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Review Article

Are measurements of non-cholesterol sterols in plasma useful in identifying susceptibility to atherosclerosis?

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Abstract

This review discusses the validity of plasma non-cholesterol sterols precursors of cholesterol synthesis and phytosterols in the identification of human atherosclerosis. There is an insufficient demonstration that these sterols are valid methods of measurement of cholesterol metabolism. All markers, including cholestanol, that derive from cholesterol synthesis may only reflect body retention of sterols and not necessarily increased intestinal absorption. Also, in most studies, conventional risk factors of atherosclerosis, such as obesity, diabetes mellitus, gender, and age were not taken into account.

Introduction

In recent years reviews related plasma non-cholesterol sterols as markers of atherosclerosis [1,2]. However, the role of these markers in atherosclerosis may be hampered by the interference of two factors, namely, doubts that these markers adequately identify alterations in cholesterol metabolism and the frequent exclusion in most studies of the interference of conventional risk factors on atherosclerosis. In one review on Cardiovascular Disease [CVD] risk, sitosterol and campesterol a generally increase or don't vary in different metabolic disorders, however, data were not corrected for the interference of the conventional multiple independent risk factors for CVD [2]. This was also the case in another review where cholesterol synthesis and intestinal absorption, in general, vary reciprocally as expected [3]. These two points are addressed in the present review.

Discussion

Validity of non-cholesterol sterols as markers of cholesterol metabolism

Since the early 1980s publications by TA Miettinen have presented plasma non-cholesterol sterol precursors of cholesterol as markers of cholesterol synthesis and phytosterols as intestinal cholesterol absorption markers [4-6]. Most papers correctly express the sterol results by plasma cholesterol concentration since non-cholesterol sterol values are dependent on the serum lipoprotein concentrations [7]. For this reason, the present review excluded investigations expressing sterol values exclusively by plasma volume [8-12] whose indiscriminate use has previously been criticized [1]. Therefore, this review analyzed only studies employing plasma sterol data properly corrected for plasma cholesterol.

Plasma phytosterols have been employed as markers of

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intestinal cholesterol absorption but their validity needs to be proven. One investigation supports their validity where the efficiency of intestinal cholesterol absorption is not related to apoE-LP phenotypes, but, as expected, plasma campesterol correlated with cholesterol absorption measured isotopically [13]. Although the study included normal controls and hyperlipidemia cases, similar plasma phytosterol correlations were disclosed in both groups [13]. Nonetheless, objection to the plasma phytosterol measurement as a method to measure cholesterol absorption was raised by the work of L Jakulj, et al [14], showing that in two groups that differed according to plasma campesterol concentrations the percent of dietary cholesterol absorbed did not differ when values were measured by combining labeled cholesterol administration with fecal sterol balance which is the gold standard procedure of intestinal cholesterol absorption measurement. Nonetheless, in their work, serum concentrations of campesterol and lathosterol varied reciprocally in the two groups as expected. Furthermore, their work improperly identified the absorption percentage with the total quantity of cholesterol absorbed. It follows from their completely different plasma lathosterol values in the two groups that substantially diverse amounts of endogenous cholesterol are excreted in bile and into the lumen of the intestine. Research has shown that the flow of cholesterol in bile is also modified when the amount of dietary cholesterol absorbed varies [6,15]. Because the marker of cholesterol synthesis [lathosterol] is 66% higher in the low campesterol as compared to the high campesterol group it is concluded that a greater mass of biliary cholesterol diminishes the absorption of dietary cholesterol and phytosterols present in the lumen of the intestine. Thus, the 25% dietary cholesterol absorption in both groups shown by L. Jakulj denotes very different total quantities of cholesterol absorbed, namely, the alimentary and biliary sources considered together as previously demonstrated [15,16]. In this sense, the work of L. Jakulk was critically evaluated by S. M Grundy [17] concluding that isotopic measurements of cholesterol absorption fail to quantify the amount absorbed due to the influence of biliary cholesterol secretion. Furthermore, their results might be biased by the interference of other factors in their cases such as a higher BMI in the low plasma campesterol group explaining greater cholesterol synthesis [6,14], and also increased plasma cholestanol likely derived from cholesterol synthesis [14].

Lathosterol, along with other markers, such as lanosterol and squalene, effectively measures cholesterol synthesis by the hepatic enzyme HMGCoA reductase activity that mirrors the simultaneously measured fecal cholesterol utilizing the balance technique [18]. Support for this conclusion on lathosterol is afforded by the gold standard fecal balance procedure utilizing labeled cholesterol [6,19]. Also, according to research on humans treated with drugs that modify cholesterol metabolism, the activity of the hepatic enzyme HMGCoA reductase agrees with the results drawn from the sterol precursors of cholesterol synthesis such as squalene, lanosterol, and lathosterol [18]. In a male population, cholesterol synthesis measured by the fecal sterol balance technique correlates with plasma concentrations of desmosterol and lathosterol [20]. Plasma lathosterol increases because it measures the synthesis rate of cholesterol that simultaneously rises when the intestinal absorption of cholesterol is blocked by dietary plant sterols [21-23], sitostanol-supplemented margarine [24], or ezetimibe [25]. Furthermore, as expected, drugs tailored to reduce cholesterol synthesis, such as statins, diminish the concentrations of cholesterol precursors in plasma [25,26]. According to several publications, plasma phytosterols vary inversely with non-cholesterol sterol precursor concentrations representing cholesterol synthesis, such as lathosterol [2,6,14,19,27-34]. This is due to the increased intake of phytosterols lowering plasma cholesterol by blocking the intestinal absorption of cholesterol thus raising the body's cholesterol synthesis rate, a situation in which under no circumstance plasma phytosterol measurements represent increased absorption of cholesterol. In conclusion, in plasma increased phytosterols may mirror decreased absorption of cholesterol from food. Furthermore, decreased plasma phytosterol signifies decreased absorption of alimentary phytosterols and cholesterol, but does not identify the total amount of cholesterol absorbed from the intestinal lumen.

