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LIFESTYLE MANAGEMENT TO REDUCE DIABETES/CARDIOVASCULAR RISK (B CONWAY AND H KEENAN, SECTION EDITORS)

Health Benefits of Fasting and Caloric Restriction

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Abstract
Purpose of Review Obesity and obesity-related diseases, largely resulting from urbanization and behavioral changes, are now of global importance. Energy restriction, though, is associated with health improvements and increased longevity. We review some important mechanisms related to calorie limitation aimed at controlling of metabolic diseases, particularly diabetes.
Recent Findings Calorie restriction triggers a complex series of intricate events, including activation of cellular stress response elements, improved autophagy, modification of apoptosis, and alteration in hormonal balance. Intermittent fasting is not only more acceptable to patients, but it also prevents some of the adverse effects of chronic calorie restriction, especially malnutrition.
Summary There are many somatic and potentially psychologic benefits of fasting or intermittent calorie restriction. However, some behavioral modifications related to abstinence of binge eating following a fasting period are crucial in maintaining the desired favorable outcomes.

Keywords Calorie restriction · Diabetes · Adipose tissue · Oxidative stress

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Introduction

It is abundantly clear that the obesity epidemic has affected most countries in the Middle East more severely [1, 2, 3•, 4, 5]. It is disconcerting that increases in the rates of obesity and type 2 diabetes continue unabated in spite of great efforts at sounding the alarm of the health costs—suggesting that the many conferences, scientific articles, and public alerts have so far had little impact in changing lifestyle choices. Another approach is to harness the health and spiritual benefits of obligatory and voluntary religious fasts, which are routinely practiced in the Middle East, as an added means of producing lasting lifestyle changes that will ultimately lead to improved health outcomes. Fasting is an age-old practice that has been prescribed in many religions and requires caloric restrictions of various durations and formats [6, 7]. Examples of religious fasting regimens are shown in Table 1. We review the mechanisms by which periodic caloric restriction, through obligatory and voluntary fasts, can lead to improved health outcomes.

Fasting by Muslims in the Middle East

Fasting during Ramadan displays some overlap with alternate-day fasting as in both instances there are recurring periods of fasting and feeding. However, alternate-day fasting involves alternating 24-h periods of fasting and feasting while water

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Table 1 Common fasts and their dietary restrictions in some religions

Religion	Timing of fast	Etiquette
Baha'i	19 days (2–10 March)	No food/drinks from sunrise to sunset
Buddhist	Usually on full-moon days and other holidays	No solid food; some liquids allowed
Catholics	Ash Wednesday and Good Friday	No meat (and no meat on Fridays during Lent). Small meals allowed
Eastern Orthodox	Fast periods include Lent, Apostles' Fast, Dormition Fast, Nativity Fast. Also includes every Wednesday and Friday	No meat, dairy products, eggs. Fish prohibited on some fast days
Hindu	New moon days, some festivals such as Shivaratri, Saraswati Puja, and Durga Puja	Can involve 24 h of full abstinence from al foods and liquids; commonly practiced with abstinence from solid food
Islam	28–30 days of Ramadan (obligatory) and each Monday and Thursday (voluntary)	No food /water from sunrise to sunset
Jewish	Yom Kippur, the Day of Atonement, and 6 other days of "minor fasts"	No food/drinks from sunset to sunset (and from sunrise to sunset for "minor fasts"
Mormon	First Sunday of each month	No food/water for two consecutive meals

intake is also allowed [6]. The data on the health benefits of fasting remain inconclusive as some studies show lower, higher, or no changes in nutrient intake during Ramadan [7]. Similar findings exist for BMI, blood metabolites profile (glucose, lipids), and the onset of cardio-metabolic diseases [7]. Fasting times vary according to geographical location and season. There are also cultural differences that likely impact dietary intake and smoking patterns.

Unique cultural practices in the Middle East and North Africa (MENA) region during Ramadan likely offset potential benefits usually achieved by caloric restriction. A meta-analysis reports that East Asian individuals displayed more significant weight loss during Ramadan when compared to West Asian populations [7]. Furthermore, others established increased energy intake in Saudi Arabia when compared to other countries [e.g., India] during Ramadan [8]. Thus, we hypothesize that individuals within the MENA countries display unique cultural/behavioral patterns that pre-dispose them to increased risk for the onset of cardio-metabolic diseases. Although the major factor[s] driving this process remain unclear, we propose that altered circadian rhythms during Ramadan may have a central role as the usual circadian rhythm among fasting Muslims in this region is significantly altered during Ramadan, with fasting individuals generally remaining awake during the night while spending most of the day sleeping [9, 10].

