Review

Review of Interventions for the Frailty Syndrome and the Role of Metformin as a Potential Pharmacologic Agent for Frailty Prevention

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ABSTRACT

Purpose: Frailty is a syndrome of vulnerability and physical decline with aging that increases risk for disability, hospitalizations, and death. To date, interventions for frailty have primarily focused on exercise and/or nutritional interventions, many of which show improvement in frailty-related characteristics, such as gait speed and lower extremity strength and function. The goal of this article was to review prior research studies investigating interventions for frailty and review the literature with regard to the role of insulin resistance and inflammation in the development of frailty. Also included is a discussion of potential therapeutic interventions for frailty.

Methods: A literature search was conducted by using PubMed and the search terms *frailty*, *interventions*, and *older adults*. This review focused on larger studies ($N \geq 100$ participants) that examined the effect of specific interventions on frailty as a primary outcome or on measures that are closely related to frailty, such as gait speed, muscle strength, and/or sarcopenia.

Findings: The results of prior studies of exercise interventions for the frailty syndrome as the primary outcome are mixed, with some but not all showing benefit. However, many exercise interventions have demonstrated improvement in components of frailty, such as strength, gait speed, and physical activity. The evidence shows that regular physical activity is beneficial for frail older adults or those at high risk of frailty and that the adverse effects related to exercise are minimal compared with the potential gains. However, questions remain as to the optimal type and duration of exercise and whether results of clinical trials are easily and feasibly implemented in a clinical setting in individuals whose motivation for exercise may be low. There is now increasing interest in pharmacologic agents that could potentially be useful in the prevention or treatment of frailty, in part based on advances in basic biology of aging research demonstrating that pharmacological agents extend lifespan in rodents. Several studies now show that obesity, insulin resistance, inflammation, and diabetes are associated with and predict frailty. Because metformin targets insulin resistance and inflammation, it is a plausible pharmacologic agent to prevent frailty. A clinical trial is underway to examine metformin's usefulness in frailty prevention.

Implications: Although the benefits of exercise are known, adherence to these regimens may be difficult for individual older adults due to lack of motivation, access, or limitations due to chronic medical

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conditions. Studies are currently underway to examine novel agents for the prevention of frailty in older adults. (*Clin Ther*. 2019;41:376–386) © 2019 Published by Elsevier Inc.

Key Words: diabetes, frailty, inflammation, insulin resistance, metformin, older adults.

INTRODUCTION

Frailty is recognized by clinicians who care for older adults as a syndrome of progressive physical decline with age.[1] Older adults identified as frail are more likely to become disabled, have medical comorbidity, and are at increased risk of hospitalization, falls, disability, and death than those not identified as frail, even after adjustment for potential confounding factors.[2] Prevalence of frailty varies based on the population examined; however, it is estimated to be 10% in the population aged >60 years and 25% in the population aged ≥80 years.[3] Although the importance of frailty and its impact on an aging US society is widely recognized, to date there are no effective interventions to prevent frailty. Data from several studies have suggested strong roles for diabetes, insulin resistance, and inflammation in the physiological basis of frailty. Therefore, targeting older adults who have insulin resistance and diabetes, which includes a large proportion of older adults, may be an effective method of preventing the onset of frailty. The purpose of the present review was to provide background research with regard to the role of inflammation and insulin resistance in the development of frailty and to review the currently available evidence with regard to interventions to prevent frailty.

MATERIALS AND METHODS

For this review, background is provided for the role of insulin resistance and diabetes in the development of frailty based on expert review and synthesis of the literature. We also provide a review of the literature with regard to interventions for the prevention or treatment of frailty. For the review of published interventions, PubMed was searched by using the search terms *frailty*, *interventions*, and *older adults, without any date restrictions*. We focused on English-language studies that reported findings of larger (N of ≥100 participants) clinical studies that examined the effect of specific interventions on the primary outcome of frailty measures or measures that were considered closely related to frailty, such as gait speed, muscle strength, and/or sarcopenia.

