8. FSSAI News. FSSAI issues draft for mandatory fortification of edible oil & packaged milk. January 2021 [Internet]. Available from: https://fssai.gov.in/upload/media/FSSAI_News_Oil_FNB_04_01_2020.pdf.

The homeoviscous adaptation to dietary lipids (HADL) hypothesis is probably incorrect

Dear Editor:

Zinöcker, Svendsen, and Dankel recently presented their homeoviscous adaptation to dietary lipids (HADL) model (1). Briefly, their model can be summarized as follows: high dietary SFA and low PUFA intake causes changes to plasma membrane fluidity that drive transfer of free cholesterol from membranes to lipoproteins, whereas a low dietary SFA and high PUFA intake does the opposite. The authors suggest several immediate implications for how we now should understand biology and the connection between diet and health.

In the following, we address issues and topics which suggest that the presented hypothesis is incorrect.

First, let us discuss the key questions posed by the authors, concerning the origin and disposal of LDL cholesterol, as this is established scientific knowledge (2). Cholesterol in plasma is transported in lipoproteins, and in humans, the majority is found in apoB-100-containing LDL particles. All apoB-100-containing lipoprotein particles originate from VLDLs, which are being continuously secreted by the liver. The main function of VLDL particles is to transport lipids, mainly triglycerides (energy), from the liver to peripheral tissues. LDL particles are the smallest VLDL remnants from which most of the triglycerides have been depleted via the function of lipoprotein lipase and hepatic lipase. Furthermore, LDL particles are continuously removed from circulation by hepatocytes via the LDL-receptor (LDLR)-dependent pathway; LDL particles can therefore accumulate in the plasma because of increased VLDL secretion and residence time or reduced LDL clearance. After degradation in lysosomes, LDL particle contents will be dispersed into various cellular pools. Cholesterol, for example, will be deposited as lipid droplets, incorporated into membranes, used for VLDL particle biosynthesis, or secreted into the bile ducts either as cholesterol or as bile salts to reach the gut for reabsorption or ultimate excretion (2).

Second, we would like to comment on a few of the statements about atherosclerosis. Although endothelial injury ("response-to-injury") may contribute, the real driver of atherosclerotic progression is the subendothelial retention of apoB-100-containing lipoprotein particles ("response-to-retention") which then launches a local, sterile inflammation (3). This means that inflammation is a consequence rather than a cause of lipid accumulation in the arterial wall. In contrast, the cholesterol molecules present in the circulation are not relevant to atherosclerosis per se. Furthermore, all apoB-100-containing particles are potentially atherogenic, and the degree of atherosclerosis progression is driven mainly by the cumulative exposure to atherogenic lipoproteins, which is determined by the absolute plasma concentration and the duration of exposure ("cholesterol burden"). Indeed, a persistently elevated concentration of LDL particles in plasma is harmful regardless of its cause (unfavorable genetic variants or an unhealthy diet), whereas a persistently low concentration is beneficial regardless of its cause [favorable genetic variants, a healthy diet, or pharmacotherapy using statins, proprotein convertase subtilisin-kexin 9 (PCSK9) inhibitors, or ezetimibe] (3).

Third, the authors should have considered the following topics while developing their hypothesis:

1) From basic science, animal models, genetic studies, and intervention trials, we know the most important determinants of the variability in plasma LDL cholesterol (3, 4). For example, number and activity of hepatic LDLRs (relevant genes include *LDLR*, *PCSK9*, *APOE*), LDL binding to LDLRs (*LDLR*, *APOB*), cholesterol biosynthesis [3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (*HMGCR*)], hepatic bile acid synthesis [cholesterol 7 alpha-hydroxylase (*CYP7A1*)], and enterocyte uptake and secretion of cholesterol [Niemann-Pick C1-Like 1, ATP-binding cassette sub-family G member 5 and 8 (*NPC1L1*, *ABCG5/G8*)].

2) All human cells can produce the cholesterol they need, and cellular cholesterol deficiency occurs only when its synthesis is defective (5–7). For example, heterozygous and homozygous familial hypercholesterolemia subjects exhibit 50% and 100% reduced cellular LDL uptake, respectively, but show no symptoms consistent with cholesterol deficiency. In contrast, cholesterol synthesis defects such as Smith–Lemli–Opitz syndrome are detrimental already in fetal life.

3) In contrast to glucose homeostasis, no hormonal system has evolved to keep plasma cholesterol concentration within a narrow range. This is because every cell can synthesize cholesterol and, accordingly, no cell has an absolute requirement for cholesterol uptake (6–8). Therefore, plasma LDL-cholesterol concentrations can be extremely low (although not 0) with few adverse effects.

4) Because free cholesterol is toxic and human cells cannot degrade cholesterol molecules, there is a balance between whole-body cholesterol input through diet and biosynthesis, and output through utilization and excretion (2, 8).

Finally, the HADL hypothesis provides at least two testable implications. The first relates to dose-response. If the physicochemical properties of dietary fatty acids affect membrane fluidity, which then determines cholesterol accretion in membranes, which then causes plasma LDL cholesterol to increase or decrease, we should be able to predict the change in LDL cholesterol based on the physicochemical properties of dietary fatty acids. Theoretically, an incrementally higher melting point of dietary fatty acids would cause incremental increases in plasma LDL cholesterol, whereas an incrementally lower melting point would do the opposite. But from controlled interventions, we find no such relation. Among the SFAs, myristic acid (14:0) increases plasma LDL cholesterol most strongly [+0.071 mM per energy percent (E%) increase in the diet], followed by palmitic acid (16:0, +0.047 mM/E%), then lauric acid (12:0, +0.01 mM/E%) (9). Among the PUFAs, both linoleic acid (18:2n–6) and α-linolenic acid (18:3n–3) reduce plasma LDL cholesterol by equal amounts (−0.017 mM/E%) (9). And importantly, of the long-chain omega-3 fatty acids, neither EPA (20:5n–3) nor DHA (22:6n–3) affects plasma LDL cholesterol (4).

