OBJECTIVE — To explore relationships between C-reactive protein (CRP), suui(proteD065 f933)uui(protinfec-0 0 6-D[(—)-(1111444.4()-19suu258.8

Table 1—*Relationships among HOMA-IR, metabolic syndrome, IFG, CRP, and pathogen burden, the GOCADAN study*

| | HOMA-IR | | Metabolic syndrome | | IFG | |
|---|---|---|---|---|---|---|
| | Model 1* | Model 2† | Model 1* | Model 2† | Model 1* | Model 2† |
| CRP quartile | | | | | | |
| 1 | 1.58 ± 1.04 | 1.62 ± 1.05 | 1 (referent) | 1 (referent) | 1 (referent) | 1 (referent) |
| 2 | 1.75 ± 1.04 | 1.63 ± 1.06 | 1.91 (0.90–4.07) | 1.90 (0.56–6.43) | 1.59 (0.81–3.11) | 2.01 (0.57–7.11) |
| 3 | 1.91 ± 1.04 | 1.66 ± 1.06 | 4.58 (2.29–9.14) | 3.51 (1.14–10.85) | 2.55 (1.37–4.76) | 2.81 (0.86–9.12) |
| 4 | 2.04 ± 1.04 | 1.73 ± 1.06 | 6.47 (3.30–12.72) | 2.82 (0.92–8.67) | 2.80 (1.51–5.17) | 2.43 (0.75–7.84) |
| P | <0.0001 | 0.341 | <0.0001 | 0.137 | 0.003 | 0.379 |
| Pathogen burden | | | | | | |
| 1 | 1.90 ± 1.11 | 1.59 ± 1.13 | 1 (referent) | 1 (referent) | — | — |
| 2 | 1.97 ± 1.06 | 1.81 ± 1.07 | 0.87 (0.29–2.60) | 0.64 (0.11–3.71) | 1 (referent)‡ | 1 (referent)‡ |
| 3 | 1.79 ± 1.03 | 1.83 ± 1.04 | 0.83 (0.30–2.25) | 0.69 (0.15–3.23) | 0.78 (0.44–1.40) | 0.94 (0.32–2.72) |
| 4 | 1.84 ± 1.03 | 1.78 ± 1.04 | 0.98 (0.36–2.66) | 0.70 (0.15–3.35) | 0.88 (0.50–1.56) | 1.08 (0.39–3.02) |
| 5 | 1.74 ± 1.06 | 1.62 ± 1.07 | 0.73 (0.25–2.15) | 0.44 (0.08–2.37) | 0.70 (0.35–1.40) | 0.89 (0.27–2.93) |
| P | 0.562 | 0.368 | 0.831 | 0.831 | 0.7118 | 0.9643 |

Data are least-square means ± SEM or odds ratio (95% CI). = 1,174 participants included in the analysis. *Adjusted for age and sex. †Adjusted for age, sex, BMI, current smoking, current drinking, physical activity, n-3 fatty acid intake, and pathogen burden (in the CRP model). ‡Categories 1 and 2 combined as reference category.

fatty acid intake. In all computations (ANOVA and logistic regression), the transformed variables for HOMA-IR and CRP were used. Participants with CRP >10 mg/l ( = 21 [1.7%]) were excluded from CRP analyses. Because participants were members of extended families, kinship was accounted for in additional analyses.

RESULTS — Of the 1,174 participants (55% women), mean BMI was 27.5 kg/m$^2$, 31.5% were overweight, and 29.1% were obese. Metabolic syndrome was present in 14.3% (11% men, 17% women). Insulin was low (median 8.1 μU/ml). Mean CRP was 1.6 mg/l (median 0.9 mg/l), and mean HCY was 7.3 μmol/l. Measures for five common pathogens averaged 3.4 per participant, and CRP was positively correlated with pathogen burden (P = 0.02). BMI, percent women, IFG (in women), CRP, glucose, insulin, and waist circumference were higher and current smoking, drinking, and physical activity were lower with increasing tertiles of HOMA-IR or in metabolic syndrome (all P < 0.001).

With increasing quartiles of CRP in the simple models (Table 1), there was a significant increasing trend in HOMA-IR (P < 0.0001) and in probabilities of metabolic syndrome and IFG (P < 0.0001 and 0.003, respectively). However, in the multivariate models, relations between HOMA-IR, metabolic syndrome, IFG, and CRP were not significant (P = 0.341, 0.137, and 0.379, respectively). Relationships of pathogen burden with HOMA-IR, metabolic syndrome, and IFG were not significant in the simple or multivariate models. For HCY, neither model was significant.

CONCLUSIONS — GOCADAN provides a unique setting for exploring relationships between inflammation, insulin resistance, and metabolic syndrome. Obesity is not pervasive, diabetes rates are low, rates of insulin resistance and other metabolic syndrome components vary, and chronic inflammation is prevalent in the population. Although CRP in univariate comparisons was higher in those with insulin resistance and metabolic syndrome, pathogen burden was not. After adjustment for confounders, no consistent relationships were observed between HOMA-IR, metabolic syndrome, or IFG and CRP or subclinical pathogen burden.

Low-grade chronic inflammation has been shown in vitro to promote insulin resistance (10). Although cross-sectional studies have demonstrated relationships between CRP and measures of insulin resistance or metabolic syndrome (11–13), longitudinal studies have varied, with CRP predictive of diabetes in some studies (14,15) but not others (3,13). In the Insulin Resistance and Atherosclerosis Study (IRAS), Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study, Augsburg study, and Atherosclerosis Risk in Communities (ARIC) study, odds of diabetes with increasing CRP became nonsignificant after adjustment for BMI or other covariates (3,13,14), suggesting that elevations in inflammatory markers seen in insulin resistance, metabolic syndrome, and diabetes are not causative but a consequence of these abnormalities. Some (15) argue that inclusion of BMI in the models represents an overadjustment, proposing that inflammation precedes obesity; however, until a causal relationship has been established, it seems prudent to focus on the complete models.

The lack of a relationship between chronic inflammation and insulin resistance and/or metabolic syndrome in this population is supported by the observation that, despite chronic subclinical infection, this population has low incidence of insulin resistance and diabetes. As in other populations, diabetes is associated with the female sex, obesity, and greater insulin resistance (6); CRP is positively associated with BMI and is higher with diabetes, smoking, and increasing pathogen burden (data not shown); thus, CRP appears to be an indicator of chronic inflammation. The reasons for the high subclinical pathogen burden are unclear; they may be related to confinement in close quarters in winter and lack of adequate medical care.

This study is limited by its cross-sectional design. Also, the high prevalence of subclinical infection may obscure relationships between obesity and insulin resistance on secretion of inflammatory cytokines. Finally, inflammatory mediators other than CRP that were not measured may be mediators.

In summary, while analyses of unique populations often lead to unexpected

findings, they can help to further understanding of complex disorders. Our study provides evidence that the inflammatory process may reflect diabetes or insulin resistance but is most likely not their cause and suggests that subclinical infection should be considered in further explorations of the inflammatory process in people with insulin resistance or metabolic syndrome.

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