RESULTS

Overview of Frailty

Although a thorough discussion of frailty definitions is beyond the scope of this review, the most commonly used methods of identifying frailty are summarized here. The model proposed by Fried et al[2] is perhaps the most extensively studied, initially developed by using data from the Cardiovascular Health Study, and has been cross-validated in several cohorts.[4–6] In this model, often referred to as the frailty phenotype model, frailty is considered a geriatric syndrome of increased vulnerability to decline and is operationalized by the presence of frailty characteristics, including muscle weakness, slowness, low physical activity, exhaustion, and weight loss.[2] Individuals with ≥3 of these 5 characteristics are categorized as frail, individuals with 1 or 2 are categorized as pre-frail, and individuals with 0 are classified as nonfrail. Interestingly, it has been shown that the increased risk for adverse outcomes such as disability, hospitalization, and death follows a stepwise pattern of increasing risk according to frailty categorization (ie, pre-frail status confers higher risk than nonfrail, and frail confers higher risk than pre-frail). Ensrud et al have proposed a modified, shortened frailty definition that assesses 3 of the 5 frailty characteristics mentioned earlier, including muscle weakness, exhaustion, and weight loss, which also predicts risk for similar adverse outcomes.[7] This definition was modeled in the SOF (Study of Osteoporotic Fractures) trial and has been referred to as the SOF index.[7,8]

An alternative model for thinking about frailty is to consider frailty as an accumulation of deficits in multiple systems that increase with age and which increase mortality risk.[9] This model, often referred to as the frailty index model, constructs a tally of deficits in multiple areas, including medical conditions, disabilities, and laboratory abnormalities. Although the frailty phenotype and frailty index definitions may have a different conceptual basis for defining the syndrome, they similarly predict future adverse health outcomes.[10]

Insulin Resistance and Diabetes in Older Adults and Relationship With Frailty Risk

Type 2 diabetes is one of the most prevalent chronic conditions in older adults. Approximately 25%−30% of older adults in the United States have diabetes and another 25%−30% have glucose intolerance, a prediabetic state.[11,12] The BLSA (Baltimore Longitudinal Study of Aging) showed a progressive decline in glucose tolerance from the third through the ninth decade of life.[13] Although the exact etiology is unknown, age-dependent decreases in pancreatic β-cell function and insulin sensitivity are believed to play important roles in the deterioration of glucose homeostasis that occurs with advancing age.[14] These factors may be related to increased adiposity, sarcopenia, and reduced physical activity.[15] Aging is also known to be associated with decreased β-cell proliferation[16] and increased β-cell susceptibility to apoptosis,[17] which is pronounced in those with impaired glucose tolerance.[18]

Several studies have reported a strong association between diabetes and frailty.[19−22] Individuals with diabetes have an ~40% increased risk of developing frailty (odds ratio, 1.40; 95% CI, 1.11−1.76),[5] and diabetes is also the most significant predictor of the onset of any 1 of the 5 frailty characteristics (using the Fried criteria) in the SALSA (San Antonio Longitudinal Study of Aging) cohort.[23] Diabetes leads to an accelerated rate of muscle loss, which worsens with increased length of time with diabetes and worse glycemic control.[24−26] However, even insulin resistance, or prediabetes, is emerging as a risk factor in sarcopenia, slow gait, and frailty development.[27−31] Barzilay et al[28] found that insulin resistance was associated with 15% increased risk of incident frailty (odds ratio, 1.15; 95% CI, 1.02−1.31).[29]