Another testable implication concerns the temporal sequence, an essential part of any cause–effect analysis. If dietary fatty acids affect membrane fluidity, which then determines cholesterol accretion in membranes, and which then causes plasma LDL cholesterol to increase or decrease, we should observe membrane remodeling before the changes in plasma LDL cholesterol. However, that is not what we observe in controlled interventions: whereas plasma LDL cholesterol responds rapidly to dietary change (days to weeks), changes in membrane lipid composition occur slowly (weeks to months) and depend largely on the rate of cell turnover (10).

In summary, the authors have presented a biased scientific rationale, and they have omitted information that directly contradicts their hypothesis. We find that the HADL hypothesis conflicts with established knowledge and, therefore, based on all the aforementioned considerations, we propose that the presented hypothesis is incorrect.

The authors report no conflicts of interest.

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References

1. Zinöcker MK, Svendsen K, Dankel SN. The homeoviscous adaptation to dietary lipids (HADL) model explains controversies over saturated fat, cholesterol, and cardiovascular disease risk. Am J Clin Nutr 2021;113(2):277–89.
2. Gurr MI, Harwood JL, Frayn KN, Murphy DJ, Michell RH. Lipids: biochemistry, biotechnology and health. 6th ed. Oxford: Wiley Blackwell; 2016.
3. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, Daemen MJ, Demer LL, Hegele RA, Nicholls SJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020;41(24):2313–30.
4. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–88.
5. Waterham HR. Defects of cholesterol biosynthesis. FEBS Lett 2006;580(23):5442–9.
6. Masana L, Girona J, Ibarretxe D, Rodríguez-Calvo R, Rosales R, Vallvé J-C, Rodríguez-Borjabad C, Guardiola M, Rodríguez M, Guaita-Esteruelas S, et al. Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels—the zero-LDL hypothesis. J Clin Lipidol 2018;12(2):292–9.e3.
7. Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. Nat Rev Dis Primers 2017;3(1):17093.
8. Dietschy JM. Regulation of cholesterol metabolism in man and in other species. Klin Wochenschr 1984;62(8):338–45.
9. Müller H, Kirkhus B, Pedersen JI. Serum cholesterol predictive equations with special emphasis on *trans* and saturated fatty acids. An analysis from designed controlled studies. Lipids 2001;36(8):783–91.
10. Arab L. Biomarkers of fat and fatty acid intake. J Nutr 2003;133(3):925S–32S.

Reply to JJ Christensen et al.

Dear Editor:

Christensen et al. suggest that the hypothesis underlying the homeoviscous adaptation to dietary lipids (HADL) model (1) is incorrect. However, none of their arguments falsify the model, and recent research into the effects of dietary fatty acids on membrane remodeling, including cholesterol incorporation, supports it.

In the fields of biophysics and molecular biology, there is currently intensive research into the mechanisms that regulate plasma membrane fluidity and thereby cell function. Intriguingly, recent studies have revealed novel molecular sensors in specific membrane compartments that enable homeostatic membrane adaptations. These mechanisms involve complementary transcriptional regulators including sterol regulatory element-binding protein (SREBP) and are influenced by fatty acid supply (2, 3). However, despite the long-known essentiality of optimal plasma membrane function, the nature and purpose of regulatory mechanisms that remodel membrane lipids, in part determined by dietary fatty acid composition, remain insufficiently described. From the cell-centric perspectives of HADL, important new questions and knowledge gaps become evident and require further investigation.

We agree that the temporal (cause–effect) issue is important. But to properly understand the dynamics of cholesterol distribution between tissues and circulating lipoproteins, we propose an expanded view from single cell types—such as nonnucleated erythrocytes which are typically used as markers of longer-term fatty acid intake—to the homeostatic dynamics of fatty acid and cholesterol redistribution across different tissues/cell types.

Support for both rapid and tissue-specific fatty acid incorporation comes from a study on fish oil supplementation in rats, showing a doubling of DHA (22:6n–3) concentrations in myocardial cells already within 2 d, whereas erythrocytes showed considerably slower and more variable fatty acid incorporation (4). Furthermore, Levental et al. (5) recently demonstrated a surprisingly rapid lipid remodeling of mammalian cellular membranes after addition of exogenous DHA. Incorporation of DHA induced lipidome-wide remodeling, most notably upregulation of saturated membrane lipids and cholesterol, resulting in recovery of membrane packing and permeability. The cholesterol incorporation was concomitant with the acyl chain remodeling, seen already 1 h after DHA introduction and with peak levels at 4 h. These findings were also confirmed in vivo within a timeframe of 2 wk (although not measured earlier) (5). As stated by Levental et al. (5): "cholesterol is rarely considered alongside fatty acids and is a major component of the remodeling we report." In sum, these empirical data demonstrate that changes in cell membrane lipids after altered fatty acid supply occur rapidly and are likely to help explain LDL-cholesterol changes observed in intervention studies. With the HADL model we propose that such adaptive changes at the cellular level are coupled with cholesterol uptake from and efflux to lipoproteins. These findings and concepts strongly motivate more research into the mechanisms that regulate plasma membrane lipid dynamics in response to diet, including temporal and cross-tissue relations.