

Original Article

Gender factors affect the association between inflammatory response and glucose homeostasis in acute illness

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ABSTRACT: Background: Systemic inflammation is associated with insulin resistance and increased plasma glucose concentrations. We hypothesized that the link between systemic inflammation and glucose control may be gender dependent.

Research methods and procedures: We studied 33 male and 30 female consecutive patients admitted to a ward of internal medicine for acute illnesses associated with increased C-reactive protein (CRP) concentrations (>10 mg/L). Patients with a previous diagnosis of diabetes mellitus and those requiring glucocorticoids, insulin or artificial nutrition were excluded.

Results: Fasting plasma glucose and CRP were determined on admission and after 1 week. On admission, CRP concentrations (106 ± 10 mg/L, mean \pm SEM) correlated directly ($r=0.46$; $p<0.001$) with fasting plasma glucose (94 ± 3 mg/dL) after logarithmic transformation in pooled patients. At the end of follow-up, patients with decreased CRP concentrations (29 men and 25 women) were selected for statistical analysis. These groups were matched for age, body mass index, initial CRP and glucose levels as well as for changes in CRP concentrations (men, $71\% \pm 3\%$; women, $73\% \pm 3\%$). In female patients the glucose concentrations were significantly decreased at the end of the follow-up period by 8.9 ± 2.9 mg/dL (Wilcoxon signed-rank test). In contrast, despite improvement of the inflammatory marker, the plasma glucose concentration did not decrease at the end of the follow-up period in males ($+6.3 \pm 3.6$ mg/dL). Changes in glucose concentration were significantly different between gender groups (Mann-Whitney U test).

Conclusion: During the recovery phase of illness, the link between a decline in inflammatory response and an improvement in glucose homeostasis is gender dependent. (*Nutritional Therapy & Metabolism* 2007; 25: 85-8)

KEY WORDS: C-reactive protein, Insulin resistance, Glucose metabolism, Male, Female

INTRODUCTION

Activation of a systemic inflammatory response in acute illness is associated with insulin resistance and variable increases in plasma glucose concentrations (1). Mechanisms involve secretion of proinflammatory cytokines and counter-regulatory hormones (2). When the underlying disease resolves, the inflammatory response abates, recovery ensues and glucose homeostasis improves. Evidence indicates that hormone responses to inflammation may be gender dependent. Sexual dimorphisms have been described for cortisol (3), growth hormone (4) and catecholamine (5, 6) secretory patterns in stress conditions. In addition, men have a higher risk for insulin resistance than women (7).

In this study, we hypothesized that the link between systemic inflammation and glucose control may be gender dependent. To confirm this hypothesis, we determined the association between changes in C-reactive protein (CRP), a marker of inflammation, and glucose levels in nondiabetic male and female patients consecutively admitted to an internal medicine ward for acute illnesses associated with systemic inflammation.

MATERIALS AND METHODS

The study was performed at the Cattinara University Hospital of Trieste, Italy. We selected 63 consecutive patients (30 women and 33 men) admitted to a ward of in-

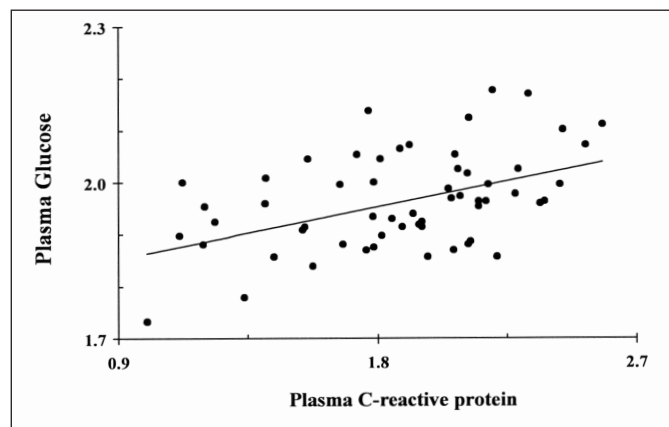


Fig. 1 - Correlation between C-reactive protein (mg/L) and glucose (mg/dL) concentrations in pooled patients on hospital admission. Values are expressed as Log10. $N=63$; $r=0.46$; $p<0.001$.

