Review Article

Intermittent fasting may optimize intestinal microbiota, adipocyte status and metabolic health

Diana Matías-Pérez PhD[1], Emilio Hernández-Bautista PhD[2], Iván Antonio García-Montalvo PhD[1]

[1] *Division of Graduate Studies and Research, Tecnológico Nacional de México/Instituto Tecnológico de Oaxaca, Oaxaca, México*
[2] *Department of Chemical and Biochemical Engineering, Tecnológico Nacional de México/Instituto Tecnológico de Oaxaca, Oaxaca, México*

The aim of this review is to provide an overview of the present association between Intermittent Fasting (IF), the Gut Microbiota (GM), and the adipocyte with respect to Metabolic Health (MH). A search was carried out through Dialnet, Scielo, Web of Science, Redalyc and PubMed, using keywords such as: "intermittent fasting", "time-restricted feeding", "gut microbiota" and "Metabolic Health". Intermittent fasting (IF) regimens promote weight loss, therefore contributing to improved metabolic health. IF beneficially participates in the modulation of the intestinal microbiome, allowing a continuous interaction with nutrients to be digested and shaping the intestinal immune responses during the development of cardiovascular disease, blood pressure and diabetes mellitus through metabolic activities.

Key Words: intermittent fasting, intestinal microbiota, metabolic health

INTRODUCTION

The globalization of the Western lifestyle, through the so-called epidemiological transition has allowed noncommunicable diseases (cardiovascular disease, diabetes mellitus and dyslipidemias) to be responsible for approximately 67% of mortality worldwide. The increase in adipose tissue is associated with a set of metabolic disorders, such as the so called Metabolic Health (MH).[1,2] The MH is characterized by a series of metabolic disorders or abnormalities that together are considered a risk factor for the development of diabetes mellitus and cardiovascular diseases, being the most important characteristics of this syndrome are: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance and prothrombotic-inflammatory situations.[1-5] If the subject presents three of the five factors according to the Adult Treatment Panel III 2014 diagnostic criteria, they will be considered with MH, these are: Waist circumference: >102 centimeters (cm) in men and >88 cm in women; blood pressure: >130/85 mmHg, fasting capillary glycemia: ≥100 mg/dL; high-density lipoprotein: <40 mg/dL in men and >50 mg/dL in women; hypertriglyceridemia: plasma triglycerides ≥150 mg/dL.[6] Poor control over dietary patterns (excess meals during the day or prolonged fasting >15 hours (h)) leads to an altered circadian rhythm, which translates into metabolic dysregulation, an altered metabolic homeostasis and increased cardiometabolic risks in these patients.[7-10] In this context, health care providers have proposed dietary improvement and structured lifestyle interventions as the first line of defense. However, due to patients poor or non-adherence to changes in their food quality and quantity, low or no physical activity and the promotion of weight loss with low-calorie diets are inadequate; since these strategies are difficult to maintain for prolonged periods of time, therefore, its effectiveness for the treatment of MH is limited. As an alternative strategy, intermittent fasting (IF) has been used to achieve progressive weight loss in obese people.[11] The alternative dietary weight loss strategies that involve restricting energy intake to certain periods of the day or prolonging the fasting interval between meals (intermittent energy restriction, IER). These strategies include intermittent fasting (IF; >60% energy restriction on 2-3 days per week, or on alternate days) and time-restricted feeding (TRF; limiting the daily period of food intake to 8-10 h or less on most days of the week).[12] Intermittent fasting is a pattern of eating in which there are alternating periods of eating and a defined phase of prolonged fasting. IF can be defined as, a voluntary abstinence from food and drink for specific periods, in addition to recurring. In IF, the subject's participation is voluntary.[11-14] The intestinal microbiota (GM) plays imp-

Corresponding Author: Dr Iván Antonio García-Montalvo, Division of Graduate Studies and Research, Tecnológico Nacional de México/Instituto Tecnológico de Oaxaca (TECNM/ITO). Avenida Ing. Víctor Bravo Ahuja No. 125 Esquina Calzada Tecnológico, C.P. 68030.
Tel: (+52)9515015016
Email: ivan.garcia@itoaxaca.edu.mx
Manuscript received 14 January 2022. Initial review completed 17 January 2022. Revision accepted 08 February 2022.
doi: 10.6133/apjcn.202203_31(1).0002

ortant roles in our organism as it has a reciprocal relationship with the circadian rhythm and eating habits. Food intake alters the inherent diurnal rhythm of the intestinal microbiome, the food content itself and feeding times play a key role in this process.[15,16] IF promotes browning of white adipose tissue and decreases obesity through modification of the intestinal microflora.[17] Time-restricted feeding contributes to the decrease of various obesogenic microorganisms and increases the proliferation of bacteria with protective functions against obesity.[18] Based on the above, the objective of this review is to provide an overview of the present relationship between Intermittent Fasting (IF) regimens and Intestinal Microbiota (GM) in patients with Metabolic Health (MH), through the search for information in the following computer resources: Web of Science, Pubmed, Redalyc, Scielo, Dialnet and Google Scholar; using and with keywords including intestinal microbiota, intermittent fasting, metabolic health and intestinal dysbiosis.

