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Review Article

Healthy aging and anti-aging treatments

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Energy Metabolism and Aging

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Aging is strongly related to energy metabolism, but the underlying processes and mechanisms are complex and incompletely understood. Restricting energy intake and reducing metabolic rate can slow the rate of aging and extend longevity, implying a reciprocal relationship between energy metabolism and life expectancy. However, increased energy expenditure has also been associated with improved health and longer life. In both experimental animals and humans, reduced body temperature has been related to extended longevity. However, recent findings on the function of thermogenic (brown or beige) adipose tissue produced intense interest in increasing the amount of energy expended for thermogenesis to prevent and/or treat obesity, improve metabolic health, and extend life. Evidence available to-date indicates that increasing adipose tissue thermogenesis by pharmacologic, environmental, or genetic interventions can indeed produce significant metabolic benefits, which are associated with improved chances for healthy aging and long life.

Keywords: Adipose tissue, beige; Adipose tissue, brown; Aging; Metabolic rate; Thermogenesis

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INTRODUCTION

All biological functions of living organisms require energy consumption or expenditure. It is, therefore, not surprising that the biological process of aging, and the regulation of longevity, are related in various ways to energy metabolism. Much of the recent and current research on the biology of aging is directed at unraveling these fascinating relationships. This includes studies of the ways in which human energy metabolism could be modified to offset some of the consequences of a so-called “Western” lifestyle in the 21st century, including an imbalance of energy intake and expenditure. In this

review article, we will briefly discuss the relationships between metabolic rate and longevity, the impact of various anti-aging interventions on energy metabolism, and the current interest in stimulating thermogenesis to promote healthy aging.

HOW ARE AGING AND LONGEVITY RELATED TO METABOLIC RATE?

In most species of animals, body temperature is identical, or very similar, to environmental temperature (eT). These exothermic (also known as poikilothermic or “cold blooded”) species include worms, snails, mus-

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sels, various marine invertebrates, insects, fish, amphibians and reptiles. In these animals, metabolic rate is determined primarily by eT , and thus is low in the cold and high in the warmth. Importantly, in these species, longevity and temperature are inversely related, where exothermic animals live longer in the cold and shorter in the warmth. Naturally, this relationship does not extend to extreme temperatures, which can be detrimental, or even lethal. The inverse relationship between eT and lifespan of exothermic species is striking, consistent, and well documented. This led early investigators to conclude that longevity is determined primarily by metabolic rate. This was long-believed to also apply to endothermic (stenothermic or “warm blooded”) animals, that is, mammals and birds that generally maintain their body temperature within very narrow limits, regardless of eT . This belief was strongly supported by the fact that body mass is a strong determinant of both metabolic rate and longevity with larger species having lower metabolic rate, and longer lifespan, than smaller species [1]. However, there are many striking departures from this relationship [2]. Birds have higher metabolic rates than mammals, but live longer (often much longer) than mammals of the same size. Some mammals (most notably bats and humans) live much longer than their body size would predict. Presumably, the ability to fly (birds and bats), and the intelligence combined with social organization in primates, greatly reduced the risk of death from predation, and thus allowed evolutionary development of life course characteristics and reproductive strategies promoting longer lifespan [3]. Interestingly, both metabolic rate and longevity of humans exceed the corresponding values measured in closely related large apes [4]. This might be related to the greater size and energy requirements of the human brain [4]. Other departures from the simple inverse relationships of metabolic rate and longevity in endotherms include species that deal with extremely low eT s by allowing their body temperature to drop for periods ranging from hours (torpor; common in small rodents) to months (hibernation; *i.e.*, ground squirrels and marmots), and possess multiple physiological adaptations to these states of low metabolic rate [5,6].

While the concept of mammalian and avian longevity being directly controlled by metabolic rate has been rejected as overly simplistic, some of its elements have been incorporated into the concept of pace-of-life being

an important determinant of aging and longevity [7]. Fast pace-of-life includes high metabolic rate, fast post-natal growth, early maturation, high fecundity, and relatively short lifespan, as observed in many species of small rodents. Slow pace-of-life, seen in larger mammals, includes lower metabolic rate, slower growth, later maturation, fewer offspring, and longer life. This concept fits well with the trade-offs between anabolism, growth, and reproduction, on the one hand, and stress resistance, repair processes, and longevity on the other [8,9]. It also fits well with the role of evolutionarily conserved cellular signaling pathways (insulin, insulin-like growth factors, and mechanistic target of rapamycin) in the control of aging [10] and with the concept of partitioning available energy resources between the processes related to growth and reproduction and those related to maintenance and repair.