TABLE I - CHARACTERISTICS OF PATIENTS WITH DECREASED C-REACTIVE PROTEIN AT THE END OF FOLLOW-UP

	Men	Women
Number	29	25
Age (years)	79.2 ± 1.8	81.7 ± 2.1
Body mass index (kg/m ²)	24.2 ± 0.9	23.7 ± 1.2
Duration of follow-up (days)	7 ± 1	7 ± 1
Initial plasma CRP (mg/L)	117 ± 16	110 ± 16
Final plasma CRP (mg/L)	40 ± 7 [§]	28 ± 5 [§]
Changes in plasma CRP (mg/L)	-77.4 ± 14.3	-82.6 ± 13.7
Initial plasma glucose (mg/dL)	92 ± 3	97 ± 4
Final plasma glucose (mg/dL)	98 ± 3	88 ± 2 [*]
Changes in plasma glucose (mg/dL)	+6.3 ± 3.6	-8.9 ± 2.9 [*]

[§] $p<0.05$, final versus initial CRP or plasma glucose (Wilcoxon signed-rank test); ^{*} $p<0.05$, women versus men (Mann-Whitney *U* test). CRP, C-reactive protein

ternal medicine for acute illnesses with plasma CRP concentrations greater than 10 mg/L. Patients with a previous diagnosis of diabetes mellitus or liver cirrhosis and those requiring glucocorticoids, insulin or artificial nutrition, either enteral or parenteral, were excluded. Mean values of age (women, 82±1 years; men, 78±2 years), body mass index (women, 24±1 kg/m²; men, 24±1 kg/m²), initial CRP (women, 95±15 mg/L; men, 114±14 mg/L) and glucose (women, 94±4 mg/dL; men, 94±3 mg/dL) concentrations were not significantly different in the 2 groups. Female patients were affected by community-acquired pneumonia (n=13), urinary tract infections (n=6), erysipelas or skin ulcers (n=3), acute coronary syndromes (n=3), atrial fibrillation (n=1),

cholangitis (n=2), ischemic stroke (n=1), and infectious arthritis (n=1). Male patients were affected by community-acquired pneumonia (n=14), urinary tract infections (n=5), erysipelas or skin ulcers (n=5), acute coronary syndromes (n=5), cholangitis (n=1), subacute thyroiditis (n=1), infectious arthritis (n=1), and diverticulitis (n=1). Plasma glucose and CRP concentrations were determined twice: after a 12-hour fast on the first morning after hospital admission and after 1 week of appropriate therapy. Plasma glucose concentrations were determined by standard methods. CRP was detected by a conventional immunoturbidimetric method (CRPLX Tinaquant, Roche Diagnostics) using automated analyzer systems. We decided a priori to select for statistical analysis those patients who had decreased CRP concentrations after 1 week of follow-up in order to determine the effect of gender on changes in fasting glucose concentrations (Tab. I). The Wilcoxon signed-rank test (2-tailed) was applied for dependent statistical comparison between 2 time points (intragroup). The Mann-Whitney *U* test (2-tailed) was used for independent statistical comparison between 2 groups. The relationship between CRP and glucose concentrations on admission was tested after logarithmic transformation using standard linear regression. The significance level was set at $p<0.05$.

