Resveratrol Use in Metabolic Syndrome

Andrew A. Bremer, MD, PhD

The link between metabolic health and longevity is intuitive and can be modified by many factors. At a molecular level, at least three main pathways exist that have been implicated in the regulation of life span in mammals—insulin/insulin-like growth factor 1 (IGF-1), tuberous sclerosis complex (TSC)/mammalian target of rapamycin (mTOR), and the sirtuins. The molecules that modulate these pathways have been shown to prevent a diverse set of age-related disorders, including cancer, cardiovascular disease (CVD), osteoporosis, and type 2 diabetes mellitus (T2DM). Resveratrol (3,4'-trihydroxystilbene), a phytoalexin and natural polyphenol whose biological effects are largely attributed to its ability to activate sirtuin 1 (SIRT1), is one such molecule that regulates a wide range of biological processes, including gene silencing, aging, cellular differentiation, and metabolism.

Initially identified in 1940 as a polyphenolic phytochemical in the white hellebore Veratrum grandiflorum, resveratrol is currently the most widely studied natural sirtuin-activating compound (STAC). It has subsequently been found in nuts, grapes, berries, and red wine. Interest in resveratrol has increased substantially over the last few years, and its broad biological activity at the cellular level has been associated with potent antioxidant, antiaging, and anti-inflammatory effects, as well as being protective against neurodegeneration and obesity/metabolic disease.

Although existing as two geometric isomers, the trans configuration is the most widely studied with the most pharmacological properties. The presence of resveratrol and related compounds in red wine has also been proposed to explain the finding that rates of CVD are lower in populations (especially European) that consume higher amounts of red wine, i.e., the “French Paradox.”

The mechanism(s) by which resveratrol activates SIRT1 remain unclear; however, proposed theories include a direct interaction with the enzyme as well as an assisted-allosteric activation mechanism, both of which result in deacetylation of target proteins. Specifically, SIRT1 deacylates key histone residues involved in the regulation of transcription, including H3-K9, H4-K16, and H1-K26, as well as multiple non-histone protein targets, including p53, forkhead box protein O1/3 (FOXO1/3), peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), and nuclear factor (NF)-κB. Resveratrol’s activation of PGC-1α has also been implicated in its protective role against metabolic disease, as well as its contribution to an increase in lipolysis and induction of adipocyte apoptosis. PGC-1α is also strongly induced by cold exposure, linking this environmental stimulus to adaptive thermogenesis; furthermore, it stimulates mitochondrial biogenesis, promotes the remodeling of muscle tissue to a metabolically more oxidative and less glycolytic fiber-type composition, and participates in the regulation of both carbohydrate and lipid metabolism.

Independent of SIRT1, resveratrol is also a direct non-selective pharmacological inhibitor of the proinflammatory cyclo-oxygenase enzymes COX1/2, possibly contributing to its anti-inflammatory properties. Moreover, the inhibition of cyclic adenosine monophosphate (cAMP) phosphodiesterases and indirect activation of AMP kinase, an important enzyme in regulating cellular energy homeostasis, may further contribute to resveratrol’s amelioration of aging-related metabolic phenotypes.

Interestingly, studies suggest that the many beneficial effects of resveratrol also mimic those induced by caloric restriction, which is related with an increase in the activity and levels of sirtuins, a family of nicotinamide adenine dinucleotide (NAD) dependent deacetylases (including SIRT1) that are central to the body’s response to diet and exercise. This intersection of caloric restriction and mild cold stress and the associated overall mitochondrial biogenesis may also account for survival during periods of cold and decreased calorie intake. Metabolically favorable properties of SIRT1 in particular include its positive associations with glucose and insulin homeostasis, control of insulin hypersecretion, lipid metabolism, fat mobilization, and adipokine secretion, as well as its regulation of mitochondrial biogenesis, muscle and fat differentiation, neurogenesis, hormone secretion, cell stress responses, and circadian rhythms. However, despite the myriad public health campaigns focused on reducing total caloric intake for the average person in efforts to prevent and/or treat cardiometabolic disease, caloric restriction is difficult for most individuals at highest risk for or affected with cardiometabolic disease to achieve and/or sustain. As such, the identification and development of small-molecule SIRT1 activators for the treatment of aging and age-related diseases, including cardiometabolic disease, are areas of active investigation.
In this issue of the Journal, Méndez-del Villar et al. describe the results of their 3-month pilot study specifically evaluating the effect of resveratrol administration on patients with metabolic syndrome (in accordance with the International Diabetes Foundation criteria), insulin sensitivity, and insulin secretion. Based on their data, they conclude that the administration of trans-resveratrol 500 mg three times per day before meals for 90 days leads to a significant loss of body weight, body mass index, fat mass, and waist circumference, as well as a decrease in the characteristic hyperinsulinemia of metabolic syndrome. Whereas another recent 12-week, placebo-controlled pilot study in non–metabolic syndrome adults assessing the safety and metabolic outcomes of resveratrol supplementation demonstrated a glucose-lowering effect of resveratrol at doses of either 300 mg/day or 1000 mg/day, Méndez-del Villar et al. did not observe such a glucose-lowering effect on either fasting glucose values or those obtained during an oral glucose tolerance test in their subjects. Whether this is due to resveratrol dosing differences, differences in the baseline characteristics of the study subjects (e.g., metabolic syndrome vs. non–metabolic syndrome), or a combination of the above and/or other factors is unknown. Fortunately, neither group of investigators reported any serious adverse events with the resveratrol supplementation.

Since no single pathway has been identified in the pathogenesis of metabolic syndrome, current management strategies still address the various components of metabolic syndrome individually by means of both lifestyle modifications and pharmacological therapy. Unfortunately, this approach is frequently associated with therapeutic failure and patient frustration, in addition to a multidrug regimen with its attendant increased risk of polypharmacy and drug-related complications. The need for safe agents that simultaneously address the multiple elements of the syndrome is thus being increasingly recognized. As such, an alternative medicine approach to metabolic syndrome is reasonable. Although prior studies have demonstrated the proof-of-concept that nutraceuticals can improve insulin sensitivity in patients with metabolic syndrome, the potential role of resveratrol in the direct treatment of metabolic syndrome has not been well-defined, highlighting the importance of Méndez-del Villar et al.’s current study. Furthermore, because resveratrol in particular seems to influence many of the metabolic pathways implicated in the development of metabolic syndrome, it may be a more effective agent than other nutraceuticals in the syndrome’s potential management and/or prevention.

Given the popularity of nutraceuticals, the fact that the majority of people who consume multiple dietary supplements consume resveratrol, and the global burden of metabolic syndrome and its associated conditions (such as obesity, T2DM, and CVD), a better understanding of the potential role of resveratrol in the syndrome’s management is needed. The study by Méndez-del Villar et al. provides an initial step in this direction; however, as the authors acknowledge, longer-term studies with larger sample sizes among different populations will be necessary to adequately evaluate the potential therapeutic and/or preventive role of resveratrol in metabolic syndrome.

Author Disclosure Statement

The contents of this article represent the author’s views and do not constitute an official position of the National Institutes of Health, Department of Health or Human Services, or the United States Government.

References

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