Disturbances in circadian rhythms are linked with cardio-metabolic diseases onset, as Ramadan fasting may affect the timing of acute coronary event presentation [11] and moreover that systemic cortisol levels are disrupted during Ramadan in a Saudi Arabian cohort, with high levels during the evenings compared to mornings [12]. Of note, such changes in cortisol levels are typically associated with the metabolic syndrome, e.g., hypercortisolemia is linked to insulin resistance due to impaired insulin secretion and increased hepatic glucose output [13, 14]. Sleep deprivation also triggers a pro-inflammatory milieu and micro/macro-vascular changes linked to impaired vascular stimulation following a flow-mediated dilation test. Altered adipokine levels also occur, with increased circulating leptin and decreased adiponectin in a Saudi Arabian cohort during Ramadan. Such an altered adipokine signature is usually linked to insulin resistance. To further compound the issue, there is excessive food intake ["gorging"] during Ramadan nights in some of these countries that will further fuel metabolic syndrome-like features such as increased weight gain and insulin resistance [15]. In addition, active/passive smoking is widespread in this region and further fuels cardio-metabolic diseases [16, 17]. For example, Ramahi et al. [17] examined a Jordanian cohort and established that indoor pollution (due to increased smoking activity) increased to unsafe levels during Ramadan after breaking of the fast. In light of these findings, we propose that altered circadian rhythms during Ramadan trigger downstream effects that eventually contribute to the onset of cardio-metabolic diseases (Fig. 1).

Intermittent Caloric Restriction [Fasting]

Calorie restriction (CR) is associated with health improvement, increased longevity, and a reduction of morbidity and mortality in animal studies [19–22]. Calorie control also benefits cardiovascular status, weight reduction, insulin sensitivity, diabetes control, cognitive function, and cancer prevention among its many effects in humans [23–26]. However, CR is difficult to practice and increases the risk of malnutrition. Intermittent fasting (IF) reduces the risk of malnutrition and is easier to follow and is gaining popularity with health experts. We review some mechanistic insights for the health benefits of IF.

Tissue Changes Following Energy Intake Restriction: Putative Mechanisms

Stress-Activated Pathways

IF activates stress-induced pathways and increases transcription of stress-induced proteins such as heat shock protein

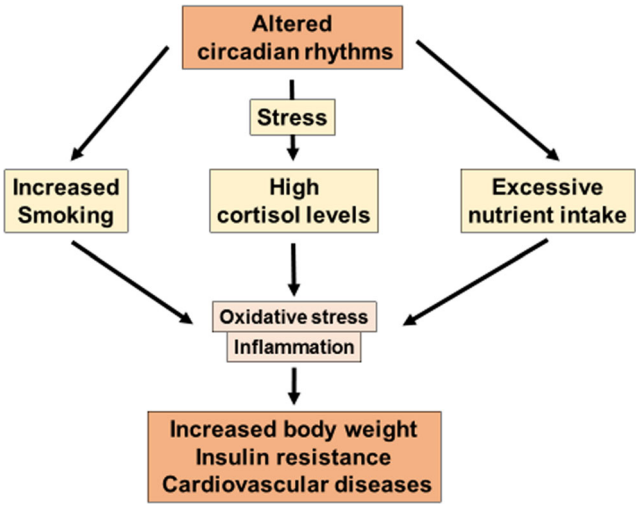

Fig. 1 Disturbances in circadian rhythms related to sleep/awake cycles, nutritional and smoking patterns may be a unifying factor that eventually contributes to the onset of cardio-metabolic diseases. Such changes can increase psycho-social stress and circulating cortisol levels, triggering oxidative stress and inflammation (systemically and target organs). Such events, with/without a genetic pre-disposition, can lead to a "tipping point" being reached that will result in pathological outcomes as indicated [18]

(HSP) 70 [27]. Increased HSPs are a generic cellular response to harsh conditions including oxidative stress [28], hypoxia [29], protein degradation [30], and energy depletion [31]. HSPs attach to unfolded or misfolded proteins and restore normal configurations [32] and have anti-inflammatory and anti-apoptotic properties [33]. Decreased levels of HSPs occur in skeletal muscles of diabetic patients, possibly related to insulin resistance [34–36]. This phenomenon may in part explain some of the metabolic benefits of IF, since elevations in HSPs mitigate insulin resistance, glucose intolerance, and diet- or obesity-induced hyperglycemia in animal studies [37].

