and deviance residuals to graphically assess the linearity of age-related effects. In order to reduce the impact of potential confounders, multivariable models adjusted for all variables that differed between diabetic and non-diabetic subjects at baseline and also treatment allocation. Thus, all models were adjusted for age, gender, diabetes, smoking, hypertension, history of prior MI, ST-depression, NSTEMI, prior revascularization, differences in medication, and treatment allocation (in OPUS-TIMI 16). All analyses were performed using Stata version 7.0 or higher.

Differences in biomarker levels were first compared between diabetics and non-diabetics. In order to allow comparison across biomarkers, the relationship between biomarkers and risk was assessed first as a continuous variable after log transformation as these variables were not normally distributed. Thus, every unit change in log biomarker reflects an approximate 2.7-fold increase in the biomarker of interest irrespective of the units. Each biomarker was also compared as a dichotomous variable (≥ median), thus allowing comparison crudely between high and low levels. We stratified the entire population by the median of each biomarker of interest into high and low biomarker groups. We examined the relationship between C-reactive protein and diabetes with respect to clinical outcomes using both unadjusted and analyses adjusted for potential confounders as shown in the results. The relative impact of inflammation in diabetics and non-diabetics was assessed in stratified analyses using inflammatory markers firstly as a log transformed continuous variable and secondly as a dichotomized variable (≥ median). The interaction between diabetes and elevated biomarker was also assessed by including an interaction term diabetes * biomarker (firstly using biomarker as a continuous and then as a dichotomous variable) in the multivariable models already described.

Finally, the inter-relationships between glucose, C-reactive protein, and cardiovascular events were examined in OPUS-TIMI
We evaluated the HR for each mmol/L increase in glucose in the two populations of interest, i.e. patients with a C-reactive protein greater than and less than the group median. The model in each case was identically constructed, using survival-time data and the Cox-proportional hazards assumption and adjusting for diabetes. We then assessed the interaction term glucose*CR-protein in a Cox proportional hazards model that adjusted for possible confounders.

**Results**

**Baseline characteristics**

Baseline characteristics stratified by diabetes status are reported in Table 1. In OPUS-TIMI 16, diabetics were more likely to be older, female, have more co-morbidities but were less likely to smoke. In addition, diabetics were more likely to have had a history of CABG and were more likely to be on a statin or an ACE inhibitor at study entry. Diabetes was associated with a higher C-reactive protein (median 9 vs. 7.8 mg/L, \( P = 0.002 \)), and a higher MCP-1 (median 190.6 vs. 170.8 pg/mL, \( P = 0.04 \)) and as expected, a higher glucose (median 10.5 vs. 6.3 mmol/L, \( P < 0.0001 \)), compared with non-diabetics. vWF levels however were not statistically different between diabetics and non-diabetics (31.8 vs. 29.6 mg/mL, \( P = 0.25 \)).

In the TACTICS-TIMI 18 cohort, diabetics similarly tended to be older, and were more likely to have hypertension and were less likely to smoke (Table 1). In addition, diabetics had a greater frequency of prior CABG and ACE inhibitor use. In TACTICS-TIMI 18, diabetes was again associated with a higher C-reactive protein (median 6.6 vs. 5.2 mg/L, \( P = 0.0005 \)) and a higher glucose (median 9.7 vs. 5.9 mmol/L, \( P < 0.0001 \)).

**Inflammation and outcome in OPUS-TIMI 16**

When analysed as a continuous variable, a unit change in log C-reactive protein (approximately reflecting a 2.7-fold increase) was associated with an increased risk of death or MI (unadjusted HR 1.14, 95% CI 1.06–1.22, \( P < 0.001 \), adjusted HR 1.09, 95% CI 1.02–1.18, \( P = 0.015 \)). Similarly, as a dichotomous variable C-reactive protein greater than or equal to median (8.1 mg/L) was associated with an increased risk of death or MI (HR, 1.35, 95% CI 1.11–1.63, \( P = 0.003 \)). After multivariable adjustment C-reactive protein greater than or equal to median remained an independent predictor of risk (adjusted HR of death or MI 1.25, 95% CI 1.02–1.52, \( P = 0.035 \)) as did history of diabetes (HR 1.30, 95% CI 1.01–1.66, \( P = 0.040 \)).