Plasma cholestanol: A marker of increased intestinal cholesterol absorption or body cholesterol retention?

Cholestanol has been considered a marker of intestinal cholesterol absorption because often cholestanol behaves similarly to the phytosterols campesterol and sitosterol utilized as cholesterol absorption markers [6,14,30,31,35-37]. In another investigation, also utilizing oral administration of isotopic cholesterol in fecal cholesterol balance, a correlation of cholesterol absorption was found with plasma cholestanol in controls and postmenopausal women, and with sitosterol and campesterol in postmenopausal women alone although the percent cholesterol absorption was similar in both groups [37]. However, considering that cholestanol is a metabolite of cholesterol, these results could be attributed to the body's sterol retention which is indistinguishable from the amount of sterol absorbed from the gut. Retention means difficulty in excreting any sterols and not necessarily increased intestinal cholesterol uptake efficiency [38]. A typical demonstration of the existence of retention mistakenly called increased absorption was demonstrated in a case of sitosterolemia a genetic disorder in which the sitosterol metabolic defect was largely corrected by liver transplantation [39]. Consequently, sitosterolemia cannot be attributed to a defect in the intestinal absorption of phytosterols but to an impediment in their bodily excretion via bile. Also, retention of sterols in the body due to difficulty in fecal excretion of sterols has long been reported in other conditions such as familial hypercholesterolemia [40] and secondary hyperlipidemias such as in experimental nephrotic syndrome [41,42].

In the presence of retention, the finding in plasma of decreased values of precursors of cholesterol synthesis suggests that the latter would have been even lower if the retention process had not taken place. This metabolic problem is exemplified in sitosterolemia, a genetic disease in which the sterol retention process typically occurs [43-48]. Accordingly, the simultaneously elevated plasma concentrations of plant

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sterols and cholestanol together with cholesterol, serve to demonstrate that blockage in their biliary excretion [38,42-48] may also combine with increased cholestanol synthesis [45]. In fact, in the genetic disease sitosterolemia, there is an increase in plasma cholestanol concentration [49] and in its synthesis by a different metabolic pathway than the regular one that occurs through the production of 7α-hydroxycholesterol [49].

Blockade of re-excretion of the alimentary cholesterol in bile as a major mechanism of plasma sterol elevation has been demonstrated in genetically hypercholesterolemic mice on a cholesterol-free diet [50] and when mice are subjected to a phytosterol-rich diet [22]. Furthermore, a higher intake of phytosterols may hinder the reabsorption of cholestanol excreted in the bile resulting in a lower plasma concentration of the latter [51]. Consequently, cholestanol may vary in the plasma due to changes in its synthesis, intestinal absorption, and excretion by bile, making it difficult to interpret its variation in plasma as a marker of intestinal absorption of cholesterol. In this regard, the presence of cholestanol in plasma was only assessed in mice and was attributed to a combination of excretion in the bile and efflux from the intestinal mucosa back into the lumen [39].

Plasma sterol measurements in the evaluation of atherosclerosis show conflicting results

Conflicting interpretations of the populational data can occur due to bias attributed to the interference of several factors such as age, gender, dietary patterns, as well as clinical conditions like diabetes, hyperlipidemia of genetic origin, obesity, metabolic syndrome, hypertension, and smoking that are independently associated with atherosclerosis [52-58]. All these factors interfere with concentration markers of synthesis or absorption of cholesterol, and often with both types of markers simultaneously. In type 2 diabetes mellitus sitosterol, campesterol, and cholestanol are increased together with synthesis markers [2]. In the latter review synthesis and absorption markers, as would be expected, differed from each other but were not corrected for BMI as required [59] on which they typically depend [60]. In type 1 diabetes mellitus sitosterol, campesterol and cholestanol are not modified, whereas desmosterol is not modified and lathosterol is either not modified or diminishes [2]. Therefore, utilizing these sterols' non-cholesterol synthesis precursors as proper methods of cholesterol synthesis measurement to identify disturbances of cholesterol metabolism in human pathologies deserves to be analyzed in all publications dealing with CVD. This becomes clear when analyzing the results of seventeen publications on the subject summarized in Table [30,31,33,35,37,61-72]. Independent risk factors that may have influenced cholesterol metabolism were not reported in only one paper [65], adjustments were duly included in another regarding age, BMI, and plasma glucose [62] and adjustments for several conventional CV risk factors were done only in six reports [30,33,37,61,62,72]. Curiously, in one of them [33] CAD cases had elevated squalene, campesterol, sitosterol, and desmosterol, but lower lathosterol which is contradictory. Data on these sterols were similar in controls and the CAD cases investigated [71]. In another study, the results of synthesis markers were discrepant: CAD-positive cases presented low desmosterol and high lathosterol levels although both are markers of cholesterol synthesis [70].

The problem becomes even more confusing with the demonstration that fecal excretion of endogenous cholesterol, an indication of cholesterol synthesis is negatively associated with carotid atherosclerosis [73]. However, this study includes a high proportion of cases treated with statins and other medications that interfere with lipoprotein metabolism.

In conclusion, in all other investigations, the results of non-cholesterol sterol markers in plasma could have been influenced by one or more conventional independent risk factors of coronary heart disease. Furthermore, variable results were obtained regarding the synthesis and absorption markers, thus questioning the validity of their usefulness in atherosclerosis. Accordingly, synthesis markers were increased in four studies [33,37,62,67], diminished in five [31,64,69,70.72], not altered in seven [30,41,61-63,69,71], not reported in three [66-68] and incongruous in three [37,62,70]. Absorption markers were increased in atherosclerosis in nine investigations [31,33,35,37,61,64,67,69,72], diminished in three [30,63,68], not altered in five [62,66,69-71] and not reported in one [65], but incongruities did not occur.

It was possible to trust the results of plasma sterols as related to atherosclerosis only in eight publications because corrections for the various conventional risk factors were provided [30,33,35,37,61,62,67,72], even though synthesis markers in plasma have been validated, nevertheless, it was not possible to conclude on studies where synthesis markers did not vary [30,35,61,63,69,71] Table 1.