Inflammation Is a Central Mechanism Underlying Frailty and Type 2 Diabetes

Inflammation plays an essential role in aging and age-related diseases.[32] Circulating inflammatory cytokines such as C-reactive protein, interleukin-6 (IL-6), interleukin-1, tumor necrosis factor (TNF)-α, and TNF soluble receptor 1 and 2 are increased with age[33] and are predictive of frailty and impairments in mobility and physical function.[34] Several studies found an association between frailty and inflammation, which is believed to be responsible for the poor stress tolerance and lack of physiological resilience observed in older adults with frailty.[35−37] Walston et al found increased mean levels of serum C-reactive protein in frail individuals, compared with nonfrail individuals (5.5 [9.8] vs 2.7 [4.0] mg/L; $P < 0.05$)[36]; and Leng et al reported that serum IL-6 concentrations were elevated in frail older adults, compared with nonfrail older adults (4.4 [2.9] vs 2.8 [1.6] pg/mL; $P < 0.05$).[37] These differences persisted after adjustment for age, sex, and race, and after exclusion of individuals with cardiovascular disease and diabetes. Our group also showed that frailty is associated with inflammation using an unbiased, high-throughput proteomics approach to screen for plasma glycoproteins and to compare these based on frailty status in community-dwelling older adults.[38] Using lectin affinity chromatography and 2-dimensional polyacrylamide gel electrophoresis, our group found that several glycoproteins differed by frailty status (transferrin, fibrinogen, haptoglobin, hemopexin precursor, kininogen-1, apolipoprotein E, leucine rich alpha-2, and glycoprotein 1). Subsequently, we used ELISA to measure these findings in plasma and found that transferrin, fibrinogen, and IL-6 plasma concentrations increased with increasing frailty category.[39] Therefore, the inflammatory state associated with frailty is believed to be beyond what is expected from age- and age-related diseases.

Type 2 diabetes is also known as an inflammatory condition, associated with increased plasma IL-6 and TNF-α concentrations[40] and enhanced activity of the transcription factor nuclear factor−κB, a master regulator of inflammatory responses.[41] Similarly, prediabetes is also a pro-inflammatory state, and the presence of inflammation in the prediabetic state predicts the onset of future diabetes.[42,43] The mechanism linking inflammation with insulin resistance is believed to be partly a result of excess glucose- and free fatty acid−induced stress to insulin-sensitive tissues, particularly adipose and liver, leading to the production of inflammatory cytokines such as TNFα, interleukin-1β, and IL-6, which further promote inflammation in other tissues, including muscle and islet cells.[14]

Review of Interventions to Prevent Frailty

Although the importance of frailty and its impact on an aging US society is widely recognized, there is no evidence to date that can support the effect of

any intervention to prevent or treat frailty.[44] There have been, however, several studies examining the effect of exercise and other nonpharmacologic interventions in older adults on outcomes highly related to frailty. The majority of these studies have examined effects on disability in activities of daily living (ADLs) and instrumental ADLs as well as lower extremity physical function, including gait speed, balance, and lower extremity strength. Although some of these studies have focused on frailty, many used different definitions to define frailty, which causes difficulty in comparing results across studies.

Nonpharmacologic Interventions for Frailty Prevention

Exercise Interventions

One of the largest trials of physical activity conducted among older adults is the LIFE (Lifestyle Interventions and Independence for Elders) study, which examined the effect of a structured physical activity program in older adults who are at increased risk for mobility disability. Specifically, inclusion criteria included men and women ages 70−89 years who were sedentary, had reduced lower extremity function based on the Short Physical Performance Battery (SPPB),[45] and who could walk 400 m in <15 min without sitting but did not have major cognitive impairment and could participate in the intervention.[46] Although the primary outcome in this study was major mobility disability (defined as the inability to complete a 400-m walk test within 15 min without sitting), subsequent analyses of the data collected from this trial examined the effect of the intervention on frailty. Initial data from the pilot phase of this study suggested that the exercise intervention reduced frailty (as measured by using the Fried criteria) at 12 months; however, this result was related primarily to its effect on increasing the physical activity level in study participants.[47] Physical activity is 1 of the 5 frailty characteristics that are components of the frailty phenotype criteria used in this study. No effect was observed with regard to gait speed or grip strength. In the subsequent larger trial of 1635 older adults, the LIFE study intervention did not reduce the frailty incidence in the intervention group compared with the control group (–0.021; 95% CI, –0.049 to 0.007).[48] In this analysis by Trombetti et al, the SOF frailty index was used, which includes measurements of gait speed, chair rise, and self-reported exhaustion. Therefore, it seems that the LIFE study intervention had an impact on physical activity but had no significant impact on gait speed and lower extremity strength. However, the LIFE study intervention did show improvement in the incidence of major mobility disability (based on the 400-m walk) and ability to rise from a chair.[46]