We explored the combined relationship between inflammation and diabetes. In unadjusted analyses, compared with non-diabetics with a C-reactive protein less than the median (reference group), diabetics with a C-reactive protein greater than or equal to median were at highest risk (HR 2.13, 95% CI 1.63–2.79, \( P < 0.0001 \)) (Figure 1A).

A similar relationship was observed using other inflammatory biomarkers (MCP-1 and vWF) (Figure 1B and C, respectively). Compared to non-diabetics with biomarker levels lesser than the median, the corresponding HR for death or MI among diabetics with a MCP-1 ≥ median (176.8 pg/mL) was 1.87 (95% CI 1.15–3.05, \( P = 0.01 \)) and for diabetics with vWF ≥ median (31.3 mg/mL) it was 2.26 (95% CI 1.23–4.14, \( P = 0.008 \)).

**Inflammation and outcome in TACTICS-TIMI 18**

When analysed as a continuous variable, a unit change in log C-reactive protein (reflecting an approximate 2.7-fold increase) tended to be associated with an increased risk of death or MI (unadjusted HR 1.19, 95% CI 0.99–1.44, \( P = 0.06 \), adjusted HR 1.20, 95% CI 0.98–1.47, \( P = 0.08 \)). Stratifying by the median C-reactive protein (5.7 mg/L), we found a similar pattern of risk as the one observed in OPUS-TIMI 16, with non-diabetics with C-reactive protein less than the median having fewest events (Kaplan–Meier rate 5.5%) and diabetics with C-reactive protein greater than or equal to 16.5 mg/L with a higher risk (HR 1.61, 95% CI 1.12–2.32, \( P = 0.010 \)).
the median experiencing the most events (Kaplan–Meier rate 11.8%) \(P = 0.017\). The unadjusted risk of death or MI among diabetic subjects with a C-reactive protein greater than or equal to the median was 2.17 (95% CI 1.12–4.18, \(P = 0.02\)). As in OPUS-TIMI 16, non-diabetics with a C-reactive protein greater than or equal to median and diabetics with a C-reactive protein less than the median had a lower risk (Figure 1D).

Multivariable analyses of death or myocardial infarction

In a multivariable model that adjusted for high-risk features and possible confounders (including age, gender, smoking, prior MI, history of hypertension, NSTEMI vs. UA, ST-depression vs. other ECG changes, treatment allocation, concomitant medical therapy, and revascularization), the combination of a C-reactive protein greater than or equal to the median and DM was associated with greatest risk in both OPUS-TIMI 16 (HR 1.63, 95% CI 1.20–2.23) and in TACTICS-TIMI 18 (HR 2.65, 95% CI 1.20–5.88) when compared with non-diabetics with C-reactive protein less than the median (reference group) (Table 2). Similar results were observed in OPUS-TIMI 16 when MCP-1 and vWF were substituted as the biomarkers of interest instead of C-reactive protein into identical models. Compared with non-diabetics/biomarker, median, diabetics/biomarker/C21 median again were at highest risk (MCP-1: HR = 1.54, 95% CI 0.86–2.75, \(P = 0.10\)) (vWF: HR = 2.08, 95% CI 1.05–4.14, \(P = 0.036\)).

Synergistic relationship between diabetes, inflammation, and outcomes

Analyses stratified by history of diabetes were performed to assess the differential impact of inflammation in each group. In unadjusted analyses, the relationship between a log unit change in each biomarker and risk tended to be greater among diabetics than non-diabetics, but differences between groups were not statistically significant (all \(P > 0.05\)).
Including the interaction term diabetes*log biomarker in the multivariable models previously described also did not demonstrate any statistically significant interactions. Similar findings were observed when using these biomarkers as dichotomized variables, as shown graphically in Figure 2. Including the interaction term diabetes*biomarker/median in the multivariable models previously described also did not demonstrate statistically significant interactions, and also attenuated the previously significant relationship between both diabetes and biomarkers with clinical risk.