Conclusion

At present, measurements of these sterols in plasma do not reliably portray the degree of human atherosclerosis. Future investigations need to provide corrections for conventional cardiovascular risk factors hoping that systematically consistent results will emerge to validate plasma sterols as markers of atherosclerosis. Furthermore, the validity of the markers can be deduced provided that the role of their retention in plasma is accounted for which is currently not feasible due to the lack of adequate methods.

Future directions

This review suggests that the presence of simultaneous plasma elevations of cholestanol, a product of cholesterol synthesis, and phytosterols may indicate an increase in sterol retention elicited by some conventional risk factors for atherosclerosis or drug action that need to be clarified in future experiments.

Author contributions

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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Table 1: Atherosclerosis is not properly identified by measurements of plasma phytosterols and non-cholesterol sterols precursors of cholesterol synthesis due to the influence of conventional cardiovascular risk factors not taken into account by several authors. The investigations shown were grouped into those showing respectively increased [31,33,35,37,61, 64,67,69,72,74], decreased [30,63,65,68], and lack of information [62,66,67,69-71] regarding plasma sterol markers of intestinal cholesterol absorption.

Investigation Study [Reference]	Atherosclerosis	Plasma sterol markers	Independent influencing factors that may hinder the results	Summary of synthesis markers	Summary of absorption markers
Postmenopausal women [332]	CAD		Several adjustments for CAD risk factors provided	↑	↑
The LURIC and YFS investigation [31,64]	All-cause and CVD mortality.	High absorption and low synthesis of cholesterol	As lathosterol increases, age and LDL-C diminish. BMI, waist, glucose, insulin, and triglycerides increase.	↓	↑
The LURIC Investigation and Young Finns Study Cohort [64]	CHD	Cholestanol increased with CHD, but not campesterol and sitosterol. Lathosterol did not vary.	Not influenced by independent risk factors	⟷	↑ cholestanol
Framingham Offspring Study cases [35]	Established CVD and carotid stenosis	higher campesterol, sitosterol, and cholestanol markers and lower desmosterol and lathosterol	Although matched for age and BMI, diabetes frequency was higher in men's and women's causes	⟷	↑ all
Postmenopausal women in Finland [37]	CAD	Correlations with absorption found by isotopic cholesterol	All cases adjusted for several risk factors	↑desmosterol ↓lathosterol	↑
Cardiovascular Risk in Young Finns Study [61]	Increased mortality	Synthesis markers not modified. Serum cholesterol correlated with campesterol	Data corrected for multiple risk factors including metabolic syndrome	⟷	↑
Japanese population [69]	CAD	Enhanced absorption and reduced synthesis of cholesterol [higher campesterol/lathosterol ratio]	A higher proportion of the male gender, frequency of DM, and metabolic syndrome. Cases were older.	↓	↑
With vs without CVD [72]	Presence of vascular disease	CVD cases: lathosterol decreased and campesterol increased	Matched for conventional risk factors for CV disease	↓	↑
Brazilian Longitudinal Study of Adult Health [ELSA] [74]	CAC = zero *vs*. CAC > zero	CAC > zero= higher desmosterol, lathosterol, campesterol, and sitosterol. Low HDL-C cases have higher desmosterol.	CAC > zero were older and BMI and cholesterol were higher. Low HDL-C cases have higher BMI and waist circumference, but lower age.	↑	↑
Brazilian UNICAMP [study in healthy volunteers] [67]	Carotid IMT	Lower lathosterol/campesterol ratio but not the individual marker values.	Carotid plaque cases: older, higher blood pressure, glucose, LDL-C, triglycerides, and hs-CRP values. Desmosterol correlated with plasma TG. Lathosterol correlated with BMI	?	?
A prospective study of men in Finland [30]	Mortality in general in 22y follow-up	High serum sitosterol predicts lower long-term mortality	Multivariate analysis performed	⟷	↓
Spanish EPIC Cohort [63]	CHD	Lathosterol and sitosterol differ between groups	Cases are heavier, hyperlipidemic, and have greater diabetes frequency	⟷	↓
EPIC-Norfolk Population Study [68]	CAD	Sitosterol/cholesterol is lower in cases than in controls. Higher levels of plasma PS are not adversely related to CAD in healthy individuals.	Cases are heavier and diabetes frequency higher.		↓
Prospective Cohort Study in Germany [65]	CV events, CV mortality, and all-cause mortality	Related to low lathosterol alone	Independent factors not informed	↓	
Framingham Offspring Study cases [62]	CHD	However, sterol markers of absorption were not predictive	Correction of the markers was provided for age, BMI, and plasma glucose.	↑ squalene desmosterol and lathosterol	⟷
Dallas Heart Study [66]	CAC + *vs*. CAC -	Sitosterol and campesterol did not differ and did not correlate with atherosclerosis	Campesterol was inversely related to fasting blood glucose and insulin.		⟷
Coronary intervention during statin therapy [69]	Non-CAD *vs*. CAD cases	In cases not treated with statins, lathosterol and campesterol do not differ between non-CAD and CAD cases.	CAD + includes a higher proportion of the male gender cases that were older, and the frequencies of DM and metabolic syndrome were higher.	⟷	⟷
Pittsburgh Epidemiology of Diabetes Complications Study [70]	CAD in type 1 diabetes mellitus	Phytosterols did not differ, but in control cases, desmosterol was higher and lathosterol lower	Age, cases with hypertension, waist/hip ratio, and medication differed between groups.	↑ desmosterol ↓ lathosterol	⟷
PROSPER Trial [71]	CHD + *vs*. CHD –	[before Pravastatin treatment]	Age, BMI, vascular disease hypertension, diabetes, and smoking were similar in both groups.	⟷	⟷

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Data availability statement

Data sharing is not applicable to this review because no new data were presented or analyzed in this study.