Another study examined the effect of an exercise program consisting of aerobic, strengthening, and balance exercises on frailty (assessed by using the Fried criteria) in 172 older adults who were pre-frail at study baseline.[49] There was no significant reduction in frailty incidence in the intervention group compared with the control group. There was an increase in walking outdoors for exercise in the intervention group, but there was no improvement in grip strength or walking speed. Although the primary outcome was not frailty, Binder et al did show that an exercise training program could improve parameters of physical function typically used to measure frailty.[50] This study enrolled 115 older adults who were sedentary and who had reduced physical performance,[51] reduced peak oxygen uptake, and self-reported disability in ADLs or instrumental ADLs. A 3-month program of supervised exercised training, which consisted of balance, coordination, flexibility, resistance, and aerobic training, was compared with a control group that consisted of a home-based, low-intensity exercise program. The intervention group exhibited improvement in lower extremity muscle strength, peak oxygen uptake, balance, and perceived health status.

Although the aforementioned studies focused on older adults who were sedentary and had poor physical function and/or disability at baseline, a different study focused on the effect of weight loss and exercise on obese older adults.[52] In this study, Villareal et al examined 107 obese (body mass index $\geq$30 kg/m^2) older adults who also had poor physical function, reduced peak oxygen uptake, and disability in ADLs or instrumental ADLs, similar to the study by Binder et al.[50] Participants were randomized to a weight management program (diet group), an exercise training program (exercise group), a combination weight management and exercise training group (diet/exercise group), or a control group for 52 weeks. The primary outcome was the

physical performance test[52]; body composition, bone mineral density, peak oxygen uptake, and health-related quality of life (QOL) were also examined. Interestingly, the diet/exercise group had the greatest improvements in physical function, peak oxygen uptake, and QOL. Although the diet group and the exercise group improved in these outcomes compared with the control group, the combination diet/exercise group had the greatest improvement. Weight loss was observed in the diet group and the diet/exercise group only, as expected, as the diet intervention included an energy deficit of 500−750 kcal/d to achieve ~10% weight loss. Furthermore, the diet/exercise group experienced less decline in lean body mass compared with the diet group alone (3% vs 5% decline). A subsequent study examined insulin sensitivity, inflammatory markers, and adipokines from these intervention groups.[53] Although the diet group showed improvement in insulin sensitivity while the exercise group did not, the diet/exercise group had the greatest improvement in insulin sensitivity. Serum C-reactive protein and TNF levels decreased in the diet/exercise group and the diet group, whereas serum adiponectin levels increased in both these groups. The exercise group did not experience any improvements in inflammatory markers or adipokines. Taken together, these findings show that exercise is beneficial to maintain muscle mass with weight loss in obese older adults, whereas weight loss is important for improved insulin sensitivity.