Improved Autophagy

IF promotes cellular autophagy [38], a process by which distorted molecules and impaired organelles are eliminated—thus providing cells with a limited supply of energy from recycled materials. Cellular senescence is associated with reduced autophagy and accumulation of malfunctioning constituents. CR attenuates the effects of aging on autophagy and maintains cellular rejuvenation [39]. The role of sirtuin-1 (SIRT-1), a NAD^+-dependent deacetylase, in the regulation of autophagy has been shown in several cell lines (including human cells). Caloric restriction stimulates sirtuin-1 activity and enhances autophagy, while its pharmacological inhibition is accompanied by decreased autophagy and accumulation of biomarkers of aging [40].

Reduction of Advance Glycation End-Products [AGEs] by Intermittent Fasting

Another putative mechanism for the beneficial effects of fasting is reduced levels of AGEs that result from non-enzymatic attachments of carbohydrate molecules to proteins, lipids, or nucleic acids, mostly during normal metabolism but also in the process of food cooking at high temperatures [41, 42]. Foods rich in AGEs include red meats, cheeses, and processed grains. There is increased production or reduced excretion of AGEs in diabetes, where this can initiate several pathophysiologic processes [43]. Mice exposed to a diet low in AGEs have extended mean and maximum life spans [44]. AGEs exert their functions through reaction with AGE receptors, which are multiligand receptors that can also be activated by other ligands with similar three-dimensional structures [45]. Activation of AGE receptors on macrophages/mesangial cells increases production of growth factors and several pro-inflammatory cytokines, including nuclear factor kappa B (NF-κB). Since AGE receptor signaling can override cellular regulatory mechanisms, it perpetuates pro-inflammatory cytokine production [46]. NF-κB and other pro-inflammatory mediators in turn increase the expression of AGE receptors [47] so that a short inflammatory circuit is turned to a long-lasting process by a positive-feedback loop. This provides a link between inflammation and oxidative stress through a positive-feedback loop whereby ROS activates AGE/RAGE signaling [47] and RAGE stimulation induces oxidative stress [48, 49]. Serum AGEs levels can be reduced by a low-calorie diet, which also reduces triglycerides, waist circumference, and body mass index BMI [50, 51]. In a study of ten patients with rheumatoid arthritis, 54 days of IF significantly decreased urinary excretion of pentosidine (an AGE) along with a reduction in severity of the rheumatologic markers [52].

Hormonal Changes

CR and IF increase adiponectin levels in humans and laboratory animals [53, 54]. This adipose-secreted protein is inversely related to body weight, adiposity, and insulin-resistance [55]. Adiponectin modulates insulin activity [56] and also reduces insullin levels and beta cell dysfunction [57, 58]. Lower levels of adiponectin occur in patients with diabetes [59]. Long-lived humans and animals have increased levels of adiponectin [60–63]. For instance, Ames mice have adiponectin levels that are three times higher than control mice [64]. It is hypothesized that the propensity of adiponectin to shift metabolism from glucose burning to fat burning reduces oxidative stress and promotes longevity [38]. Dietary manipulation of four strains of mice *[obese-prone C57BL/6, genetically obese ob/ob, obese-resistant A/J and peroxisome proliferator-activated receptor-α gene knockout]* strongly

suggests that it is the amount of calories, rather than the fat content, that is the major determinant of adiponectin secretion [65]. Adiponectin also mediates the cardiovascular benefits of IF as shown in animal studies [66]; however, its prognostic value in human disease has been questioned as higher levels of adiponectin are associated with less favorable outcomes in congestive heart failure [54] (Fig. 2).

Tissue and Metabolic Changes

Adipose Tissue

The complex role of adipose tissue (AT), white and brown (WAT and BAT, respectively) in overall energetic homeostasis, in both physiological and pathological conditions is intricately linked with lipid (fatty acid, FA) metabolism in AT- and non-AT (muscle, heart), where the liver acts as an integrative metabolic organ (Figs. 3 and 4).