References

1. Quintão ECR. Plasma Non-cholesterol Sterols as Markers of Cholesterol Synthesis and Intestinal Absorption: A Critical Review. Curr Pharm Des. 2020;26(40):5152-5162. doi: 10.2174/1381612826666200730220230. PMID: 32744960.

2. Mashnafi S, Plat J, Mensink RP, Baumgartner S. Non-Cholesterol Sterol Concentrations as Biomarkers for Cholesterol Absorption and Synthesis in Different Metabolic Disorders: A Systematic Review. Nutrients. 2019 Jan 9;11(1):124. doi: 10.3390/nu11010124. PMID: 30634478; PMCID: PMC6356200.

3. Lupattelli G, De Vuono S, Mannarino E. Patterns of cholesterol metabolism: pathophysiological and therapeutic implications for dyslipidemias and the metabolic syndrome. Nutr Metab Cardiovasc Dis. 2011 Sep;21(9):620-7. doi: 10.1016/j.numecd.2011.04.010. Epub 2011 Aug 19. PMID: 21855307.

4. Miettinen TA, Tilvis R. Comparison of different components in the fractional conversion of mevalonate to cholesterol with cholesterol synthesis and serum methyl sterols. Scand J Clin Lab Invest. 1981 Sep;41(5):507-12. doi: 10.3109/00365518109090490. PMID: 7313530.

5. Miettinen TA, Gylling H, Strandberg T, Sarna S. Baseline serum cholestanol as predictor of recurrent coronary events in subgroup of Scandinavian simvastatin survival study. Finnish 4S Investigators. BMJ. 1998 Apr 11;316(7138):1127-30. doi: 10.1136/bmj.316.7138.1127. PMID: 9552949; PMCID: PMC28514.

6. Gylling H, Miettinen TA. Inheritance of cholesterol metabolism of probands with high or low cholesterol absorption. J Lipid Res. 2002 Sep;43(9):1472-6. doi: 10.1194/jlr.m200155-jlr200. PMID: 12235179.

7. Kuksis A. Plasma non-cholesterol sterols. J Chromatogr A. 2001 Nov 23;935(1-2):203-36. doi: 10.1016/s0021-9673(01)01226-2. PMID: 11762775.

8. Gelzo M, Di Taranto MD, Sica C, Boscia A, Papagni F, Fortunato G, Corso G, Dello Russo A. Age-related changes of cholestanol and lathosterol plasma concentrations: an explorative study. Lipids Health Dis. 2019 Dec 30;18(1):235. doi: 10.1186/s12944-019-1176-3. PMID: 31888647; PMCID: PMC6937658.

9. Baila-Rueda L, Lamiquiz-Moneo I, Jarauta E, Mateo-Gallego R, Perez-Calahorra S, Marco-Benedí V, Bea AM, Cenarro A, Civeira F. Association between non-cholesterol sterol concentrations and Achilles tendon thickness in patients with genetic familial hypercholesterolemia. J Transl Med. 2018 Jan 15;16(1):6. doi: 10.1186/s12967-018-1380-3. PMID: 29334954; PMCID: PMC5769342.

10. Windler E, Zyriax BC, Kuipers F, Linseisen J, Boeing H. Association of plasma phytosterol concentrations with incident coronary heart disease Data from the CORA study, a case-control study of coronary artery disease in women. Atherosclerosis. 2009 Mar;203(1):284-90. doi: 10.1016/j.atherosclerosis.2008.06.014. Epub 2008 Jun 26. PMID: 18656878.

11. Sonoda M, Sakamoto K, Miyauchi T, Sanada J, Nakamura K, Arima T, Kuriyama M, Nagata K, Osame M, Miyahara K. Risk factors in normolipidemic male patients with coronary artery disease in Japanese. Jpn Circ J. 1992 Aug;56(8):829-36. doi: 10.1253/jcj.56.829. PMID: 1527895.

12. Yoshida H, Tada H, Ito K, Kishimoto Y, Yanai H, Okamura T, Ikewaki K, Inagaki K, Shoji T, Bujo H, Miida T, Yoshida M, Kuzuya M, Yamashita S. Reference Intervals of Serum Non-Cholesterol Sterols by Gender in Healthy Japanese Individuals. J Atheroscler Thromb. 2020 May 1;27(5):409-417. doi: 10.5551/jat.50187. Epub 2019 Sep 5. PMID: 31484845; PMCID: PMC7242229.

13. Von Bergmann K, Lütjohann D, Lindenthal B, Steinmetz A. Efficiency of intestinal cholesterol absorption in humans is not related to apoE phenotype. J Lipid Res. 2003 Jan;44(1):193-7. doi: 10.1194/jlr.m200319-jlr200. PMID: 12518038.

14. Jakulj L, Mohammed H, van Dijk TH, Boer T, Turner S, Groen AK, Vissers MN, Stroes ES. Plasma plant sterols serve as poor markers of cholesterol absorption in man. J Lipid Res. 2013 Apr;54(4):1144-50. doi: 10.1194/jlr.P031021. Epub 2012 Nov 25. PMID: 23178226; PMCID: PMC3605990.

15. Quintão E, Grundy SM, Ahrens EH Jr. Effects of dietary cholesterol on the regulation of total body cholesterol in man. J Lipid Res. 1971 Mar;12(2):233-47. PMID: 5108133.

16. Connor WE, Lin DS. The intestinal absorption of dietary cholesterol by hypercholesterolemic (type II) and normocholesterolemic humans. J Clin Invest. 1974 Apr;53(4):1062-70. doi: 10.1172/JCI107643. PMID: 4815075; PMCID: PMC333091.

17. Grundy SM. Plasma noncholesterol sterols as indicators of cholesterol absorption. J Lipid Res. 2013 Apr;54(4):873-5. doi: 10.1194/jlr.E036806. Epub 2013 Feb 12. PMID: 23402986; PMCID: PMC3605993.

18. Björkhem I, Miettinen T, Reihnér E, Ewerth S, Angelin B, Einarsson K. Correlation between serum levels of some cholesterol precursors and activity of HMG-CoA reductase in human liver. J Lipid Res. 1987 Oct;28(10):1137-43. PMID: 3681138.