PHYSIOLOGICAL BASES OF FASTING

During the fasting phase, a coordinated alteration of metabolic and transcriptional mechanisms is induced. After 12 to 36 h of fasting, the body has decreased blood glucose concentration, decreased liver glycogen stores, and hepatic production of fat-derived ketone bodies, or ketones, which are used as energy for the brain.[19,20] Glucose sensitive neurons respond by activating sympathetic neurons, for example, norepinephrine released in the stomach allows the stimulation of ghrelin secretion, which affects the release of growth hormone, thereby maintaining plasma glucose concentration.[21,22] The fasting biological environment causes an elevated glucagon/insulin ratio, which facilitates the mobilization of free fatty acids towards the liver, being a sufficient stimulus to form ketone bodies (30% of free fatty acids present in adipose tissue are converted in the liver to ketone bodies). In the physiological condition of prolonged fasting for several days, ketones become the preferred fuel source of the brain, providing between 65-70% of its energy needs, becoming a more efficient source of energy in the muscles and brain, improving bioenergetics, as well as the connective activity of neurons.[20] When insulinemia is low, the liver forms ketone bodies from acetyl-CoA. Under these conditions, lipolysis is active and increases in adipose tissue, releasing increasing amounts of fatty acids. A quantity of these substances is taken up by the liver, where β-oxidation is activated, with a consequent production of acetyl-CoA. As the anabolic pathways that acetyl-CoA could follow are blocked, such as the synthesis of fatty acids and cholesterol due to the absence of insulin and the consequent deactivation of the regulatory enzymes of these processes, acetyl-CoA is channeled into the formation ketone bodies (Acetoacetate, Beta-hydroxybutyrate and Acetone).[23] Beta-hydroxybutyrate (BHB) is involved in signaling functions by inducing transcription of brain-derived neurotrophic factor derivatives (BDNF), which is a regulator of neuronal function that stimulates mitochondrial biogenesis, maintains the synaptic structure, regulates the production and survival of new neurons, and increases their resistance to injury and disease. Fasting induces peroxisome proliferator activated receptor gamma 1 alpha protein expression (PGC-1 alpha), involved in the modulation of genes associated with the metabolism of carbohydrates and fatty acids. Also, fasting suppresses inflammation by reducing the expression of proinflammatory cytokines (Interleukin 6; IL-6, and Tumor Necrosis Factor α; TNF-α).[23] The stimulation of gluconeogenesis is manifested through a negative nitrogen balance because during the first five days of fasting about 75 g of protein can be catabolized daily. Glycemia decreases during fasting, reaching a plateau around the third day, this fall is due to the depletion of hepatic glycogen and the delay of gluconeogenesis (Figure 1), derived from this, it remains low for about a week. With continuous fasting, several mechanisms are produced by which glycemia is normalized (the tissues metabolize more easily fatty acids and ketone bodies; gluconeogenesis is intensified, producing 30 to 35 g/d of carbohydrates from amino acids and glycerol).[23,24] During IF, lipid metabolism is influenced by altering the hormonal activities of leptin, adiponectin, and ghrelin. Leptin is associated with a pro inflammatory state, while adiponectin is associated with increased sensitivity to insulin. Ghrelin can stimulate neurogenesis. Leptin decreases but adiponectin and ghrelin increase, these alterations are probably beneficial for the bioenergetics of neurons and the maintenance of neural pathways.[25,26] IF not only consist of not eating, but doing it at specific time intervals, that is, establishing intervals of 12 h where meals are organized and 12 h where fasting takes place, although some studies propose fasting for 16 h and eating for the remaining 8 h.[26-28]

RELATIONSHIP BETWEEN THE INTESTINAL MICROBIOTA AND METABOLIC HEALTH

The intestinal microbiota (GM) participates both in the digestion and the fermentation of complex carbohydrates, the synthesis of vitamins, the development and maturation of the immune system of the gastrointestinal mucosa, the defense against intestinal pathogens, as well as, in direct interaction with the enteric nervous system through the release of endocrine mediators in the interstitial tissue.[29] Also, GM regulates the innate and adaptive mechanisms of immune homeostasis. These bidirectional mechanisms of action are related to the epithelial and immune cells that act as an epithelial barrier, and to tolerance to the microorganisms present in the intestine. The latter are represented by the multitude of bacteria that constitute the microbiota, whether residents or transients, such as viruses, fungi, and sometimes even parasites. The intestinal mucosal epithelium participates in events of absorption, mucus production, secretion of antimicrobial peptides, various hormones, and antigen sampling. Beneath the epithelial layer, in the lamina propria, a series of innate and adaptive immune cells are located, including B cells, T cells, macrophages, dendrite cells, and innate lymphoid cells, responsible for immune responses.[30,31] The secretion of substances by GM involves short chain fatty acids (acetate, butyrate, and propionate), neurotransmitters (serotonin, dopamine, noradrenaline, gamma amino butyric acid, tryptophan, serotonin, dopamine), bile acids, hypothalamic-pituitary-adrenal axis hormones (cortisol), gastrointestinal hormones (leptin and PYY).[32] There are several neurotransmitters and hormones involved in this pro-

