Serum fatty acid composition and indices of stearoyl-CoA desaturase activity are associated with systemic inflammation: longitudinal analyses in middle-aged men

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Altered fatty acid (FA) composition is related to insulin resistance and CVD. One possible mediator may be inflammation, but longitudinal data relating FA composition to inflammation taking insulin resistance into account are limited. We investigated the long-term association between FA composition and C-reactive protein (CRP) concentrations in a large population-based cohort study in 767 men followed for 20 years. The association between FA composition in serum cholesteryl esters at age 50 and CRP concentrations at age 70 was investigated using linear regression. In addition, desaturase activities (stearoyl-CoA desaturase-1 (SCD-1), Δ5- and Δ6-desaturase) were estimated using FA product-to-precursor ratios. Insulin resistance was measured directly at follow-up by euglycaemic clamp. After adjusting for confounders (smoking, physical activity, alcohol intake, obesity and erythrocyte sedimentation rate) CRP concentrations were inversely associated with the proportion of 18:2ω6 and positively associated with 16:1ω7. After adding insulin resistance to the model, 18:2ω6 (P=0.002) and 16:1ω7 (P=0.003) concentrations were inversely associated with the proportion of 18:2ω6 (P=0.002) and 16:1ω7 (P=0.004) and estimated SCD-1 (P=0.005) and Δ6-desaturase (P=0.002) activities. After adding insulin resistance to the model, 18:2ω6, 16:1ω7 and SCD-1 remained significant predictors of CRP. A FA composition indicating low intake of 18:2ω6, high intake of SFA and high SCD-1 activity is, in a Swedish population of middle-aged men, associated with CRP concentrations 20 years later, even independently of obesity and insulin resistance.

C-reactive protein: Fatty acids: SCD-1: Inflammation

Serum fatty acid (FA) composition is a consequence of dietary fat but also of endogenous FA desaturation. Desaturation is catalysed by enzymes introducing a double bond in the FA chains. Stearoyl-CoA desaturase-1 (SCD-1) synthesizes MUFA from SFA, whereas Δ5- and Δ6-desaturases catalyse the synthesis of highly unsaturated FA.

FA composition in cholesteryl esters (CE) has been associated with insulin resistance and CVD. A potential mediating role of low-grade inflammation in the association between FA composition and insulin resistance is still unknown.

Low-grade inflammation as assessed by C-reactive protein (CRP) is related to insulin resistance and CVD. A potential anti-inflammatory effect of n-3 FA has previously been indicated. No larger studies have, however, investigated the long-term relationship between overall FA composition and CRP. Furthermore, no studies have examined the role of FA desaturases on inflammation, despite high SCD-1 activity index being linked to obesity and insulin resistance. We investigated the longitudinal association between dietary fat quality as assessed by CE FA composition at age 50, and CRP concentrations 20 years later in 767 healthy men, also taking several important confounders into account, including insulin resistance measured by a gold standard technique.

Methods

Subjects

Subjects participated in the Swedish cohort, Uppsala Longitudinal Study of Adult Men (http://www.pubcare.uu.se/ULSAM/). Subjects (n 1020) had measures of serum CE FA composition at age 50 and CRP at age 70. Exclusion criteria were CRP concentration >10 mg/l, diabetes (fasting blood glucose ≥6.1 mmol/l), CVD (ICD-8 codes 401–443) or malignancy at baseline, and usage of lipid-lowering medicine or glucocorticoids at age 50 or 70. After exclusions, the

Abbreviations: CE, cholesteryl esters; CRP, C-reactive protein; FA, fatty acid; HOMA-IR, homeostasis model assessment of insulin resistance index; SCD-1, stearoyl-CoA desaturase-1.

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Results

Baseline characteristics are presented as means and standard deviations; variables with skewed distribution are presented as median (Q1–Q3): BMI, 24·7 (sd 2·9) kg/m²; 14·0, 1·1 (sd 0·2) %; 16·0, 1·1 (sd 1·0) %; 16·1, n = 7, 3·4 (2·9–4·1) %; 18·0, 1·1 (1·0–1·3) %; 18·1, n = 9, 19·0 (sd 2·4) %; 18·2, n = 6, 54·9 (sd 4·7) %; 18·3, n = 6, 0·6 (0·5–0·8) %; 18·3, n = 3, 0·7 (sd 0·2) %; 20·3, n = 6, 0·6 (sd 0·1) %; 20·4, n = 4, 4·8 (sd 0·9) %; 20·5, n = 3, 1·2 (0·9–1·6) %; 22·6, n = 3, 0·7 (sd 0·2) %; Δ5-desaturase, 8·8 (sd 2·2); Δ6-desaturase, 0·011 (0·008–0·015); SCD-1, 0·29 (0·26–0·35); CRP concentration at age 70, 1·9 (0·9–3·8) mg/l.