19. Kempen HJ, Glatz JF, Gevers Leuven JA, van der Voort HA, Katan MB. Serum lathosterol concentration is an indicator of whole-body cholesterol synthesis in humans. J Lipid Res. 1988 Sep;29(9):1149-55. PMID: 3183524.

20. Miettinen TA, Tilvis RS, Kesäniemi YA. Serum plant sterols and cholesterol precursors reflect cholesterol absorption and synthesis in volunteers of a randomly selected male population. Am J Epidemiol. 1990 Jan;131(1):20-31. doi: 10.1093/oxfordjournals.aje.a115479. PMID: 2293749.

21. Nunes VS, Ilha AOG, Ferreira GDS, Bombo RPA, Afonso MS, Lavrador MSF, Machado RM, Nakandakare ER, Quintão ECR, Lottenberg AM. Plasma lathosterol measures rates of cholesterol synthesis and efficiency of dietary phytosterols in reducing the plasma cholesterol concentration. Clinics (Sao Paulo). 2022 Apr 6;77:100028. doi: 10.1016/j.clinsp.2022.100028. PMID: 35397367; PMCID: PMC8989763.

22. Nunes VS, da Silva EJ, Ferreira GDS, de Assis SIS, Cazita PM, Nakandakare ER, Zago VHS, de Faria EC, Quintão ECR. The Plasma Distribution of Non-cholesterol Sterol Precursors and Products of Cholesterol Synthesis and Phytosterols Depend on HDL Concentration. Front Nutr. 2022 Mar 1;9:723555. doi: 10.3389/fnut.2022.723555. PMID: 35299760; PMCID: PMC8921769.

23. Nunes VS, Cazita PM, Catanozi S, Nakandakare ER, Quintão ECR. Phytosterol containing diet increases plasma and whole body concentration of phytosterols in apoE-KO but not in LDLR-KO mice. J Bioenerg Biomembr. 2019 Apr;51(2):131-136. doi: 10.1007/s10863-019-09786-8. Epub 2019 Feb 9. PMID: 30739226.

24. Thuluva SC, Igel M, Giesa U, Lütjohann D, Sudhop T, von Bergmann K. Ratio of lathosterol to campesterol in serum predicts the cholesterol-lowering effect of sitostanol-supplemented margarine. Int J Clin Pharmacol Ther. 2005 Jul;43(7):305-10. doi: 10.5414/cpp43305. PMID: 16035372.

25. Wu AH. Biomarkers for cholesterol absorption and synthesis in hyperlipidemic patients: role for therapeutic selection. Clin Lab Med. 2014 Mar;34(1):157-66, viii. doi: 10.1016/j.cll.2013.11.010. PMID: 24507794.

26. Jakulj L, Vissers MN, Groen AK, Hutten BA, Lutjohann D, Veltri EP, Kastelein JJ. Baseline cholesterol absorption and the response to ezetimibe/simvastatin therapy: a post-hoc analysis of the ENHANCE trial. J Lipid Res. 2010 Apr;51(4):755-62. doi: 10.1194/jlr.M001487. Epub 2009 Oct 14. PMID: 19828909; PMCID: PMC2842149.

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27. Noto D, Cefalù AB, Barraco G, Fayer F, Minà M, Yue P, Tarugi P, Schonfeld G, Averna MR. Plasma non-cholesterol sterols in primary hypobetalipoproteinemia. Atherosclerosis. 2011 Jun;216(2):409-13. doi: 10.1016/j.atherosclerosis.2010.10.050. Epub 2011 Feb 1. PMID: 21492858.

28. García-Otín AL, Cofán M, Junyent M, Recalde D, Cenarro A, Pocoví M, Ros E, Civeira F. Increased intestinal cholesterol absorption in autosomal dominant hypercholesterolemia and no mutations in the low-density lipoprotein receptor or apolipoprotein B genes. J Clin Endocrinol Metab. 2007 Sep;92(9):3667-73. doi: 10.1210/jc.2006-2567. Epub 2007 Jun 12. PMID: 17566095.

29. van Himbergen TM, Otokozawa S, Matthan NR, Schaefer EJ, Buchsbaum A, Ai M, van Tits LJ, de Graaf J, Stalenhoef AF. Familial combined hyperlipidemia is associated with alterations in the cholesterol synthesis pathway. Arterioscler Thromb Vasc Biol. 2010 Jan;30(1):113-20. doi: 10.1161/ATVBAHA.109.196550. Epub 2009 Oct 15. PMID: 19834104; PMCID: PMC2813691.

30. Strandberg TE, Gylling H, Tilvis RS, Miettinen TA. Serum plant and other noncholesterol sterols, cholesterol metabolism and 22-year mortality among middle-aged men. Atherosclerosis. 2010 May;210(1):282-7. doi: 10.1016/j.atherosclerosis.2009.11.007. Epub 2009 Nov 13. PMID: 19962145.

31. Silbernagel G, Fauler G, Hoffmann MM, Lütjohann D, Winkelmann BR, Boehm BO, März W. The associations of cholesterol metabolism and plasma plant sterols with all-cause and cardiovascular mortality. J Lipid Res. 2010 Aug;51(8):2384-93. doi: 10.1194/jlr.P002899. Epub 2010 Mar 14. PMID: 20228406; PMCID: PMC2903788.

32. Lupattelli G, Pirro M, Siepi D, Mannarino MR, Roscini AR, Vaudo G, Pasqualini L, Schillaci G, Mannarino E. Non-cholesterol sterols in different forms of primary hyperlipemias. Nutr Metab Cardiovasc Dis. 2012 Mar;22(3):231-6. doi: 10.1016/j.numecd.2010.05.010. Epub 2010 Aug 13. PMID: 20708389.