There are three sources of FA: food intake, storage from white adipose tissue (WAT), and de novo synthesis (mainly in liver and also in AT). Together with other lipids, FA from different sources (in the form of triacylglycerols, TAG) are packaged in lipoprotein particles: chylomicrons in the intestine and VLDL (very-low-density lipoproteins) in the liver and through lymphatic or blood vessels move to capillary of extrahepatic tissues [67, 68].

All aspects of AT biology are connected with the development of metabolic disorders, including metabolic syndrome, obesity, cardiovascular diseases, type II diabetes, cancer, and neurodegenerative disorders. This involves the following specific alterations: morphological and cellular (hypertrophy/hyperplasia/atrophy), metabolic (ratio of lipolysis/lipogenesis and degree of re-esterification and releasing of adipocyte FA, level of FFA in circulation, and balance of re-esterification of FA between AT and liver), and physiological and endocrine (production of adipocytokines with depot-specific signature).

IF affects WAT cellularity at the level of the size of adipocytes. Studies in humans show that enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes [69]. Increases in fat cell size ("hypertrophic obesity") play a more important role in metabolic diseases than increases in fat cell number ("hyperplastic obesity") [70]. The authors suggest that larger adipocytes have higher capacity for TAG synthesis and lipolysis. Consequently, higher FA release from WAT and flux of FFA in circulations contribute to metabolic diseases [70]. Another study [71] reports that inguinal (subcutaneous depot) and epididymal (visceral depot) fat cells were smaller in IF. The large reduction in adipocyte size of both WAT depots correlates with their increased insulin sensitivity, likely due to increases in insulin receptor number [72]. Studies in animals and humans demonstrate that IF and CR positively modulate the secretory signatures of adipocyte cytokines by decreasing secretion of pro-inflammatory mediators and the development of a pro-inflammatory phenotype in WAT [73, 74••].

Experiments by Ding et al. [75•] showed that fasting for up to 24 h significantly reduced the body weight of both male and female mice, with moderate reductions in weight of subcutaneous visceral fat depots. Recent results of Fabbiano et al. [76] show that long-term CR or IF regimens stimulate browning of WAT. Indeed, induction of "browning" in WAT or transplantation of BAT is considered by some to have a therapeutic potential [77]. Stimulation of "browning" in WAT by dietary means can influence body weight and the potential success of anti-obesity therapies. Hence, even though induction of "browning" in WAT is logically contrary to the physiological response to negative energy balance due to IF and

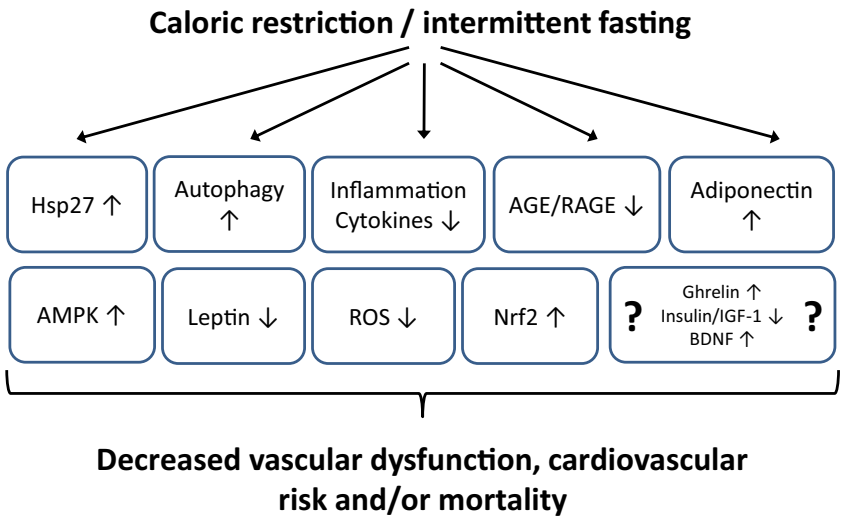

Fig. 2 Some of the mechanisms involved in cardiovascular effects of intermittent fasting

