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Re: "Effects of Short-Term Hypothyroidism on the Lipid Transfer to High-Density Lipoprotein and Other Parameters Related to Lipoprotein Metabolism in Patients Submitted to Thyroidectomy for Thyroid Cancer" by Sigal et al. (Thyroid 2019;29:53-58)

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Re: “Effects of Short-Term Hypothyroidism
on the Lipid Transfer to High-Density Lipoprotein
and Other Parameters Related to Lipoprotein
Metabolism in Patients Submitted to Thyroidectomy
for Thyroid Cancer” by Sigal *et al.*
(*Thyroid* 2019;29:53–58)

Robin P.F. Dullaart

Dear Editor:

The profound effects of hypothyroidism on lipoprotein metabolism have been known for decades. Such effects include high-density lipoprotein (HDL) cholesterol elevations, as confirmed in the recent study by Sigal *et al.* (1). Given the well-established inverse association of HDL cholesterol concentrations with atherosclerotic cardiovascular disease, there is continued interest in discerning the mechanisms that contribute to changes in HDL that occur during hypothyroidism. Among other pathways, the cholesteryl ester transfer protein (CETP)-mediated transfer of cholesteryl esters from HDL to apolipoprotein B-containing (triglyceride-rich) lipoproteins provides a key regulatory step in HDL metabolism. High HDL cholesterol levels are observed in genetic *CETP* deficiency, whereas HDL cholesterol increases consequent to pharmacological *CETP* inhibition (2). As appreciated by Sigal *et al.*, several previous studies have demonstrated that hypothyroidism may decrease plasma cholesteryl ester transfer (*CETP*) mass or activity, measured either as the transfer of radiolabeled cholesteryl esters from endogenous HDL toward apolipoprotein B-containing (triglyceride-rich) lipoproteins (referred to in the study by Sigal *et al.*) (1), or as the transfer/exchange of radiolabeled cholesteryl esters between exogenously added low density lipoproteins and HDL (3), the latter type of assay reflecting the plasma level of active *CETP* independent from the endogenous plasma lipoproteins (3). In general, these earlier findings are consistent with an effect of low thyroid hormone status to impair the *CETP*-mediated cholesteryl ester transfer process, thereby conceivably contributing to an increase in HDL cholesterol.

The assay system used in the study by Sigal *et al.* (1) is based on the transfer of radiolabeled cholesteryl esters, unesterified cholesterol, triglycerides, and phospholipids

from an artificial nanoparticle lipid emulsion to endogenous plasma HDL (4). With this assay system as a readout, they observed no effect of hypothyroidism on the accumulation of cholesteryl esters and other lipids in HDL (1). Notably, after adjustment for HDL cholesterol, as a crude measure of HDL mass, the transfer of cholesteryl esters, unesterified cholesterol, triglycerides, and phospholipids from the lipid emulsion to HDL were all attenuated in hypothyroidism (1). However, this assay system does not allow the specific contributions of *CETP*, lecithin:cholesterol acyltransferase (*LCAT*), and phospholipid transfer protein to the accumulation in the HDL fraction of the various radiolabeled lipids tested to be appropriately appreciated. Obviously, the lack of effect of hypothyroidism on cholesteryl ester transport from the lipid emulsion to HDL, as now reported by Sigal *et al.*, does not explain why HDL cholesterol is increased in hypothyroidism. Moreover, Sigal *et al.* did not observe changes in *CETP* and *LCAT* mass or changes in HDL size and lipid composition during hypothyroidism (1), the latter finding contrasting with our earlier observations (3).

Taken together, we question the utility of the nanoparticle lipid emulsion assay system, as employed in the report by Sigal *et al.* (1), to interrogate specific abnormalities in key regulatory pathways involving HDL metabolism in the hypothyroid state. We propose to discern further the effect of thyroid dysfunction on metrics of HDL function, including its ability to promote cellular cholesterol efflux and its anti-inflammatory capacity, in order to understand better the role of HDL in hypothyroidism-associated atherosclerosis development.

References

1. Sigal GA, Tavoni T, Silva B, Kalil Filho R, Brandão LG, Maranhão RC 2019 Effects of short-term hypothyroidism

- on the lipid transfer to high-density lipoprotein and other parameters related to lipoprotein metabolism in patients submitted to thyroidectomy for thyroid cancer. *Thyroid* **29**:53–58.
2. Dullaart RP, Sluiter WJ 2008 Common variation in the CETP gene and the implications for cardiovascular disease and its treatment: an updated analysis. *Pharmacogenomics* **9**: 747–763.
 3. Dullaart RP, Hoogenberg K, Groener JE, Dikkeschei LD, Erkelens DW, Doorenbos H 1990 The activity of cholesteryl ester transfer protein is decreased in hypothyroidism: a possible contribution to alterations in high-density lipoproteins. *Eur J Clin Invest* **20**:581–587.
 4. Lo Prete AC, Dina CH, Azevedo CH, Puk CG, Lopes NH, Hueb WA, Maranhão RC 2009 *In vitro* simultaneous transfer

of lipids to HDL in coronary artery disease and in statin treatment. *Lipids* **44**:917–924.

