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Influence of Intermittent Fasting on Circulating Inflammatory and Oxidative Stress Markers in Obese Individuals: A Review

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ABSTRACT

Background Obesity entails low-grade chronic inflammation and oxidative stress, which result in metabolic disorders, such as insulin resistance, cardiovascular disease, and non-alcoholic fatty liver disease. These risks can be alleviated by dietary interventions that inhibit inflammatory and oxidative stress. Intermittent fasting (IF) is one of these strategies that are alternating feeding and fasting.

Material and Methods: PubMed and MEDLINE based systematic literature search was performed on human clinical trials, meta-analyses and narrative reviews published within 15 years. The keywords were used as follows: intermittent fasting, time-restricted feeding, alternate-day fasting, obesity, inflammation, CRP, TNF-a, oxidative stress, 8-isoprostane, malondialdehyde. Articles that included obese or overweight adults with a measure of circulating inflammatory (CRP, IL-6, TNF-a or oxidative stress (malondialdehyde, 8-isoprostane, catalase) were identified.

Findings: It has been shown that intermittent fasting can lead to a drop in some pro-inflammatory factors- TNF-a and C-reactive protein (CRP) reduction have been observed (1,2). The evidence of the improvement of the oxidative stress markers (e.g., the decrease in malondialdehyde, increases in catalase activity, etc.) in the overweight/obese groups is also emerging (3). The findings are however heterogeneous, especially of interleukin-6 (IL-6) and other markers and most of the trials are short term or small-scale trials.

Conclusion: The intermittent fasting can be considered a promising non-pharmacological intervention to reduce systemic inflammation and oxidative stress in obese patients, which may be the cause of other metabolic issues. However, further, more rigorous, better-powered trials are needed to elucidate best regimens and mechanistic circuits. .

KEYWORDS: intermittent fasting, inflammation, oxidative stress, obesity, C-reactive protein, malondialdehyde.

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INTRODUCTION

Obesity has now been identified as a chronic disease with systemic implications, with an excessive amount of adiposity that puts a person at risk of health hazards. Besides the direct influence on the growth of adipose tissue, obesity is characterised by the continued low-grade inflammation and increased oxidative stress. The pro-inflammatory cytokines released by adipocytes in the hypertrophied adipose tissue tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6) and elevates levels of the circulating C-reactive Protein (CRP); these inflammatory conditions help to promote insulin resistance, endothelial dysfunction and metabolic dysregulation (1). At the same time, an excess of calories in the body and metabolic overload in obese people contribute to the overproduction of reactive oxygen species (ROS), the deterioration of mitochondrial activity and exhaustion of the antioxidant defence system, which increases oxidative stress (2). Chronic inflammation and oxidative stress are two processes that play a significant role as the mediators of obesity-related complications such as type 2 diabetes mellitus, non-alcoholic fatty liver disease, and cardiovascular disease.

It is against this backdrop that dietary interventions that are not only focused on weight reduction but also adjustment of inflammation and oxidative stress aroused interest. Intermittent fasting (IF) is one of such interventions. In contrast to the continuous caloric restriction, IF focuses on when food is consumed and alternates between eating and starvation. Some of the most common ones are time-restricted eating (TRE), alternate-day fasting (ADF) and a 5:2 diet. IF induces metabolic changes:

the substitution of a glucose metabolism with a fatty acid/ketone metabolism, the activation of the autophagy process, and the enhancement of mitochondrial efficiency (3). Such adaptations can lead to the reduction of ROS production, the enhancement of antioxidant reaction and reduction of inflammatory signalling (3,4).

Mechanistically, in the process of. fasting, the glycogen stores are emptied and lipolysis is triggered, which favors the synthesis of ketone bodies like b-hydroxybutyrate. These metabolites are known to suppress NLRP3 inflammasome, inhibit NF-kB activation hence suppress systemic inflammation (4). At the same time, the fasting process activates nutrient-sensing pathways such as AMPK and sirtuins, which promote mitochondrial biogenesis, assists in antioxidant enzyme expression (e.g., superoxide dismutase, catalase), and cell resilience to oxidative stress (3). There is animal and human research indicating that IF can decrease signs of oxidative stress and enhance vascular and metabolic wellbeing (5). It has been suggested that the synergistic action of the decreased inflammatory response and oxidative stress is the basis of the metabolic health advantages of IF.

Nevertheless, the metabolic and weight-loss impact of IF has been comparatively well-documented, whereas the particular impact of IF on the circulating inflammatory and oxidative stress biomarkers in obese patients have been less evident. Cases of CRP/or TNF-a reduction, some with minimal impact on IL-6; oxidative stress measures, including malondialdehyde or 8-isoprostane, have only been examined in limited settings (6). Also, heterogeneity in fasting regimes, duration of intervention, weight loss attained, and study groups make it difficult to interpret. The knowledge of whether IF has effects on these biomarkers independently of weight loss, and the extent of its effects in people undergoing obesity are pertinent to developing specific interventions to reduce the metabolic risk factors.

This review, therefore, attempts to integrate the existing information on the effect of intermittent fasting on systemic inflammatory and oxidative stress levels in obese or overweight human populations. We emphasize the mechanistic pathways, followed by a critical analysis of the findings of human trials and gaps, as well as recommendations of future investigations.

