Review Article

Trans Fatty Acids: Are Its Cardiovascular Risks Fully Appreciated?

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ABSTRACT

Objective: The goal of this article was to review the causal link between trans fatty acids (TFA) produced from partially hydrogenated vegetable oil (PHVO) and cardiovascular disease (CVD) risk and its likely mechanisms. The potential risk of TFA from ruminant dairy and meats, which are currently the major sources of dietary TFA, is also discussed.

Methods: Evidence was derived from observational studies of large cohorts followed up prospectively; from randomized controlled trials of clinical interventions; and from specific case-control studies that investigated biomarkers in tissues. Searches included PubMed and Medline from 1990 to 2013.

Results: Despite TFA from PHVO being associated more strongly with CVD risk than even saturated fats, it may prove difficult to totally eliminate PHVO from all foods. This raises the issue of the lower limit of TFA consumption below which CVD risk is not increased. Limits of $<1\%$ of total energy have been suggested. The major mechanism underlying the increased CVD risk from TFA is an increase in LDL-C and Lp(a) lipoproteins and a decrease in HDL-C; increased inflammation and adverse effects on vascular function have also been shown. Both PHVO and ruminant TFA comprise a range of isomers, some specific to each source but including a substantial commonality that supports findings of similar adverse effects at equivalent intakes of TFA. However, the amount of TFA in ruminant fat is relatively small; this limits the CVD risk from eating ruminant products, an inference supported by analysis of prospective cohort studies.

Conclusions: Two key challenges to the health industry arise from this evidence. They must first determine whether a small intake of TFA from PHVO is safe and what constitutes a safe amount. They must also determine whether TFA from ruminant fat in currently consumed amounts represent limited cardiovascular risk that is balanced by the nutritional benefits of dairy products. (*Clin Ther*. 2014;36:315–321)

Key words: biomarkers, cardiovascular risk, ruminant fat, TFA isomers, trans fatty acids.

INTRODUCTION

The coordinated actions to reduce, if not eliminate, the harmful effects of trans fatty acids (TFA) in foods is one of the few modern success stories in nutrition. Scientific observations and clinical studies have led to collaboration between nutritionists, food regulators, and food industry to diminish the impact of dietary TFA on human health, particularly with regard to coronary heart disease (CHD). Although the initial focus on this public health problem has rightly been on the hardening of vegetable oils through which partial hydrogenation of vegetable oils (PHVO) occurs, it has become apparent that the major remaining contribution now comes from ruminant TFA (ie, dairy products, lamb, beef), which has been regarded as originating from "natural sources." In an editorial, Mensink and Nestel[1] questioned whether there are evidence-based reasons for assuming that the 2

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sources of TFA would differ in their effects on cardiovascular risk. They concluded that the risks from both were similar; however, because risk is a function of the amounts present in national diets, the considerably lower consumption of ruminant TFA than that which prevailed for PHVO ruminant TFA may present a lower risk. The variety of TFA isomers derived from ruminant and industrial sources are not identical, although substantial commonality exists.[2] Differences in the respective TFA isomers are therefore unlikely to confer different outcomes.

Regulators also have difficulty in defining the lowest level of TFA that may be harmless because that has not been unequivocally determined but has a bearing on the lower intake of TFA from ruminant fats. It is therefore important to be reassured that prospective cohort studies, complemented by studies of an ever-growing list of biomarkers of CHD risk, provide the consistency and strength on which to base policies related to dietary TFA. Currently, the consensus is overwhelming that such reassurance is justified even while important exceptions are acknowledged. The present article examined the pros and cons of the evidence as well as focused on unresolved issues.

METHODS

Evidence was sourced from observational studies of large cohorts followed up prospectively; from randomized controlled trials of clinical interventions; and from specific case-control studies that investigated biomarkers in tissues.

RESULTS

Consensus That Industrially Produced TFA are Causally Linked to CHD Risk and Outcomes

The Spectrum of TFA Isomers in Ruminant and Industrial Products

The difference between *trans* and *cis* conformation around a double bond relates to the position of the hydrogen atoms around the double bond. This isomeric difference results in differing biological properties. Thus, whereas natural *cis* configurations are kinked or bent at every double bond, *trans* configurations lead to straight molecules.

Ruminant TFA are formed in the rumen of such animals in which bacterial actions on feed unsaturated fatty acids convert naturally occurring *cis* to *trans* forms.[2] Whether this allows the claim of natural is a moot point. The major ruminant TFA is vaccenic acid; depending on nomenclature, vaccenic acid is *trans* C18:1 (n-7), a monounsaturated fatty acid at carbon 7 where it is in the *trans* conformation. Trans C16:1 (n-7), a *trans* form of palmitoleic acid, is a minor component but has gained importance through its biomarker status of dairy consumption. Diunsaturated forms are also found, and when the 2 double bonds are at adjacent carbons, these fatty acids are called conjugated linoleic acids (CLA). They are important because they have been attributed many beneficial properties regarding CHD.[3] CLA of the *cis*-9, *trans*-11 type, the naturally occurring ruminant trans diunsaturated fatty acid, can also be synthesized in humans from vaccenic acid.

In contrast, PHVO contains among its many isoforms the major TFA elaidic acid (*trans* C18:1n-11), which is the *trans* isomer of oleic acid. CLA isomers are formed as 2 major species, 1 of which resembles that in ruminant fat. There is substantial overlap in isomers present in ruminant and PHVO, although both sources of fats also have their specific TFA. Longer chain TFAs in the C22 to C24 range are found after hydrogenation of marine oils, a common substrate for hard margarines.

Prospective Cohort Studies

The most convincing evidence is based on prospective cohort studies. Weaknesses implicit in such studies include the dependence on use of food questionnaires and misclassification due to inaccurate recall of eating habits. Furthermore, patterns of food consumption changed over the long periods of the major prospective cohort studies. Correction for this variation is possible, as are adjustments for confounding factors; nevertheless, the strength of the evidence is inferior to that of randomized controlled trials, which are unlikely to occur with respect to cardiovascular outcome studies. Among the best studies are the Nurses' Health Study[4] and the Health Professionals Follow-up Study.[5] Both were large, excellently designed and executed, and had extensive follow-up periods. Meta-analyses of the best of the prospective studies provide pooled calculations that resolve minor discrepancies among studies.

The Nurses' Health Study has the strength of having estimated both the consumption of TFA and the effect of this consumption on hard CHD end points at various times (ie, after 8, 14, and 20 years).[4] The associations between TFA intake and CHD were significant at each time point as the number of incident cases