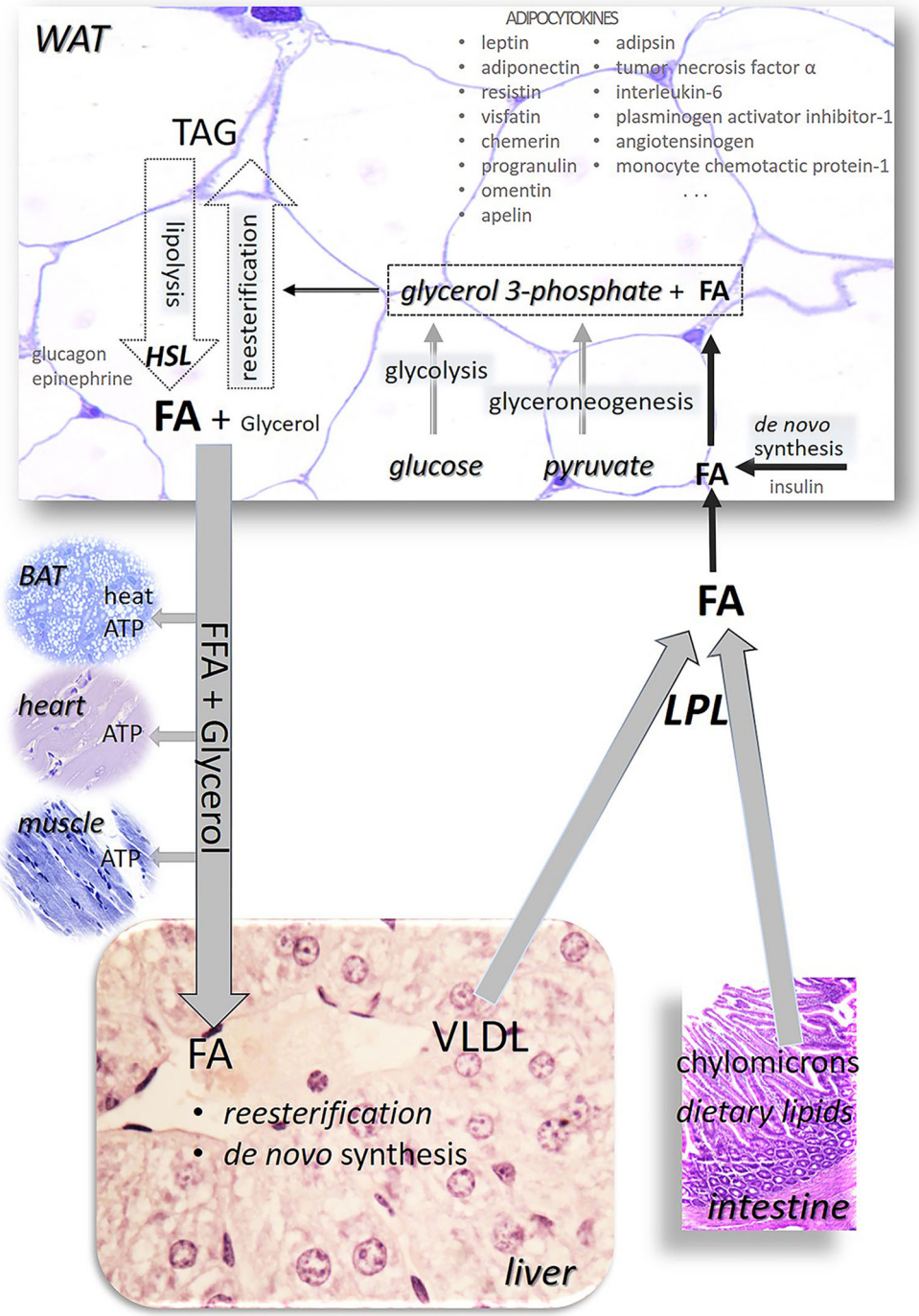

Fig. 3 General overview of lipid metabolic pathways in the body with the accent to white adipose tissue (WAT) biology (for explanation see text). BAT, brown adipose tissue; TAG, triacylglycerols; FA, fatty acids; FFA, free fatty acids; VLDL, very-low-density lipoproteins; LPL, lipoprotein lipase; HSL, hormone sensitive lipase

CR, it should be kept in mind that different food constituents and intermediary metabolites can induce browning of WAT. For example, lactate and the ketone body β-hydroxybutyrate [78] are strong "browning" inducers, while the amino acid L-arginine improves all metabolic aspects in WAT and BAT, and has the potential to induce "browning" [79, 80]. Similar effects are also produced by exercise training where "browning" of WAT occurs in visceral and especially subcutaneous adipose depots [80].