WHAT IS THE INFLUENCE OF AGING ON THE METABOLIC RATE?

Progressive decline in physical strength, speed of movements, energy level, and ability to recover from injury, diseases, or environmental insults (resilience) as well as reduced thermogenesis (feeling cold) are among the well-known correlates, and almost certainly effects, of aging. Reduced walking speed and increased difficulty walking for a long distance are among the most consistent functional changes during human aging and are used in geriatric medicine to assess the progression of aging, development of frailty, and risk of neurodegenerative disorders [11-13]. These observations and age-related decrease in the levels of several anabolic hormones indicate that aging has a major impact on energy metabolism. In fact, an age-related decline in basal metabolic rate was described in both humans [14] and experimental animals [15-17]. However, there is also evidence that metabolic rate does not always decline with age, and may, in fact, increase due to age-related increases in chronic, low-grade, “sterile” inflammation [18]. This is a result of an accumulation of intra-abdominal adipose tissue that possess an increased abundance of senescent cells, as well as a hypoxic microenvironment, which together, lead to an increased secretion of proinflammatory factors [19]. Thus, age-related changes in metabolic rate in human cohorts representative of the general population can be very different from what is seen in exceptionally healthy individuals [20]

in whom inflammation may not override the effects of age on metabolic rate.

ENERGY METABOLISM IS ASSOCIATED WITH EXTREME LONGEVITY

Body temperature is related to metabolic rate, and there is evidence that reduced body temperature favors longevity. Thus, calorie restriction, the most effective way of slowing aging and increasing lifespan of laboratory animals, also results in reduced body temperature in mice [21] as well as in humans [22]. Importantly, this association is very likely to be causal. Bioengineering mice to produce animals with reduced core body temperature increased median lifespan in both females and males [23]. In humans, lower body temperature has been associated with calorie restriction [22] as well as with longevity [24]. A recent publication reported intriguing evidence that mean body temperature in United State adults has been decreasing during the last 157 years by 0.03°C per birth decade [25]. The authors suggested that this may have contributed to improvements in health and longevity during this period.

We felt that some novel insights into the relationships of aging to energy metabolism can be gained by comparing animals with mutations which predispose them to slow aging and extreme longevity to their genetically normal (wild type) siblings. In mice, various naturally occurring mutations and targeted disruption of genes related to growth hormone (GH) signaling produce syndromes of GH deficiency and GH resistance, which are associated with remarkable extension of longevity in both sexes [reviewed in 8,26-29]. We expected to find evidence for reduced metabolism in these long-lived animals, particularly in those mutants which, in addition to being GH-deficient, are also hypothyroid and have a marked reduction in body temperature [30]. However, metabolic rate in these remarkably long-lived mice (assessed by oxygen consumption per unit of body mass) was significantly increased, rather than reduced [31]. We believe that this unexpected finding reflects increased heat loss in these diminutive mutants housed in a standard room temperature of 23°C, and the consequent need for increased thermogenesis. In support of this interpretation, differences of metabolic rate between mutant mice and wild type animals could be diminished or even completely eliminated by

housing them in a temperature of 30°C [32], considered a thermoneutral temperature for mice [33]. In addition to revealing differences in metabolic rate, indirect calorimetry studies of GH-deficient and GH-resistant mice showed a reduction in respiratory quotient (RQ; a ratio of the production of carbon dioxide to consumption of oxygen) [31,32]. A reduced RQ indicates an increased reliance on fatty acids as opposed to glucose as an energy substrate. Differences in RQ between normal and mutant mice also could be eliminated by housing at increased temperature [32]. An increased usage of lipids as metabolic fuel is associated with improved mitochondrial function, and a reduced production of harmful molecules that cause oxidative stress, both of which are likely mechanisms of aging.