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Response to Dullaart re: “Effects of Short-Term Hypothyroidism on the Lipid Transfer to High-Density Lipoprotein and Other Parameters Related to Lipoprotein Metabolism in Patients Submitted to Thyroidectomy for Thyroid Cancer”

Gilbert A. Sigal, Thauany M. Tavoni, Bruna M.O. Silva, Roberto Kalil Filho, Lenine G. Brandão, and Raul C. Maranhão

Dear Editor:

We are pleased to have received the comments of Dr. Dullaart (1) who illustrates the difficulties of sorting out the multifaceted functions of high-density lipoprotein (HDL) and how they relate to atherogenesis and other pathophysiologic processes, and the design and interpretation of functional tests for HDL (2). In this respect, lipid transfers among lipoprotein classes play a crucial role in HDL formation and remodeling, and are determinants of HDL lipid composition and of the content of >80 proteins present in HDL fraction. In this respect, subjects with cholesteryl ester transfer protein deficiency show important proteomic changes in the HDL fraction (3). The HDL fraction, which contains the majority of lecithin-cholesterol acyltransferase (LCAT) and apo A-I, the LCAT cofactor, is the main system responsible for cholesterol esterification, a process that is essential for cholesterol stabilization in the plasma and that creates driving gradients of reverse cholesterol transport. In this setting, the entry of cholesterol into HDL from the other lipoprotein classes to undergo esterification is of great importance for cholesterol homeostasis. These considerations were the chief

motivations for the development of an *in vitro* assay in our laboratory, which determines the simultaneous transfer of the esterified and unesterified cholesterol forms, triglycerides and phospholipids to HDL to approach the dynamics of lipid transfers in the plasma. This is a practical and reproducible method, which can eventually undergo automatization for the clinical laboratory (4).

In previous studies, we showed in patients with coronary artery disease (CAD) that a lower entry of unesterified cholesterol and esterified cholesterol into the HDL fraction is an independent CAD predictor (5). In subsequent studies, harmful life-style habits and diseases (sedentary life style, bedridden subjects, familial hypercholesterolemia, heart transplantation, and metabolic syndrome) were associated with lower transfer of cholesterol to HDL patients. Because lipid transfers are bidirectional and in the current assay only the HDL entry but not the HDL exit of the four lipids is measured, decreased or increased transfer of a given lipid to HDL is not necessarily accompanied by changes in the lipid composition of HDL as occurred in our recent study.

The four lipid transfers are not only defined by the action of the transfer proteins and the enzymes acting on plasma lipid

metabolism but also by the number particles and composition of the other lipoprotein classes that compete with HDL to receive lipids, and there are probably other still unknown mechanisms at play. As emphasized by Dr. Dullaart, these intervening factors are not individually characterized in the *in vitro* assay, which deals with the resultant fluxes from all these variables.

Dr. Dullaart suggests that in hypothyroidism, tests such as the cholesterol efflux from cells and a measurement of the HDL anti-inflammatory capacity (6) should be performed. In fact, Jung *et al.* (7) found that the cholesterol efflux was diminished in hypothyroidism but did not improve after hormone substitution. To our knowledge, HDL anti-inflammatory assays have not been reported in hypothyroid patients, and we agree that this would be an important piece of information in this field.

In conclusion, in our study, there was a trend for diminished transfer of lipids in hypothyroidism that was corrected by the increase in the recipient HDL fraction; HDL-cholesterol elevation in those patients occurred through apparently unrelated mechanisms. Those findings suggest alterations in the complex process of lipid exchanges among lipoproteins, but the importance of these alterations to overall cholesterol homeostasis under thyroid hormone deficiency is indeed difficult to characterize.

References

1. Dullaart RPF 2019 Re: "Effects of short-term hypothyroidism on the lipid transfer to high-density lipoprotein and other parameters related to lipoprotein metabolism in patients submitted to thyroidectomy for thyroid cancer" by Sigal *et al.* (Thyroid 2019;29:53–58). Thyroid **29**:1027–1028.
2. deGoma EM, deGoma RL, Rader DJ 2008 Beyond high-density lipoprotein cholesterol levels evaluating high-density lipoprotein function as influenced by novel therapeutic approaches. J Am Coll Cardiol **51**:2199–2211.
3. Okada T, Ohama T, Takafuji K, Kanno K, Matsuda H, Sairyo M, Zhu Y, Saga A, Kobayashi T, Masuda D, Koseki M, Nishida M, Sakata Y, Yamashita S 2019 Shotgun proteomic analysis reveals proteome alterations in HDL of patients with cholesteryl ester transfer protein deficiency. J Clin Lipidol **13**:317–325.
4. Lo Prete AC, Dina CH, Azevedo CH, Puk CG, Lopes NH, Hueb WA, Maranhão RC 2009 In vitro simultaneous transfer of lipids to HDL in coronary artery disease and in statin treatment. Lipids **44**:917–924.
5. Maranhão RC, Freitas FR 2014 HDL metabolism and atheroprotection: predictive value of lipid transfers. Adv Clin Chem **65**:1–41.
6. Dullaart RP, Annema W, Tio RA, Tietge UJ 2014 The HDL anti-inflammatory function is impaired in myocardial infarction and may predict new cardiac events independent of HDL cholesterol. Clin Chim Acta **433**:34–38.
7. Jung KY, Hahn HY, Han SK, Park YJ, Cho BY, Moon MK 2017 Association between thyroid function and lipid profiles, apolipoproteins, and high-density lipoprotein function. J Clin Lipidol **11**:1347–1353.

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