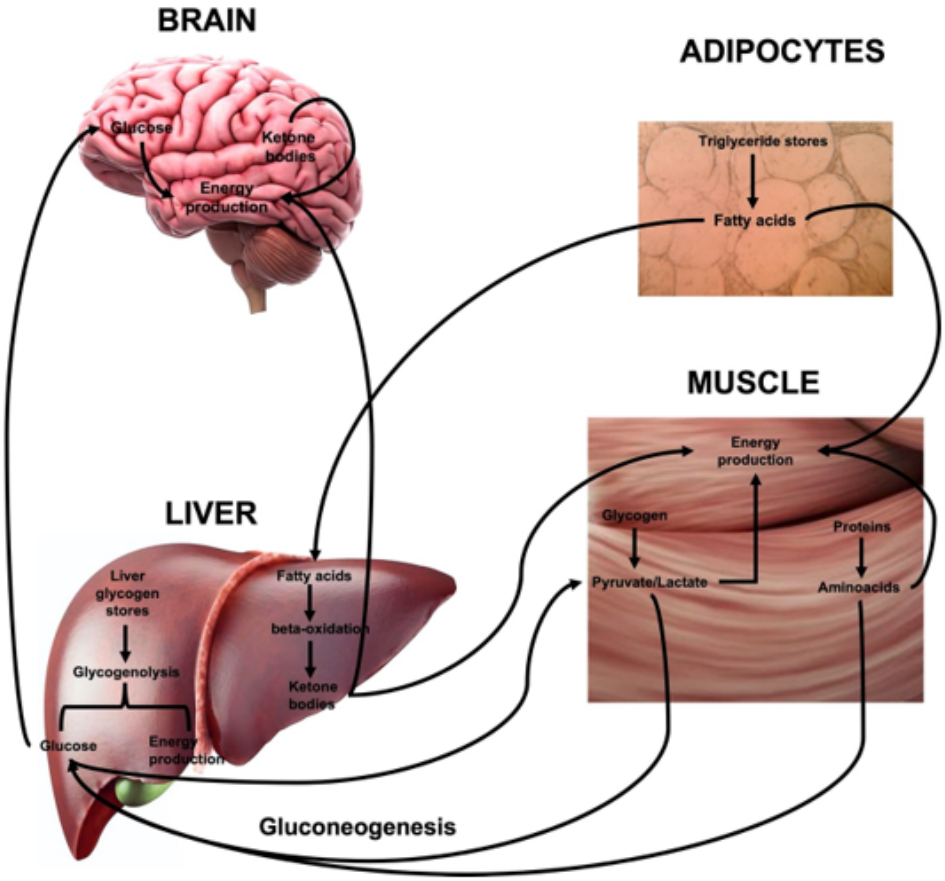

Figure 1. Metabolism and utilization of ketone bodies in intermittent fasting.

cess, there is a group called incretins (intestinal secretion of insulin) that are produced by enteroendocrine cells distributed throughout the digestive tract, from the stomach to the distal colon. Incretins enhance insulin secretion in response to glycemia, regulating it and are responsible for around 70% of the postprandial insulin concentration. The two most important are gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP1). Propionate modulates energy homeostasis by activating sympathetic neurons mediated by GPR41 (G41 protein-coupled receptor), in contrast to ketone bodies. The ability to modulate sympathetic outflow provides another mechanism that links the intestinal microbiota with the enteric nervous system, energy expenditure, and metabolic homeostasis.[32,33] Some bacteria producing these molecules with endocrine activity are Lactobacillus and Bacteroides. GM is fluctuating throughout growth and development, susceptible to modifications associated with diet, birth pathway and even systemic diseases. The loss of functional balance in GM is called dysbiosis, and it has been associated with MH, through GM-mediated endocrine signaling in insulin resistance and chronic inflammation. In MH, the intestinal microbiota is implicated due to its involvement in the development of obesity by increasing energy and stimulating inflammation, lipopolysaccharides (LPS) from the membranes of Gram-negative bacteria and other molecular patterns associated with microbial pathogens (PAMPs) promote inflammation, which is associated with early processes in obesity and the development of insulin resistance.[34] One of the proposed mechanisms is that the deterioration of the intestinal microbiota with a specific or modified composition leads to an increase in intestinal permeability and subsequently, to a high concentration of systemic bacterial products such as LPS (metabolic endotoxemia).[35,36] The intestinal composition of an adult is stable; however, it depends on multiple factors (environment, diet, lifestyle, and diseases). Short term and long term diets have been shown to alter the gut microbiota; in the case of short term diets, the composition of the gut microbiota reverts to its primitive state; therefore, a stable modification of the composition of the intestinal microbiota requires long term nutritional adaptations.[37,38] Insulin resistance is recognized as an indispensable part of the pathophysiology of MH, leading to compensatory hyperinsulinemia, however, this long term mechanism favors the development of obesity, contributing to the progressive failure of the beta-pancreatic cells, and triggering dysglycemia and diabetes mellitus. Nevertheless, insulin resistance does not develop homogeneously in each of the insulin sensitive tissues and their functions (regulation of lipid metabolism, cell proliferation, vascular tone, and appetite modulation). Specific changes in GM composition have been associated with the development of insulin resistance, derived from the overgrowth of microbial species with elevated short chain fatty acid fermentative activity, high pyruvate metabolism and potentiation of the pentose phosphate pathway of fatty acid biosynthesis, and glycerolipid metabolism; thus favoring the accumulation of adiposity, the development and progression of obesity and insulin resistance.[39-41] The intestinal microbiota of obese patients presents less biodiversity than that of normal weight patients, those individuals with less biodiver-

sity tend to present greater adiposity, insulin resistance, dyslipidemia and a more pronounced inflammatory phenotype compared to those with high biodiversity. The presence in the intestinal microbiota of high concentrations of Staphylococcus aureus and low concentrations of Bifidobacterium spp in childhood predict the future appearance of overweight or obesity. In relation to the predominant microbiota, changes observed in its composition and function are related to a higher risk of type 2 diabetes, which is assoaciated to an increase in the number of *Bacteroides* and *Clostridium*.[42,43] The contribution of dietary fat alters the composition of the intestinal microbiota, increasing gram-negative bacterial populations and altering the intestinal barrier function. These events lead to increased plasma concentrations of LPS and the subsequent development of a low-grade inflammatory state that facilitates the development of insulin resistance and type 2 diabetes mellitus (T2D).[44]