Diabetes Mellitus

A popular method of IF involves 1 day of eating followed by a day of fasting, while others suggest 20 h of fasting followed by 4 h of eating time or 16 h of fasting followed by 8 h of eating [81]. Several clinical trials have compared IF vs CR; however, to our knowledge, there is no clinical study comparing the various IF protocols with each other. For instance, Adrienne et al. compared IF and CR in type II diabetic patients

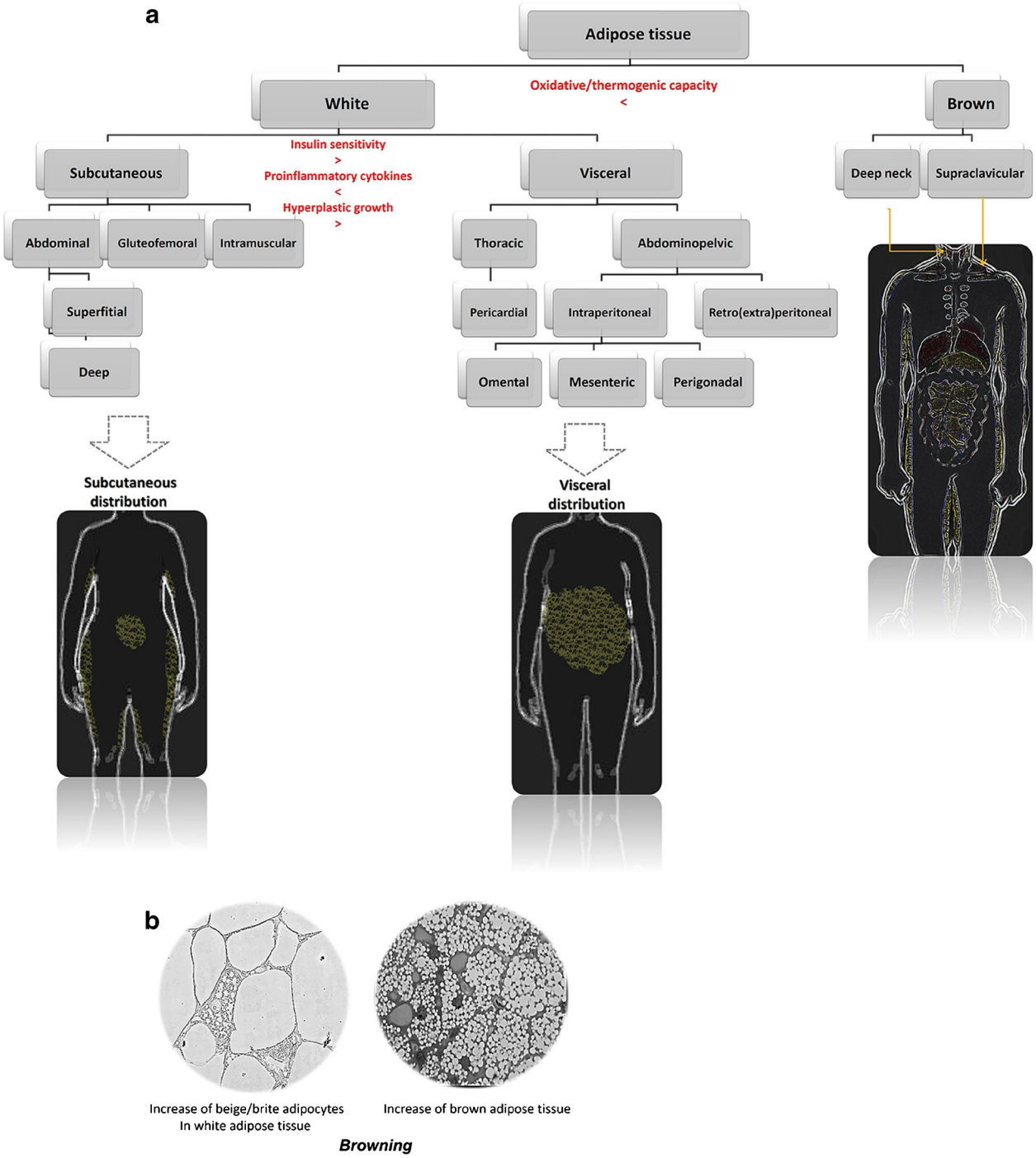

Fig. 4 The main depots of human adipose tissue (AT) types according to their relative amounts, functional specificities and the clinical significance are listed (**a**). Discrete functional-metabolic, endocrine and expanding characteristics of human AT depots, primarily that of subcutaneous- and the visceral depots, can influence metabolic health/risk. Thus, in contrast to subcutaneous depots, visceral depots are less sensitive to insulin, express higher levels of pro-inflammatory adipocytokines and grow mostly by adipocyte hypertrophy. Accordingly, subjects with more visceral AT can have a restricted (short term) capacity to buffer high calorie (nutritional) overload, and ultimately develop a higher risk insulin resistance and diabetes. Depots of AT in humans are predominantly white fat which is able to store lipids and have limited numbers of mitochondria. In contrast, brown and beige/bright adipocytes contain significantly more mitochondria that are rich in uncoupling protein-1 (UCP1), which regulates oxidative phosphorylation from ATP synthesis and energy dissipating as heat. Some depots of AT in newborn babies (interscapular), as well as in adults (deep neck, supraclavicular) are brown fat (**a**, right), and bright UCP1 containing adipocytes can be found within various AT depots, visceral and subcutaneous. Increases of the relative amounts of brown adipose tissue, brown/bright adipocytes in white AT, and the brown-like functional characteristics of white adipocytes—browning (**b**), may have greater relevance in obesity and diabetes type 2 treatment

[82]. They found that even though CR is superior in terms of weight reduction, CR and intermittent fasting had comparable effects in visceral fat mass reduction, fasting insulin, and insulin resistance. IF also improves metabolic parameters in non-diabetic individuals [83]. Data related to adherence rates were not reported in the study [83]. Intermittent fasting diminishes fat mass while preserving lean body mass, as opposed to daily CR, which results in reduced fat and lean body mass [74••, 84].

