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REVIEW

The role of serum non-cholesterol sterols as surrogate markers of absolute cholesterol synthesis and absorption

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Squalene

Abstract *Aims:* To study the whole-body cholesterol metabolism in man, cholesterol synthesis and absorption need to be measured. Because of the complicated methods of the measurements, new approaches were developed including the analysis of serum non-cholesterol sterols. In current lipidologic papers and even in intervention studies, serum non-cholesterol sterols are frequently used as surrogate markers of cholesterol metabolism without any validation to the absolute metabolic variables. The present review compares serum non-cholesterol sterols with absolute measurements of cholesterol synthesis and absorption in published papers to find out whether the serum markers are valid indicators of cholesterol metabolism in various conditions.
Data synthesis: During statin treatment, during interventions of dietary fat, and in type 2 diabetes the relative and absolute variables of cholesterol synthesis and absorption were frequently but not constantly correlated with each other. In some occasions, especially in subjects with apolipoprotein E3/4 and E4/4 phenotypes, the relative metabolic markers were even more sensitive than the absolute ones to reflect changes in cholesterol metabolism during dietary interventions. Even in general population at very high absorption the homeostasis of cholesterol metabolism is disturbed damaging the validity of the serum markers.
Conclusions: It is worth using several instead of only one precursor and absorption sterol marker for making conclusions of altered synthesis or absorption of cholesterol, and even then the presence of at least some absolute measurement is valuable. During consumption of plant sterol-enriched diets and in situations of interfered cholesterol homeostasis the relative

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markers do not adequately reflect cholesterol metabolism. Accordingly, the validity of the relative markers of cholesterol metabolism should not be considered as self-evident.

Introduction

Absolute measurement of human cholesterol synthesis is time consuming and methodologically complicated requiring, e.g. sterol balance technique. The latter, which is the golden standard to measure cholesterol synthesis, requires the determinations of dietary intake and output of cholesterol. Cholesterol output is determined from fecal samples by analyzing neutral sterols of cholesterol origin and bile acids. Cholesterol synthesis is calculated by subtracting the output from the dietary intake of cholesterol. In most occasions, the value is negative indicating that the body synthesizes more cholesterol as compared to the dietary consumption. Thus, in a group of 63 fifty-year old men randomly selected from a general population, only one had high enough dietary cholesterol to result in positive sterol balance value [1]. Sterol balance technique requires steady-state cholesterol metabolism indicated by stable serum cholesterol level, stable dietary cholesterol intake, and stable sterol balance values. The latter can be obtained after a several-day food records and stool collections. For the latter one, unabsorbable intestinal marker is used to stabilize the fecal flow. Currently, sitostanol has been used for this purpose. Original measurement of cholesterol synthesis with the sterol balance technique was developed for almost 50 years ago [2,3]. However, even today, the same method is principally the only way to reliably measure absolute cholesterol synthesis.

The addition of absorption percent of dietary cholesterol to the data obtained with sterol balance technique increases markedly the information on cholesterol metabolism. The change of ^{14}C-cholesterol/^{H3}sitostanol ratio in stools vs ingested markers allows to calculate the percentage of dietary cholesterol absorption, which in general is considered to measure the overall percentage of cholesterol absorption (called absolute cholesterol absorption in the following). Currently, stable isotopes (D-cholesterol/D-sitostanol) with subsequent mass-spectrometric analysis have been used for this purpose [4,5]. The combination of cholesterol absorption and sterol balance data allows us to calculate several other variables of cholesterol metabolism, e.g. the absolute absorption of intestinal, dietary, biliary, or endogenous cholesterol.

Serum non-cholesterol sterols

Owing to the complicated methods of evaluating sterol balance and cholesterol absorption, new approaches have been developed using the measurement of serum non-cholesterol sterols. The initial determination of the cholesterol precursors with gas-liquid chromatography (GLC) suggested that they were related to cholesterol synthesis in normal situation as well as in many clinical conditions [6]. After further development of the GLC-methodology [7], additional determinations indicated that serum plant sterol [8] and cholestanol [9] levels, especially their ratios to serum cholesterol, were positively related to absolute cholesterol absorption in a random male population [10]. These papers concluded that the type of dietary fat, dietary plant sterols and absolute absorption, absolute synthesis, and biliary secretion of cholesterol are all significantly associated with the serum contents of non-cholesterol sterols, including cholesterol precursors, cholestanol, and plant sterols. Most current articles and reviews accept serum non-cholesterol sterols to reflect the absolute synthesis and absorption of cholesterol without any inclusion of absolute information on variables of cholesterol metabolism. The present paper compares the relative variables of cholesterol metabolism, the serum non-cholesterol sterols, with the absolute measurements of cholesterol metabolism to find out whether the serum markers are valid indicators of absolute cholesterol metabolism in various conditions.

Statin treatment

In a recent study [11], the serum synthesis markers as ratios to cholesterol were correlated with absolute cholesterol synthesis at baseline and on statin treatment in a small group of hypercholesterolemic patients. Serum cholestenol, desmosterol, and lathosterol were assayed as the synthesis markers and cholestanol, sitosterol, and campesterol as the absorption markers. At baseline, the synthesis sterol markers were positively related to absolute synthesis and negatively to absolute absorption of cholesterol, and the absorption sterol markers were positively related to absolute absorption and negatively to absolute synthesis of cholesterol, respectively. Serum lathosterol ratios to cholesterol, cholestanol, and sitosterol consistently correlated with the ratio of absolute cholesterol synthesis (mg/kg/d)/absolute cholesterol absorption (%) (r-range $+0.456$ to $+0.727$, $p < 0.05$ for each) at baseline and on statin treatment. Serum desmosterol ratios to cholesterol, cholestanol, and sitosterol correlated with absolute synthesis/absolute absorption of cholesterol on statin treatment in the whole study population. In addition, the correlation was significant also in poor responders characterized by a smaller change in lathosterol/cholestanol and LDL cholesterol level from baseline than in good responders.

Studying the regression equation between the cholestenol ratio to cholesterol and absolute synthesis/absorption of cholesterol in more detail, a decrease of the cholestenol to cholesterol ratio at baseline by 1 lowers cholesterol synthesis by 5.03 mg/d/kg for one % of absorption. As expected, the respective value after 16 weeks on statin treatment was smaller, viz 3.79. Even though the absorption marker sterols were interrelated, serum campesterol was not related to the absolute ratios of synthesis/absorption.