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Hyporesponders and Hyperresponders to Changes in Diet

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Summary

Evidence is presented that some human subjects may have a consistently low or high response of serum cholesterol to dietary cholesterol. Responsiveness to dietary cholesterol appears to be associated with responsiveness to dietary saturated fatty acids. On the average, hyperresponders have a higher habitual cholesterol intake, higher levels of HDL cholesterol and a lower body weight than hyporesponders. The mechanisms underlying hypo- and hyperresponsiveness to either dietary cholesterol or saturated fatty acids have not yet been revealed. A possible mechanism is discussed. The phenomenon of hyporesponsiveness and hyperresponsiveness may have implications for the counselling of subjects who attempt to lower their serum cholesterol by diet. However, identification of true hyporesponders and hyperresponders is greatly hampered by within-person fluctuations of the level of serum cholesterol. No simple test is available to discriminate hyporesponders from hyperresponders. As yet, monitoring a person's response to diet should be based on relatively large numbers of serum cholesterol determinations.

Hyporeaktivität und Hyperreaktivität gegenüber Diätänderungen

Es wird gezeigt, daß bei einigen Patienten ein ständiges hohes oder niedriges Ansprechen des Serumcholesterinspiegels auf mit der Nahrung zugeführtes Cholesterin besteht. Das Ansprechen auf zugeführtes Cholesterin scheint mit der Reagibilität auf mit der Nahrung aufgenommene gesättigte Fettsäuren in Zusammenhang zu stehen. Im Durchschnitt nehmen Hyperreaktive gewohnheitsmäßig mehr Cholesterin zu sich, weisen höhere HDL-Cholesterinspiegel auf und haben ein niedrigeres Körpergewicht als Hyporeaktive. Die Wirkungsmechanismen, die zu einer Hyporeaktivität bzw. Hyperreaktivität auf zugeführtes Cholesterin oder gesättigte Fettsäuren führen, sind noch ungeklärt. Ein möglicher Mechanismus wird diskutiert. Das Vorliegen einer entsprechenden Reaktivität kann sich auf die Ernährungsberatung auswirken (Herabsetzung des Serumcholesterinspiegels durch diätetische Maßnahmen). Da jedoch die Serumcholesterinspiegel zeitlich innerhalb einer und derselben Person stark schwanken können, ist es gar nicht so leicht, jemanden als Hypo- oder Hyperreaktiven zu identifizieren. Es gibt hierfür keinen einfachen Test. Wie bisher sollte die Überwachung des Ansprechens eines Patienten auf Diätformulierungen mittels relativ häufiger Serumcholesterinbestimmungen erfolgen.

Introduction

The level of serum cholesterol in man is sensitive to the type of fat and the amount of cholesterol in the diet. The quantitative effects of these dietary components can be predicted using empirical formulas (1–3). However, such predictions of serum cholesterol changes only hold good for group means and not for individual subjects. It has often been suggested that in certain individuals (hyporesponders) the level of serum cholesterol is relatively insensitive to dietary challenge whereas in others (hyperresponders) the effect of diet is much more pronounced.

The subject of hyporesponsiveness and hyperresponsiveness is of both practical and scientific interest. Patients with hypercholesterolaemia generally receive dietary advice from clinicians to lower their serum cholesterol levels. Frequently, such advice turns out to be ineffective. Although lack of compliance may be involved, it is possible that certain patients are insensitive to cholesterol-lowering diets and need a different form of therapy. It is assumed here that subjects who are hyporesponsive or hyperresponsive to cholesterol-lowering diets are likewise hyporesponsive or hyperresponsive to hypercholesterolaemic diets. From the scientific point of view elucidation of the mechanism underlying responsiveness may shed more light on the relations between dietary components and cholesterol metabolism.

