INDIVIDUAL RESPONSIVENESS OF SERUM CHOLESTEROL TO DIETARY CHANGES

An apparent lack of response to a lipid-lowering diet can be caused by one or a combination of factors. The most significant are lack of patient compliance, analytical error, random fluctuations in serum cholesterol and a habitual diet already low in saturated fat and cholesterol. True hyporesponsiveness to dietary change is rare. It is important, therefore, to know how to determine when a response or lack of response is true.

By Anton C. Beynen, PhD, and Martijn B. Katan, PhD

Dietary treatment is necessary in the management of all forms of hyperlipidemia, either as the sole approach or in combination with drug therapy. The common lipid-lowering diet is similar to the diet recommended by authoritative bodies for general use by populations with high incidence of coronary artery disease. In overweight patients, such a diet is combined with restriction of energy intake until a target body weight is attained. Unfortunately, maintaining the weight loss can be extremely difficult. Rare forms of hypertriglyceridemia, particularly the chylomicronemia syndrome (Type I hyperlipoproteinemia) and severe familial hypertriglyceridemia (Type V) may require a different diet, characterized by very low fat content.

Frequently, the response of serum cholesterol to a lipid-lowering diet is disappointingly insignificant. Such an apparent lack of responsiveness to dietary change can be ascribed to either poor adherence, analytical error, diet-independent random fluctuations in serum cholesterol concentration, or individually-determined insensitivity to the lipid-lowering diet. In addition, the patient may already have been

DR. BEYVEN is Utrecht University Foundation Professor of Experimental Animal Nutrition, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands.

DR. KATAN is Associate Professor of Human Nutrition, Wageningen University, and Nutrition Foundation Professor, Nijmegen University School of Medicine, Nijmegen, The Netherlands.
Figure 1. How random fluctuations in serum cholesterol might be responsible for the appearance of hypo- and hyperresponders. The continuous lines in figures (a) and (b) represent hypothetical continuous recordings of serum cholesterol in patients participating in a dietary trial. Serum cholesterol is known to fluctuate within subjects with a periodicity of two to three days and an amplitude as indicated in the figure. The fictitious patients first receive a diet high in saturated fat and cholesterol, which produces a mean cholesterol level of 6.5 mmol/L (250 mg/dL) and then a cholesterol-lowering diet, which produces a mean level of serum cholesterol of 5.5 mmol/L (212 mg/dL). In (a), the timing of the actual blood samples (x) is such that the observed response appears much larger than the actual mean response of 1 mmol/L. In (b), the reverse is the case. These data are simulated, but they represent the actual variability of serum cholesterol levels and indicate how random errors may misrepresent the actual response to dietary modifications. Reproduced with permission from Katan, MB. Lipid Review 4:73, 1990.

following a lipid-lowering diet. This article will elaborate on these causes of hyporesponsiveness to lipid-lowering diets.

RANDOM ERRORS
Random errors may simulate a lack of responsiveness if the pretreatment value is erroneously low and/or the value obtained during treatment erroneously high. The reverse also may occur and can lead to unwarranted claims about the effectiveness of certain diets or nostrums. Errors can fall into two categories: those due to laboratory procedures and those due to natural fluctuations in the patient.

Analytical errors. Laboratory procedures and variations in blood sampling techniques introduce random errors. Even a single homogenous serum pool will yield a range of values if analyzed repeatedly. This variability has implications for the ability to monitor the effectiveness of cholesterol-lowering treatment in individual patients.

The extent of variability is usually reported in terms of the standard deviation (SD). The formula for calculating the SD is such that for a series of measurements, 66% of the values differ from the mean of the series by no more than one SD, and 95% differ from the mean by, at most, twice the SD. Careful standardization can reduce the random fluctuations within one laboratory down to a relative SD (i.e., the SD divided by the mean cholesterol concentration) of less than 0.7%. Clinical practice, however, lags behind these developments; in the United States, a typical relative SD is
3.5%. Of even more serious concern are the systematic differences (bias) between different laboratories. In one American survey, 5,000 laboratories produced values for a single serum pool that ranged from 4.7 mmol/L to 9.8 mmol/L, and this after arbitrary removal of the 107 most extreme values, which ran from 2.6 mmol/L to 13.5 mmol/L. The true value of the pool was 6.79 mmol/L.

It is useful to improve patient preparation and laboratory quality. Posture is important — if the patient has been standing before venepuncture at one occasion and lying down at the next, his cholesterol level will have fallen by an average of 10% simply through hemodilution. Acute infections can lead to large changes in cholesterol levels, and necessitate postponement of the measurement. Good laboratory practice and stringent quality control are of the utmost importance. Laboratories should provide data on their performance in blind external proficiency tests. Measures such as these may cut the SD by half.

**Random fluctuations.** Lack of awareness of diet-independent, within-person fluctuations of serum cholesterol concentrations can yield misleading results about the efficacy of a lipid-lowering therapy. The serum cholesterol concentration of one individual fluctuates with a coefficient of variation of 5% to 10% around his or her mean value (Figure 1). Because cholesterol levels vary, the differences between consecutive cholesterol measurements will also fluctuate.