METABOLIC HEALTH AS A THERAPEUTIC TARGET OF INTERMITTENT FASTING

The first line of therapy for metabolic health is aggressive diet and lifestyle interventions (reducing caloric intake, adopting a healthier eating plan, and increasing physical activity), however, these interventions are insufficient to effectively control the disease, rather, it may gradually get worse, and patients are often given medications to treat their symptoms. Treatment of the metabolic health is important to prevent progression to T2D and reduce morbidity and mortality from T2D or cardiovascular diseases. Within the mechanism of participation of intermittent fasting and the relationship with the metabolic health, we can mention the mechanistic objective of rapamycin (mTOR), a serine-threonine kinase that participates as an intracellular energy sensor, stimulating the response to growth factors and increasing amino acids or glucose. Low glucose or amino acid concentrations during fasting are associated with decreased mTOR activity. Fasting regulates mTOR activity, which stimulates autophagy, cell repair, and increases mitochondrial biogenesis. Another cell mediator of interest is sirtuins (sirtuin 3), which is in the mitochondria of metabolically active tissues (heart, kidney and skeletal muscle) stimulating in response to fasting and exercise.[6,44-46] The IF cycle model of feeding with established fasting and feeding periods, generates adaptive cellular responses since cells participate in tissue specific processes of growth and plasticity during the feeding period, stress resistance and suppression of inflammation, as well as delayed aging. These functions are dependent on diet, gender, and genetic factors. Total dietary energy intake and the duration of fasting between meals favour changes in bioenergetic levels such as: NAD, ATP, and acetyl CoA. These energy transporters activate proteins that mediate cellular function and stress resistance, thereby generating neuroendocrine and adaptive responses to low glucose concentration.[47] The two main types of IF are: alternate-day fasting and time-restricted fasting. In alternate day fasting, the subset may consist of 24 h fasts followed by a 24 h period of feeding that can be performed several times a week, as noted by the 5:2 strategy, in which there are 2 fasting days mixed with 5 unrestricted days. For time-restricted fasting, variations include 16 h fasts with 8 h feeding times, and 20 h fasts with 4 h feeding times. IF is involved in the main features that compose the metabolic health spectrum, such as its participation in the control of dyslipidemias, blood pressure, obesity, and T2D.[19]

IF has been used as a dietary intervention strategy, periodic energy restriction has been shown to decrease the risks of aging and associated conditions, in addition to providing satisfactory results in terms of body weight control and metabolic health in study patients,[48] as well as cardiovascular disease and dyslipidemia. Also, IF reduces markers of systemic inflammation and oxidative stress associated with atherosclerosis. It has been reported that individuals who did not eat breakfast have a higher risk of atherosclerosis compared to those who ingested high calories at breakfast. Individuals who did not eat breakfast compared to the high caloric intake group showed unfavorable parameters: higher percentage of central obesity, body weight, body mass index, waist circumference, dyslipidemia and glycemia. Stanislawski et al (2021), mention that the intestinal microbiota plays a fundamental role in the development of obesity in addition to contributing to weight loss. Dysbiosis has been linked to the pathogenesis of obesity in both animal models and humans, derived from the mechanism involving energy homeostasis/nutrients absorption, inflammatory pathways, appetite regulation, and/or the generation of small molecules that alter metabolism. Weight loss has been shown to result in changes in the intestinal microbiota and there is evidence that the intestinal microbiota and gut-derived metabolites may be important mediators of the response to dietary energy restriction. In work conducted by these researchers they compared the weight loss produced by intermittent fasting (IF, restriction of 80% of energy intake for three nonconsecutive days per week with no restriction of intake on the intervening days) with the current standard of care dietary approach to weight loss of daily caloric restriction (DCR), both groups targeting an equivalent weekly energy deficit (34%), receiving identical exercise prescriptions and a comprehensive behavioral weight loss program based on the group.[49] In their conclusions, they demonstrated that the gut microbiota is involved in the regulation of body weight and contributes to responsiveness during a weight loss intervention. During the first three months of a lifestyle-based weight loss intervention that included an energy restricted diet and increased physical activity, the intestinal microbiota of the participants changed significantly. The initial composition of the intestinal microbiota predicted the change in waist circumference at three months and that numerous bacterial taxa were associated with improvements in weight and waist circumference measurements. This leads to the fact that the structure of the intestinal microbiota community can influence the response to weight loss efforts, which is critical to understand more fully, as the intestinal microbiota profiles can be altered through various means, such as probiotics/prebiotics, personalized diet changes, or targeting of intestinal microbiota pathways and metabolites.[49,50] Obesity: IF is effective for weight loss compared to the use of standard diets.[51,52] Another study found that it was effective for weight loss and cardiovascular health in overweight and normal