In recent years, systematic reviews have been conducted to synthesize studies testing the effect of exercise interventions on frailty and its related outcomes among older adults. A meta-analysis by Chou et al examined the effect of exercise on physical function, ADL disability, and QOL in older adults.[54] This meta-analysis focused on single or comprehensive training programs compared with usual care on the measures of gait speed, balance, ADL disability, and QOL. In a combined analysis of 1068 participants in 8 clinical trials, exercise led to an improvement in gait speed (by 0.07 m/second; 95% CI, 0.02−0.11; $P = 0.005$), balance (improvement in a Berg Balance Scale score of 1.7; 95% CI, 0.6−2.8; $P = 0.003$), and ADL disability (mean difference on the Barthel index of 5.33; 95% CI, 1.01−9.64; $P = 0.02$). There was no improvement observed in the Timed Up and Go test or in QOL. Another study by de Labra et al was a systematic review of randomized controlled trials of exercise interventions to manage frailty in older adults.[55] Of 507 articles that were identified through literature review, 9 met the inclusion criteria. Inclusion criteria were that the study was an original randomized controlled trial of either aerobic or resistance training and that the primary outcomes were domains of frailty, physical capacity, and/or functional capacity. This review found that frail older adults do benefit from exercise interventions; however, the optimal exercise program is not clear. Lastly, in an expert review of exercise interventions for frailty, Liu and Fielding analyzed several studies of short- or long-term aerobic and resistance exercise for frailty in older adults.[56] In summary, the evidence shows that regular physical activity is beneficial for frail older adults or those at high risk of frailty and that the adverse events related to exercise are minimal compared with the potential gains.

Multicomponent Interventions

Two studies by Fairhall et al and Cameron et al examined the effect of a multifactorial intervention on preventing frailty in older adults with pre-frailty.[57,58] This randomized clinical trial randomized 216 older adults who met the Fried criteria for pre-frailty to a 12-month interdisciplinary intervention that targeted characteristics of frailty, or usual care. The intervention consisted of methods to address the Fried frailty characteristics of unintentional weight loss, exhaustion, low physical activity, muscle weakness, and slow gait. For weight loss, a dietitian evaluated the nutritional intake of participants with weight loss and offered nutritional supplementation for participants with low body mass index (<18.5 kg/m^2). Home-delivered meals were also recommended if appropriate. For participants with exhaustion, a referral to mental health services (a psychologist or psychiatrist) was made for those who had increased score on the geriatric depression scale. For those with social isolation, opportunities to encourage social engagement were offered through day activities as well as telephone contact with volunteers. To address low physical activity, muscle weakness, and slow gait, a physiotherapist provided 10 total home visits to prescribe a home exercise program for participants to follow over the 12-month study period. Exercises included balance and strengthening for both upper and lower extremities. The study determined that

there was lower prevalence of frailty in the intervention group compared with the control group at 12 months, with a 14.7% reduction ($P = 0.02$). The intervention group also improved in lower extremity strength as measured by the SPPB (between-group difference of 1.44 points; $P < 0.001$). There were no significant differences between the intervention and control group with regard to ADL disability, depression, or health-related QOL.

Another study examined the effect of both dietary supplementation and exercise on bone and body composition in 217 frail older adults.[59] In this study from the Netherlands, an unconventional method for defining frailty was used that consisted of use of home care services, meals-on-wheels services, lack of regular exercise, recent weight loss, and body mass index $\leq$25 kg/m^2. Participants were randomized to 1 of 4 treatment groups: (1) nutrition; (2) exercise; (3) combination nutrition and exercise; and (4) control. The nutrition intervention entailed the consumption of 2 nutrient-dense products per day, which consisted of fruit and dairy products. The exercise intervention consisted of muscle strength, coordination, flexibility, and endurance exercises. The control group had social visits and educational lectures implemented by a creative therapist. After a 17-week follow-up period, a small increase in lean body mass was observed in the exercise group (increase of 0.2 [1.4] kg; $P < 0.05$), and a small increase in bone mineral density was observed in the nutrition group (increase of 0.006 [0.014] g/cm^2; $P < 0.05$). There were no observed benefits for the combination nutrition and exercise group.