We are currently investigating the effect of long-term exposure to different eTs on aging-sensitive traits and longevity of wild-type and GH-mutant mice. We have recently reported that life-long exposure to increased (thermoneutral) temperature does not eliminate the longevity advantage of GH-resistant *Ghr*^{-/-} mice [34].

There is increasing evidence that studying mice living at temperatures corresponding to their thermoneutral zone is important for obtaining data that can be “translatable” to humans [35-37]. Standard animal room temperature is believed to produce conditions of mild cold stress for the mice [33], while most humans live and work in spaces that are heated and/or air-conditioned which, together with wearing weather-appropriate clothing, produces conditions approaching thermoneutrality.

As we mentioned earlier, we hypothesize that in “standard” 23°C housing temperature (that is cool for mice), the diminutive long-lived GH-related mutants devote a large part of their energy budget to thermogenesis. In support of this hypothesis, *Ghr*^{-/-} and Ames dwarf mice have an increased amount of brown adipose tissue (BAT) [38,39]. Measuring expression of thermogenesis-related genes in this tissue indicates that BAT is more metabolically active in these mutants than in normal animals from the same strain [38,39]. The role of BAT in thermogenesis, and the potential health benefits of stimulating BAT function, will be discussed in subsequent sections of this article.

BROWN, WHITE, AND BEIGE ADIPOSE TISSUE

Adipose tissue has multiple functions that are critical for health and survival. In contemporary, well-nourished humans, it is the largest organ in the body. In mammals, there are three types of adipose tissue: white adipose tissue (WAT), BAT, and beige adipose tissue [40,41]. The principal function of WAT is energy storage, which involves accumulation of lipids, which form large lipid droplets in individual white adipocytes. In addition to storing lipids, WAT secretes a multitude of bioactive factors, including leptin, which is important in the regulation of appetite, various proinflammatory molecules, and adiponectin, which enhances sensitivity to insulin and exhibits anti-inflammatory and anti-atherogenic activity [42]. WAT is widely distributed, but most of it is present beneath the skin (subcutaneous WAT) and in the abdominal cavity (visceral WAT).

Technological and economic development during the twentieth and twenty-first century led to conditions which promote accumulation of WAT, leading to obesity, which now afflicts more than a quarter of adults in developed nations. Although genetic predisposition plays a role, these conditions essentially reflect a shift in energy metabolism, involving an unequal balance of energy expenditure and consumption. Inflammation of WAT is a result of this imbalance, and it leads to increased risk of type 2 diabetes, cancer, and cardiovascular disease [19,43,44]. There is increasing evidence that obesity also increases the risk of Alzheimer's disease and other age-related neuropathology [45-49], and likely accelerates the rate of aging [50]. These effects of obesity certainly increase mortality rate, and represent one of the key public health issues of the modern world. In this context, the potential of preventing and/or treating obesity by increasing thermogenic functions of adipose tissue is a focus of intense ongoing research.

BAT has a higher concentration of mitochondria than WAT and is responsible for non-shivering thermogenesis. BAT uses thermogenin, also known as uncoupling protein-1 (UCP1), to uncouple the electron transport chain from ATP production, resulting in the production of chemical energy in the form of heat [51]. To maintain this futile process, BAT must consume and expend energy from circulating glucose and lipids. Indeed, while BAT in mice may constitute only a few hundred milligrams, it can consume more than

half of ingested lipids and glucose when maximally stimulated [52]. In humans, BAT was once thought to be present only in newborns, and would disappear during adolescence. Studies have now shown that BAT is still present in adult humans [53-57]. BAT can be found surrounding the circulatory system to dissipate heat, and can be found near the heart, lungs, and kidney. In humans, the largest depot of BAT can be found in the supraclavicular region [56,58,59]. Fifty grams of BAT mass accounts for 3% to 5% of a human subject's basal metabolic rate [60]. In mice, BAT differs anatomically from human BAT because it is concentrated in specific depots (*e.g.*, the interscapular depot), whereas in humans, brown adipocytes tend to be dispersed within white adipose depots.