weight adults, mentioning that daily calorie restriction versus intermittent restriction is equally effective in reducing weight and fat mass.[11] In a randomized trial, they concluded that there is no superior adherence, weight loss, weight maintenance, or cardioprotection versus daily caloric restriction, although IF may be more effective for not losing lean mass.[53] Through a meta-analysis, the authors found that skipping breakfast increases the risk of over-weight/obesity by 48% in cross-sectional studies and 44% in cohort studies.[54] T2D: Two studies showed that 24 h IF (4:3), 3 times per week successfully reversed insulin resistance in patients with prediabetes or T2D, thereby reducing glycosylated hemoglobin concentrations, oxidative stress, and appetite control.[55] The study group consisted of patients were older adult, with a high percentage of women and smokers, who had consumed a diet with a higher intake of calories per day, animal protein, total fat, cholesterol, processed foods, alcoholic beverages and, on the other hand, consumed less dietary fiber, vegetables, and whole grains.[56] Another study reported that the alternate-day fasting group that underwent a 75% alternate-day caloric restriction had a 10±4% reduction in LDL and a 17±5% reduction in triglycerides after 12 weeks.[57] Another study, obese patients showed an improvement in HDL and LDL concentrations after 12 weeks of alternate day fasting combined with exercise.[57] Blood pressure: IF has been shown to reduce systolic and diastolic blood pressure. In a study of men with prediabetes, a mean reduction in systolic blood pressure of 11±4 mmHg and a reduction in diastolic blood pressure of 10±4 mmHg was observed after 5 weeks of fasting for 18 h periods.[58] Through the analysis of heart rate and blood pressure, it was concluded that those patients who perform IF have a lower frequency component in the variability of diastolic blood pressure, a marker of sympathetic tone. IF is considered to have the ability to reduce blood pressure, thus improving mortality from noncommunicable diseases such as cardiovascular diseases.[59,60] Some lifestyle modifications can promote metabolic health, such as: Sleep, there is evidence through observational studies that eating at night is associated with a reduced duration and poor quality of sleep, which can later lead to insulin resistance and thus increase the risk of obesity, diseases cardiovascular and diabetes. Altered circadian timing due to these behaviors can lead to circadian desynchronization affecting normal sleep patterns.[61-64] The metabolic disturbances associated with sleep loss may be mediated by the overgrowth of specific gut bacteria. The end products of bacterial species that grow in response to sleep loss can induce fatigue. The positive effects of intermittent fasting on sleep latency and sleep efficiency may be due to its effect on the intestinal microbiota, probiotic supplementation improves subjective sleep quality.[65] Energy consumption, most fasting regimens reduce the total number of hours available for eating and thereby may reduce overall energy consumption and risk of obesity. A dysregulation in working hours (shift or night) has shown alterations in the hormones that regulate appetite (leptin, ghrelin and xenin) that can lead to increases in total energy intake.[66-68]

ADIPOCYTE STATUS AND INTERMITTENT FASTING

The adipocyte is a cell with the ability to generate and receive information from its environment and intervene in the low-intensity chronic inflammatory process resulting from obesity. In the increase in the amount of adipose tissue, two processes are involved: the increase in size of adipocytes and the increase in the number of adipocytes. Under normal conditions, 80% of adipose tissue is in the subcutaneous cellular tissue, while visceral adipose tissue represents less than 20% of total body fat in men and approximately 6% in women. Subcutaneous abdominal fat deposits are located below the regional skin. In the lower body segment, all fatty deposits are subcutaneous; the two main sites of accumulation are the femoral and gluteal regions. Visceral adipose tissue is made up of smaller adipocytes, with less storage capacity, is more vascularized, and has greater sympathetic innervation and a large number of β3-adrenergic receptors, which facilitates greater metabolic activity.[69] There are two types of adipose tissue, and therefore two different types of adipocytes that form them: Brown or brown adipose tissue is responsible for thermogenesis; its colour is due to the large amount of hemoprotein cytochrome oxidase, and the mitochondria it possesses express high amounts of uncoupling protein (UCP), UCP that produce uncoupled oxidative phosphorylation with the consequent dissipation of energy in the form of heat; White adipose tissue is the most abundant in the adult human body and therefore the largest energy reservoir as already mentioned, in the form of triacylglycerides, coming from chylomicrons and VLDL circulating. Due to its wide distribution, it is an excellent thermal insulator and plays an important role in maintaining body temperature, being considered the main buffer system for energy balance.[70,71] White adipose tissue releases secretion products that are involved in the regulation of energy intake-expenditure and glucose homeostasis, or both (leptin, adiponectin, resistin, visfatin, acylation-stimulating protein or ASP), immune inflammatory response (TNF-α, IL-6, IL-1, C-reactive protein, serum amyloid A, haptoglobin, monocyte chemoattractant protein 1), vascular function (angiotensinogen, angiotensin, resistin), blood coagulation (PAI1, tissue factor), complement pathway (adipsin), growth factors (TGF-β), in angiogenesis (VEFG) and reproductive function.[69,72,73] The adipose tissue of obese patients is characterized by hypertrophy and hyperplasia of adipocytes and by changes in their metabolic functions, the adipocyte being the largest producer of inflammatory adipokines in these conditions.[74-77] There are several mechanisms capable of inducing inflammatory pathways: By extracellular mediators such as cytokines and lipids; Due to intracellular stress, such as stress on the endoplasmic reticulum system, understood as an increase in its functional demands induced by obesity, which causes changes in architecture, increased protein and lipid synthesis, and disturbances in energy flows and of intracellular nutrients in adipose tissue.[78] Mention is made below of some ways in which the role played by intermittent fasting and adipocytes can be seen:

Li et., mention that, while activation of beige thermogenesis is a promising approach for treatment of obesity-

associated diseases, there are currently no known pharmacological means to induce beiging in humans. Intermittent fasting is an effective and natural strategy for weight control. Every other day fasting (EODF) regimen selectively stimulates beige fat development within white adipose tissue, and dramatically ameliorates obesity, insulin resistance and hepatic steatosis. EODF treatment results in a shift in the gut microbiota composition leading to the elevation of the fermentation products acetate and lactate, and the selective upregulation of monocarboxylate transporter expression in beige cells.[79] Harney et al., establish that, intermittent fasting is a beneficial dietary treatment for obesity. A key change in subcutaneous white adipose tissue (scWAT) and visceral white adipose tissue (vWAT) depots is an increase in mitochondrial protein content after EODF. This effect is correlated with increased fatty acid synthesis enzymes in both white adipose tissue (WAT) depots but not in brown adipose tissue. EODF treatment downregulates lipolysis specifically in vWAT, mediated by a large decrease in the abundance of the catecholamine receptor (ADRB3). Enrichment analysis highlights downregulation of inflammatory collagen IV specifically in vWAT, allowing improved insulin sensitivity.[80]

CONCLUSIONS

In conclusion, we can say that intermittent fasting is a strategy to be considered today as it has wide applications not only for weight loss, but also for improving the health of people with metabolic health disorders (dyslipidemia, hypertension, T2D and/or overweight). Evidence has been found that IF participates beneficially in modulating the intestinal microbiome, allowing a continuous interaction with nutrients to digest and shape intestinal immune responses during the development of cardiovascular disease through metabolic activities. The implementation of the IF may favor the relationship between intestinal microbiota and the pathogenesis of obesity, metabolic health, and even T2D, by influencing body weight, proinflammatory activity, and insulin resistance, as well as neurodegenerative diseases. It has been found that IF collaborates in the reduction of plasma LPS, which has been recognized as a possible trigger of the systemic inflammatory response and atherosclerotic cardiovascular disease, in the same way IF is important in the increase of anti-inflammatory cytokines and in situations of metabolic oxidative stress.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

REFERENCES

1. Hyder AA, Wosu AC, Gibson DG, Labrique AB, Ali J, Pariyo GW. Noncommunicable disease risk factors and mobile phones: a proposed research agenda. J Med Internet Res. 2017;19:e133.
2. Mercer AJ. Updating the epidemiological transition model. Epidemiol Infect. 2018;146:680-7.
3. Fonseca É, Figueredo N, Rocha T, Nogueira I, Melo J, Silva B et al. Metabolic syndrome and insulin resistance by HOMA-IR in menopause. Int J Cardiovasc Sci. 2018;31: 201-8.
4. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clin Dermatol. 2018;36:14-20.
5. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001;24:683-9.
6. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-5.
7. Lahsen R. Metabolic syndrome and diabetes. Rev Med Clin. 2014;25:47-52.
8. Ruiz MH, Pérez-Díez S, Navas-Carretero S, Martínez JA. Alimentary and lifestyle changes as a strategy in the prevention of metabolic syndrome and diabetes mellitus type 2: Milestones and perspectives. Sist Sanit Navar. 2016; 39:21.
9. Peinado-Martínez M, Dager-Vergara I, Quintero-Molano K, Mogollón-Pérez M, Puello-Ospina A. Metabolic syndrome in adults: a narrative review of the literature. Arch De Medicina. 2021;17:1-5.
10. Espinoza-Díaz C, Paredes-Pintado J, Lozada-Martínez G, Verdezoto-Nuñez B, Gómez-Félix G, Flores-Fiallos E. Gut microbiota in the pathogenesis of metabolic syndrome: A new piece in the neuro-endocrine puzzle. Rev Sindro. 2019; 9:11-6.
11. Welton S, Minty R, O'Driscoll T, Willms H, Poirier D, Madden S, Kelly L. Intermittent fasting and weight loss: Systematic review. Can Fam Physician. 2020;66:117-25.
12. Rynders CA, Thomas EA, Zaman A, Pan Z, Catenacci VA, Melanson EL. Effectiveness of in-termittent fasting and time-restricted feeding compared to continuous energy restriction for weight loss. Nutrients. 2019;11:2442.
13. Chaix A, Lin T, Le HD, Chang MW, Panda S. Time-restricted feeding prevents obesity and metabolic syndrome in mice lacking a circadian clock. Cell Metab. 2019;29:303-19. e4.
14. Antoni R, Johnston KL, Collins AL, Robertson MD. Intermittent vs. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in over-weight/obese participants. Br J Nutr. 2018;119:507-16.
15. Ussar S, Griffin NW, Bezy O, Fujisaka S, Vienberg S, Softic S, Deng L, Bry L, Gordon JI, Kahn CR. Interactions between gut microbiota, host genetics and diet modulate the predisposition to obesity and metabolic syndrome. Cell Metab. 2015;22:516-30.
16. Ozkul C, Yalinay M, Karakan T. Structural changes in gut microbiome after Ramadan fasting: a pilot study. Beneficial Microbes. 2020;11:227-33.
17. Cignarella F, Cantoni C, Ghezzi L, Salter A, Dorsett Y, Chen L et al. Intermittent fasting confers protection in cns autoimmunity by altering the gut microbiota. Cell Metab. 2018;27:1222-35e6.
18. Harvie M, Howell A. Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight, and normal weight patients-a narrative review of human and animal evidence. Behav Sci. 2017;7:4.
19. Green A, Bishop RE. Ketoacidosis - Where do the protons come from? Trends Biochem Sci. 2019;44:484-9.