VIVE2 (Vitality, Independence, and Vigor Study) recently examined the effect of a 6-month exercise intervention as well as a nutritional supplement consisting of both protein and vitamin D on lower extremity function, body composition, and muscle strength and quality.[60,61] Participants (N = 149) who were enrolled were similar to those who participated in the LIFE study in that they were mobility limited (SPPB score $\leq$9). In addition, all subjects had vitamin D levels between 9 and 24 ng/mL at baseline. The exercise intervention consisted of 3 supervised center-based physical activity sessions per week, including walking, lower-extremity strength exercises, balance, and flexibility, similar to the LIFE study trial.[62] All subjects participated in the physical activity component of the intervention but were randomized to receive the nutritional supplement. At 6 months, both groups improved significantly in gait speed on the 400-m walk, with an average increase of 0.08 m/second in the intervention group and an increase of 0.11 m/second in the placebo group.[61] There was no significant difference between the 2 groups. Similarly, SPPB scores significantly improved in both groups (by 2.1 points in the intervention group and by 2.6 points in the placebo group), with no significant difference between the groups. Interestingly, with regard to body composition and muscle strength and quality, the intervention group experienced reduced thigh intramuscular fat, with a decrease of 12% compared with only a 5% decrease in the control group ($P = 0.049$).[60] Therefore, while in this study, the addition of a nutritional supplement had no additive effects to exercise with regard to gait speed and lower extremity function, those who received the protein and vitamin D supplementation reported greater reductions in intramuscular fat.

Although it is accepted that exercise is a useful tool for the prevention and treatment of frailty, questions remain as to the optimal type and duration of exercise. Furthermore, whether findings from any clinical trial are feasibly implemented in a clinical setting and whether the beneficial effects of exercise are sustainable beyond the period of training is not clear. There is some evidence, however, that engagement and regular contact from a patient's primary care physician along with a prescription for exercise,[63] as well as additional staff support and patient contact,[64] can have a greater impact on future exercise success. Lastly, the majority of studies focused on improving physical function in older adults who are already frail, while few studies examined the prevention of frailty.

Pharmacologic Interventions for Frailty

There is no known pharmacologic intervention for the prevention of frailty. However, because of major advances in understanding the molecular basis of aging,[65] there is now tremendous interest in agents that may potentially modify human aging and health span.[66,67] The development of pharmaceutical interventions for frailty, however, is in part hindered by the lack of a consensus definition for frailty. The International Conference on Frailty & Sarcopenia Research recently formed a task force to address concerns related to translational research on frailty

and sarcopenia.[44,68] The task force consensus is that potential agents should target the underlying biology of sarcopenia and that further research is needed to identify the optimal target population as well as several other issues, including the most appropriate secondary outcomes to examine in such trials.[68] Although recent large trials such as the LIFE study focused on sedentary older adults with existing reduced lower extremity function, other populations might also be appropriate. The nature of the population will likely depend in large part on the pharmacologic agent proposed and examined.

The ENRGISE (Enabling Reduction of Low-Grade Inflammation in Seniors) study is currently being conducted (clinicaltrials.gov number NCT02676466); it will examine the effect of fish oil and angiotensin receptor blockade on systemic inflammation (IL-6) and gait speed.[69] This study aims to enroll 300 subjects with mobility impairment and high baseline levels of inflammation and to follow the effect of the drug intervention versus placebo over 6 months for a pilot phase of the study; evaluation of the drug effect on gait speed on the 400-m walk and IL-6 are the primary outcomes. The rationale for this study is that age-related renal dysfunction and atherosclerosis may be major contributors to the inflammation observed with aging.

