

Fatty acids, inflammation, and the metabolic syndrome^{1,2}

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The metabolic syndrome is a locus of 5 biologic indexes that together, in combinations of ≥ 3 , predict the development of cardiovascular disease and type 2 diabetes. Although these 5 indexes—hypertension, insulin resistance, central adiposity, hypertriglyceridemia, and low HDL cholesterol concentrations—are readily measured in clinical medicine, mechanistically they seem to have little in common. The emerging information linking basal (ie, constitutive) inflammation with the metabolic syndrome and obesity (1) may either make this picture even more complex, or it may provide a mechanistic link between these indexes.

In this issue of the Journal, Klein-Platat et al (2) report that overweight preteen adolescents have higher plasma concentrations of C-reactive protein and interleukin 6 than do normal-weight control subjects. Fatty acid composition analysis of the subjects' plasma phospholipid and cholesteryl ester (CE) fractions also uncovered differences between normal-weight and overweight groups, including higher saturated fatty acids and lower n-3 polyunsaturated fatty acids in the overweight group, particularly in the phospholipid fraction. These distortions in the phospholipid fatty acid composition were even more pronounced in the subgroup of overweight subjects who met the criteria for the metabolic syndrome. In addition, the metabolic syndrome subgroup also showed a marked elevation in palmitoleic acid (16:1n-7) in both the phospholipid and CE fractions.

It is tempting to conclude that the increased saturated fatty acid concentrations and reduced n-3 fatty acid concentrations in the overweight subjects in the present study (2) were due to poor diet. Furthermore, because n-3 fatty acids have antiinflammatory properties, a reduced intake of fish and leafy greens might also explain the higher concentrations of plasma interleukin 6 and C-reactive protein. However, dietary differences do not offer a direct explanation for the elevated 16:1n-7 concentrations in phospholipids and CEs that were associated with the metabolic syndrome. This fatty acid is unusual in the human diet (the only common dietary source being macadamia nuts), but it is readily produced in humans by the enzyme stearoyl-CoA desaturase-1 (also called δ -9 desaturase).

In a prior report, Kunesova et al (3) noted significant within-pair concordances for 16:1n-7 across multiple serum and adipose lipid fractions in adult identical twins who lived apart, and they also noted that 16:1n-7 in adipose and serum triacylglycerols correlated with body mass index and adiposity, as measured by both skin fold thicknesses and hydrodensitometry. This group also reported strong within-pair concordances for multiple

essential polyunsaturated fatty acids in serum phosphatidyl choline, but not in CEs or triacylglycerols. These observations indicate that genotype exerts a strong influence on both the nonessential and the essential fatty acid composition, particularly in membrane components, independent of diet.

So what role does constitutive inflammation play? Is it secondary to diet or genotype-driven fatty acid differences, or does it have a more direct causal role? Given that we now understand leptin to be a proinflammatory cytokine (4), it is interesting to look in retrospect at serum and tissue fatty acids in the Zucker fatty rat, which lacks the leptin receptor and maintains high serum leptin concentrations. In these animals, 16:1n-7 is dramatically elevated in all lipid fractions in the obese genotype, whereas membrane polyunsaturated fatty acids are abnormal because of maldistribution between the phospholipid and CE fractions (5). Furthermore, when these animals were fed γ -linolenic acid (18:3n-6), an antiinflammatory fatty acid that also corrected the principal membrane polyunsaturated abnormality, both food intake and weight gain were selectively reduced in the obese, but not in the lean, genotype (5, 6). These results suggest a close and causal relation between inflammation and tissue fatty acid distribution, with implications for both insulin resistance (7) and weight gain.

Clearly, dietary fat, both the specific type and the total amount, can affect tissue fatty acid composition, cell-mediated inflammatory processes (8), and inflammation-mediated disease outcome (9). However, the twin study by Kunesova et al (3) and the differences between lean and obese Zucker rats that were fed the same diet emphasize the importance of genotype in the postabsorptive metabolism and distribution of both essential and nonessential fatty acids. Given an understanding of specific genes or gene combinations on fatty acid metabolism, we will be better able to use dietary intervention for person-specific health benefits.


It is also clear that understanding the interrelations within and between different fatty acid classes and their effects on other metabolic processes will not be easy. Difficulties in understanding these relations include the wide variations in fatty acid composition between different lipid fractions in the same tissue and also between the same fractions in different tissues. Although

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both serum and plasma are convenient analytes, their phospholipid fractions differ substantially from those of most fixed tissues (5) and may not adequately reflect the fatty acid composition of the target organ in question. Thus, the lack of a relation between phospholipid polyunsaturated fatty acids and insulin sensitivity in the study by Klein-Platat et al (2) may be due to their analysis of plasma lipids rather than an insulin-responsive organ membrane, such as skeletal muscle (7).

The most consistent observation in studies of fatty acid composition in obesity is the strong correlation between 16:1n-7 and adiposity (2, 3, 5, 10). This monounsaturated product derived from palmitic acid (16:0) is clearly not produced by the isolated activation of stearoyl-CoA desaturase-1, because all of these studies showed increases in the precursor 16:0 pool as well (although to a proportionately lesser degree). Because 16:1n-7 has a relatively short metabolic half-life, its tissue accumulation in obesity is therefore most likely a result of increased production via de novo lipogenesis. It follows that 16:1n-7 might be evaluated as a biomarker for weight gain and its pathway of production explored as a target for therapeutic intervention.

In conclusion, the report by Klein-Platat et al (2) is an excellent first step toward understanding the metabolic interactions between dietary fatty acids, endogenous fatty acid partitioning, inflammation, and obesity. Improved understanding of these processes could lead to the rational therapeutic use of essential fatty acids of both the n-3 and n-6 families to prevent and treat the metabolic syndrome. However, changes in dietary fat composition alone may not be sufficient to overcome the downstream metabolic effects of the postabsorptive maldistribution of essential fatty acids in fixed tissue membranes. The interactions between inflammation, insulin sensitivity, membrane abnormalities, and de novo lipogenesis offer a host of targets for future research. 

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