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The adult table: Chronic intermittent fasting improves β cell health only in adults

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Intermittent fasting (IF) improves metabolic health in some individuals but increases health risks in others. Matta et al. now show that IF oppositely affects β cells depending on age: beneficial at old but deleterious at young age.

Eat like a python: this is how intermittent fasting (IF), characterized by alternating periods of fasting and feeding, has traditionally been endorsed as diet intervention against a sedentary lifestyle and obesity-related metabolic syndrome. The benefits of IF extend beyond weight loss to improved metabolism and stress response and increased longevity.[1,2] The scientific evidence supporting these benefits, so far, is based on studies carried out in middle- and old-aged subjects. How intermittent fasting would affect organs at younger ages remains elusive.

In their article, Matta et al.[3] describe age-dependent effects of IF on glucose metabolism, especially on pancreatic β cell function. The metabolic effects of short-term (5 weeks) and long-term (10 weeks) IF were studied on young (2 months), middle-aged (8 months), and old-aged (18 months) mice. The study showed that while short-term IF improved glucose homeostasis and insulin sensitivity independently of age, the impact of chronic IF on pancreatic β cells is conditioned by age. While it improved glucose tolerance and β cell function in old mice, it led to impaired function and maturation and reduced β cell mass in young mice (Figure 1).

Islets isolated from old mice exposed to long-term IF secreted more insulin in response to glucose, showing the beneficial effect of IF on glucose-stimulated insulin secretion (GSIS). Conversely, islets from young mice under chronic IF showed lower GSIS compared to no-IF controls and reduced expression of many important functionality genes, such as MAFA, GLUT2, and NKX6.1, which is reminiscent of the effects of type 2 diabetes in both humans and mice. Islets showed an overall reduction in the proliferation and total numbers of α and β cells, suggesting that both cell types need continuous access to nutrients to maintain proper survival and function. Surprisingly, glucose homeostasis was not affected by the loss in islet cells, and young mice showed generally lower glucose levels during the glucose tolerance test, compared to older mice. This raises the question of whether glycemia impairment may only be seen when these mice age.

Together, the findings presented by Matta et al.[3] suggest that critical pathways in cellular growth adaptation to the nutritional status should not be switched off for too long in actively growing individuals. A growth-related sensitivity to prolonged fasting in younger individuals might disrupt pancreatic islet development and glucose regulatory mechanisms.

Another recent study in mice shows similar results achieved through caloric restriction (CR).[4] CR generally reduces the workload on β cells, leading to improved insulin sensitivity, thus lessening the demand for insulin production. With aging, CR keeps β cell autophagy mechanisms and mitochondrial function intact, prevents cellular senescence, and maintains longevity.[4] However, the lack of nutrient challenges maintains a lower β cell number. If these cells are suddenly confronted with a high-fat diet, they show a deficient compensatory response. This is similar to the observations reported by Matta et al.[3] in young mice exposed to chronic IF early in life, where a sufficient number of β cells might not have been made, leading to insufficient β cell compensation and growth.

Aging is associated with reduced metabolic flexibility, insulin sensitivity, and increased visceral fat. β cells decline with aging, with diminished β cell function, accompanied by an age-dependent reduction of the β cell maturation factor PDX-1, a higher susceptibility of human islets to glucose-induced apoptosis,[5] and an increase in β cell senescence. Decreasing the number of overworked aged β cells is an effective strategy to restore β cell function and identity.[6] Hypothetically, this could be achieved via IF by inducing "β cell rest," which would reduce a constant metabolic demand and the need for insulin secretion and thus improve β cell viability. In human islets, resting induced by the inhibition of constant insulin secretion, for example by K_{ATP} channel openers,[7] improves β cell survival. Such experiments have all been performed in islets from organ donors beyond adulthood, and effects before adolescence remain therefore unknown.

