Butter increases high-density lipoprotein functional capacity: is this compensation for its adverse effect on serum low-density lipoprotein cholesterol?

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Butter increases HDL functional capacity: is this compensation for its adverse effect on serum LDL-cholesterol?

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Controversy over the dietary guidelines to reduce saturated fatty acids (SFA) rests heavily on the lack of evidence from meta-analyses for a direct association between dietary SFA and lower CVD mortality[1,2]. Evidence that a lower intake of SFA reduces CVD events has been reported, and can be explained, in part, by the lowering of serum LDL-cholesterol[2], a causal risk factor for the development of CVD[3]. Somewhat counter intuitively, the effects of SFA on the putatively beneficial serum HDL-cholesterol run in parallel to that of LDL-cholesterol, but how these diet-induced changes in HDL-cholesterol impact on CVD risk, is less clear.

The effects of dietary SFA on serum LDL-cholesterol depend on what macronutrient (unsaturated fatty acids and/or carbohydrate) replaces the SFA[4], and other constituents in the food, including its specific SFA content, and other components of the food matrix, such as protein, minerals, fiber[5]. The study by Brassard *et al*[6], examines these phenomena in relation to HDL-cholesterol, but extends its analysis to the substructure and function of HDL with relevance to the potential cardio-protective role of this lipoprotein.

A strong inverse association exists between serum HDL-cholesterol and CVD risk in populations, and underlies the diagnostic value of low serum HDL-cholesterol and the total cholesterol to HDL-cholesterol ratio as a discriminating marker of CVD risk[7]. In comparison, there is relatively little evidence that raising low serum HDL cholesterol decreases CVD risk. There is increasing evidence to suggest that the measurement of the amount of cholesterol in HDL may be inadequate as a biomarker of CVD risk[8]. HDL is a vehicle for the extracellular transport of cholesterol from peripheral tissues to the liver, a process known as reverse cholesterol transport. While difficult to measure directly in vivo, this process can be assessed as the capacity of HDL taken from participants, ex-vivo, to perform efflux of radiolabelled cholesterol from cultured cells.

The study by Brassard *et al*[6], is a secondary analysis of a randomly controlled intervention trial[9] that confirmed earlier reports that equivalent amounts of SFA from cheese had a lesser effect in elevating serum LDL-cholesterol than butter[10,11]. This was attributed to a food matrix effect of cheese that was proposed to reduce the absorption of SFA in the gut, and thus its capacity to raise LDL cholesterol. This so-called 'cheese-matrix' effect may originate from a combination of factors, involving the composition of fat, protein or calcium in cheese, and/or its effects upon the microbiome and fermentation in the gut[5]. The first paper on this study, examined four test diets, each of 4 weeks, in a total of 92 abdominally obese men and women, in a randomly controlled cross-over design[9]. Two of the diets were rich in SFA (12.4-12.6%E) from butter and cheese, while the other diets replaced SFA (5.8%E) with either monounsaturated fat from olive oil or polyunsaturated fat from corn oil. The test diets were compared with a low fat (5.8%E SFA, 25%E total fat) high carbohydrate (59%E) control. In the present study[6], the principal outcome was HDL-mediated cholesterol efflux capacity (CEC), as measured by the capacity of apo B free serum from 46 participants to remove radiolabelled cholesterol (3H-cholesterol) from J774 macrophages cultured under basal conditions. A secondary outcome included the distribution of serum HDL subclasses known to be involved in cholesterol efflux, and thus informative with respect to CEC.

The butter and MUFA-rich diets increased CEC relative to cheese (4.3% and 4.7%, respectively). The effects of butter were significant in men (+6%), but not women, and for MUFA, significant in women, but not men. The differential effects of butter and cheese diets on the distribution of serum HDL subclasses were complex, but interpreted to be consistent with CEC being attenuated on the cheese relative to butter diet. Contrary to the findings in the first paper of this study[9], the relative increase in serum LDL cholesterol in butter versus cheese diets did not reach statistical significance in this secondary analysis, presumably because of the smaller subgroup of participants. The relative effects of butter over cheese on CEC are concluded to arise from the higher circulating LDL or oxysterols derived from LDL. This possibility is further supported by a significant correlation between the change in serum LDL-cholesterol in men, but not women.

These findings provide new evidence to show that increased HDL-cholesterol, but more critically increased HDL-mediated CEC, induced by SFA in butter, may arise as compensation for the increase in LDL-cholesterol. Whether this compensation exerts an overall benefit on CVD risk is unknown, and may ultimately depend on the extent to which it counteracts the adverse impact of butter in raising LDL-cholesterol. In contrast, the significant increase in HDL-mediated CEC in women after the MUFA-rich diet could be interpreted as being of greater benefit in reducing CVD risk, since this diet lowered serum LDL cholesterol relative to butter and cheese. Another interesting aspect of this study is whether the men and women had any characteristics that could explain why they were more responsive to SFA in butter and MUFA, respectively. This raises the important question; does the extent of compensation vary between different individuals, and if so, what are the determinants of this variability?

This study of Brassard *et al*[6], provides new insight into the extent of the cheese-matrix effect on HDL function, further highlighting the importance of the nature of SFA-rich foods in the management of CVD risk. The adverse effect of SFA in butter in raising serum LDL-cholesterol is well established. Whether increased HDL-mediated CEC compensates for this effect in any way is unclear, and will require confirmation in large human intervention studies with this, and other measures of HDL function.

References

1. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:398-406.
2. Hooper L, Martin N, Abdelhamid A. Cochrane corner: what are the effects of reducing saturated fat intake on cardiovascular disease and mortality? Heart. 2015;101:1938-40.
3. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, at al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459-72.
4. Micha R, Mozaffarian D.Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. Lipids. 2010;45:893-905.
5. Hjerpsted J, Tholstrup T. Cheese and Cardiovascular Disease Risk: A Review of the Evidence and Discussion of Possible Mechanisms. Crit Rev Food Sci Nutr. 2016;56:1389-403.
6. Brassard d, Arsenault BJ, Boyer M, Bernic D, Tessier-Greier M, Tolbot D, Tremblay A, Levy E, Asztalos B, Jones PJH et al. Saturated fats from butter but not from cheese increase HLS-mediated cholesterol efflux capacity from J774 macrophages in men and women with abdominal obesity. J. Nutr. 2018. (in press)

7. Castelli WP1, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. Ann Epidemiol. 1992;2:23-8.
8. Arsenault BJ, Despres JP, HDL-cholesterol is not HLD – don't judge the book by its cover. NAT. Rev. Cardiol.2012;9:557-8.
9. Brassard D, Tessier-Grenier M, Allaire J, Rajendiran E, She Y, Ramprasath V, Gigleux I, Talbot D, Levy E, Tremblay A, Jones PJ, Couture P, Lamarche B. 809.Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. Am J Clin Nutr. 2017;105:800-809.
10. Hjerpsted J, Leedo E, Tholstrup T. Cheese intake in large amounts lowers LDL-cholesterol concentrations compared with butter intake of equal fat content. Am J Clin Nutr. 2011;94:1479-84.
11. Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. Eur J Clin Nutr. 2005;59:1059-63.

Declarations of interest.

BAG has no declarations of interest. JAL is an expert on the Government Scientific Advisory Committee for Nutrition (SACN), UK and the Saturated Fat Working Group for SACN.