If a patient is following a constant diet, differences between sequential cholesterol measurements will fluctuate around zero, with an SD equal to the square root of 2 multiplied by the SD of the cholesterol level. If the SD of the cholesterol level is 0.5 mmol/L (caused by a combination of within-patient and laboratory fluctuations), the SD of the difference between any two values will be 0.7 mmol/L and so will the SD of any change in level caused by therapy.

The apparent lack of responsiveness to dietary change can be ascribed to either poor adherence, analytical error, diet-independent random fluctuations in serum cholesterol concentration, or individually-determined insensitivity to the lipid-lowering diet.

If the number of cholesterol observations is increased to four before and four after the start of treatment, one can replace a difference between two casual samples by a difference between the means of two series of four and obtain a more reliable impression of the effect of treatment. The SD, however, decreases only with the square root of the number of observations. As a result, the SD of the difference will be 0.35 instead of 0.7 and any change in cholesterol will carry an uncertainty of $2 \times 0.35 = 0.7$ mmol/L; clearly still unacceptable if trying to pick up a change of 1.0 mmol/L. Hence, this proves the need for careful laboratory standardization, patient preparation and multiple blood sampling.

If multiple determinations are needed to characterize a patient’s serum cholesterol, at what intervals should the samples be obtained? In one study which obtained a number of blood samples in volunteers under semimeabolic ward conditions, the intra-individual SD increased as a function of the time between successive blood samples and reached a plateau after approximately four days. Thus, the range of cholesterol or high-density lipoprotein (HDL) values that exists within an individual was covered most efficiently by spacing measurements at least four days apart. Values obtained within 24 hours of each other were usually fairly similar: if one value was higher than the true average, the chances were that the other value would also be higher, and the average of the two would not be much closer to the true mean than either measurement separately. Therefore, multiple measurements should be spaced at least four days apart.

**DIETARY COMPLIANCE**

For the individual care of hyperlipidemic patients, dietary instruction is best provided by a professional dietician, whose skills are necessary to ensure the nutritional adequacy of the diet, to individualize the diet to the patient’s taste, energy needs and specific metabolic disorder, and to promote compliance. Access to trained dieticians is not
always possible, but nurses and other paramedics have also been employed successfully in helping maintain patient compliance. It may also be appropriate for general dietary guidelines to be provided by the physician, who should be able to offer qualitative advice to mildly hyperlipidemic patients. In this situation, the physician has an indispensable role in motivating the patient to comply with the diet and explaining the reasons for its use. Referral to a dietician becomes mandatory, however, if the adequate plasma lipid response is not observed.

Nutritional change is seldom attained in a single session of instruction. Several months should be allowed for adapting to the diet, which involves altering habits and preferences, cooking techniques and food purchasing. Some authorities on behavior modification advocate stepwise changes in eating pattern.

Figure 2. Relationship between the individual responses of serum cholesterol to a change in dietary cholesterol observed in two different experiments. In experiment 1, the volunteers successively consumed 10 mg and 55 mg of cholesterol/MJ; in experiment 3, these values were 15 mg/MJ and 85 mg/MJ. Reproduced with permission from Beynen, AC, Katan, MB, Van Zutphen, LFM. Ernährungs Umschau 32:356, 1985.
TRUE HYPO- AND HYPERRESPONSIVENESS

With a limited number of blood samples, individual responses to dietary change cannot be measured precisely enough to allow classification of true hypo- and hyperresponsiveness (Table). In one study, six volunteers first abstained from cholesterol-rich products for 10 days, 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 the other. However, the hyperresponders in the first experiment were not necessarily hyperresponders in the second experiment; in addition, those initially classified as hyporesponders were not consistently unresponsive in the second experiment.

All differences between individuals are not caused entirely by chance. In repeated trials it has been demonstrated that modest, stable differences in responsiveness of serum cholesterol to dietary cholesterol exist in humans (Figure 2). From these experiments it is also clear that there will always be subjects who appear to be hyperresponsive in one experiment and hyporesponsive in another.8-8

The wide scatter of responses seen in single experiments and in clinical settings is due largely to irreproducible chance fluctuations. After correction for intra-individual fluctuations of serum cholesterol, the true width of the responsiveness distribution on an increase in cholesterol intake from about 100 mg/day to 750 mg/day was found to be rather small. Assuming that the distribution is gaussian, then 16% of the subjects would have a cholesterolemic response of either less than half of the mean response or more than 150% of the mean. Only approximately 2% would show no increase at all.8 A lack of responsiveness to dietary change should be ascribed to poor adherence or to chance before the hyporesponse concept is invoked.

Response to saturated fatty acids. The question has been addressed whether human subjects who are hypo- or hyperresponsive to dietary cholesterol are also hypo- or hyperresponsive, respectively, to saturated fatty acids in their diet.9 Subjects who participated in controlled trials on the effect of dietary cholesterol were also tested for their response to saturated versus polyunsaturated fatty acids. 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 three weeks and then changed to 5% for the next three weeks. The polyunsaturated:saturated fatty acids ratios were 1.91 and 0.22, respectively. The increase in serum cholesterol with the increased intake of saturated fatty acids was positively correlated with the mean response to dietary cholesterol in 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.

CONCLUSION

Although true individual differences in susceptibility to dietary change undoubtedly exist, the wide range of responses observed in single trials and in clinical settings is largely an artifact caused by poor adherence and/or accumulation of random errors.

REFERENCES