

More on the Chinese red-yeast-rice supplement and its cholesterol-lowering effect

Dear Sir:

I follow with great interest the heated legal, ethical, and purely medical controversies surrounding the therapeutic value of fermented Chinese red yeast rice in cardiovascular diseases. Some of the debated issues are addressed by the authors of a recent publication in the Journal (1).

The study by Heber et al (1) indicates that very short-term supplementation of patients with hyperlipidemia with red yeast rice reduced total cholesterol, LDL-cholesterol, and total triacylglycerol concentrations modestly. Unfortunately, only 42 patients were included in the treatment group. Differences in total cholesterol, LDL-cholesterol, and triacylglycerol between the treatment and control groups were modestly significant ($P < 0.05$; Table 2 from reference 1). Total cholesterol decreased from baseline by 16.8% at week 8 and by 16.1% at week 12 in the treatment group and was 18.1% lower at week 8 and 16.1% lower at week 12 in the treatment group than in the control group.

An analysis of the Chinese red-yeast-rice supplement by Heber et al indicated the presence of nine 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in addition to sterols, isoflavones, glycerides, and other substances. The authors' conclusion was that the effect of red yeast rice on the cholesterol concentration could not be explained by its constituent monacolin K alone (also known as mevinolin or lovastatin), but was the combined effect of monacolins and other substances in the red-yeast-rice supplement.

The inhibition of cholesterol biosynthesis by statins (including lovastatin) is a well-accepted fact and Heber et al assumed that the effect of the red-yeast-rice supplement followed the same pathway; however, they presented no evidence in support of this assertion. In the United states, 6 different HMG-CoA reductase inhibitors (known as statins) are currently marketed, all of which control endogenous cholesterol biosynthesis at the mevalonate level. A schematic representation of this complex pathway was presented by Bliznakov and Wilkins (2). Yet, this multistep process can be affected at various other levels, with different biochemical and clinical consequences. The potent effect of statins at the mevalonate level is, unfortunately, not specific and results in parallel inhibition of several nonsterol isoprenoid end products, including coenzyme Q₁₀ (CoQ₁₀) and dolichol. If the cholesterol biosynthetic pathway is impaired below the farnesyl pyrophosphate branch point of the mevalonate pathway, CoQ₁₀ biosynthesis is not inhibited. The CoQ₁₀-lowering effect of statins and its compensation by administration of CoQ₁₀ was described 10 y ago and since then has been confirmed in numerous studies of animals and humans.

CoQ₁₀, also designated ubiquinone, is a naturally occurring, fat-soluble, vitamin-like nutrient—a quinone—with character-

istics common to vitamins. Like vitamins, CoQ₁₀ is essential to the healthy functioning of all cells in an organism. The fundamental role of CoQ₁₀ as an electron and proton carrier for the cellular energy transduction in mitochondria is well established. In addition, CoQ₁₀ is involved in the stabilization of cell membranes, thus preserving cellular integrity and function, and is a potent scavenger of reactive oxygen species, preventing oxidative injury to DNA, lipids, proteins, and other molecules. This action retards or prevents the development of many cardiovascular and possibly neoplastic and neurodegenerative disease states. The biomedical and clinical aspects of CoQ₁₀ have been the subject of 14 international symposia, and the clinical effectiveness of CoQ₁₀ in cardiovascular diseases (a system with high energy demand) was reviewed recently (3, 4). A compilation of the indications for clinical use of CoQ₁₀ was presented by Bliznakov and Wilkins (2). In summary, many studies substantiate the strong relations between CoQ₁₀ deficiency, disease states, and clinical improvement after CoQ₁₀ treatment.

Despite numerous clinical trials documenting a generally good safety profile, side effects resulting from treatment with statins occur. Some of the adverse reactions—myalgia; myopathies; rhabdomyolysis; gastrointestinal symptoms, including hepatic injury; and the initiation or accelerated progression of cataracts and neoplasia—could be a direct or indirect consequence of the CoQ₁₀-deficiency state associated with statin treatment. It was suggested that CoQ₁₀ supplementation should be considered during extended therapy with statins to support cellular bioenergetic demands (2). Moreover, the possibility of an additive or synergistic therapeutic effect of CoQ₁₀ when administered with statins should be considered.