Hyporesponders and Hyperresponders to Dietary Cholesterol

The existence of human hyporesponders and hyperresponders to dietary cholesterol has been frequently assumed (4, 5), but has proved very difficult to substantiate experimentally. A major problem in studies with humans in this area is that the response of serum cholesterol to dietary cholesterol is relatively small (6), and any particular measurement contains a large error term contributed by spontaneous, diet-independent fluctuations of serum cholesterol level (7, 8). If one is only interested in the mean effect of a certain diet factor on serum cholesterol in man then this within-subject variability is usually eliminated by measuring the average response to a dietary challenge in a group of 10 to 30 subjects. Such a number of subjects yields a reasonably precise estimate of the population mean response. However, if one demands the same precision in estimating the inherent responsiveness of one particular subject, then one theoretically needs to perform 10 to 30 response experiments with this individual, which is impracticable. As a result, serious attempts to estimate the extent of differences in responsiveness to dietary cholesterol between individuals have been rare, and where they have been made the results are highly imprecise.

In 1926 *Mjassnikow* (9), and in 1933 *Okey* and *Stewart* (10) reported that the mean serum cholesterol concentration of human subjects increased somewhat on cholesterol-sup-

Tab. 1 Changes in serum cholesterol levels in six human volunteers after daily consumption of six egg yolks for 10 days.

	Change in serum cholesterol (%)					
	Subject A	Subject B	Subject C	Subject D	Subject E	Subject F
Expt 1	+ 5	− 3	+ 17	+ 17	+ 27	+ 5
Expt 2	+ 16	+ 12	+ 26	+ 25	+ 4	+ 3

Twelve months elapsed between Expt 1 and Expt 2; the design was otherwise identical. The pre-experimental and experimental serum cholesterol values were both based on two blood samples obtained on successive days. After *Katan* and *Beynen* (12).

Tab. 2 Effect of egg-yolk cholesterol on serum cholesterol in three controlled trials with the same subjects.

	Change in serum cholesterol (mmol/l)	
	Hyporesponders	Hyperresponders
	(n = 15)	(n = 17)
Selection trial	− 0.01 ± 0.21	+ 0.96 ± 0.27
First reproducibility trial	+ 0.06 ± 0.35	+ 0.28 ± 0.38*
Second reproducibility trial	+ 0.47 ± 0.26	+ 0.82 ± 0.35**

Results are expressed as means ± SD. Change significantly different from that in the hyporesponders (one-tailed Stundent's t test): *, $P < 0.05$; **, $P < 0.005$. Based on *Katan* et al. (13).

plemented diets, but that there was a considerable variability in observed individual responses. A similar inter-individual variation in cholesterolaemic response was seen in most experimental studies that followed, and the concept of hyperresponders and hyporesponders to dietary cholesterol became widely accepted. However, in the numerous studies in which the effect of dietary cholesterol on serum cholesterol in humans was assessed (11), the response to the dietary challenge in a given subject was usually measured in one study only. The serum cholesterol concentration of one individual fluctuates with a coefficient of variation of 5 to 10% around his or her mean value (7, 8). These fluctuations are independent of the diet and are of the same order of magnitude as the usual response to dietary cholesterol loads, which even with extreme dietary loads rarely exceed 20% (6). As a result, individual responses cannot be measured precisely enough to allow classification of subjects as hyporesponsive or hyperresponsive. Table 1 illustrates this. Six volunteers first abstained from cholesterol-rich products for 10 days, and then took six egg yolks per day for another 10 days. The study was repeated with the same subjects one year later. The average response for the group was fairly similar from one experiment to another, but the "hyperresponders" in the first experiment were not necessarily hyperresponders in the second experiment, and neither were those initially classified as hyporesponders consistently unresponsive the second time. Similar experiments were performed already in 1942 by *Messinger* and coworkers (6). They fed patients a dietary supplement of 150 g of egg-yolk powder per day emulsified in milk, providing 3750 mg cholesterol. The experiment was repeated in four of these patients and the response was reproducible in only two of them. The patient who displayed the highest cholesterolaemic response in the first experiment showed the lowest response in the second experiment. These two studies illustrate that the variability in the response to dietary cholesterol observed in single short-term experiments by itself does not prove the existence of human hyperresponders and hyporesponders, because this variation could be largely explained by random within-person fluctuations in the level of serum cholesterol.