Synergistic relationship between glycaemia, C-reactive protein, and outcomes

In OPUS-TIMI 16, the correlation coefficient between glucose and C-reactive protein was 0.14 (P < 0.0001), which was identical in both NSTEMI and in unstable angina subjects. After adjusting for a history of diabetes, the risk associated with a 1 mmol/L increase in glucose was greater among those with a C-reactive protein greater than or equal to median (HR 1.07, 95% CI 1.03–1.11) vs. those with a C-reactive protein less than the median (HR 1.02, 95% CI 0.97–1.06) (Figure 3). This difference in risk was statistically different (P interaction = 0.045). After adjusting for age, gender, smoking, prior MI, ST-depression, treatment allocation, concomitant medical therapy, prior revascularization, glucose, and C-reactive protein in a multivariable model, the interaction term glucose*C-reactive protein was significantly associated with increased risk of death or MI (P = 0.01). Using vWF or MCP-1 as the biomarker of interest produced directionally similar but not statistically interaction significant results (glucose*vWF, P interaction = 0.62; glucose*MCP-1, P interaction = 0.46). Directionally similar results were observed in TACTICS-TIMI 18 (P interaction = 0.48).
Discussion

Diabetes has been associated with an elevated C-reactive protein in stable patients, and the present findings extend this observation to the ACS setting. In addition to higher levels of C-reactive protein, patients with diabetes in our study also had higher levels of MCP-1 and tended towards higher levels of vWF. These findings suggest that diabetic patients have a generalized higher inflammatory state compared with non-diabetic patients, even in the context of ACS. Most importantly, we found evidence of synergism between hyperglycaemia and inflammation with respect to their adverse association with prognosis in this setting, such that the risk of recurrent events associated with hyperglycaemia was magnified in patients with evidence of greater inflammatory activation.

Irrespective of diabetic status, an elevated (non-fasting) glucose in the peri-ACS period is associated with increased risk of future cardiovascular events. Of interest was our observation in OPUS-TIMI 16 that the clinical risk associated with a 1 mmol/L rise in glucose, was more marked among those with a higher C-reactive protein. The synergistic relationship between glucose, C-reactive protein, and risk of clinical events remained statistically significant after multivariable adjustment. Directionally similar relationships were observed with respect to C-reactive protein in TACTICS-TIMI 18 and for other inflammatory markers in OPUS-TIMI 16. These findings suggest that the important deleterious biological interactions between glucose and C-reactive protein observed in vitro could also be of clinically relevance in ACS patients. While C-reactive protein is the best characterized inflammatory marker studied in ACS, the consistent directionality across three different inflammatory markers in OPUS-TIMI 16 supports the hypothesis that there is a synergistic interaction between a generalized inflammatory process and hyperglycaemia beyond any specific biomarker. Of note also subjects with high biomarkers and diabetes were at highest risk. Increased inflammation tended to be associated with greater risk in diabetics than non-diabetics although formal testing for interaction was not significant. While the potential mechanisms which underlie the greater clinical risk observed in diabetic patients are likely multifactorial, the present observations lead us to hypothesize that the presence of greater inflammation and a synergistic interaction between hyperglycaemia and inflammation could contribute to the increased cardiovascular risk.

