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Dodging physical activity and healthy diet: can resveratrol take the edge off the consequences of your lifestyle?

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While >800 million people live in conditions of food insecurity with great impact on their health status (1), health in Western societies is challenged by the opposite: too much, too sweet, and too fatty food intake combined with too little physical activity. Although there is very compelling evidence that physical activity and dietary modification are the most potent, cheapest, and easiest ways to prevent lifestyle-related chronic diseases (2), long-term adherence to dietary and exercise training interventions is challenging (3). Accordingly, it may be questioned whether these are the means that will alleviate the burden of lifestyle-related diseases.

As a result, a rationale exists for exploring dietary and other compounds that can mimic exercise and energy restriction, presumably to reduce the need for eating healthy and being physically active.

Resveratrol is one such dietary shortcut proposed to prevent and cure lifestyle-related diseases (4). Resveratrol is a naturally occurring polyphenol found in various fruits, nuts, and vegetables and is also sold as a dietary supplement. In a mouse model where early death follows a high-fat diet compared with mice fed an unpurified diet, resveratrol supplementation improved insulin sensitivity, increased mitochondrial number, and increased mouse life span (5). This fundamental finding was related to activation of the health span–regulating NAD⁺-dependent histone deacetylase, Sirtuin 1. Sirtuin 1 was later also shown to be upregulated in parallel with improved metabolic health in obese subjects after resveratrol supplementation (6). In addition, resveratrol supplementation has also been shown to activate some of the same molecular pathways as physical activity, including peroxisome proliferator-activated receptor γ coactivator 1 α (7). Collectively, resveratrol has been shown to improve insulin sensitivity and skeletal muscle mitochondrial function and to decrease liver fat accumulation in various models ranging from banana flies to humans. However, a substantial number of clinical trials in humans investigating the effects of resveratrol on blood pressure, glucose homeostasis, insulin sensitivity, and blood cholesterol have presented inconsistent findings (8–10). It is of course difficult to translate findings from animals to humans, and the dose and duration of resveratrol supplementation may be a key limitation to most clinical studies reporting null findings.

To help address this shortcoming, de Ligt et al. (11) designed a much-needed randomized placebo-controlled trial to investigate the effects of long-term resveratrol treatment in overweight and obese subjects, published in the current issue of *The American Journal of Clinical Nutrition*. The clinical trial tested the effects of 6 mo of resveratrol supplementation on several metabolic parameters, including insulin sensitivity, blood glucose, blood cholesterol, intrahepatic lipid content, body composition, resting energy metabolism, blood pressure, physical performance, quality of life, and quality of sleep.

The design was simple and solid. In a parallel-group, double-blind clinical trial, 41 overweight to obese (inclusion BMI range: 27–35 kg/m²) men and women (aged 40–70 y) were randomly assigned to either 150 mg *trans*-resveratrol or placebo daily for 6 mo. By mass spectrometry, the plasma content of resveratrol was verified on a monthly basis and adherence to the supplementation was strictly followed.

Aside from lower glycated hemoglobin (HbA1c) and improved knee flexor muscle endurance in the resveratrol arm, none of the outcome measures were different in the 2 treatment arms. This is a somewhat surprising finding, because both the dosage and duration of resveratrol treatment were carefully chosen in order to reveal positive effects on insulin sensitivity and other parameters related to metabolic health in overweight subjects.

So why did 6 mo of resveratrol treatment not improve Matsuda index or glucose AUC during an oral-glucose-tolerance test? Why were free fatty acids, triacylglycerol, and cholesterol concentrations completely unaffected? Why were both resting metabolic rate and physical performance in activity of daily living not improved by resveratrol treatment? And likewise, why did intrahepatic lipid content and whole-body fat remain unchanged?

The authors point toward one of the usual suspects for the lack of changes after half a year of resveratrol treatment: the supplement dosage. Trials that report improved glucose homeostasis or insulin sensitivity typically used resveratrol dosages of <500 mg/d, but a high dosage is not consistently more effective

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than a low dosage (12, 13). Indeed, the most recent meta-analyses suggest that, irrespective of dosage, resveratrol treatment does not improve glucose homeostasis, insulin sensitivity, or blood cholesterol in overweight nondiabetic subjects (8, 9). Another potential shortcoming of the present trial was, as the authors note, its small sample size and therefore limited power.

An interesting observation of the study was that HbA1c concentrations were 1.8 mmol/mol lower in the resveratrol arm than in the placebo arm when adjusted for preintervention HbA1c concentrations. As the authors note, observing decreased HbA1c and with no change in fasting plasma glucose could imply an effect of resveratrol on hemoglobin glycosylation or even erythrocyte life span, rather than an accumulated effect of lower plasma glucose during the past 3 mo. Given the reports of increased longevity after treatment with resveratrol in simple organisms and single cells (14), this explanation seems plausible and certainly raises a number of new research questions and putative therapeutic targets of resveratrol.

In sum, the overall effects of 6 mo of resveratrol treatment are limited and the article by de Ligt et al. adds to the body of literature that questions the positive effects of resveratrol on human health. Future studies are needed to determine whether a higher dosage or longer duration of resveratrol supplementation can meaningfully mimic a healthy diet and physical activity.

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