Heber et al disclose that “there were no serious adverse effects in any of the 88 subjects randomly assigned” to treatment with the red-yeast-rice supplement or placebo. Note that there were only 42 subjects in the red-yeast-rice treatment group and the length of the treatment, unfortunately, was only 12 wk. It is premature to assume the lack of toxicity on the basis of this short-term study. Cendella (5) attests that the ocular safety of statins can be established only after 10–20 y of clinical experience. Recently, Jeppesen et al (6) reported 7 cases of peripheral neuropathy associated with longer-term (1–7 y) statin therapy. The fact that fermented red yeast rice has been used in China since 800 AD is an interesting part of bygone medical folklore, but is not an indication of efficacy or of the lack of toxic effects.

Obviously, it is important to measure blood CoQ₁₀ concentrations in patients treated with the Chinese red-yeast-rice supplement. If the CoQ₁₀ concentration is not affected, this will imply a mechanism different from the mechanism accepted for cholesterol reduction by statins and will heighten the clinical interest in this product.



Another critical point not addressed by Heber et al is the standardization of the Chinese red-yeast-rice supplement. Various methods of preparation and potencies were used in the Chinese studies and in the trial reported by Heber et al. Neither the manufacturing method nor the origin of the product used were reported. Furthermore, it is not clear whether the Chinese red-yeast-rice supplement analyzed by Heber et al (Table 1 from reference 1) is the same preparation that was used in the clinical study. Nor is the relation between this "new" red-yeast-rice product and Cholestin clear.

HMG-CoA reductase inhibitors (statins), developed since 1987, are considered the first generation of cholesterol-lowering agents contributing to the pharmacologic armament against cardiovascular diseases. We now need a second generation of cholesterol-lowering agents with much more specific effects and which do not inhibit concomitantly the biosynthesis of other products involved in the physiologic control of cardiovascular and other diseases, such as CoQ₁₀. The publication by Heber et al does not make it evident whether the fermented Chinese red-yeast-rice supplement they studied fulfills the criteria for this second generation of lipid-lowering agents.

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Reply to EG Bliznakov

Dear Sir:

Bliznakov, in his letter, "More on the Chinese red-yeast-rice supplement and its cholesterol-lowering effect," brings up some issues that are outside the scope of our paper regarding the use of Chinese red yeast rice to lower cholesterol (1) and other issues that are irrelevant to the scientific and public health significance of our work.

First, he states that the study was "very short-term." We believe that the duration of our study, 12 wk, was more than adequate to determine the effects of an inhibitor of cholesterol biosynthesis on serum lipids; our patients had already achieved a maximal effect by

week 8. In our view, the only reason to conduct longer and larger studies would be to directly test the efficacy of Chinese red yeast rice in preventing heart attacks, as was done in studies with several statins, as cited in our paper (2–5). Furthermore, the utility of cholesterol as an intermediate biomarker for myocardial infarction has been well established in men and women with cholesterol concentrations >6.2 mmol/L (240 mg/dL) as well as in those with cholesterol concentrations between 5.2 and 6.2 mmol/L (200 and 240 mg/dL). For every 1% reduction in total cholesterol, there is a 2% reduction in the risk of fatal and nonfatal myocardial infarction (6, 7). After we showed a marked 16–18% reduction in cholesterol concentrations, we completed the scope of work for our phase 2 study. Only large-scale phase 3 studies can answer ultimate questions of the public health effect of the widespread use of Chinese red yeast rice as a food ingredient (8) or dietary supplement (1).

Second, it is not clear to me why Bliznakov objected to the number of patients in the trial ($n = 83$, with 42 in the treatment group) because our findings were both clinically and statistically significant. In fact, although the difference in total cholesterol from baseline was significant ($P < 0.05$), the difference from baseline in LDL cholesterol was highly significant ($P < 0.001$). Although we do not wish to promote the common myth in the literature that greater levels of statistical significance indicate more clinically significant differences, the data we collected were both physiologically and statistically significant.

Third, I agree with Bliznakov that more research is needed on both the mechanisms of action and the effects of the other 9 monacolins in Chinese red yeast rice, and we recently applied for federal funds to conduct research on the cellular and molecular aspects of the actions of this monocolin mixture compared with those of lovastatin, including its effects on coenzyme Q₁₀, which is a potent antioxidant carried on LDLs.

Fourth, we reported that the red-yeast-rice product we used was produced by the traditional solid-phase fermentation method. The preparation used in our study was identical to the proprietary product Cholestin, now available as a dietary supplement (Pharmanex, Inc, San Francisco).

