

Metabolic and Molecular Adaptations to Dietary Restriction in Humans

Abstract:

Billions of dollars are spent every year to treat highly prevalent chronic diseases, which are largely preventable with the implementation of the best healthy lifestyle practices. Modern medicine focuses on diagnosing and treating clinically evident chronic diseases one at the time, mainly with drugs and surgery. The problem of this approach is that many age-associated chronic diseases begin early in life and progress over decades of unhealthy lifestyles, which promote the incremental accumulation of metabolic and molecular damage leading to multiple medical conditions (Fontana et al. *Nature* 2014).

Evidence from experimental studies indicates that the age-associated accumulation of molecular damage can be prevented or greatly delayed by dietary, genetic and pharmacological manipulations that down-regulate key cellular nutrient-sensing and inflammatory pathways (Fontana et al. *Science* 2010). For example, restricting calorie or protein intake in mice or introducing mutations in nutrient-sensing pathways can extend lifespans by as much as 50%. These 'Methuselah mice' are more likely than controls to die without apparent disease (Ikeno et al. 2013).

In Rhesus monkeys dietary restriction (DR) also increases lifespan and protects against obesity, diabetes, cancer, heart disease, brain ageing and frailty (Mattison et al. *Nat Comm.* 2017), and in humans, it causes physiologic, metabolic and molecular changes that protect against these pathologies (Fontana & Klein. *JAMA* 2007; Most et al. *Ageing Res Rev.* 2017). Moreover, recent findings indicate that meal timing is crucial, with both intermittent fasting and time restricted feeding improving health and function in the absence of changes in overall intake. Lowered intake of particular nutrients is also key in mediating some of the effects of DR, with protein and specific amino acids and nutritional modulation of the microbiome playing prominent roles (Fontana & Partridge. *Cell* 2015).

More studies are needed to understand the interactions between single nutrient modifications and calorie intake, and the interpersonal variations in the effectiveness of these interventions, so that we can develop new personalized mechanism-based nutritional and lifestyle interventions for the prevention and treatment of multiple age-related diseases that share common pathophysiological features and are the leading drivers of rising health-care costs.

Biography:

Prof. Luigi Fontana is Leonard P. Ullmann Chair of Translational Metabolic Health at the Charles Perkins Centre, University of Sydney, Australia where he directs the Healthy Longevity Research and Clinical Program. He is also a Professor of Medicine and Nutrition in the Faculty of Medicine and Health at the University of Sydney and a Clinical Academic in the Department of Endocrinology at the Royal Prince Alfred Hospital. He is an internationally recognized physician scientist and one of the world's leaders in the field of nutrition and healthy longevity in humans. His pioneering studies on the effects of dietary restriction in humans have opened a new area of nutrition-related research that holds tremendous promise for the prevention of age-related chronic diseases and for the understanding of the biology of human aging. Dr. Fontana's is the recipient of three prestigious awards: the 2009 AFAR Breakthroughs in Gerontology Award and the 2011 Glenn Award for and the 2016 AFAR Vincent Cristofalo Award. He has published over

120 manuscripts in prestigious journals including Science, Nature, Cell, New England Journal of Medicine, JAMA, Cell Metabolism, Circulation, JACC, Diabetes, and PNAS. He is also a Scientific Member of the Board of Directors of the American Aging Association.