20. Westman EC, Tondt J, Maguire E, Yancy WS. Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus. Expert Rev Endocrinol Metab. 2018;13:263-72.
21. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab. 2014;19:181-92.
22. Washburn RL, Cox JE, Muhlestein JB, May HT, Carlquist JF, Le VT, Anderson JL, Horne BD. Pilot study of novel intermittent fasting effects on metabolomic and trimethylamine N-oxide changes during 24-hour water-only fasting in the FEELGOOD trial. Nutrients. 2019;11:246.
23. García de Lorenzo y Mateos A, Rodríguez-Montes JA. Metabolism in fasting and injury. Its role in the development of disease-related malnutrition. Nutr Hosp Supplements. 2013;6:1-9. (In Spanish)
24. Myers MG, Olson DP. Central nervous system control of metabolism. Nature. 2012;491:357-63.
25. Aubert G, Martin OJ, Horton JL, Lai L, Vega RB, Leone TC et al. The failing heart relies on ketone bodies as a fuel. Circulation. 2016;133:698-705.
26. Li C, Sadraie B, Steckhan N, Kessler C, Stange R, Jeitler M, Michalsen A. Effects of a one-week fasting therapy in patients with type-2 diabetes mellitus and metabolic syndrome-A randomized controlled explorative study. Exp Clin Endocrinol Diabetes. 2017;125:618-24.
27. Saini A, Al-Shanti N, Stewart CE. Waste management-cytokines, growth factors and caquexia. Cytokine Growth Factor Rev. 2006;17:475-86.
28. Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: A randomized trial in young overweight women. Int J Obes. 2011;35:714-27.
29. Rodríguez JM, Murphy K, Stanton C, Ross RP, Kober OI, Juge N et al. The composition of gut microbiota throughout life, with an emphasis on early life. Microb Ecology Health Dis. 2015;26:26050.
30. McDermont AJ, Huffnagle GB. The microbiome and regulation of mucosal immunity. Immunology. 2014;142: 24-31.
31. McLoughlin RM, Millis RH. Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. J Allergy Clin Imunol. 2011;127:1097-107.
32. Farías M, Silva C, Rozowski J. Gut microbiota: role in obesity. Rev Chil Nutr. 2011;38:228-33.
33. Devaraj S, Hemarajata P, Versalovic J. The human gut microbiota and body metabolism: Implications with obesity and diabetes. Acta Bioquím Clín Latin. 2013;47:421-34.
34. Velikonja A, Lipoglavšek L, Zorec M, Orel R, Avguštin G. Alterations in gut microbiota composition and metabolic parameters after dietary intervention with barley beta glucans in patients with high risk for metabolic syndrome development. Anaerobe. 2019;55:67-77.
35. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016;8:42.
36. Cani PD. Human gut microbiome: Hopes, threats and promises. Gut. 2018;67:1716-25.
37. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. PNAS. 2010;107:14691-6.
38. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505:559-60.
39. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. New Eng J Med. 2016; 375:2369-79.
40. Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G et al. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome. 2017;5:14.
41. Frost F, Storck LJ, Kacprowski T, Gärtner S, Rühlemann M, Bang C et al. A structured weight loss program increases gut microbiota phylogenetic diversity and reduces levels of Collinsella in obese type 2 diabetics: a pilot study. PLoS One. 2019;14:e0219489.
42. Gotteland M. The role of the gut microbiota in the development of obesity and type-2 diabetes. Rev Chil Endocrinol Diabetes. 2013;6:155-62.
43. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014; 514:184-6.
44. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. Natl Health Stat Report. 2009;13:1-7.
45. Chung H, Chou W, Sears DD, Patterson RE, Webster NJ, Ellies LG. Time-restricted feeding improves insulin resistance and hepatic steatosis in a mouse model of postmenopausal obesity. Metabolism. 2016; 65:1743-54.
46. Finkel T. The metabolic regulation of aging. Nat Med. 2015; 21:1416-23.
47. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. Science. 2018;362:770-5.
48. Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, Ingram DK, Lane MA, Mattson MP. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci U. S. A. 2003;100:6216-20.
49. Stanislawski MA, Frank DN, Borengasser SJ, Ostendorf DM, Ir D, Jambal P et al. The gut microbiota during a behavioral weight loss intervention. Nutrients. 2021;13:3248.
50. Kunnackal GJ, Wang L, Nanavati J, Twose C, Singh R, Mullin G. Dietary alteration of the gut microbiome and its impact on weight and fat mass: A systematic review and meta-analysis. Genes. 2018;9:167.
51. Harvie M, Howell A. Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight, and normal weight patients-a narrative review of human and animal evidence. Behav Sci. 2017;7:4.
52. Harris L, Hamilton S, Azevedo LB, Olajide J, De Brún C, Waller G et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: A systematic review and meta-analysis. JBI Database System Rev and Implement Rep. 2018;16:507-47.
53. Trepanowski JF, Kroeger CM, Barnosky A, Klempel MC, Bhutani S, Hoddy KK et al. Effect of alternate day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. JAMA Intern Med. 2017;177:930-8.
54. Ma X, Chen Q, Pu Y, Guo M, Jiang Z, Huang W, Long Y, Xu Y. Skipping breakfast is associated with over-weight and obesity: A systematic review and meta-analysis. Obes Res Clin Pract. 2020;14:1-8.
55. Furmli S, Elmasry R, Ramos M, Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. BMJ Case Rep. 2018;2018: bcr2017221854.
56. Varady KA, Bhutani S, Klempel MC, Kroeger CM. Comparison of effects of diet versus exercise weight loss