In univariate analyses, the proportions of 16·1, n = 7 (r = 0·13, P = 0·0002); 18·1, n = 9 (r = 0·20, P < 0·0001) and 18·3, n = 6 (r = 0·09, P = 0·012) were positively correlated, whereas 18·2, n = 6 (r = 0·18, P < 0·0001) was inversely related to CRP concentrations 20 years later. Δ6-Desaturase and SCD-1, but not Δ5-Desaturase, were significantly related to CRP (r = 0·11, P = 0·0014 and r = 0·13, P = 0·0004, respectively).

In the multivariate model (n = 594) including BMI, smoking, physical activity and erythrocyte sedimentation rate at age 50 and alcohol consumption at age 70, the positive correlation with CRP remained for 16·1, n = 7 (P = 0·0008); 18·1, n = 9 (P = 0·0003), Δ6-desaturase (P = 0·022) and SCD-1 (P = 0·005), as well as the inverse correlation with 18·2, n = 6 (P = 0·002). When additionally adjusting for insulin resistance, 16·1, n = 7 (P = 0·008), 18·1, n = 9 (P = 0·010), 18·2, n = 6 (P = 0·012) and SCD-1 (P = 0·003) were associated with CRP in the model with HOMA-IR at baseline (n = 482), whereas only 18·1, n = 9 (P = 0·002), 18·2, n = 6 (P = 0·023) and SCD-1 (P = 0·047) were related in the model with M at follow-up (n = 570). 20·5, n = 3 was positively related to CRP in the multivariate models without insulin resistance and with HOMA-IR (P = 0·036 and P = 0·015, respectively). The univariate association between 20·5, n = 3 and CRP was, however, non-significant.

The univariate associations remained after excluding subjects with CRP concentrations > 5 mg/l (n = 635), except for 16·1, n = 7 (P = 0·062). Only 18·1, n = 9 was related in multivariate analysis. Excluding subjects with CVD or non-steroidal anti-inflammatory drug use at follow-up did not change the results appreciably.

When analysing the relationship between CE FA composition at age 70 and CRP, only 320 subjects were included and 14·0 was not assessed. 18·2, n = 6 (r = 0·11, P = 0·041), 20·3, n = 6 (r = 0·25, P < 0·0001), Δ5-desaturase (r = 0·13, P = 0·020) and Δ6-desaturase (r = 0·13, P = 0·026) were correlated to CRP. Only 20·3, n = 6 was correlated when adjusting for BMI, smoking, physical activity and alcohol intake at age 70 (n = 221) as well as when additionally adjusting for insulin sensitivity (M) at age 70 (n = 220).

Discussion

In this longitudinal study, serum FA composition in CE at age 50 was related to CRP concentrations 20 years later among 767 Swedish men. It is the first study to demonstrate a link between estimated SCD-1 and inflammation, which is of interest since high SCD-1 activity has been linked to diabetes and obesity(18,19). CRP were positively associated with SCD-1 and the proportion of 18·1, n = 9, and inversely associated with 18·2, n = 6, independently of BMI, smoking, physical activity, alcohol intake, erythrocyte sedimentation rate and insulin.
resistance. The present results accord with previous findings from this population where a similar FA pattern was related to the metabolic syndrome\(^{27}\), insulin resistance\(^{24}\) and CVD\(^{5,6}\).

