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VIEWPOINT

Saturated fatty acids are not off the hook

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Abstract A recent meta-analysis by Chowdhury et al. (2014) has disclaimed the association between coronary artery diseases and either circulating blood levels or the intake of total saturated fatty acids (SFA). Scrutiny revealed that two of the eight studies included in the meta-analysis focused on the proportion of pentadecanoic acid (C15:0) and heptadecanoic acid (C17:0) and their impact on cardiovascular disease (CVD) risk. These odd-chain fatty acids are markers for milk or ruminant fat intake. Both studies indicated inverse associations between milk-fat intake and first-ever myocardial infarction. Neither of the two studies described the association between total circulating blood SFA on coronary outcomes.

In contrast to the cardioprotective effects of dairy consumption, we expected that an elevated intake of palmitic acid (C16:0) and stearic acid (C18:0) *de novo* may raise CVD risk. Thus, it is of particular importance to differentiate the effects of individual circulating SFA on cardiovascular outcomes.

Excluding the studies that evaluated the association of fatty acids from milk fat and cardiovascular outcomes revealed a positive association of total SFA blood levels and coronary outcome (RR 1.21, CI 1.04–1.40). Therefore, results obtained from studies of C15:0 and C17:0 cannot be mixed with results from studies of other SFA because of the opposite physiological effects of regular consumption of foods rich in C16:0 and C18:0 compared to high intake of milk or ruminant fat. In our opinion, it is vital to analyze the impact of individual SFA on CVD incidence in order to draw prudent conclusions.

Several studies revealed an association between high intake of fat rich in saturated fatty acids (SFA) and increased incidence of cardiovascular diseases (CVD) [1–4]. The effect of dietary SFA may result mostly from their effects on CVD risk factors, *i.e.* increasing low-density lipoprotein cholesterol (LDL-C). Currently, the contribution of dietary SFA to CVD risk is still under discussion because recent systematic reviews and meta-analyses of prospective cohort studies reported no significant association

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between SFA intake estimated by food frequency questionnaires (FFQ), 24 h recalls or circulating blood SFA levels and CVD risk [5–8].

On closer examination, these studies and meta-analyses mostly found weak but not significant associations between dietary SFA intake and cardiovascular events. Mente et al. [6] evaluated the impact of SFA intake (divided as quantiles) in 11 cohorts (n = 160,673) and reported a relative risk (RR) of 1.06 (0.96–1.15) for coronary outcomes. In the Kuopio Ischemic Heart Disease Risk Factor Study (n = 1981), Virtanen et al. [8] found higher incidence rates of coronary heart disease (CHD) in men with high SFA intake. During the average follow-up of 21.4 years, 183 fatal and 382 nonfatal CHD events occurred. The study revealed that intake of SFA or *trans* fatty acids was not associated with CHD risk, whereas intake of monounsaturated fatty acids (MUFA) was associated with increased risk; intake of polyunsaturated fatty acids (PUFA) decreased risk of fatal CHD. However, dividing the collective according to median SFA intake (energy %) into quartiles (median SFA intakes: 13.4, 16.6, 19.1, 22.8 energy %) showed increases of the hazard ratios (HR) from 1.0, 1.10 (0.7–1.73), 1.16 (0.73–1.86) to 1.29 (0.79–2.08) for fatal CHD and from 1.0, 0.81 (0.6–1.11), 0.89 (0.65–1.22) to 1.14 (0.83–1.57) for nonfatal CHD. The correlation between total fat consumption and risk of nonfatal CHD was statistically significant ($p < 0.05$).

In a recent large meta-analysis in *Annals of Internal Medicine*, Chowdhury and colleagues analyzed prospective observational studies and randomized controlled trials for the association of dietary, supplementary and circulating fatty acids with coronary outcomes [9]. Among other findings, blood concentrations and documented dietary intake of SFA were disclaimed to correlate with coronary outcomes. The analysis of the relation between documented dietary SFA intake and cardiovascular events was based on 20 studies with 276,763 participants (10,155 events). The RR for SFA intake was 1.03 (95% CI, 0.98–1.07) when the top and bottom thirds of baseline dietary fatty acid intake were compared. Closer examination of the studies included showed RRs <1.0 in six studies, whereas in 14 studies RRs were ≥1.0. The confidence intervals were wide within each study and none of the studies suggested a significant association.

The results of the meta-analysis by Chowdhury and colleagues gave rise to misleading headlines like ‘Animal fat is not bad for the heart’ in the lay press [10]. Consumers may therefore continue evidently unhealthy dietary habits in response to such simplified messages.

But, are there good reasons that would explain the apparent absence of evidence? The answer is yes, in the sense that there is an urgent need for improving the quantification of the dietary intake of nutrients. Existing tools for evaluating dietary intake, such as FFQ, 24 h recalls, etc., do not accurately reflect actual food intake [11,12]. Overreporting of ‘healthy foods’, such as vegetables and fruits, and in particular underreporting of ‘unhealthy foods’, such as highly processed calorie-dense and nutrient-poor foods as well as alcohol, are major pitfalls of these questionnaires. Ferrari et al. evaluated under- and overreporting and their determinants in a 24-h diet recall sub-study of the European Prospective Investigation into Cancer and Nutrition (EPIC) study cohorts [11]. In total, 35,955 men and women, aged 35–74 years, participated in the nested EPIC calibration sub-studies. In these studies, overreporting had only minor impact but the percentage of subjects identified as extreme underreporters was 13.8% and 10.3% in women and men, respectively. Interestingly, BMI (or weight), gender and age were particularly associated with underreporting.

Underreporting of energy consumption by self-reporting is another well-recognized issue. For example, 544 participants of the Women’s Health Initiative Dietary Modification Trial completed a double-labeled water protocol, 24-h urine collection and self-reports of diet (FFQ), exercise, and lifestyle habits; 111 women repeated all reports after 6 months. Valid biomarkers, such as urinary nitrogen as a marker for protein intake and the doubly labeled water protocol as a marker for total energy expenditure, confirmed that underreporting of nutrient consumption from self-reported FFQ was common, and the extent of misreporting was predicted by age, BMI, and race/ethnicity. Women of the intervention group underreported energy intake by 32% (*vs.* 27% in the comparison group) and protein intake by 15% (*vs.* 10%). Younger women showed higher underreporting of energy and protein, while higher BMI predicted increased underreporting of energy and increased overreporting of the percentage of energy derived from protein [12].

In addition to the bias due to the above outlined inaccuracy of dietary self-reports, this kind of documentation of dietary intake has further shortcomings: Databases used for calculating nutrient intake are based mainly on unique nutrient analyses of the included foods and data on seasonal or regional differences as well as differences of species, animal care and feeding conditions are not considered. Further, individual inherent characteristics of study subjects, such as metabolic rate, genetic variations, hormonal milieu, disease status, and lifestyle (*e.g.* physical activity) are often not taken into account. Finally, it is quite difficult for study participants to estimate sufficiently precise the amount of the food they have eaten per meal [13].

The occurrence of systematic bias in dietary self-reports indicates the urgent need for analyzing biomarkers that better reflect dietary intake. The analysis of circulating fatty acids has been considered as a more appropriate way than the dietary assessment by questionnaires. Ruiz-Núñez et al. [14] investigated the relations between fatty acid status, as concentrations of fatty acids in serum cholesterol esters (CE) and red blood cells (RBC) on the one hand and serum total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and TC/HDL-C ratio on the other hand in five Tanzanian and one Dutch ethnic groups.