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BASIC RESEARCH

# Cardioprotective benefits of dietary spermidine

> the cardioprotective benefits of oral spermidine are dependent on autophagy

Oral supplementation of a natural polyamine spermidine in rodent models of cardiovascular disease is associated with reduced cardiac hypertrophy, preserved diastolic function, and prolonged lifespan. This finding comes from a study published in *Nature Medicine*, which proposes a new and feasible strategy for the treatment of heart disease using spermidine-enriched diets.

Autophagy, a physiological process that involves the degradation and turnover of long-lived proteins for new cell formation, can help to minimize the functional decline of ageing cardiomyocytes. Oral supplementation of spermidine has been shown to prolong lifespan and health span through induction of autophagy in yeast, flies, and worms. Eisenberg and colleagues sought to assess the potential cardioprotective effects of spermidine supplementation in both a mouse model of physiological cardiac ageing and a rat model of high-salt-induced congestive heart failure.

The effect of oral spermidine supplementation on lifespan and cardiac structural and functional parameters were tested in wild-type C57BL/6 mice. Female mice given lifelong access to drinking water supplemented with spermidine had a significantly extended median lifespan compared with control mice that received normal drinking water. This prolonged lifespan was also maintained in pre-aged male and female mice that received spermidine later in life (to enhance translational applicability to humans). Furthermore, spermidine supplementation in these mice reversed age-related hypertrophy, improved diastolic function, and reduced left ventricular (LV) stiffness.

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Transcriptome and proteome analyses of cardiac tissue extracts from the aged mice were performed to determine whether dietary spermidine influenced cardiomyocyte mechanoelastic functionality. Spermidine-supplemented mice had a favourable molecular phenotype, with regards to components of the cytoskeletal apparatus and inflammatory processes. Furthermore, spermidine reversed the age-related decline in mitochondrial respiratory function and mitochondria-related metabolite levels. These improvements coincided with an increase in titin phosphorylation, which is known to reduce cardiomyocyte stiffness.

The investigators further hypothesized that spermidine acts as a potent inducer of autophagy. To measure autophagic flux, mice aged 13 months were given spermidine in their last 4 weeks of life along with leupeptin, an inhibitor of autophagosome turnover. Leupeptin treatment increased levels of the autophagosome marker LC3-II, suggesting that spermidine elevates autophagic flux *in vivo*. The investigators subsequently sought to determine whether the cardioprotective effects of spermidine were dependant on autophagy in $Atg5^{-/-}$ mice with a cardiomyocyte-specific autophagy defect. Importantly, spermidine-induced reduction of LV hypertrophy was seen in $Atg5^{+/+}$ mice, but not in $Atg5^{-/-}$ mice. Spermidine-treated $Atg5^{-/-}$ mice also had impaired diastolic and systolic function, indicating that the cardioprotective benefits of oral spermidine are dependent on autophagy.

The effect of dietary spermidine on hypertension-induced congestive heart failure was also tested using Dahl salt-sensitive rats fed a high-salt diet. Spermidine-treated rats had reduced systemic blood pressure, attenuated cardiac hypertrophy, improved diastolic function, reduced LV stiffness, and increased titin phosphorylation compared with untreated rats, thus delaying their progression to heart failure.

Finally, these preclinical findings were corroborated in a prospective, population-based patient cohort study, in which dietary spermidine was found to correlate with decreased blood pressure and a lower incidence of cardiovascular disease.

In an accompanying editorial, Rafael de Cabo and Pácido Navas question whether the cardioprotective effects of spermidine can be translated to humans. Given that spermidine is present in many foods, "it could be relatively easy for most people to get the benefits of spermidine through dietary modifications or by supplementation, and thus validate its potential as a new therapeutic approach for cardioprotection against ageing," they conclude.

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**ORIGINAL ARTICLE** Eisenberg, T. *et al.* Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat. Med.* **22**, 1428–1438 (2016)