The spatial (anatomical) and functional separation of BAT and WAT is not absolute. Under some circumstances (for example, prolonged cold exposure), white adipocytes can express UCP1, acquire other characteristics of brown adipocytes, and assume a role in thermogenesis and maintenance of body temperature. This process is referred to as "beiging," and the resulting type of adipose tissue is classified as beige [41,52]. Beige adipose tissue is sometimes referred to as brite. It is also possible for BAT cells to lose their thermogenic properties and to start resembling white adipocytes. This is called whitening of BAT. Physiologically, BAT and beige fat have widely overlapping (if not identical) functions, and thus, beiging of white fat and stimulation of BAT and beige adipocytes function are expected to produce nearly identical metabolic benefits [61]. It has been suggested that human BAT corresponds more closely to beige rather than brown fat in the mouse, but this is still a matter of some debate [57]. Interestingly, BAT development and metabolic health can be shaped during fetal development by maternal exercise [62].

BENEFITS OF VARIOUS MEANS OF STIMULATING BROWN ADIPOSE TISSUE FUNCTION AND PROMOTING BEIGING OF WHITE ADIPOSE TISSUE

Age- and obesity-related declines in BAT mass and its thermogenic activity are associated with an increase in WAT, and this association is almost certainly causal. In humans, BAT mass has been shown to be inversely correlated with body mass index (BMI) [54], and thus

increase in adiposity and reduction of BAT may form a vicious circle [56,58]. Moreover, BAT levels decline with age [58], although this can be prevented through interventions that stimulate the beiging of fat [63]. Indeed, the decrease in BAT as a result of increased BMI and age raises the possibility that promoting BAT may combat both obesity and age-related metabolic disorders. Methods of improving BAT thermogenesis and promoting formation of beige fat, along with some of the mechanisms which control the function of these tissues, are discussed below. Understanding these mechanisms should identify targets for development of pharmacological interventions.

1. Cold exposure

Cold exposure has been shown to directly increase energy expenditure. The results of a recent study of the effects of outdoor temperatures showed that the energy expenditure and the skin temperature of the supraclavicular region increased with cold exposure [59]. This indicates that BAT concentrated in that region effectively induced non-shivering thermogenesis to produce heat, thereby increasing energy expenditure. It was recently reported that presence of active BAT determines cold-induced increase in energy expenditure in humans [64]. Cold exposure has also been proven to induce white fat beiging [65]. This can reverse the deterioration of BAT with age due to oxidative stress [65], which holds potential in treating metabolic disorders. In mice fed a high fat diet, chronic exposure to low temperature reduced obesity by enhancing BAT thermogenesis [66]. Importantly, intermittent exposure to cold was shown to improve control of blood glucose (“sugar”) levels in patients with type 2 diabetes [67]. In this study, acclimating patients to 15°C, over a 10-day period, while wearing only light clothing resulted in a 43% increase in insulin sensitivity. These, and similar findings, led to suggestions that lower setting of temperature controls in the house, sleeping under lighter covers, having windows open during the night, and using other means of reducing ambient temperature and stimulating thermogenesis are likely to have beneficial effects on body composition and metabolic health [68-71].

Additional evidence for beneficial effects of cold exposure was obtained from studies of individuals practicing winter (cold water) swimming, an extreme sport which is increasingly popular in various countries [72]. Practitioners of this sport swim regularly in natural

bodies of water through most, or all, of winter in locations where water temperature drops to 1°C to 5°C. Winter swimming produces a host of physiological responses including regional changes in blood flow, acute responses to the stress of cold water immersion (including transient increases in sympathetic tone and cortisol levels), adaptation to this stress, and stimulation of both shivering and non-shivering thermogenesis. Beneficial metabolic effects include improved insulin sensitivity and reduced insulin levels [73,74], as well as a reduction of and enhanced activity of anti-oxidant enzymes [75]. Although effects of increased thermogenesis in cold water swimmers are difficult (if not impossible) to separate from the effects of exercise and the hormetic responses to repeated stress, the observed physiological changes would be expected to reduce risk of chronic disease and to promote healthy aging. A pronounced reduction in the insulin levels and enhanced insulin sensitivity [73,74] are of particular note in this context. For the readers who might be interested in starting cold water swimming, we should add that this can be risky, particularly for those with some pre-existing heart conditions and generally untrained individuals without prior adaptation to cold [72,76]. Please consult with your physician first!

It appears that the potential benefits of immersion in cool water, rather than extremely cold water, have not been extensively explored. Although intensive exercise produces heat, therefore negating the effects of cold exposure, relaxed swimming in cooler water could potentially stimulate non-shivering thermogenesis due to water's evaporative cooling effect.