Dietary modification is a critical factor in the management of diabetes. In a 20-year longitudinal study of Rhesus monkeys, CR lowered age-related diseases including diabetes, where 5 of 38 control animals developed diabetes and another 11 being pre-diabetic, while animals experiencing CR showed no impairment of glucose homeostasis [85]. IF leads to similar outcomes in both diabetic and pre-diabetic individuals, as a 1-kg reduction of body weight is associated with 16% reduction in diabetes risk [86]. A number of studies confirm the effectiveness of IF in reducing risk factors for diabetes or its complications. For instance, intermittent fasting reduces visceral fat, an important site for producing TNF-α in diabetic patients [87]. Reductions of visceral fat after 6 to 24 weeks of IF have been reported in several studies [74••, 88–91]. In almost all of these investigations, reductions of visceral fat paralleled loss of body weight. IF decreases fasting glucose and insulin levels in non-obese [92], overweight/obese [90, 91], and diabetic individuals [93] with simultaneous improvements in insulin sensitivity.

Several mechanisms have been proposed to explain the modifying effects of CR on glucose metabolism. First, reduced energy intake reduces pancreatic cell apoptosis, as shown in diabetic rats where caloric restriction attenuates beta cell apoptosis [94]. Improved insulin sensitivity increases the expression of SIRT-1 [94]. It is likely that SIRT-1 adjusts hepatic gluconeogenic/glycolytic pathways in response to CR. SIRT-1 increases hepatic glucose output by affecting PPARγ co-activator alpha [PGC]-1α [95]. Overexpression of SIRT-1 in mice increases metabolic rate and reduces weight, blood cholesterol, adipokines, fasting blood sugar, and insulin levels [96]. In other words, SIRT-1 activity promotes the beneficial effects of CR. The life extending effects of CR is lost in SIRT1 deficient mice [97]. Six months of CR in overweight adolescents also increased expression of SIRT-1 and other genes whose protein products are essential for mitochondrial function [98].