We carried out three controlled dietary trials with the same subjects to study the question whether individuals do exist with a consistently high or low serum cholesterol response to dietary cholesterol (13). In each trial the volunteers successively consumed a low-cholesterol and a high-cholesterol diet, the cholesterol component of the diets (provided by egg yolk) being the only variable. Subgroups of putative hyporesponders and hyperresponding subjects, with mean serum cholesterol increases of 0 and 19%, respectively, were selected from a larger population in a first trial and then underwent a second and a third experiment. Although the response in each subject was only partly reproducible, the selected hyperresponders showed significantly higher serum cholesterol responses in the second and third trial than the hyporesponders (Table 2). Standardised regression coefficients for individual responses in two experiments ranged from 0.34 to 0.53 (n = 32).

Under less controlled conditions we found similar results. In 1976 *Bronsgeest-Schoute* et al. (14) studied the serum cholesterol response to discontinuation of egg consumption in subjects who habitually consumed at least one egg/day. When eggs were eliminated from the diet, daily cholesterol intake decreased from about 800 mg to 300 mg. Mean serum cholesterol fell only slightly (by 3%), but the individual responses varied from −20% to +8%. In 1982, 34 of these subjects were re-investigated (15), and at our request they again eliminated eggs and egg-containing products from their diet. The differences in serum cholesterol response between individuals were partly reproducible; the individual responses in 1976 and 1982 were positively correlated ($r = 0.32$, $n = 34$, $P < 0.05$).

In the study on the reproducibility of the effect of cessation of egg consumption (15), the observed consistent response could theoretically be caused by the consistent, individually-determined replacement of eggs by either low-fat, low-cholesterol foods or by cheese or fat-rich meat. In order to exclude this possibility a follow-up study with controlled diets, differing in their cholesterol content only, was performed (16). Two subjects who were hyperresponsive in both 1976 and 1982 again showed a marked change in serum cholesterol in the study with controlled diets. Three out of the four putative hyporesponders who participated in the follow-up study showed the predicted lack of serum cholesterol response (16).

Thus it appears that at least part of the cholesterolaemic response to dietary cholesterol in man is individually determined. It is also clear that one will always find subjects who appear hyperresponsive in one experiment and hyporesponsive in another. This is caused by the diet-independent within-person variability of serum cholesterol. In our controlled

studies (13) we calculated that the within-person error variance was still responsible for about 25% of the apparent variance in response between subjects even if we used 12 independent blood samples to determine each person's response to dietary cholesterol. Thus it is probably fallacious to characterise a patient as hyperresponsive or hyporesponsive to diet therapy if this is based on the results of a few blood samples only. A large number of serum cholesterol measurements is needed before and after the dietary challenge, and even then the observed response should be interpreted with caution.

Hyporesponders and hyperresponders to saturated fatty acids

In man the nature of the fat in the diet is more important as a determinant of the serum cholesterol concentration than the amount of cholesterol. Thus it is relevant to know whether hyporesponders and hyperresponders to dietary fatty acid composition also exist, and whether hyperresponders to dietary cholesterol are also hyperresponsive to saturated fatty acids and other dietary components that affect serum cholesterol levels. Such information may also provide clues to the mechanisms underlying the inter-individual variation in the cholesterolaemic response to diet.

We studied the question whether human subjects hyporesponsive or hyperresponsive to dietary cholesterol are also hyporesponsive or hyperresponsive, respectively, to saturated fatty acids in the diet. Twenty three subjects who participated in the three controlled trials on the effect of dietary cholesterol (13) were also tested for their response to saturated versus polyunsaturated fatty acids. In this experiment cholesterol intake was kept constant at an average of 41 mg/MJ (almost 500 mg/day), but the energy percentage of dietary polyunsaturated fatty acids was kept at 21% for the first 3 weeks and then changed to 5% for the next 3 weeks; the polyunsaturated : saturated fatty acids ratios were 1.91 and 0.22, respectively. The response of serum cholesterol to the change in dietary fatty acid composition in this experiment was positively correlated with the mean response to dietary cholesterol in the three preceding experiments ($r = 0.50$; $n = 23$; $P < 0.05$). This indicates that in humans hyperresponsiveness to dietary cholesterol is associated with hyperresponsiveness to saturated fat.