33. Rajaratnam RA, Gylling H, Miettinen TA. Independent association of serum squalene and noncholesterol sterols with coronary artery disease in postmenopausal women. J Am Coll Cardiol. 2000 Apr;35(5):1185-91. doi: 10.1016/s0735-1097(00)00527-1. PMID: 10758959.

34. Krawczyk M, Lütjohann D, Schirin-Sokhan R, Villarroel L, Nervi F, Pimentel F, Lammert F, Miquel JF. Phytosterol and cholesterol precursor levels indicate increased cholesterol excretion and biosynthesis in gallstone disease. Hepatology. 2012 May;55(5):1507-17. doi: 10.1002/hep.25563. Epub 2012 Apr 4. PMID: 22213168.

35. Matthan NR, Pencina M, LaRocque JM, Jacques PF, D'Agostino RB, Schaefer EJ, Lichtenstein AH. Alterations in cholesterol absorption/synthesis markers characterize Framingham offspring study participants with CHD. J Lipid Res. 2009 Sep;50(9):1927-35. doi: 10.1194/jlr.P900039-JLR200. Epub 2009 May 12. PMID: 19436064; PMCID: PMC2724787.

36. Baila-Rueda L, Pérez-Ruiz MR, Jarauta E, Tejedor MT, Mateo-Gallego R, Lamiquiz-Moneo I, de Castro-Orós I, Cenarro A, Civeira F. Cosegregation of serum cholesterol with cholesterol intestinal absorption markers in families with primary hypercholesterolemia without mutations in LDLR, APOB, PCSK9 and APOE genes. Atherosclerosis. 2016 Mar;246:202-7. doi: 10.1016/j.atherosclerosis.2016.01.005. Epub 2016 Jan 6. PMID: 26802983.

37. Gylling H, Hallikainen M, Rajaratnam RA, Simonen P, Pihlajamäki J, Laakso M, Miettinen TA. The metabolism of plant sterols is disturbed in postmenopausal women with coronary artery disease. Metabolism. 2009 Mar;58(3):401-7. doi: 10.1016/j.metabol.2008.10.015. PMID: 19217458.

38. Igel M, Giesa U, Lutjohann D, von Bergmann K. Comparison of the intestinal uptake of cholesterol, plant sterols, and stanols in mice. J Lipid Res. 2003 Mar;44(3):533-8. doi: 10.1194/jlr.M200393-JLR200. Epub 2002 Dec 16. PMID: 12562824.

39. Miettinen TA, Klett EL, Gylling H, Isoniemi H, Patel SB. Liver transplantation in a patient with sitosterolemia and cirrhosis. Gastroenterology. 2006 Feb;130(2):542-7. doi: 10.1053/j.gastro.2005.10.022. PMID: 16472606; PMCID: PMC1391914.

40. Quintão EC, Sperotto G. The role of dietary cholesterol in the regulation of human body cholesterol metabolism. Adv Lipid Res. 1987;22:173-88. doi: 10.1016/b978-0-12-024922-0.50009-6. PMID: 3328489.

41. Goldberg AC, Eliaschewitz FG, Quintão EC. Origin of hypercholesterolemia in chronic experimental nephrotic syndrome. Kidney Int. 1977 Jul;12(1):23-7. doi: 10.1038/ki.1977.75. PMID: 894913.

42. Goldberg AC, Oliveira HC, Quintão EC, McNamara DJ. Increased hepatitic cholesterol production due to liver hypertrophy in rat experimental nephrosis. Biochim Biophys Acta. 1982 Jan 15;710(1):71-5. doi: 10.1016/0005-2760(82)90191-6. PMID: 7055597.

43. Bhattacharyya AK, Connor WE, Lin DS, McMurry MM, Shulman RS. Sluggish sitosterol turnover and hepatic failure to excrete sitosterol into bile cause expansion of body pool of sitosterol in patients with sitosterolemia and xanthomatosis. Arterioscler Thromb. 1991 Sep-Oct;11(5):1287-94. doi: 10.1161/01.atv.11.5.1287. PMID: 1911714.

44. Salen G, Shore V, Tint GS, Forte T, Shefer S, Horak I, Horak E, Dayal B, Nguyen L, Batta AK, et al. Increased sitosterol absorption, decreased removal, and expanded body pools compensate for reduced cholesterol synthesis in sitosterolemia with xanthomatosis. J Lipid Res. 1989 Sep;30(9):1319-30. PMID: 2600539.

45. Salen G, Kwiterovich PO Jr, Shefer S, Tint GS, Horak I, Shore V, Dayal B, Horak E. Increased plasma cholestanol and 5 alpha-saturated plant sterol derivatives in subjects with sitosterolemia and xanthomatosis. J Lipid Res. 1985 Feb;26(2):203-9. PMID: 3989379.

46. Patel SB, Salen G, Hidaka H, Kwiterovich PO, Stalenhoef AF, Miettinen TA, Grundy SM, Lee MH, Rubenstein JS, Polymeropoulos MH, Brownstein MJ. Mapping a gene involved in regulating dietary cholesterol absorption. The sitosterolemia locus is found at chromosome 2p21. J Clin Invest. 1998 Sep 1;102(5):1041-4. doi: 10.1172/JCI3963. PMID: 9727073; PMCID: PMC508970.

47. Klett EL, Lu K, Kosters A, Vink E, Lee MH, Altenburg M, Shefer S, Batta AK, Yu H, Chen J, Klein R, Looije N, Oude-Elferink R, Groen AK, Maeda N, Salen G, Patel SB. A mouse model of sitosterolemia: absence of Abcg8/sterolin-2 results in failure to secrete biliary cholesterol. BMC Med. 2004 Mar 24;2:5. doi: 10.1186/1741-7015-2-5. PMID: 15040800; PMCID: PMC394351.

48. Salen G, Patel S, Batta AK. Sitosterolemia. Cardiovasc Drug Rev. 2002 Winter;20(4):255-70. doi: 10.1111/j.1527-3466.2002.tb00096.x. PMID: 12481199.