Since this is an observational study, only speculations about possible mechanisms can be made. The positive correlations between MUFA and CRP may first seem surprising since MUFA generally is associated with beneficial health effects. However, MUFA in CE in Swedish populations at the time of the study reflects intake of foods containing high SFA rather than olive oil which was rarely consumed\(^{25}\). Similarly, in US populations, MUFA in CE reflected SFA intake rather than MUFA intake\(^{21}\), suggesting that the present correlation between CRP and MUFA probably reflects high meat and dairy fat intake. Why then was SFA not significantly related to CRP? Increased intake of SFA may increase the SCD-1 activity to keep the membrane concentration of 16:0 low to retain fluidity and prevent impaired cell signalling\(^{4,20}\). Inflammation could also be promoted by the metabolic disorder state associated with elevated SCD-1 activity rather than by the SFA intake per se. The SCD-1 activity index (16:1/16:0:16), however, seems to be an excellent marker of SFA intake rather than MUFA intake\(^{21}\), suggesting that the present correlation between CRP and MUFA probably reflects high meat and dairy fat intake. Why then was SFA not significantly related to CRP? Increased intake of SFA may increase the SCD-1 activity to keep the membrane concentration of 16:0 low to retain fluidity and prevent impaired cell signalling\(^{4,20}\). Inflammation could also be promoted by the metabolic disorder state associated with elevated SCD-1 activity rather than by the SFA intake per se. The SCD-1 activity index (16:1/16:0:16), however, seems to be an excellent marker of SFA intake, at least as good as individual serum SFA\(^{21}\) (E Warenjö, unpublished results). A role of SFA in inflammation is in line with in vitro data showing that stimulation of cells with 16:0 increases IL-6 mRNA expression and protein production\(^{22,23}\). IL-6 in turn induces CRP production. Interestingly, 18:2n-6 inhibited 16:0-induced IL-6 up-regulation\(^{22}\). Since 18:2n-6 in plasma reflects the dietary intake\(^{2}\), a diet high in this FA may contribute to lower CRP concentrations.

When associating FA composition at age 70 to CRP, the cross-sectional results partly differed from those assessed at age 50, possibly due to the lower power at that time-point. The data should therefore be interpreted cautiously. The divergence may, however, also depend on a different response to diet caused by ageing. High proportion of 20:3n-6 and low Δ5-desaturase activity have previously been associated with the metabolic syndrome\(^{21}\) and CVD\(^{37}\). Little data exist concerning CE FA composition and CRP concentrations. In a Spanish study, 18:2n-6 and n-3 FA were inversely associated with CRP\(^{31}\). Similarly, in a French population CRP was inversely associated with 18:3n-3 and 20:5n-3\(^{12}\). A large Italian study also reported an inverse relationship between 18:3n-3 and CRP\(^{17}\). We found no inverse association between n-3 FA and CRP, a result that accords with controlled trials\(^{24}\). Divergences in results may depend on differences in background diet and inflammation status among populations.

There are limitations to the present study. In this observational study, no conclusions regarding causality can be drawn. Desaturase activities were only estimated but may give an indication of the FA desaturation pattern. There are studies suggesting that these ratios reflect desaturase activity. In man, both SCD-1 mRNA expression in adipose tissue and serum SCD-1 ratio increased after rosiglitazone treatment\(^{25}\). Inhibition of SCD-1 is reflected by 16:1/16:0 in human hepatoma cells\(^{18}\). Since we had no measure of CRP at age 50, we adjusted for erythrocyte sedimentation rate to address the possibility that subclinical inflammation at baseline explained the longitudinal correlations. Interestingly the relationships remained, supporting the possibility that FA composition may precede inflammation. Another limitation is that no food records were assessed at baseline to support FA composition data. Only men at the same age participated, with no data for women or other ethnic groups. Strengths include the longitudinal design, the large sample with complete FA composition data and adjustments of several relevant covariates including directly measured insulin resistance at follow-up. Serum FA composition is, compared to dietary registration, a more objective method that limits reporting bias. FA composition was assessed in CE which may not be directly translated to FA composition in phospholipids, but overall differences between fractions should probably not play a significant role when interpreting or comparing data.

In conclusion, among healthy middle-aged men, a serum FA pattern indicating high intake of SFA and low PUFA (18:2n-6) in a Swedish population predicted CRP concentrations 20 years later, even independently of obesity and insulin resistance. This dietary pattern was accompanied by increased estimated SCD-1 activity, which may be a consequence of such a FA pattern and/or reflect a novel link between lipogenic activity and inflammation independent of diet. Studies measuring SCD-1 activity directly will be required to answer the latter question. Our independent associations over a long time period motivate investigation of whether a specific FA intake could prevent or decrease inflammation, i.e. investigation in controlled studies of whether a diet relatively high in 18:2n-6 and low in SFA may decrease low-grade inflammation.

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References