Pathophysiology

Hyperglycaemia increases the binding of inflammatory cells to the endothelium, as well as increasing inflammatory cytokine production in monocytes. This may not only drive atherogenesis but could result in plaque instability at vulnerable sites. Chronically, high glucose concentrations lead to the non-enzymatic irreversible glycation of circulating proteins called ‘advanced glycation end products’ (AGE). AGE induce a number of deleterious effects in endothelial and inflammatory cells, including the production of inflammatory cytokines and procoagulants which could play a role in atherothrombosis. Additionally, hyperglycaemia amplifies the deleterious effects of atherogenic substrates such as low-density lipoprotein cholesterol (LDL-C) and oxidized LDL-C. When combined, these observations support the hypothesis that hyperglycaemia itself and the products of chronic hyperglycaemia induce inflammation. In vitro hyperglycaemia acts synergistically with the inflammatory mediator C-reactive protein resulting in the increased production of adhesion molecules and MCP-1 by the vessel wall. This could potentially result in a greater number of inflammatory cells accumulating at vulnerable sites along the vessel wall, thus triggering plaque instability. Additionally, hyperglycaemia is associated with a prothrombotic state and increased platelet activation, in stable patients. Thus, in the ACS setting high levels of vWF in combination with the potentially prothrombotic effects of hyperglycaemia could result in more recurrent thrombotic events among diabetic patients. We observed that diabetic patients with either a high MCP-1 or vWF were at greatest risk, thus extending prior laboratory observations to a clinical setting.

Clinical implications

Despite the clinical benefits from treatments during ACS such as the adjunctive use of glycoprotein IIb and IIa inhibitors or percutaneous intervention, diabetic patients with ACS remain at higher risk than non-diabetic patients. Our observations in OPUS-TIMI 16 and from the invasive arm of TACTICS-TIMI 18 suggest that patients with both hyperglycaemia and inflammation appear to be at particularly higher risk, despite aggressive medical management. Our observations suggest that both hyperglycaemia and inflammation might be important future targets for clinical risk reduction in diabetics with ACS. Newer agents, such as thiazolidinediones have been shown to reduce cardiovascular events in diabetic patients with evidence of prior macrovascular disease. In addition to improving glycemic control, thiazolidinediones reduce inflammation independently of glycemic control and future trials should assess the potential benefits of this class of drug in the future management of diabetic patients with ACS.

Limitations

The analyses presented here are exploratory and therefore should be considered hypothesis generating. We used a clinical history of diabetes rather than any formal testing to establish diabetes. If anything, errors in ascertainment are likely to reduce the strength of any associations as some non-diabetic patients may have had diabetes. Additionally, we had no information about the acute management or hyperglycaemia, or the use of oral hypoglycaemic agents or insulin during the study period, beyond the use of these agents at study entry and these factors could have influenced our findings. While we have attempted to adjust for potential confounders using multivariable models, we cannot exclude the possibility that unidentified confounders could still explain our observations. It should also be noted that inflammation was broadly assessed as high and low after dichotomising data by the population median. Therefore, the present data may not necessarily be extended to inflammation if considered as a continuous variable. Notwithstanding these limitations, we measured three separate markers of inflammation in OPUS-TIMI 16 that showed directionality similar associations with respect to clinical outcomes.
outcome, and observed similar results with respect to C-reactive protein in TACTICS-TIMI 18. We did observe statistically a significant interaction between glucose and C-reactive protein when used as continuous variables, and favourable trends were observed for vWF and MCP-1. We broadly assessed the concept of inflammation for each biomarker by stratifying the population above and below the median for the purposes of assessing potential mechanisms only rather than to provide a diagnostic tool for individual biomarkers for further clinical management. Nevertheless, the present findings are provocative and given the important burden of diabetes in patients with ACS, further exploration of these observations may be warranted.

Conclusions

Even in the context of ACS diabetic patients have more inflammation than non-diabetic patients, and diabetic patients with increased inflammatory markers have the highest risk of adverse events. While inflammation is a risk factor for adverse events, we observed that this risk was further increased by a synergistic relationship between inflammation and high glucose levels. As both inflammation and hyperglycaemia are more common among diabetic patients, the interaction between hyperglycaemia and inflammation may play an important role in the high cardiovascular risk observed among diabetic patients with ACS. Strategies that better control inflammation or glycaemia may be of clinical importance in the management of diabetic patients with ACS and should be assessed in future trials.

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