2. Dietary polyphenols

Polyphenols are micronutrients with multiple phenol groups. Some polyphenols have antioxidant properties, and can benefit metabolic health by targeting the sympathetic nervous system (SNS), which is responsible for adrenergic signaling. The SNS is importantly involved in thermoregulatory processes because it signals to interscapular BAT to induce heat production through activation UCP1 [77]. Various kinds of natural polyphenols can induce SNS signaling, and therefore BAT stimulation. Naringenin is a citrus flavonoid that was tested in human white adipocyte tissue cultures (hADSC) to determine if it induces browning. Studies of Rebello et al [78] showed that naringenin increased the expression of UCP1 and adipose triglyceride lipase,

which are both involved in thermogenesis. Oxygen consumption rates increased in naringenin-treated hADSC, signifying that it caused an increase in energy expenditure. Naringenin also increased glucose transporter type 4, adiponectin, and carbohydrate-responsive element-binding protein levels, which are all associated with improving insulin sensitivity [78]. These findings suggest that naringenin could potentially be used for treating obesity and diabetes.

Resveratrol is a polyphenol found in red cabbage, spinach, berries, red grapes and wine, and peanuts. In addition to its impact on sirtuins and on metabolism of carbohydrates and lipids [79,80], resveratrol can have beneficial effects on the gut microbiome [66]. It can improve gut function and activate metabolites in the intestinal tract through gut microflora mediated-biotransformation [66]. These actions can increase the beiging of WAT tissue.

Green tea extract which contains epigallocatechin gallate can promote weight loss by stimulating thermogenesis. This effect is most likely due to inhibition of the degradation of norepinephrine and the resulting increase in the sympathetic stimulation of BAT [81].

Many other natural plant-derived polyphenols, including thyme and chysin, have been shown to enhance lipolysis [63]. Magnolol and Honokiol are components of bark extracts from Asian trees that have been used for medicinal purposes and have been found to induce thermogenesis, leading to increased lipolysis and reduced lipogenesis [63]. These natural sources of dietary polyphenols may offer possible safe treatment option for inducing lipolysis in obese patients by stimulating the SNS and initiating the beiging of WAT.

Dietary polyphenols combined with cold exposure is another potential treatment method for increasing energy expenditure in obese patients. Capsinoids are known to cause thermogenic activation, increasing energy expenditure through recruiting active BAT during cold exposure [63]. This method has been shown to be effective in patients with low BAT levels as well, meaning this treatment could combat BAT degeneration due to aging. Capsinoid food sources include chili peppers such as jalapeno and cayenne. Coupling a natural dietary polyphenol supplement with cold exposure could offer a safe and natural way to stimulate WAT beiging and raising energy expenditure levels in obese individuals.

3. Oxidative stress

The amount of BAT and its thermogenic functions tend to decline during aging [58]. Oxidative stress is believed to be one of the key mechanisms of aging [82]. The role of oxidative stress in age-related changes in BAT was tested through exposing BAT cells to hydrogen peroxide, an oxidative agent. This caused a decline in BAT cells. Importantly, it was also shown that antioxidant treatment reduced the effects of oxidative stress and reversed BAT activity decline [60]. Mitochondrial dysfunction can develop during aging, causing a decrease in fuel oxidation overall and a buildup of reactive oxidative species [60]. These reactive species are likely responsible for an increase in metabolic dysfunction rates with age, but antioxidant supplements could reduce these effects and reverse BAT deterioration.

4. Endogenous compounds: lipokines and bile acids

Although drugs such as mirabegron are appealing since they can activate BAT, they tend to have undesirable off-target effects, such as tachycardia. Therefore, there has been an emphasis on finding physiological compounds that can target, and activate, BAT. Lipokines, or lipids that are secreted from adipose tissue and have signaling properties, are a novel class of lipid, some of which have been able to increase BAT function. For example, 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) is secreted from activated BAT, and acts in an autocrine manner to stimulate lipid uptake into brown adipocytes [83]. Another example is 12-hydroxyeicosapentaenoic acid (12-HEPE), which is secreted from BAT and acts in an endocrine manner to increase glucose uptake [84]. While it does act as an endocrine lipokine, it is also able to stimulate BAT-specific uptake of glucose as well. Therefore, treatment with 12,13-diHOME and 12-HEPE has the potential to decrease the abundance of circulating lipids and glucose through disposal by BAT. Unfortunately, there is currently no available data on the effects of these lipids on lifespan.