49. Salen G, Batta AK, Tint GS, Shefer S, Ness GC. Inverse relationship between plasma cholestanol concentrations and bile acid synthesis in sitosterolemia. J Lipid Res. 1994 Oct;35(10):1878-87. PMID: 7852865.

50. Nunes VS, Cazita PM, Catanozi S, Nakandakare ER, Quintão ECR. Cholesterol metabolism in mice models of genetic hypercholesterolemia. J Physiol Biochem. 2020 Aug;76(3):437-443. doi: 10.1007/s13105-020-00753-1. Epub 2020 Jun 17. PMID: 32557226.

51. Lin X, Racette SB, Ma L, Wallendorf M, Spearie CA, Ostlund RE Jr. Plasma biomarker of dietary phytosterol intake. PLoS One. 2015 Feb 10;10(2):e0116912. doi: 10.1371/journal.pone.0116912. PMID: 25668184; PMCID: PMC4323197.

52. Shoda J, Miyamoto J, Kano M, Ikegami T, Matsuzaki Y, Tanaka N, Osuga T, Miyazaki H. Simultaneous determination of plasma mevalonate and 7alpha-hydroxy-4-cholesten-3-one levels in hyperlipoproteinemia: convenient indices for estimating hepatic defects of cholesterol and bile acid syntheses and biliary cholesterol supersaturation. Hepatology. 1997 Jan;25(1):18-26. doi: 10.1053/jhep.1997.v25.pm0008985259. PMID: 8985259.

53. Baila-Rueda L, Mateo-Gallego R, Pérez-Calahorra S, Lamiquiz-Moneo I, de Castro-Orós I, Cenarro A, Civeira F. Effect of different fat-enriched meats on non-cholesterol sterols and oxysterols as markers of cholesterol metabolism: Results of a randomized and cross-over clinical trial. Nutr Metab Cardiovasc Dis. 2015 Sep;25(9):853-859. doi: 10.1016/j.numecd.2015.06.008. Epub 2015 Jun 23. PMID: 26232911.

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54. Cofán M, Escurriol V, García-Otín AL, Moreno-Iribas C, Larrañaga N, Sánchez MJ, Tormo MJ, Redondo ML, González CA, Corella D, Pocoví M, Civeira F, Ros E. Association of plasma markers of cholesterol homeostasis with metabolic syndrome components. A cross-sectional study. Nutr Metab Cardiovasc Dis. 2011 Sep;21(9):651-7. doi: 10.1016/j.numecd.2010.01.005. Epub 2010 May 31. PMID: 20554170.

55. Weingärtner O, Weingärtner N, Scheller B, Lütjohann D, Gräber S, Schäfers HJ, Böhm M, Laufs U. Alterations in cholesterol homeostasis are associated with coronary heart disease in patients with aortic stenosis. Coron Artery Dis. 2009 Sep;20(6):376-82. doi: 10.1097/MCA.0b013e32832fa947. PMID: 19620855.

56. Assmann G, Cullen P, Erbey J, Ramey DR, Kannenberg F, Schulte H. Plasma sitosterol elevations are associated with an increased incidence of coronary events in men: results of a nested case-control analysis of the Prospective Cardiovascular Münster (PROCAM) study. Nutr Metab Cardiovasc Dis. 2006 Jan;16(1):13-21. doi: 10.1016/j.numecd.2005.04.001. Epub 2005 Jul 28. PMID: 16399487.

57. Nunes VS, Leança CC, Panzoldo NB, Parra E, Cazita PM, Nakandakare ER, de Faria EC, Quintão EC. HDL-C concentration is related to markers of absorption and of cholesterol synthesis: Study in subjects with low vs. high HDL-C. Clin Chim Acta. 2011 Jan 14;412(1-2):176-80. doi: 10.1016/j.cca.2010.09.039. Epub 2010 Oct 7. PMID: 20932966.

58. Leança CC, Nunes VS, Panzoldo NB, Zago VS, Parra ES, Cazita PM, Jauhiainen M, Passarelli M, Nakandakare ER, de Faria EC, Quintão EC. Metabolism of plasma cholesterol and lipoprotein parameters are related to a higher degree of insulin sensitivity in high HDL-C healthy normal weight subjects. Cardiovasc Diabetol. 2013 Nov 22;12:173. doi: 10.1186/1475-2840-12-173. PMID: 24267726; PMCID: PMC4222276.

59. Simonen P, Gylling H, Miettinen TA. The validity of serum squalene and non-cholesterol sterols as surrogate markers of cholesterol synthesis and absorption in type 2 diabetes. Atherosclerosis. 2008 Apr;197(2):883-8. doi: 10.1016/j.atherosclerosis.2007.08.003. Epub 2007 Sep 17. PMID: 17875306.

60. Simonen PP, Gylling H, Miettinen TA. The distribution of squalene and non-cholesterol sterols in lipoproteins in type 2 diabetes. Atherosclerosis. 2007 Sep;194(1):222-9. doi: 10.1016/j.atherosclerosis.2006.07.030. Epub 2006 Sep 11. PMID: 16963050.

61. Miettinen TA, Gylling H, Hallikainen M, Juonala M, Räsänen L, Viikari J, Raitakari OT. Relation of non-cholesterol sterols to coronary risk factors and carotid intima-media thickness: the Cardiovascular Risk in Young Finns Study. Atherosclerosis. 2010 Apr;209(2):592-7. doi: 10.1016/j.atherosclerosis.2009.10.013. Epub 2009 Oct 20. PMID: 19963215.

62. Matthan NR, Zhu L, Pencina M, D'Agostino RB, Schaefer EJ, Lichtenstein AH. Sex-specific differences in the predictive value of cholesterol homeostasis markers and 10-year cardiovascular disease event rate in Framingham Offspring Study participants. J Am Heart Assoc. 2013 Feb 19;2(1):e005066. doi: 10.1161/JAHA.112.005066. PMID: 23525441; PMCID: PMC3603247.