The aggravating effects of oxidative stress in the pathogenesis of diabetes and its complications [99] include impeding the ability of endothelial cells to combat glucotoxicity associated with an array of the cardiovascular consequences of diabetes [100]. Hyperglycemia triggers several pathways that lead to the mitochondrial and non-mitochondrial production of reactive oxygen species [ROS] that participates in the pathogenesis of diabetes-induced vascular damage [101]. Increased levels ROS inhibit the activity of glyceraldehyde-3-phosphate dehydrogenase [GAPDH] and lead to increased concentrations of glyceraldehyde-3-phosphate [GA3P] and other upstream glycolytic intermediates. Levels of methylglyoxal, which are elevated by GA3P, lead to [i] increased production of AGE and [ii] activation of protein kinase C (PKC), which has a number of effects including reduced activity of endothelial nitric oxide synthase [eNOS], production of ROS by the phagocyte NADPH oxidase isoform, over-activity of the coagulation system, increased expression of some growth factors, and stimulation of NF-κB all of which promote an inflammatory state. Non-mitochondrial origins of ROS include NAD[P]H oxidase, xanthine oxidase, uncoupled eNOS, lipoxygenase, cyclooxygenase, cytochrome P450 enzymes, and other hemoproteins [102].

CR boosts the activity of endogenous antioxidant systems. In a study of 46 overweight [BMI 25–29.9] individuals, 6 months of CR increased plasma glutathione peroxidase activity and reduced plasma protein carbonyl levels, which were associated with non-significant decreases in plasma 8-epi-prostaglandin F2α levels [103]. The antioxidant effects of CR manifest several days after initiation of the diet, as shown in a study of 40 overweight/obese women [BMI 32 ± 5.8] where F2-isoprostane concentrations were reduced after 5 days of a 25% CR diet [104].

Many epidemiologic studies indicate an association between reduced food intake and lower cardiovascular diseases [105, 106]. As mentioned before, CR reduces oxidative stress in endothelial cells, a phenomenon that is associated with increased expression of eNOS. SIRT-1 acetylates lysine residues to enhance eNOS activity [107]. Greater bioavailability of eNOS-derived nitric oxide (NO), associated with decreased ROS, reduces blood pressure in both animal and human studies following CR [108, 109]. Apart from its vasodilating effects, NO also reduces oxidative stress and has anti-inflammatory properties [110]. Furthermore, the anti-proliferative effects of NO in vascular smooth muscle coupled with its inhibitory action on platelet aggregation and inflammatory cell adhesion play a significant role in prevention of atherosclerosis [105]. Several cytokines [e.g., IL-6, IL-1β, IL-17A, TNF-α] are positively correlated with cardiovascular outcome [111] and CR suppresses inflammatory pathways.

In light of the fact that the majority of parameters that are changed by caloric restriction and IF [e.g., nuclear factor erythroid 2-related factor 2 (Nrf2) activation, decreased oxidative stress, lower leptin levels, activation of AMP-activated protein kinase (AMPK), higher adiponectin levels, suppressed AGE/RAGE signaling and inflammation] is associated with decreased cardiovascular risk and mortality, it is not surprising that CR/IF is highly beneficial for the aging heart and

vasculature [112]. This evidence is supported by a systematic review of three randomized controlled clinical trials of fasting in humans reporting improvements in weight and other risk-related outcomes as well as two observational clinical outcome studies of fasting in humans showing an association with a lower prevalence of coronary artery disease or new onset of diabetes [113].

Conclusion

This brief overview summarizes some of the mechanisms that are activated by intermittent fasting. The benefits of fasting are described in some detail based on findings from experimental animal studies, and epidemiologic studies that confirm beneficial outcomes in human populations. Despite the many efforts to increase awareness of the obesity/diabetes epidemic that appears to be affecting the Middle East to a greater extent than other regions, the prevalence of cardio-metabolic diseases continues unabated [1, 2, 3•, 5]. A solution, at least in part, may be found in religious edicts in the Middle East where people of various religious persuasions fast regularly. In spite of the well-known health benefits of intermittent caloric restriction, the prevalence of obesity continues to escalate, with seemingly little efforts for limiting overall energy intake. Fasting or periodic calorie restriction also prevents unwanted effects of chronic energy restriction such as malnutrition. Intermittent fasting, by acting as acute intermittent stressor, activates stress-response pathways that lead to improvement in well-being. Finding optimal methods of fasting, in terms of the intensity of calorie restriction and duration is proposed as a method to alleviate many metabolic diseases. The requirement of many religions in the Middle East to fast, either as obligatory fasts or optional fasts, not only fulfills religious obligations but has the added benefit of stemming the rising tide of obesity in the region.

Compliance with Ethical Standards

Conflict of Interest Saeid Golbidi, Andreas Daiber, Bato Korac, Huige Li, M. Faadiel Essop, and Ismail Laher declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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