regimens on LDL and HDL particle size in obese adults. Lipids Health Dis. 2011;10:119.
57. Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA. Alternate day fasting, and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. Obesity (Silver Spring). 2013;21: 1370-9.
58. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. Cell Metab. 2018;27: 1212-21.
59. Dong T, Sandesara P, Dhindsa D, Mehta A, Arneson L, Dollar A, Taub P, Sperling L. Intermittent Fasting: A heart healthy dietary pattern? Am J Med. 2020;133:901-7.
60. Chandrasekar B, Nelson J, Colston J, Freeman G. Calorie restriction attenuates inflammatory responses to myocardial ischemiareperfusion injury. Am J Physiol Heart Circ Physiol. 2001;280:H2094-102.
61. Antelmi E, Vinai P, Pizza F, Marcatelli M, Speciale M, Provini F. Nocturnal eating is part of the clinical spectrum of restless legs syndrome and an underestimated risk factor for increased body mass index. SleepMed. 2014;15:168-72.
62. Yamaguchi M, Uemura H, Katsuura-Kamano S, Nakamoto M, Hiyoshi M, Takami H, Sawachika F, Juta T, Arisawa K. Relationship of dietary factors and habits with sleep-wake regularity. Asia Pac J Clin Nutr. 2013;22:457-65.
63. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. J Sleep Res. 2009;18: 148-58.
64. Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: The evidence, the possible mechanisms, and the future. Sleep Med Rev. 2010; 4:191-203.
65. McStay M, Gabel K, Cienfuegos S, Ezpeleta M, Lin S, Varady KA. Intermittent fasting and sleep: a review of human trials. Nutrients. 2021;13:3489.
66. Schiavo-Cardozo D, Lima MM, Pareja JC, Geloneze B. Appetite-regulating hormones from the upper gut: disrupted control of xenin and ghrelin in night workers. Clin Endocrinol. 2013;79:807-11.
67. Crispim CA, Waterhouse J, Dâmaso AR, Zimberg IZ, Padilha HG, Oyama LM, Tufik S, de Mello MT. Hormonal appetite control is altered by shift work: a preliminary study. Metab Clin Exp. 2011;60:1726-35.
68. Wirth MD, Burch J, Shivappa N, Steck SE, Hurley TG, Vena JE, Hébert JR. Dietary inflammatory index scores differ by shift work status: NHANES 2005 to 2010. J Occup Environ Med. 2014;56:145-8.
69. Fonseca-Alaniz MH, Takada J, Alonso-Vale MI, Lima FB. Adipose tissue as an endocrine organ: from theory to practice. J Pediatr (Rio J). 2007;83(5 Suppl):S192-203.
70. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends Endocrinol Metab. 2000;11:327-32.
71. Godínez S, Marmolejo G, Márquez E, Slordla J, Baeza R. Visceral fat and its importance in obesity. Rev Endocrinol Nutr. 2002;10:121-7.
72. Fruhbeck G, Gómez-Ambrosi J, Muruzabal J, Burrel MA. The adipocyte: a model for integration of endocrine and metabolic signalling in energy metabolism regulation. Am J Physiol Endocrinol Metabol. 2001;280:E827-47.
73. Manzur F, Alvear C, Alayón AN. Adipocytes, visceral obesity, inflammation and cardiovascular disease. Rev Colomb de Cardiol. 2010;17:207-13.
74. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003; 112:1821-30.
75. Blüher M, Wilson-Fritch L, Leszyk J, Laustsen PG, Corvera S, Kahn CR. Role of insulin action and cell size on protein expression patterns in adipocytes. J Biol Chem. 2004;279: 31902-9.
76. Skurk C, Alberti-Huber CH. Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab. 2007;92:1023-33.
77. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam Horm. 2006; 74:443-77.
78. Wellen KE, Hotamisligil GS. Inflammation, stress and diabetes. J Clin Invest. 2005;115:1111-19.
79. Li G, Xie C, Lu S, Nichols RG, Tian Y, Li L et al. Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota. Cell Metab. 2017;26:672-85.
80. Harney DJ, Cielesh M, Chu R, Cooke KC, James DE, Stöckli J, Larance M. Proteomics analysis of adipose depots after intermittent fasting reveals visceral fat preservation mechanisms. Cell Rep. 2021; 34:108804.