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Review article

Effects of intermittent fasting on metabolism in men☆

Fernanda Reis de Azevedo[a,*], *Dimas Ikeoka*[b], *Bruno Caramelli*[a]

[a] *Interdisciplinary Medicine in Cardiology Unit, Heart Institute (InCor), Medical School, Universidade de São Paulo, São Paulo, SP, Brazil*
[b] *Second Department of Surgery, Post-operative Care Unit, Medical School, Universidade de São Paulo, São Paulo, SP, Brazil*

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ABSTRACT

This review analyzes the available literature on the impact of intermittent fasting (IF), a nutritional intervention, on different aspects of metabolism. The epidemic of metabolic disturbances, such as obesity, metabolic syndrome (MS), and diabetes mellitus type 2 has led to an increase in the prevalence of cardiovascular diseases, and affected patients might significantly benefit from modifications in nutritional habits. Recent experimental studies have elucidated some of the metabolic mechanisms involved with IF. Animal models have shown positive changes in glucose (lower plasma glucose and insulin levels) and in lipid metabolism (reduced visceral fat tissue and increased plasma adiponectin level), and an increased resistance to stress. Despite the limited number of samples studied, positive results have been reported on the impact of IF for human health. IF is reported to improve the lipid profile; to decrease inflammatory responses, reflected by changes in serum adipokine levels; and to change the expression of genes related to inflammatory response and other factors. Studies on obese individuals have shown that patient compliance was greater for IF than other traditional nutritional approaches (calorie restriction), and IF was found to be associated with low oxidative stress. Recent reports suggest that IF exerts a positive impact on the metabolic derangements commonly associated with cardiovascular diseases, and that it may be a viable and accessible intervention for most individuals. Therefore, further clinical studies are essential to test the effectiveness of IF in preventing and controlling metabolic and cardiovascular diseases.

Efeitos do jejum intermitente no metabolismo humano

Palavras-chave:
Jejum
Doença cardiovascular
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Restrição calórica
Dislipidemia

RESUMO

Esta revisão traz uma análise de dados disponíveis na literatura sobre o impacto do jejum intermitente, uma modalidade de intervenção nutricional, em diferentes aspectos do metabolismo. A epidemia de anormalidades metabólicas, como obesidade, síndrome metabólica e diabetes mellitus tipo 2, tem ocasionado um aumento na prevalência de doenças cardiovasculares, condições em que os indivíduos afetados apresentam importantes melhorias advindas de modificação nos hábitos alimentares. Estudos experimentais recentes têm elucidado a modulação do metabolismo por jejum intermitente. Testes com

☆ Study conducted at the Interdisciplinary Medicine in Cardiology Unit, Instituto do Coração (InCor), São Paulo, SP, Brazil.

* Corresponding author: Interdisciplinary Medicine in Cardiology Unit, Heart Institute (InCor), Av. Dr. Enéas de Carvalho Aguiar, 44, Cerqueira César, São Paulo, SP, 05403-000, Brazil.
E-mail: freis@usp.br (F.R.d. Azevedo).

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animais têm mostrado alterações positivas no metabolismo glicídico (valores menores de glicemia e insulinemia) e lipídico (redução no volume de gordura visceral e aumento nos valores de adiponectina plasmática), além de uma maior resistência ao estresse. Apesar dos estudos disponíveis apresentarem populações muito reduzidas, observaram-se resultados positivos com esta intervenção também na saúde humana. Os resultados indicam melhorias no perfil lipídico, redução de respostas inflamatórias, com redução na liberação de adipocinas inflamatórias e alterações na expressão de genes relacionados com a resposta inflamatória e de outros fatores. Em indivíduos obesos observou-se uma melhor adesão ao jejum intermitente em relação a intervenções tradicionais (restrição calórica), além da redução no estresse oxidativo desta população. Dessa maneira, por se tratar de uma intervenção viável e acessível para a maioria dos indivíduos, novos estudos clínicos são necessários para testar a eficácia desta intervenção na prevenção e no controle de doenças metabólicas e cardiovasculares.

