Journal of Clinical Lipidology (2018) ■, ■–■

Journal of Clinical Lipidology

Original Article

Saturated fatty acids and mortality in patients referred for coronary angiography—The Ludwigshafen Risk and Cardiovascular Health study

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KEYWORDS:
Saturated fatty acids;
Palmitic acid;
Stearic acid;
Mortality;
Coronary artery disease

BACKGROUND: Saturated fatty acids are thought to be harmful by increasing the risk for cardiovascular events.

OBJECTIVE: We examined the associations of erythrocyte saturated fatty acids with total and cardiovascular mortality in patients referred for coronary angiography.

METHODS: Red blood cell saturated fatty acid (RBC SFA) proportions were measured by gas chromatography at baseline in 3259 participants of the Ludwigshafen Risk and Cardiovascular Health study. Associations of saturated fatty acid concentrations with mortality were investigated using Cox proportional hazards regression.

RESULTS: During a median follow-up of 9.9 years, 975 patients (29.9%) died and 614 patients (18.8%) died of cardiovascular causes. The proportion of palmitic acid (PA, C16:0) ranged from 15.1% to 27.4% with a mean (standard deviation) of 21.9% (1.15%) and was associated with an increased risk for mortality in models adjusted for conventional cardiovascular risk factors. An increase of 1-standard deviation in PA was associated with a hazard ratio (95% confidence interval) of 1.08 (1.01–1.16) for all cause and 1.05 (0.96–1.15) for cardiovascular mortality after adjustment for cardiovascular risk factors. For the other investigated RBC SFA (C14:0, C18:0, C20:0, C22:0, and C24:0), there was no association with mortality and also not for the sum of all saturated fatty acids.

CONCLUSIONS: Our results reveal association with increased mortality risk only for PA but not for the other RBC SFAs or the sum of all RBC SFAs and emphasize the need to investigate each fatty acid individually rather than studying groups of fatty acids.

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Submitted August 25, 2017. Accepted for publication January 12, 2018.

1933-2874/
https://doi.org/10.1016/j.jacl.2018.01.007

Introduction

Saturated fatty acids (SFAs) are often regarded as a homogeneous group of fatty acids that are a key factor promoting elevated total serum cholesterol and low density lipoprotein (LDL) cholesterol concentrations, and thus coronary heart disease (CHD), since the 1960s.[1] Consequently, medical societies recommended to lower the intake of SFAs[1] and these recommendations are still in place. The current European guidelines for cardiovascular disease prevention, for example, state "Saturated fatty acid intake should be reduced to a maximum of 10% of energy intake by replacing it with polyunsaturated fatty acids."[2] The evidence-based guidelines of the German Nutrition Society evaluated the evidence for the prevention of the widespread diseases, for example, obesity, type 2 diabetes mellitus, hypertension, metabolic syndrome, CHD, and stroke by the intake of fat or different types of fatty acids.[3] The authors found the evidence convincing that reduced intake of total fat, specifically SFA, and a higher intake of polyunsaturated fatty acids (PUFAs) reduce the concentration of total cholesterol (TC) and LDL cholesterol. Despite the effects on total and LDL cholesterol, the evidence that reduced intake of total fat and SFA has no effect on CHD was rated by the authors as "possible." In a recent meta-analysis, Chowdhury et al evaluated dietary and circulating SFA with 14–18 carbon atoms and reported no impact of these fatty acids on the relative risk (RR) for coronary outcomes.[4] On the other hand, Wang et al[5] recently reported in their meta-analysis an association of higher SFA intake with increased mortality. Epidemiologic studies on the associations of individual very long-chain SFAs with more than 20 C atoms in erythrocytes are scarce[6,7] and do not support an elevated cardiovascular risk. The publications mentioned question cardiovascular guidelines recommending limited consumption of SFA, and the controversies regarding SFA are described in a recent review.[8]

There is a consensus that LDL particles are causally involved in the development of CHD. However, neither TC nor the widely used LDL cholesterol concentration appears to be good predictors for cardiovascular events.[9] In part, this may be due to the heterogeneity of LDL particles with especially small dense LDL thought to be most atherogenic.[10] Recently, we demonstrated that higher levels of the polyunsaturated omega-3 fatty acid docosahexaenoic acid, which elevates LDL, were associated with lower total mortality and cardiovascular mortality (CVM), and the same to be true for eicosapentaenoic acid (EPA), which has no impact on LDL.[11] Our findings did not support the uncritical use of LDL as a surrogate parameter in conjunction with fatty acids. Moreover, we recently reported that higher erythrocyte levels of natural trans fatty acids that originate from ruminant fat are associated with lower total and CVM, while the low levels of industrially produced trans fatty acids we observed in Germany were not associated with elevated mortality.[12] Together with the distinct biological properties of specific fatty acids and their metabolites,[13] our findings question the use of generalizing umbrella terms such as "trans fatty acids" or "polyunsaturated fatty acids." Whether prognostic differences exist between individual SFA in erythrocytes was unknown. Therefore, we investigated the associations of individual erythrocyte SFA with total mortality and CVM and with several conventional and nonconventional cardiovascular risk factors in the framework of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study.

Methods

Study populations

The LURIC study included 3316 Caucasians hospitalized for coronary angiography between 1997 and 2000 at a tertiary care center in south western Germany.[14] Clinical indications for angiography were chest pain or a positive noninvasive stress test suggestive of myocardial ischemia. To limit clinical heterogeneity, individuals suffering from acute illnesses other than acute coronary syndrome, chronic noncardiac diseases, and a history of malignancy within the 5 past years were excluded. The study was approved by the ethics committee at the "Landesärztekammer Rheinland-Pfalz" and was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants. Clinical definitions are supplied in the Supplementary. Information on vital status was obtained from local registries. Death certificates and medical records of local hospitals and autopsy data were reviewed independently by 2 experienced clinicians who were blinded to patient characteristics and who classified the causes of death. During a median follow-up of 10.0 years (range 0.1–11.9 years) 995 (30%) participants died.

Laboratory procedures

Fasting blood samples were obtained by venipuncture in the early morning. Cholesterol and triglycerides were measured with enzymatic reagents from WAKO (Neuss, Germany) on an Olympus AU640 analyzer (Center Valley, PA). Lipoproteins were separated by a combined ultracentrifugation precipitation method (β-quantification), as described previously.[14] Erythrocyte fatty acid composition was analyzed by gas chromatography as previously described[15] at Omegametrix GmbH (Martinsried, Germany). RBC SFAs were measured in 3259 participants of the LURIC study.

Statistical analyses

The primary aim of our study was to examine the association of individual SFA with all-cause mortality using Cox proportional hazard models. The proportional hazard assumption was checked by examination of scaled Schoenfeld residuals. Adjustments were carried out including