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Intermittent Fasting Enhanced the Cognitive Function in Older Adults with Mild Cognitive Impairment by Inducing Biochemical and Metabolic changes: A 3-Year Progressive Study

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Received: 17 August 2020; Accepted: 28 August 2020; Published: 30 August 2020



Abstract: Intermittent fasting (IF) refers to various dietary regimens that cycle between a period of non-fasting and a period of total fasting. This study aimed to determine the effects of IF on cognitive function among elderly individuals who practice IF who have mild cognitive impairment (MCI). A total of 99 elderly subjects with MCI of Malay ethnicity without any terminal illness were recruited from a larger cohort study, LRGs TUA. The subjects were divided into three groups, comprising those who were regularly practicing IF (r-IF), irregularly practicing IF (i-IF), and non-fasters (n-IF). Upon 36 months of follow-up, more MCI subjects in the r-IF group reverted to successful aging with no cognitive impairment and diseases (24.3%) compared to those in i-IF (14.2%) and n-IF groups (3.7%). The r-IF group's subjects exhibited significant increment in superoxide dismutase (SOD) activity and reduction in body weight, levels of insulin, fasting blood glucose, malondialdehyde (MDA), C-reactive protein (CRP), and DNA damage. Moreover, metabolomics analysis showed that IF may modulate cognitive function via various metabolite pathways, including the synthesis and degradation of ketone bodies, butanoate metabolism, pyruvate metabolism, and glycolysis and gluconeogenesis pathways. Overall, the MCI-afflicted older adults who practiced IF regularly had better cognitive scores and reverted to better cognitive function at 36 months follow-up.

Keywords: DNA damage; intermittent fasting; metabolomics; mild cognitive impairment; oxidative stress; inflammation; older adults

1. Introduction

Neurodegenerative diseases, a heterogeneous group of disorders, are characterized by slow progressive loss of neurons [1]. Although the precise etiology underlying neurodegeneration has not been fully elucidated, oxidative stress has been suggested as one of the contributing factors of various neurodegenerative diseases and accelerated aging [2–5]. Levels of oxidative damage correlate significantly with the neurodegenerative impairment in various populations. For these reasons, there is a great

interest among researchers in finding ways to protect against oxidative damage and potentially treat neurodegenerative diseases, especially among individuals with mild cognitive impairment (MCI). MCI is a pre-stage for dementia, and it is known to be reversible. Previous research has reported that MCI is associated with impairment of glucose metabolism in the brain, dietary composition, and caloric intake [6].

Dietary approaches are suggested as more viable and non-invasive ways to prevent MCI incidence and to promote the reversion of MCI among the general public. Caloric restriction (CR) is one of the dietary regimens that have been shown to produce positive health effects. However, several alternative hypotheses argued that CR could cause damage to protein, lipids, and nucleic acids through the accumulation of reactive oxygen species (ROS) or reactive nitrogen species (RNS) [7]. Moreover, the compliance to long-term hypocaloric diet is inadequate, and other approaches more acceptable from the older adult perspective are needed. Thus, intermittent fasting (IF) is another approach that represents an alternative and more physiological way to prevent the deleterious effect of chronic excess of food intake [8].

IF is an umbrella term referring to various dietary regimens that cycle between a period of non-fasting and a period (long or short) of total fasting [9]. IF was intended as an alternative regimen that takes advantage of CR benefits, without eliciting any negative side effects from severe CR that causes malnourishment. Several studies support the idea that IF and CR activate similar biological mechanisms [10]. Interestingly, IF also reduces body weight the same as CR, but the difference is that CR produces loss of muscle mass and adipose tissue whereas IF reduces the adipose tissues whilst preserving muscle mass both in human and animal models [11]. Many scientific studies have been carried out, finding that IF gives beneficial health improvement by prolonging the lifespan and prevention of other chronic diseases including cardiovascular diseases, different forms of cancer, diabetes, and renal diseases [12,13].

Although previous studies have demonstrated the beneficial effects of IF with or without CR amongst an older population, most of these studies focused on healthy and obese people with no or limited MCI only. Fasting CR conducted among older adult men for 3 months via a clinical trial using a combination regime of CR with 2 days/weeks of Muslim sunnah fasting showed that CR with IF could improve metabolic parameters and quality of life, and alleviate the depression among these older subjects [12]. IF was also reported as one of the factors for reducing the risk of cognitive impairment among older adults in a large cohort conducted in Malaysia [14]. For these reasons, there is a need to identify the health benefits of IF among older adults with MCI. Hence, this study aims to investigate the effects of IF on biochemical profile, cognitive function, oxidative stress, genome health, and inflammatory responses among older adults with MCI. Besides this, this study also aims to identify the neuroprotective metabolites among older adults with MCI who practice IF since the human metabolomics data on this aspect remain unavailable.

2. Materials and Methods

2.1. Sample Size Calculation

The sample size was calculated using G*power software. F-test (analysis of covariance (ANCOVA): fixed effects, omnibus, one-way) was used to calculate the sample size. In this study, the effect of medium size (f) and error probability (α) were set to 0.40 and 0.05, respectively, while power ($1-\beta$) was 0.80.

2.2. Subject Recruitment

This study is a part of the longitudinal study on the neuroprotective model for healthy longevity (LRGS TUA) involving Malaysian older adults from four states in Malaysia with the highest prevalence of older adults aged 60 years and above [15]. Only Muslim subjects with MCI adhering to Petersen's criteria were recruited in this study [16]. Subjects were recruited for baseline analysis from May 2012 to February 2013 and were followed up for 36 months. Out of the 967 Malay subjects, only 118 subjects fulfilled the criteria. However, 19 subjects could not be followed up at 36 months because they could not be contacted, died, moved, could not complete all the study tests, or refused to follow this study