Material and Methods: The systematic literature search was performed in PubMed and MEDLINE regarding human clinical trials, meta-analyses, and narrative reviews that have been published within the past 15 years. The keywords were intermittent fasting, time-restricted feeding, alternate-day fasting, obesity, inflammation, CRP, TNF-a, oxidative stress, 8-isoprostane, malondialdehyde. Research papers that included obese or overweight adults with the measurement of inflammatory markers (CRP, IL-6, TNF-a) or oxidative stress markers (malondialdehyde, 8-isoprostane, catalase) were included.

DISCUSSION

The accumulated literature on the effects of intermittent fasting (IF) on circulating inflammatory and oxidative stress markers in obese subjects shows some potential and uncertainty to the research. Mechanistically, IF is likely to be anti-inflammatory and anti-oxidative. Fasting regimes induce the metabolic switch to fatty acid oxidation and ketogenesis, which produces b-hydroxybutyrate, which prevents NLRP3 inflammasome and suppresses NF-kB signalling, consequently decreasing the production of pro-inflammatory cytokines (3,4). Along with it, nutrient deficiency causes the activation of the AMPK and SIRT1, which increase the rate of mitochondrial biogenesis, enhance redox homeostasis, up-express antioxidant enzymes (e.g., superoxide dismutase, catalase) and down-regulate the production of ROS (3). The animal interventions have always shown a decrease in the oxidative stress parameters of malondialdehyde (MDA) and a high level of total antioxidant capacity (TAC) under the fasting conditions (6,7).

To consider human data, a recent systematic review of IF and inflammatory biomarkers showed significant changes in TNF-a (standardised mean difference [SMD] [?] -0.31, p = 0.009) and CRP (SMD [?] -0.19, p = 0.04) in comparison with controls (2). Nevertheless, the effect of IL-6 was not significant (SMD [?] -0.13, p = 0.37) (2). The other meta-analysis established that IF has a CRP-reducing effect on obese/overweight individuals, especially when weight loss was attained (1). The initial TRE study (16 h fast/8 h if the experiment lasted 4 weeks) did not demonstrate any significant reduction in IL-6 or hs-CRP nor in TNF-a or IL-1b in older overweight adults; however, the reduction in oxidative stress marker 8-isoprostane was minimal (8). These conflicting findings point to how complicated biomarker modulation is.

The effect sizes appear to be attenuated especially when focusing on the obese populations. Indicatively, a 12-month comparison of adults with obesity observed that TRE or caloric restriction resulted in a mean loss of weight at 4-5 percent, but no significant alteration in TNF-a, IL-6 or CRP (9). This indicates that the extent of losing weight, the length of intervention, or the underlying state of metabolism might mediate the response of biomarkers. A trial on oxidative stress front reported that, in overweight/obese post-menopausal women with rheumatoid arthritis, 16:8 IF diet over 8 weeks had significant lowering of MDA and increased catalase activity over control albeit with comorbidity (10). Therefore, the generalisation is weak even though the markers of oxidative stress appear more receptive in some sub-groups.

There are a number of reasons that can explain heterogeneity in findings. To start with, a good number of IF trials induced weight loss simultaneously; considering that weight loss alone lowers inflammation and oxidative stress, it is hard to separate the independent influence of fasting (1). Second, the length of interventions has not been long (less than 12 weeks) and has restricted long-term evaluation. Third, there are differences in the selection of the markers (CRP, IL-6, TNF-a, leptin, adiponectin, 8-isoprostane, MDA, catalase, TAC) which makes meta-analysis difficult. Fourth, there are differences in fasting schedules (TRE, ADF, 5:2) based on fasting length and eating periods, which can affect the response of biomarkers (2). Lastly, the metabolic status of a baseline (level of obesity, insulin resistance or not) and the dietary intake and physical activity are not the same, which depend on the results.

To be used practically, the results are provisional evidence of IF as an intervention to decrease systemic inflammation and oxidative stress in obese patients, in combination with moderate weight reduction and lifestyle modifications. Researchers and clinicians are to assume that >5% weight loss, regular fasting procedures, and sufficient period of time might be needed to improve biomarkers ([?]12-16 weeks). Notably, future RCTs ought to standardise the fasting regimens, provide sufficient sample size and duration, obese populations in particular, and the weight-loss independent and dependent changes on the biomarkers.

CONCLUSION

In short, intermittent fasting is potentially meaningful in regulating the circulation of inflammatory and oxidative stress biomarkers in obese people. Anti-inflammatory and antioxidative properties are biologically plausible through mechanistic reasons such as the activation of ketogenesis, the AMPK/SIRT1 signatures, autophagy and better mitochondrial/antioxidant performance. Human evidence shows IF has the ability to decrease pro-inflammatory i.e. TNF-a and CRP, and in some selective studies, oxidative stress i.e. MDA, catalase. The findings are however, heterogeneous, especially that of IL-6 and other biomarkers and appear to be moderated by factors like the extent of weight loss, fasting regimen, length of interventions, and initial metabolic condition.

In this way, although intermittent fasting can be suggested as an effective non-pharmacological method of decreasing systemic inflammation and oxidative stress in obesity, it must be viewed as a component of a larger lifestyle approach. Its effects will probably be improved by weight management, physical activity, the quality of the diet and possibly circadian alignment. To apply IF to clinical practice, more well-designed long-term studies in obese populations are required, to determine the best fasting regimens, whether the changes in biomarkers not dependent on weight loss are beneficial, and whether the effects of decreasing inflammation and oxidative stress on reducing obesity-related complications are apparent.

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