Finally, I do not share Bliznakov's view that "we now need a second generation of cholesterol-lowering agents with much more specific effects." Many physicians have patients who have lost weight and follow a healthy diet and lifestyle, but still have elevated cholesterol concentrations. Are we to prescribe statins for these millions of patients? As a society, we are faced with rapidly increasing health care costs, including significant amounts of money spent for prescription drugs. Dietary supplements such as Chinese red yeast rice provide an alternative to prescription drugs. Because they may cost less and do not require a prescription, they are more accessible and may be used more widely. Research sponsored by the Office of Dietary Supplements Research of the National Institutes of Health in conjunction with other divisions of the National Institutes of Health and funding from private foundations will, I hope, provide the scientific base to address many of the public's concerns regarding dietary supplements.

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Low energy expenditure as a contributor to infant obesity

Dear Sir:

Stunkard et al (1) reported data on energy intake and energy expenditure in infants born to lean and overweight mothers and concluded that excessive energy intake, rather than low energy expenditure, is the cause of obesity in infants at high risk of excess weight gain. They also suggested that their results specifically refute the results of an earlier study conducted by 2 of us (2), and therefore by implication also a previous collaborative study by Stunkard (3) and work by other groups (4, 5). We take issue with the interpretation of the new study by Stunkard et al (1) on several grounds, in particular because their results are actually consistent with ours, not contradictory.

In particular, Stunkard et al did not study infants becoming overweight. With mean weight-for-length percentiles decreasing from approximately the 50th percentile at 3 mo of age to the 37th percentile at 12 mo in both low-risk infants (born to lean mothers) and high-risk infants (born to overweight mothers), these were infants who became relatively leaner over time, with no significant difference in actual weight gain between groups. This is a critical difference from the original study by Roberts et al (2), in which infants with a wide range of weight gains were included in the high-risk group and in which 2 groups of high-risk subjects could therefore be distinguished: those who became overweight and those who did not. Thus, what Stunkard et al actually found is that high-risk infants who remain lean do not have low energy expenditures, a finding identical to the original observation of Roberts et al (2) in normally growing infants of overweight mothers and a finding also reported by other groups (6, 7). This is an entirely unrelated

finding to the original report of Roberts et al (2) that high-risk infants who gain excess weight have low rates of energy expenditure. Thus, far from refuting the findings of Roberts et al (2), Stunkard et al (1) actually provide further supporting evidence for one aspect of the original results. The further observation of Stunkard et al that weight gain is positively associated with energy intake in lean infants is consistent with the previous report by Roberts (8) of excess energy intake (as well as low energy expenditure) in high-risk infants.

Our second concern with the interpretation of the study by Stunkard et al is the implication that either low energy expenditure or high energy intake is the cause of obesity in infancy. Why not both? The concept of one single determinant of energy balance is far too simplistic given the wealth of data from studies in adults showing the capacity of humans for both overeating and reduced energy expenditure (9–11). We suggested previously that both overeating and underexpenditure may facilitate weight gain in genetically predisposed infants becoming overweight, depending on environmental circumstances (12). This suggestion is also entirely consistent with laboratory studies of genetically obese rodents showing that both overeating and underexpenditure can facilitate excess weight gain early in life, with overeating being the dominant mechanism if circumstances permit (13, 14). If food is plentiful, young *ob/ob* mice will overeat and gain weight, but if food intake is controlled, energy expenditure will drop to facilitate weight gain. Given that the *OB* gene has been identified in humans (15), the same hierarchy of mechanisms likely exists in some infants also. However, conclusive evidence of the usual importance of low energy expenditure in the development of obesity in different groups of infants is needed. Obtaining such information will require more than simple observational studies to account for the possibility that a hypometabolic state may be easily rectified by excess weight gain and the possibility that hypometabolism may occur transiently at different ages in different infants.

Finally, even if Stunkard et al can in the future identify a group of infants who actually become overweight without exhibiting low energy expenditure, and within the same time period as in previous studies (time frame being an important factor because an infant who becomes overweight by 2 y of age may be metabolically different from one who is overweight by 6 mo), would this mean that low energy expenditure is never a cause of excess weight gain in infancy? Or, would it mean that, compared with infants in the studies in which low energy expenditure was identified as a problem, the infants studied by Stunkard et al were genetically different or subject to different environmental constraints? We strongly suggest that the latter possibility is more likely to be correct in view of the supporting data given above and because obesity is much more prevalent today in the United States (therefore being more likely to be precipitated by favorable environmental circumstances) than it was in England 15 y ago when the original cohort of Roberts et al (2) was identified.

Scientific progress in this area is clearly needed and will be furthered by careful studies identifying the underlying causes of excess weight gain in individual infants. What will not further scientific progress is the use of observational data from nonobese, slowly growing infants to explain the causes of obesity. We can see several good uses for the new data of Stunkard et al (1) on