Developing a new treatment paradigm for disease prevention and healthy aging

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ABSTRACT

An increasingly prevalent pattern of risk factors has emerged in middle-aged and older adults that includes the presence of type 2 diabetes or prediabetes, overweight or obese weight status with central obesity and very high body fat, low cardiorespiratory fitness (CRF), low strength, and a low lean-body-mass-to-body-fat ratio. Traditionally, these problems have been approached with a low-fat and low-calorie diet and with lower to moderate intensity activity such as walking. While the treatment has some clear benefits, this approach may no longer be optimal because it does not reflect more recent findings from nutrition and exercise sciences. Specifically, these fields have gained a greater understanding of the metabolic and functional importance of focusing on reducing body fat and central obesity while maintaining or even increasing lean body mass, a quality weight loss, and how to efficiently and effectively increase CRF and strength. Evidence is presented for shifting the treatment paradigm for disease prevention and healthy aging to include the DASH nutrition pattern but with additional protein, higher intensity, brief aerobic training, effort-based, brief resistance training, and structured physical activity. Recent interventions based on social cognitive theory for initiating and then maintaining health behavior changes show the feasibility and efficacy of the approach we are advocating especially within a multiple health behavior change format and the potential for translating the new treatment paradigm into practice.

KEYWORDS

Diabetes, Quality weight loss, Treatment paradigm, Multiple health behaviors

IMPORTANCE OF THE PROBLEM, USUAL TREATMENT, CHANGING THE TREATMENT PARADIGM

A pressing public health problem is the high prevalence of engagement in multiple, poor health behaviors, creating patterns of high risk for morbidity and mortality and contributing to considerable individual and societal financial burden [1, 2]. One pattern that is becoming increasingly prevalent is the combination of prediabetes, overweight or obese weight status, cen-

Implications

Practice: Treatment needs to reflect both the high prevalence of a multiple risk pattern and recent findings from nutrition and exercise sciences that point to a different set of intervention components delivered in different modalities and representing a new paradigm for disease prevention and healthy aging.

Policy: The high prevalence of a pattern of multiple risk factors foretells considerable individual and societal burden unless new approaches reflecting advances in psychological, nutrition, and exercise sciences and demonstrating long-term maintenance of behavior changes that can be attractive to health care insurers are translated into practice.

Research: Research within a new treatment paradigm needs to focus on improvement of components of multiple health behavior change interventions and especially on their overall feasibility and strategies for their translation into practice.

tral obesity (increased visceral adipose tissue), and low cardiorespiratory fitness (CRF) with gradual loss of lean body mass and strength [3], which further increases the risks for type 2 diabetes (T2D), cardiovascular diseases, and some cancers, disabilities, and premature death [4]. The prevalence of T2D, based on fasting glucose or hemoglobin A1c levels in adults, aged 45–64 years old, is ~14 %, and the prevalence of prediabetes for adults >20 years old is ~35 % [5]. For adults over 65 years old, the prevalence of T2D is ~27 % and the prevalence of prediabetes is ~50 % [5].

Overweight, not just obesity weight status, is often comorbid for central obesity (waist circumference (WC) ≥102 cm for men and ≥88 cm for women) [3], which is associated with increased risk of T2D, especially for women [6]. Overweight individuals with large WC's, though at high risk, are often not identified for interventions [6, 7]. The normal age-related loss of lean body mass beginning in middle age or earlier for physically inactive people [7] also renders the usual interpretation of body mass index (BMI) suspect in that it does not account for the

large percentage of body fat and body fat distribution, particularly intra-abdominal, increased visceral fat associated with the risk of T2D. Thus, the overall problem may be *underestimated* [7–9].