RESULTS

On admission, values of CRP concentrations (median: 84 mg/L; range: 10-381 mg/L) directly correlated (pooled patients, $r=0.46$, $n=63$; $p<0.001$; female, $r=0.48$, $n=30$; $p<0.01$; male, $r=0.48$, $n=33$; $p<0.01$) with fasting plasma glucose (median: 91 mg/dL; range: 54-150 mg/dL) (Tab. I). At the end of the follow-up period, plasma CRP concentrations had decreased in 88% and 83% of the male and female patients, respectively. The characteristics of male and female patients who exhibited decreased inflammation at the end of the follow-up period are described in Table I. Age, body mass index, CRP and glucose concentrations on admission were not significantly different in the gender groups. Mean CRP concentration decreased by 62%±5% in men and by 69%±4% in women. In female patients, plasma glucose concentrations significantly decreased at the end of the follow-up period by 7%±3%. In contrast, despite an improvement of the inflammatory marker, the plasma glucose concentration did not change significantly at the end of the follow-up period in males. Changes in glucose concentration were significantly different between gender groups (Tab. I). There was no direct relationship between CRP and plasma glucose at the end of the study.

DISCUSSION

In our study we analyzed the gender dependence of the association between systemic inflammation and changes in glucose homeostasis in the context of acute illness. We found that CRP and glucose concentrations decreased in parallel during the recovery phase in postmenopausal women, while, in spite of an improvement in the inflammatory marker, the plasma glucose concentration did not change significantly in males. The relationship between glycemic status and CRP, observed in nondiabetic patients affected by acute illness, is likely to be related to changes in insulin resistance rather than changes in insulin secretion (8). Activation of a systemic inflammatory response in acute illness is associated with secretion of proinflammatory cytokines and counter-regulatory hormones, directly leading to insulin resistance (2). The degree of insulin resistance appears to be directly proportional to the severity of the inflammatory response (1). A large epidemiological study has demonstrated a weak association ($r=0.14$) between high-sensitivity CRP and fasting glucose in 1000 healthy subjects (9). In our study, this association was much stronger ($r=0.46$), suggesting that an inflammatory response is a major determinant of glucose homeostasis in nondiabetic patients affected by acute illness.

Although in physiological conditions men have a higher risk of insulin resistance than women (7), gender differences in hormonal responses to stress have been poorly investigated. Regulation of the hypothalamic-pituitary-adrenal axis appears to be more responsive during experimental inflammatory stress in female experimental animals (3). In contrast, the catecholamine response to hypoglycemia and strenuous exercise is attenuated in women (5, 6). Women are characterized by a faster recovery of the pulsatile growth hormone secretory pattern compared to men during protracted critical illness (4). These and other unidentified gender differences may account for a closer association between decreases in inflammation and improvement in glucose metabolism during recovery from acute illness in women. Most of the patients enrolled in our study had normal fasting plasma glucose on admission and showed small changes during the follow-up period because they were not critically ill and because all diabetics and those requiring insulin treatment were excluded. Nonetheless, our experiment design enabled us to demonstrate a significant relationship between inflammatory response and glucose homeostasis. We may predict that the gender differences observed in our patients at near-normal glucose levels could also apply to critically ill patients with severe hyperglycemia, who are at greater risk of infection complications and mortality (10-12).

CONCLUSION

We studied nondiabetic patients admitted to a ward of internal medicine for acute illnesses associated with activation of systemic inflammation. On admission, the degree of inflammation, as determined by plasma CRP concentrations, closely correlated with fasting plasma glucose in both male and female patients. This suggests a cause-effect relationship between activation of inflammatory mediators and changes in glucose homeostasis (1, 2). After 1 week of appropriate therapy, the CRP levels decreased in 86% of patients. Such decline in systemic inflammation was paralleled by small but significant decreases in fasting plasma glucose only in female patients. Thus, in the recovery phase of illness, the link between a decline in inflammatory response and improvement of glucose homeostasis is gender dependent, being slightly less efficient in men than in postmenopausal women. The clinical impact of such a gender-dependent relationship between systemic inflammation and glucose homeostasis needs to be investigated in patients with severe hyperglycemia.

ACKNOWLEDGMENT

This study was supported by a grant from the Italian Ministry of Education, University and Research (MIUR) (COFIN 2003).

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Received: September 27, 2006

Accepted: April 18, 2007