63. Escurriol V, Cofán M, Moreno-Iribas C, Larrañaga N, Martínez C, Navarro C, Rodríguez L, González CA, Corella D, Ros E. Phytosterol plasma concentrations and coronary heart disease in the prospective Spanish EPIC cohort. J Lipid Res. 2010 Mar;51(3):618-24. doi: 10.1194/jlr.P000471. Epub 2009 Sep 28. PMID: 19786566; PMCID: PMC2817591.

64. Silbernagel G, Chapman MJ, Genser B, Kleber ME, Fauler G, Scharnagl H, Grammer TB, Boehm BO, Mäkelä KM, Kähönen M, Carmena R, Rietzschel ER, Bruckert E, Deanfield JE, Miettinen TA, Raitakari OT, Lehtimäki T, März W. High intestinal cholesterol absorption is associated with cardiovascular disease and risk alleles in ABCG8 and ABO: evidence from the LURIC and YFS cohorts and from a meta-analysis. J Am Coll Cardiol. 2013 Jul 23;62(4):291-9. doi: 10.1016/j.jacc.2013.01.100. Epub 2013 May 22. PMID: 23707316.

65. Weingärtner O, Lütjohann D, Meyer S, Fuhrmann A, Cremers B, Seiler-Mußler S, Schött HF, Kerksiek A, Friedrichs S, Ulbricht U, Zawada A, Laufs U, Schulze PC, Scheller B, Fliser D, Böhm M, Sijbrands E, Heine GH. Low serum lathosterol levels associate with fatal cardiovascular disease and excess all-cause mortality: a prospective cohort study. Clin Res Cardiol. 2019 Dec;108(12):1381-1385. doi: 10.1007/s00392-019-01474-2. Epub 2019 Apr 4. PMID: 30949753.

66. Wilund KR, Yu L, Xu F, Vega GL, Grundy SM, Cohen JC, Hobbs HH. No association between plasma levels of plant sterols and atherosclerosis in mice and men. Arterioscler Thromb Vasc Biol. 2004 Dec;24(12):2326-32. doi: 10.1161/01.ATV.0000149140.00499.92. Epub 2004 Oct 28. PMID: 15514206.

67. Nunes VS, de Campos EVS, Baracat J, França V, Gomes ÉIL, Coelho RP, Nakandakare ER, Zago VHS, de Faria EC, Quintão ECR. Plasma Campesterol Is Positively Associated with Carotid Plaques in Asymptomatic Subjects. Int J Mol Sci. 2022 Oct 9;23(19):11997. doi: 10.3390/ijms231911997. PMID: 36233298; PMCID: PMC9569444.

68. Pinedo S, Vissers MN, von Bergmann K, Elharchaoui K, Lütjohann D, Luben R, Wareham NJ, Kastelein JJ, Khaw KT, Boekholdt SM. Plasma levels of plant sterols and the risk of coronary artery disease: the prospective EPIC-Norfolk Population Study. J Lipid Res. 2007 Jan;48(1):139-44. doi: 10.1194/jlr.M600371-JLR200. Epub 2006 Oct 30. PMID: 17074925.

69. Nasu K, Terashima M, Habara M, Ko E, Ito T, Yokota D, Ishizuka S, Kurita T, Kimura M, Kinoshita Y, Asakura Y, Tsuchikane E, Katoh O, Suzuki T. Impact of cholesterol metabolism on coronary plaque vulnerability of target vessels: a combined analysis of virtual histology intravascular ultrasound and optical coherence tomography. JACC Cardiovasc Interv. 2013 Jul;6(7):746-55. doi: 10.1016/j.jcin.2013.02.018. Epub 2013 Jun 14. PMID: 23769651.

70. Shay CM, Evans RW, Orchard TJ. Do plant sterol concentrations correlate with coronary artery disease in type 1 diabetes? A report from the Pittsburgh Epidemiology of Diabetes Complications Study. J Diabetes. 2009 Jun;1(2):112-7. doi: 10.1111/j.1753-0407.2009.00012.x. PMID: 20827426; PMCID: PMC2933944.

71. Matthan NR, Resteghini N, Robertson M, Ford I, Shepherd J, Packard C, Buckley BM, Jukema JW, Lichtenstein AH, Schaefer EJ; PROSPER Group. Cholesterol absorption and synthesis markers in individuals with and without a CHD event during pravastatin therapy: insights from the PROSPER trial. J Lipid Res. 2010 Jan;51(1):202-9. doi: 10.1194/jlr.M900032-JLR200. PMID: 19578163; PMCID: PMC2789780.

72. Weingärtner O, Lütjohann D, Vanmierlo T, Müller S, Günther L, Herrmann W, Böhm M, Laufs U, Herrmann M. Markers of enhanced cholesterol absorption are a strong predictor for cardiovascular diseases in patients without diabetes mellitus. Chem Phys Lipids. 2011 Sep;164(6):451-6. doi: 10.1016/j.chemphyslip.2011.03.008. Epub 2011 Apr 8. PMID: 21501602.

73. Lin X, Racette SB, Ma L, Wallendorf M, Dávila-Román VG, Ostlund RE Jr. Endogenous Cholesterol Excretion Is Negatively Associated With Carotid Intima-Media Thickness in Humans. Arterioscler Thromb Vasc Biol. 2017 Dec;37(12):2364-2369. doi: 10.1161/ATVBAHA.117.310081. Epub 2017 Oct 5. PMID: 28982667; PMCID: PMC5699927.

74. Nunes VS, Bensenor IM, Lotufo PA, Passarelli M, Nakandakare ER, Quintão ECR. The coronary artery calcium score is linked to plasma cholesterol synthesis and absorption markers: Brazilian Longitudinal Study of Adult Health. Biosci Rep. 2020 Jul 31;40(7):BSR20201094. doi: 10.1042/BSR20201094. PMID: 32579186; PMCID: PMC7332684.

Citation: Rocha Quintão EC (2023) Are measurements of non-cholesterol sterols in plasma useful in identifying susceptibility to atherosclerosis? Arch Prev Med 8(1): 001-007. DOI: https://dx.doi.org/10.17352/apm.000031