Beyond tuning metabolic stress, IF impacts the immune response as well, and this effect may also be age dependent. IF can modulate several inflammatory processes, such as cytokine production and T cell activation, via reduction of adipose-tissue-derived leptin and metabolites with anti-inflammatory properties, like β-hydroxybutyrate and short-chain fatty acids.[8] This is advantageous for older individuals experiencing chronic, low-grade inflammation. However, young individuals might need these stimuli to grow and develop a fully functional immune system.

The mechanism behind the observation made by Matta et al. remains to be solved.

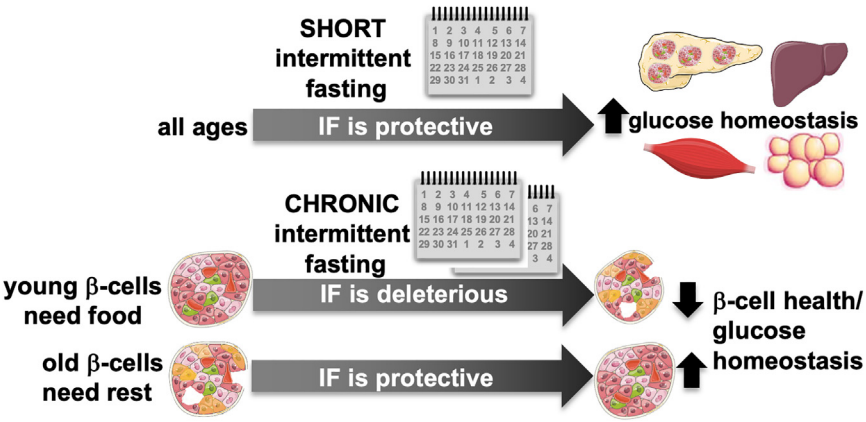

Figure 1. Intermittent fasting (IF) is beneficial for all at short term but chronically deleterious at a young age

Findings in mice show that short-term IF improves glucose metabolism (insulin secretion and action) at all ages, but chronic IF, over 2 months, impairs β cell function and maturation at a young age, whereas it improves it at older ages. Young β cells need constant nutrition to drive growth, reach maturity, and achieve full functionality, while in aged cells, IF induces rest and protects against constant nutritional challenge and the associated senescence, dysfunction, apoptosis, and aging-induced inflammation.

Metabolic benefits of IF cannot be explained simply by weight loss or lesser radical formation induced by constant food intake.[1,2] The conserved mechanistic target of rapamycin (mTOR) cascade, which links nutrient supply to glucose and lipid homeostasis, protein synthesis, inflammation, and cell growth, could be a plausible mediator of the age-dependent IF effect on β cells.[9] In response to meals, glucose, lipid, and amino acid levels peak, resulting in insulin secretion, protein and organelle synthesis, growth, and proliferation. On the contrary, during fasting, both plasma glucose and insulin are at a basal level. The latter is driven by mTOR silencing and autophagy activation, leading to cellular homeostasis being shifted toward recycling cellular waste, removing damaged molecules, repairing, and resting. Such resting phase is essential for cellular health and maintenance of insulin sensitivity, as insulin receptors do not degrade but remain highly sensitive for the next feeding period.

Although mTOR activation wasn't investigated by Matta et al.,[3] and the activation state isn't evidenced in the RNA-seq datasets, the age-dependent results are fully in line with the mTOR plasticity and its regulation in β cells during aging. Cells and organs require mTOR activation to proliferate and grow; however, due to the decline in intracellular repair machinery with age, the burden of damaged products increases with chronic mTOR hyperactivation, resulting in β cell malfunction,[10] which may be improved by IF.

The new data solve one aspect of the debate about the best dietary intervention: overall, metabolic benefits of short-term fasting and resting are independent of age. However, chronic IF is deleterious for β cells at younger but beneficial at older ages. Clinical studies are needed to prove these findings in humans, where it will also be interesting to compare the effects of IF on lean versus overweight individuals at different ages. What is safe for adults: *if* you want to keep your functional β cells, follow IF.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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