Lee Nunn

Clinical Internship Spring 2022

Literature Review

Does Intermittent Fasting (IF) help prevent stroke and improve outcomes in post-stroke patients by improving insulin resistance (IR)?

Intermittent fasting (IF) is a dietary plan that can take several forms including calorie restriction (CR), alternate day fasting (ADF) with periods of *ad libitum* feeding, and time-restricted feeding (TRF) where all calories are consumed within a certain number of hours in a given day.[1,2] Popular forms of TRF are 18/6 and 16/8 where the majority of a 24-hour period is spent fasting. Current research has shown that prophylactic IF extends lifespan and reduces the impact of cardiovascular disease (CVD) including myocardial infarction and stroke.[2,3] Lifestyle factors such as obesity and physical inactivity are known to increase the risk of CVD due to pro-inflammatory changes associated with central adiposity.[4] It has also been established that central adiposity promotes insulin resistance (IR) leading to type 2 diabetes mellitus (T2DM) and hyperinsulinemia, known risk factors for stroke. Patients with T2DM have less favorable post-stroke outcomes due to decreased plasticity in the CNS.[5] This review summarizes the metabolic rationale for why IF may indeed help prevent stroke and minimize negative outcomes in post-stroke patients.

Stroke is but one of a number of CVD outcomes that are associated with a metabolically dysregulated phenotype. This collection of maladaptive metabolic, renal, thrombotic, and inflammatory dysfunctions is known as Cardiometabolic Syndrome (CMS) and includes insulin resistance and impaired glucose tolerance, dyslipidemia (elevated triglycerides and lowered HDL-C), hypertension, and central adiposity.[6] Due to its prevalence, CMS is now recognized as a disease by the World Health Organization (WHO) and the American Society of Endocrinology (ASE). People with CMS are 3 times more likely to

have an adverse cardiac event, including myocardial infarction or stroke, than those without the syndrome.

Metabolic dysfunctions are induced by increased consumption of calorie-dense highly refined diets.[6] White adipose tissue (WAT), mainly stored around the gluteal regions and viscera, is an active endocrine tissue that produces adipokines (hormones) such as adiponectin, an anti-inflammatory mediator that sensitizes cells to the effects of insulin, and leptin, a metabolic enhancer and satiety signaling hormone. Excess adipose tissue leads to a decrease in adiponectin and an increase in leptin secretion promoting an inflammatory state.[4] A lack of satiety signaling and downregulation of metabolism leads to increased hunger signals and additional positive energy balance creating a cycle that promotes WAT accumulation and metabolic dysfunction.

From a molecular energy utilization standpoint, a dietary intervention of IF enables systemic energy changes to be switched at the cellular level from utilizing glucose as the preferred energy-producing substrate to ketone bodies which are predominantly derived from fat stores. This metabolic switching increases NAD^+ levels which induce Sirtuin 1 (SIRT1). The Sirtuin family of proteins is known to upregulate autophagy, a process by which cellular components are degraded and recycled removing cellular waste and decreasing inflammation. In nerve cells, autophagy has been found to be neuroprotective. Elevated levels of NAD^+ also uncouple mitochondria by activating mitochondrial uncoupling proteins (UCP2 and UCP4) promoting mitochondrial biogenesis. This promotes more efficient oxidative phosphorylation and glycolysis which increases energy substrate utilization leading to sensitization to insulin. In addition, induction of SIRT1 inhibits proinflammatory pathway mediators such as FoxO1 and NF-kB by reducing their gene expression. In terms of post-stroke patients, it has been demonstrated that IF extensively alters post-ischemic gene expression which modulates metabolism, cell survival, and growth factors such as VEGF and HSP70 promoting neuroplasticity.[7]

According to a meta-analysis conducted by Lau *et al*., the prevalence of diabetes in stroke patients is 28% with the rate in ischemic stroke patients at 33% and hemorrhagic stroke patients at 26%. After any stroke, acute hyperglycemia and diabetes were associated with higher mortality, longer hospital stays with higher readmissions, and increased stroke recurrence.[5] In a population of 242 acute ischemic stroke patients, those with diabetes or pre-diabetes were associated with poor early prognosis (30-day modified Ranking Scale [mRS] score 2-6).[8] Allaf *et al.* conducted a meta-analysis of randomized controlled trials concluding that even though IF was superior to *ad libitum* feeding in reducing weight, there was no clinical significance in improving cardiometabolic risk in the short term.[1]

The current literature supports IF as a dietary intervention for reversing insulin resistance and hyperinsulinemia due to excess caloric intake. However, results have been mixed when a dietary IF intervention has been applied to a high cardiometabolic risk patient population. From a metabolic standpoint, it has been demonstrated that IF improves both lipid and glucose metabolism leading to improved glucose tolerance via increased insulin sensitivity, but some trials have not produced overwhelmingly positive results possibly due to the short duration of follow-up.

A diet composed mainly of vegetables, fruits, nuts, seeds, and high-quality protein sources is important for health and longevity. Controlling the amount of food consumed is immensely beneficial as it promotes multiple cellular and molecular protective mechanisms and simultaneously prevents toxic mechanisms. IF provides a non-pharmaceutical intervention for weight management thereby decreasing WAT and subsequent cardiometabolic risks. It is a flexible and easy-to-adopt dietary modification that helps to mitigate metabolic dysfunction like insulin resistance, and thus the devastating cardiometabolic age-related diseases of myocardial infarction, stroke, and dementia.

1. Allaf M, Elghazaly H, Mohamed OG, et al. Intermittent fasting for the prevention of cardiovascular disease. *Cochrane Database Syst Rev*. Jan 29 2021;1(1):Cd013496. doi:10.1002/14651858.CD013496.pub2
2. Fann DY, Ng GY, Poh L, Arumugam TV. Positive effects of intermittent fasting in ischemic stroke. *Exp Gerontol*. Mar 2017;89:93-102. doi:10.1016/j.exger.2017.01.014
3. Kim J, Kang SW, Mallilankaraman K, et al. Transcriptome analysis reveals intermittent fasting-induced genetic changes in ischemic stroke. *Hum Mol Genet*. Jul 1 2018;27(13):2405. doi:10.1093/hmg/ddy138
4. Guerreiro VA, Carvalho D, Freitas P. Obesity, Adipose Tissue, and Inflammation Answered in Questions. *J Obes*. 2022;2022:2252516. doi:10.1155/2022/2252516
5. Lau LH, Lew J, Borschmann K, Thijs V, Ekinci EI. Prevalence of diabetes and its effects on stroke outcomes: A meta-analysis and literature review. *J Diabetes Investig*. May 2019;10(3):780-792. doi:10.1111/jdi.12932
6. Dwaib HS, AlZaim I, Eid AH, Obeid O, El-Yazbi AF. Modulatory Effect of Intermittent Fasting on Adipose Tissue Inflammation: Amelioration of Cardiovascular Dysfunction in Early Metabolic Impairment. *Front Pharmacol*. 2021;12:626313. doi:10.3389/fphar.2021.626313
7. Vemuganti R, Arumugam TV. Much ado about eating: Intermittent fasting and post-stroke neuroprotection. *J Cereb Blood Flow Metab*. Jul 2021;41(7):1791-1793. doi:10.1177/0271678x211009362
8. Tanaka R, Ueno Y, Miyamoto N, et al. Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. *J Neurol Sci*. Sep 15 2013;332(1-2):45-50. doi:10.1016/j.jns.2013.06.010