Free fatty acids, cardiovascular mortality, and cardiometabolic stress

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This editorial refers to 'Elevated plasma free fatty acids predict sudden cardiac death: a 6.85-year follow-up of 3315 patients after coronary angiography' by S. Pilz et al., on page 2763

Free fatty acids (FFAs) are non-esterified fatty acids that circulate in the bloodstream predominantly bound to albumin. FFAs are released from adipocyte triglyceride stores by lipolysis and from phospholipids by the action of phospholipases. Release of FFAs, as well as uptake of circulating FFAs by tissues such as skeletal muscle and liver, is regulated by the action of insulin and modulated by adrenergic activity. FFAs represent a significant energy source, being oxidized by myocardium, skeletal muscle, liver, and kidney. Specific FFAs may also directly regulate cellular function, either by exchange with membrane phospholipid fatty acids or in their role as natural ligands of cytoplasmic nuclear receptors, such as peroxisome proliferator-activated receptors.

Utilizing data from a prospective cohort study of 3315 German patients with suspected acute coronary syndrome undergoing coronary angiography in 1997–2000, Pilz et al.1 evaluated associations between total fasting FFA, measured using stored blood from the time of angiography, and risk of mortality over 6.9 years. Results had previously been reported for total mortality and cardiovascular mortality at 5.4 years;2 this report evaluates sudden cardiac death (SCD) and includes additional follow-up time. After adjustment for traditional risk factors, medication use, left ventricular function, and levels of C-reactive protein, homocysteine, creatinine, B-type natriuretic protein (BNP), and noradrenaline, higher FFA levels were independently associated with SCD (P trend = 0.01), with 76% higher risk comparing extreme quartiles [relative risk (RR) = 1.76, 95% confidence interval (CI) = 1.03–3.00]. Notably, results were very similar for other cardiovascular deaths (RR = 1.78, 95% CI = 1.14–2.78), indicating lack of specificity for SCD in contrast to a prior report from the Paris Prospective Study among men free of known coronary disease, in whom FFA levels were associated with higher risk of SCD but not other fatal myocardial infarctions3. These associations with cardiovascular mortality were present following multivariable adjustment for a broad range of other potential risk factors, indicating that, among these risk factors, FFA levels are a strong independent predictor of SCD and other cardiovascular deaths.

The paramount question is whether this observed relationship is causal (i.e. FFAs directly increase cardiovascular mortality) or non-causal (i.e. higher FFA levels are a marker of underlying metabolic or adrenergic stress that raises risk). If the former, then any treatment which lowers FFA levels would reduce risk. If the latter, then only treatments which improve the underlying cardiometabolic dysfunction would reduce risk. This question, similarly to the uncertainty surrounding other novel risk factors for cardiovascular disease (e.g. C-reactive protein), has major scientific and clinical implications.

Observed associations of FFA levels with insulin resistance,4,5 heart failure,6 or high catecholamine states7 do not help answer this question, as once again FFAs may simply be a marker of the underlying cardiometabolic dysfunction that raises clinical risk. For example, in Pilz et al.,1 FFA levels were associated (in unadjusted analyses) with greater left ventricular dysfunction, BNP levels, and noradrenaline levels, consistent with prior reports of elevated FFAs in states of adrenergic stress7 known to increase cardiovascular mortality. Higher FFA levels were also strongly associated (in unadjusted analyses) with multiple indices of metabolic dysfunction, including greater prevalent diabetes, hypertension, adiposity, insulin resistance, blood pressure, triglyceride levels, and C-reactive protein levels.

One common denominator of these latter conditions—often considered together as a ‘metabolic syndrome’—appears to be adipocyte and endothelial dysfunction (due to mitochondrial, endoplasmic reticulum, and/or oxidative stress8), caused by excess caloric intake, inadequate physical activity, chronic weight gain (visceral adiposity), specific dietary factors (e.g. low intake of whole grains; high intake of refined carbohydrates or trans fat), and...
smoking. Interventions directed at these underlying lifestyle risk factors are the clearest way to improve the underlying metabolic stress marked by higher FFA levels and ensure reductions in clinical risk. Modest changes in caloric intake, physical activity, dietary habits, and body weight significantly reduce metabolic stress, improving insulin resistance, blood pressure, lipid levels, and systemic inflammation, and lowering risk of diabetes and cardiovascular events.\textsuperscript{9–13} Unfortunately, data on physical activity and dietary habits were not collected by Pilz et al., so the associations of these behaviours with FFA levels (or the confounding of the FFA–mortality association by these behaviours) could not be assessed.

Some evidence suggests that FFAs, in addition to marking underlying cardiometabolic stress, may also casually increase cardiovascular risk. As reviewed by Oliver,\textsuperscript{7} increased FFAs due to heparin-induced lipolysis or direct intravenous injection induce ventricular arrhythmias in animal experiments, while inhibition of adipose tissue lipolysis lowers arrhythmic events. Such effects may be related to increased myocardial oxygen consumption (especially in ischaemic zones) due to lower efficiency of FFA oxidation, compared with glucose oxidation, or direct toxicity of FFAs on myocardial cell membranes, ion pumps, or mitochondrial function.\textsuperscript{7} FFAs also appear to induce peripheral insulin resistance in skeletal muscle and possibly the liver, with associated intracellular accumulation of muscle and hepatic fat stores.\textsuperscript{4,5}

Nevertheless, even a direct effect of FFAs on peripheral or hepatic insulin resistance, if clearly substantiated in humans, would not imply that all pharmacological interventions that reduce FFA levels would necessarily lower cardiac risk. While peripheral insulin resistance and circulating glucose levels might improve from such treatment and reduce microvascular complications such as retinopathy and glomerulopathy, macrovascular (cardiac) complications might be less affected, as the latter may result from underlying adipocyte and endothelial stress (more proximal risk factors) rather than peripheral insulin resistance or elevated plasma glucose (downstream risk factors). The difference between the targeting of these proximal vs. distal risk factors might explain, for example, the disappointing results for reducing coronary events of drug treatments that improve glucose control but do not affect the underlying adipocyte dysfunction or its causes.\textsuperscript{14}

The strong independent association of FFAs with cardiovascular mortality demonstrated by Pilz et al. should stimulate further investigation of how FFAs—the forgotten risk factor\textsuperscript{7}—relate to and impact cardiovascular risk. Although based on current evidence the potential causality of the relationship should not be overemphasized, it is clear that circulating FFA levels provide an additional indication of underlying cardiometabolic stress—and associated higher clinical risk—that is not currently provided by other measures (including glucose, insulin, serum lipids, BNP, C-reactive protein, and noradrenaline levels). It remains to be seen whether acute or chronic effects of FFAs predominate; and whether fasting, post-prandial, or catecholamine-induced levels of FFAs are most relevant. The potentially differential effects of specific individual FFAs (i.e. of varying chain lengths and locations and numbers of unsaturated bonds) will likely prove to be particularly interesting and informative, and deserve further careful investigation.

Whether FFAs are only an independent risk marker of specific underlying pathophysiology (metabolic stress, catecholamine excess) or also directly impact cardiovascular risk, interventions to reduce FFA levels should target the underlying cardiometabolic stress (e.g. at the level of the adipocyte). This could be achieved by the development of novel drugs or, more simply and directly, by basic lifestyle measures such as smoking cessation, greater physical activity, modest dietary change (e.g. reduced calories, consumption of whole grains in place of refined carbohydrates, reduced trans fats), and modest weight loss.

Conflict of interest: none declared.

References