Metformin, a biguanide, is the most widely used oral antidiabetic drug that is generally recommended for first-line medical treatment of type 2 diabetes.[70] Early initiation of metformin at the time of diagnosis, when glycosylated hemoglobin levels are not significantly elevated, has been associated with improved glycemic control over time and decreased long-term complications.[71] Metformin has been shown to be highly effective at reducing the onset of diabetes by 31% in 3234 prediabetic adults over a period of 2.8 years in the DPP (Diabetes Prevention Program) study[72] and at reducing systemic inflammation.[73] Results of animal studies suggest that metformin has life extension properties and improves health span.[74] Metformin is believed to activate AMP-activated protein kinase (AMPK), a major cellular regulator of lipid and glucose metabolism.[75,76] Because AMPK interacts with the mammalian target of rapamycin pathway,[77] metformin has modulating effects on a pathway known to play a major role in lifespan extension.[65] Metformin also upregulates peroxisome proliferator–activated receptor gamma coactivator 1-alpha, a master regulator of mitochondrial function, and nrf2, a transcription factor that controls antioxidant programs.[78] Because these molecules (AMPK, mammalian target of rapamycin, and peroxisome proliferator–activated receptor gamma coactivator 1-alpha) are interconnected through cellular signaling networks implicated in the modulation of the aging process, it has been postulated that metformin could slow aging and age-related diseases.[77] Furthermore, observational studies indicate that metformin reduces mortality and frailty.[79,80]

Despite the strong link between insulin resistance and diabetes with frailty, it is unknown whether an insulin sensitizer such as metformin can attenuate frailty. However, evidence supports that the detrimental effect of insulin resistance on aging muscle is potentially modifiable. For instance, although Lee et al showed that men with prediabetes or diabetes had greater loss in lean muscle mass compared with normoglycemic men,[31] those treated with insulin sensitizers such as metformin or thiazolidinediones during this time period (3.5 years) experienced less decline in muscle mass compared with those not treated with insulin sensitizers.[81] A similar effect was observed in older women treated with insulin sensitizers.[82] In fact, those treated with insulin sensitizers had essentially the same decline (–0.10 m/second) as women without diabetes (–0.11 m/seconds), whereas those with diabetes not treated with insulin sensitizers had the greatest decline (–0.17 m/second; $P < 0.05$). The evidence therefore suggests that diabetes and prediabetes have detrimental effects on aging muscle and that insulin sensitizers may ameliorate these effects.[81,82]

We are currently conducting a randomized clinical trial of metformin for the prevention of frailty in older adults with prediabetes (clinicaltrials.gov identifier number NCT02570672). We selected older adults with prediabetes given their increased risk for developing frailty.[29] Furthermore, this population has a clinical indication for metformin.[72] We aim to study 120 subjects taking metformin versus placebo for 2 years. The primary outcome is frailty (Fried criteria), and secondary outcomes are systemic inflammation, insulin resistance (as measured by using the insulin clamp technique), muscle tissue inflammation, and insulin signaling and AMPK activity/phosphorylation in muscle tissue. With this

study, we hope to shed light on the potential benefit of metformin on frailty in older adults with prediabetes.

In addition, the TAME (Targeting Aging with Metformin) study aims to determine the effect of metformin on the prevention of a composite outcome of age-related diseases and conditions.[77] This study is planned as a multisite clinical trial.

DISCUSSION

Current research studies are primarily using nonpharmacologic approaches to improve frailty outcomes. These interventions most often include exercise and/or nutritional interventions, and the effectiveness of these interventions is varied. Although the benefits of exercise are known, few older adults are meeting the current recommendation guidelines for physical activity. In fact, almost 30% of adults aged $\geq$50 years are sedentary,[83] which may be due in part to the fact that many older adults have existing disability and comorbid medical conditions that make it difficult to exercise.[84] Because of major advances in the biology of aging research, we now have potential pharmacologic interventions that may prove useful for aging-related outcomes such as frailty.[44,66] Currently, we are at the dawn of an exciting time in translational geroscience, in which we have the potential to discover one or more novel interventions to intervene on frailty and promote healthy aging. Challenges remain as to safely conducting such research, choosing agents with more potential for benefit as opposed to harm, and selecting the most appropriate target populations for such interventions.

CONFLICTS OF INTEREST

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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All authors performed the literature review, writing, and synthesis of information for the manuscript.

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