Characteristics of hyporesponders and hyperresponders

The characteristics of hyporesponders and hyperresponders to dietary cholesterol are of interest for several reasons. First, knowledge of the hyperresponder profile may help in identifying beforehand which patients will benefit most from dietary therapy. Secondly, the characteristics of hyporesponders and hyperresponders may provide clues as to the metabolic basis not only for hyporesponsiveness and hyperresponsiveness, but also for the effects of diet on serum cholesterol levels in general.

In our controlled studies with low-cholesterol and high-cholesterol diets (13) we found no relation of responsiveness with age, sex, intestinal transit time, ratio of primary to secondary steroids in the faeces and within-subject variability of serum cholesterol while on a constant diet (17). Both serum total and HDL_2 cholesterol on the low- and high-cholesterol diets were positively associated with responsiveness to dietary cholesterol. It should be stressed that the values for serum total cholesterol and those for calculating the responsiveness variable were based on independent sets of measurements. Thus hyperresponders tended to have higher levels of serum total, but also of HDL_2 cholesterol concentrations than hyporesponders.

Body mass index, total body cholesterol synthesis (based on sterol balance data) and the habitual intake of cholesterol were negatively associated with the cholesterolaemic response to dietary cholesterol. Multivariate analysis was performed to take into account the correlations among the variables with predictive value. It then appeared that body mass index and body cholesterol synthesis did not longer contribute significantly to the explanation of variance in responsiveness (17).

In conclusion, our repeated controlled studies suggest that a low habitual cholesterol intake, a high serum HDL_2 cholesterol level, or a low body weight do not make one less susceptible to dietary-cholesterol-induced hypercholesterolaemia. The negative association of the response of serum cholesterol with body mass index and the positive association with HDL cholesterol were also seen in the other cohort discussed above, where the effect of cessation of egg consumption on serum cholesterol was studied in subjects who habitually consumed at least one egg/day (15). Similar associations were reported by *Oh* and *Miller* (18).

Underlying mechanisms

On the basis of literature data we proposed earlier that after cholesterol feeding hyporesponders suppress cholesterol synthesis more effectively than hyperresponders (19, 20). Thus in hyperresponders the increased amounts of ingested cholesterol are not compensated for, and eventually lead to an increase in serum cholesterol. At this moment we feel that individual differences in the efficiency of absorption of intestinal luminal cholesterol could be the primary determinant of the phenomenon of hyporesponsiveness and of hyperresponsiveness. This idea is based on animal studies with different species of monkeys. In three studies hyperresponsive monkeys absorbed a significantly higher percentage of dietary cholesterol than did hyporesponders (21–23).

Hyperresponsiveness to dietary cholesterol is associated with responsiveness to dietary saturated fatty acids, pointing to a common metabolic pathway. However, it is not yet possible to illustrate this in molecular terms. A possible chain of events is that a high efficiency of cholesterol absorption in the hyperresponders produces an increased influx of cholesterol into the liver. This results in a higher hepatic efflux of cholesterol in low density lipoprotein (LDL) or its precursors, after cholesterol consumption. About 90% of the increase in cholesterol found in serum after cholesterol feeding resides in LDL particles (24). A role for hepatic lipoprotein secretion in determining responsiveness can be derived by combining the results of the trial of *Ginsberg* et al. (25), in which the response to dietary cholesterol was minimal, with those of *Packard* et al. (24), who observed a large response of serum cholesterol to a dietary load. In the hyperresponders studied by *Packard* et al. (24), unlike the hyporesponders of *Ginsberg* et al. (25), there was a pronounced increase in LDL production after cholesterol feeding. The dietary cholesterol-induced enhancement of LDL synthesis in hyperresponders may involve direct synthesis of LDL or of intermediate density lipoproteins (IDL) by the liver. *Nestel* and *Billington* (26) have recently shown that in man cholesterol feeding caused an increase in IDL-apo B production, and that this increase was directly correlated with the rise in serum cholesterol. The stimulation of LDL production accounts for the increase in LDL cholesterol in serum.

The number of hepatic LDL receptors, which may be already decreased in hyperresponders (27), will decrease further through downregulation (28). The receptor-mediated LDL clearance decreases, but the absolute amount of LDL cholesterol taken up by the cells via the receptor and by the receptor-independent pathway increases because of the increased level of LDL cholesterol. In this way a new equilibrium is reached in which LDL production equals LDL catabolism.

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