Introduction

The human genotype is believed to have evolved from 600,000 BC to 25,000 BC, when humans were hunter-gatherers.[1] During this period, major energy oscillations appear to have selected genes that regulate metabolism for efficient nutrient usage and increased fat storage, which represents an evolutionary benefit consistent with the thrifty genotype theory proposed by James V. Neel.[2] While the environment changed drastically with urbanization and easy availability of food, the genotype remains largely unaltered. This imbalance has resulted in an epidemic of conditions characterized by metabolic disturbances, such as obesity, metabolic syndrome (MS), and diabetes mellitus type 2 (DM2).[1,3,4]

While obesity is easily defined by body composition (body mass index [BMI] > 30 kg/m^2), and DM2 by elevated blood glucose levels, MS is recognized by a cluster of metabolic markers whose importance and contribution have greatly changed over time. Despite this difference, the three conditions have common pathophysiological backgrounds. Firstly, all these conditions involve insulin resistance, elevated levels of plasma lipids, and increased levels of chronic inflammatory mediators. Secondly, the consequent metabolic profile considerably increases cardiovascular risk. Finally, individuals with any of these conditions can benefit from significant lifestyle changes.[5–7] Notably, modification of nutritional habits is now considered extremely important for reducing cardiovascular risk.[8,9]

Intermittent fasting (IF) is an interventional strategy wherein individuals are subjected to varying periods of fasting. IF has recently attracted attention because experimental studies have highlighted its potential for correcting metabolic abnormalities.[10] This regimen has also shown better adherence than other methods.[11]

This review analyzes existing data on the impact of IF on different aspects of metabolism.

Methodology

Experimental studies and clinical trials on IF available in the PubMed database at the time of manuscript preparation were reviewed. Animal and human studies were searched for by using the key words "intermittent fasting," "alternate day fasting," and "starvation" either alone or combined with "cardiovascular risk," "obesity," and "metabolic syndrome."

The first search retrieved over 22,000 results, mostly by using the keyword "starvation" alone (21,735). A detailed search yielded 26 articles on the impact of fasting or IF on metabolic parameters related to cardiovascular risk.

Pathophysiological basis of obesity and MS

Obesity and MS were the main outcomes analyzed in the studies on IF.

Adipose tissue is now known to function as an endocrine organ involved in regulating metabolism, rather than a passive reservoir for energy storage.[12] Adipocytes, mesenchymal cells, and infiltrating macrophages together produce cytokines and adipokines that have important regulatory effects on inflammation, insulin sensitivity, coagulation, vascular homeostasis, appetite, energy expenditure, etc. When this production is deregulated, e.g., by excessive adipose tissue, the organism appears to develop low-grade chronic inflammation, leading to insulin resistance and cardiovascular disease.[13] Adipocytes produce important proinflammatory adipokines, such as leptin, tumor necrosis factor alpha (TNF-α), resistin, angiotensinogen, interleukin-6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1), as well as nonesterified fatty acids and C-reactive protein (CRP), which are atherogenic.[14,15]

Certain adipokines have cardioprotective action, such as adiponectin, which is abundant in human circulation. Adiponectin was primarily investigated for its ability to promote insulin sensitivity by suppressing gluconeogenesis and increasing fatty acid oxidation, which in turn reduce triglyceride accumulation in the liver.[13,16] Moreover, adiponectin regulates endothelial function by increasing the production of endothelial nitric oxide; by inhibiting endothelial cell activation and endothelium–leukocyte interaction; by enhancing phagocytosis; and by suppressing macrophage activation, macrophage-to-foam cell transformation, and platelet aggregation.[17–19]

Adipokines might represent the evolutionary pathway that led excessively nourished humans to obesity, insulin resistance, MS, and cardiovascular disease. Indeed, obese patients