Another type of endogenous compound that can stimulate BAT are bile acids. Bile acids normally function in the gastrointestinal tract to emulsify consumed fat, however, they have garnered considerable attention as endocrine molecules in recent years, particularly in terms of glucose metabolism [reviewed in 85].

Interestingly, several studies have suggested that bile acids are able to stimulate BAT activation, and even protect mice from diet-induced obesity [86,87]. Interestingly, bile acids have been shown to play a beneficial role in aged animals, particularly in the context of glucose metabolism [88]. Although an attempt to extend longevity through the use of a particular bile acid, ursodeoxycholic acid was unsuccessful [89], there does appear to be a role of bile acids and aging. For example, the long-lived “little” mice have drastically higher levels of many bile acids [90], which appears to be at least partially controlled by growth hormone signaling in the liver [91]. Moreover, treating progeroid mice with cholic acid was able to significantly extend longevity [92]. To what extent bile acids can impact BAT and longevity is still unknown.

STUDIES OF THE REGULATION OF DEVELOPMENT AND FUNCTION OF BROWN AND BEIGE FAT SUGGEST NOVEL TARGETS FOR INTERVENTION

Thermogenesis involves shuttling fatty acids to BAT or beige fat cells to produce heat rather than storing them in WAT [51]. This process in BAT is activated during cold exposure [51,93]. Targeting this mechanism of fatty acid redistribution could be beneficial for treating obesity and accompanying metabolic diseases, such as cardiovascular disease and diabetes and have been related to excess triglyceride storage in WAT.

Central nervous system control of BAT thermogenesis involves guanylate cyclase 2C receptors in the hypothalamus and it was recently shown that activation of these receptors by treatment with linaclotide reduced body weight of obese mice without changing their food intake [94]. This beneficial metabolic effect was related to inducing increased energy expenditure for BAT thermogenesis. Linaclotide is a drug approved for treatment of irritable bowel syndrome with constipation.

Research in this field is very active and several novel approaches to stimulating energy expenditure in order to improve metabolic health have been reported while this article was being finalized. Treating mice with an orally bioavailable mitochondrial uncoupler, BAM15, was shown to increase nutrient oxidation, and decrease adiposity without altering food intake, and

improve insulin sensitivity [95]. These actions reversed diet-induced obesity and would be expected to promote healthy aging. A derivative of amphetamine modified to prevent its entry into the brain and acting as sympathofacilitator was reported to increase lipolysis, thermogenesis, and heat dissipation in mice, thus protecting the animals from obesity without having undesirable cardiovascular and central nervous system effects of amphetamine [96]. Disulfiram, which is approved treatment of alcohol addiction, was recently shown to reverse diet-induced obesity and metabolic dysfunction in mice by increasing energy expenditure [97]. An implantable wireless optogenetic device was shown to activate thermogenesis selectively in adipocytes by a mechanism independent of beta-adrenergic pathway [98]. In mice, this innovative treatment could increase thermogenesis and whole-body energy expenditure and prevent diet-induced weight gain [98]. Results of these and other recent studies identify new avenues that could be explored to stimulate activity of BAT and beige fat in people to produce metabolic changes that reduce a risk of age-related disease likely leading to extended longevity.

CONCLUSIONS

Age-related changes in body composition and in the risk of diabetes and other chronic diseases are related to energy metabolism. Activation of BAT and conversion of WAT to thermogenic beige fat can increase utilization of fat for thermogenesis (heat production) leading to reduced adiposity, improved glucose homeostasis, and healthier metabolism. Increasing energy expenditure for thermogenesis by cold exposure or by dietary or pharmacological interventions holds promise for reducing and/or preventing obesity and improving chances for healthy aging and long life.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Article conception & design: AB. Data acquisition: AB. Data analysis and interpretation: AB. Writing of the manuscript: AB, KH, EH, SB, JD. Receiving grant: AB, EH, JD. Approval of final manuscript: AB.

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