Objective

Age-related chronic diseases (ArCD) are complex non-linear processes that depends on a large number of interconnected genetic and metabolic pathways which should be tackled with a many faceted preventive strategy. Calorie-dense diet and sedentary lifestyle are responsible of the growing prevalence of metabolic syndrome (MetS), which, together with tobacco, is the major preventable cause of ArCD, mediated by the increased availability of insulin, growth factors, and inflammatory cytokines. In animals, calorie restriction (CR) is the most potent dietary intervention for preventing ArCD and prolonging life. In humans, we and others have shown that a sustainable CR, resulting in decreased prevalence of MetS, can be obtained through a comprehensive change in dietary habits, reducing animal food and refined carbohydrates, and increasing whole grain cereal products, legumes and vegetables, according to the Mediterranean and macrobiotic diet principles. Metformin (MET), an antidiabetic drug associated with decreased cancer incidence, activates the same gene pathways activated by CR, including AMPK/TSC, which reduces energy consuming processes, and cell proliferation (through the inhibition of mTOR). We propose a placebo controlled randomised trial to test whether treatment with MET, with or without associated CR, reduces the incidence of major chronic diseases, such as cancer, myocardial infarction, stroke, and diabetes. We estimated that randomizing 2,000 women and men aged 55-74 at high risk of developing ArCD because of MetS, shall provide over 90% power (at alpha = 0.05) to detect a significant 25 to 33% reduction of ArCD incidence in 5 years. In a subsample of the cohort we shall study the genetic and epigenetic mechanisms of the preventive action of metformin and CR.
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