Standard treatments for diabetes prevention, such as primarily relying on lower to moderate intensity physical activity (i.e., walking) and traditional dietary approaches (i.e., lower calories, moderate protein, and lower fat), while providing clear benefits [13, 14], may now *not* be optimal to meet the challenges of the increasingly prevalent constellation of risk factors nor reflect more current findings from nutrition and exercise sciences. Walking or other similar moderate physical activity (PA) used in the Diabetes Prevention Program and the recently completed Look Ahead trials provides no real stimulus for increasing and retaining lean body mass and strength and affecting the attendant risks or for efficiently increasing and maintaining CRF > 1.5 metabolic equivalent of tasks (METs), with CRF strongly and inversely associated with cardiovascular disease (CVD) risk and all-cause mortality [15]. Similarly, nutritional patterns entailing large caloric reductions and only-moderate protein consumption can result in the loss of lean body mass and appear inadequate for preserving or increasing lean body mass with resistance training (RT), which is a central part of exercise guidelines [16]. Reduced lean body mass is associated with insulin resistance and prediabetes [17–19]. In the Look Ahead protocol, for example, only 1,200 to 1,500 kcal/day with a minimum of 15 % calories from protein was recommended during the initial weight loss phase for people weighing < 114 kg. However, even with 20 % kilocalorie from protein, this is likely inadequate to maintain lean body mass (e.g., 20 % protein, 1,350 kcal/day, 90 kg bodyweight, 0.75 g protein/kg, below the current RDA). Recent reviews, noted below, suggest that for middle-aged and older adults, RT may be optimized by consuming ~1.2 g of protein per kilogram of bodyweight, 108 g of protein per day for a person weighing 90 kg, with 20–30 g of protein in several meals throughout the day [20, 21]. Moreover, following usual energy restricted, lower to moderate protein diets and usual physical activity, cycles of weight loss and *regain* can result in a loss of lean body mass and additional gains in body fat in middle-aged and older adults, even for longer-term programs that effectively reduce weight and only show minimal weight regain [22, 23].

Gaining body fat also seems to set the stage for further loss of lean body mass [24]. There is an emerging research base showing the functional and metabolic importance of retention of lean body mass [2, 17, 18], and an approach is needed that *preserves, as much as possible, lean body mass*. Low CRF also exacerbates cardiovascular risk in people with T2D [25], and both strength and CRF independently and jointly affect morbidity and mortality risks [26–28]. Typically, improving CRF is approached by moderate intensity endurance aerobic training (AT) or, more currently, extended interval training. However, recent research by different investigators described later has shown that very *brief* AT can effectively increase CRF and

favorably affect other risk factors and can be effectively used with RT.

A *paradigm shift* for disease prevention and healthy aging, distinct, evidence-based, and also free from recent revelations of ‘myths’ about traditional weight loss [29], needs to occur. Such a paradigm involves moving away from a focus on overweight and obesity weight status and the usual weight loss approach, to a focus on the reduction of excess body fat while retaining or even increasing lean body mass. This is the goal of *body composition change, a quality weight loss, and concurrent risk reduction* through multiple health behavior changes that includes a healthful nutrition pattern and not a restrictive ‘diet’, brief targeted resistance training, very brief aerobic training, and physical activity to create a new healthy phenotype—lower body fat, retained lean body mass, higher CRF, and increased strength. A nutrition plan such as dietary approaches to stop hypertension (DASH) [10], in conjunction with other treatment components, can result in the loss of body fat while retaining or even increasing lean body mass, strength, and CRF [11, 12].

DASH NUTRITION

DASH [10] is considered an optimal dietary pattern and *not an energy-restricted diet*. The aim is the replacement of energy-dense, nutrient-poor food choices with nutrient-rich healthful food choices, which have lower energy content and would result in meeting macro- as well as micronutrient recommendations. Importantly, such an approach could result in fat mass loss while allowing lean mass accretion through additional protein consumption and RT. DASH’s meal composition and plans for *distributing protein throughout the day* are considered ideal (see later) [21]. DASH is low in saturated fat and emphasizes consumption of fruits, vegetables, low-fat dairy products, whole-grain products, fish, poultry, smaller portions of lean meats and nuts, with minimal sweets, added sugars, and sugar-sweetened beverages. In addition, DASH can be the focus of treatment because recent evidence shows (1) the ready adaptability and enhanced metabolic and CVD risk benefits with DASH plus additional protein [30], (2) modest weight loss through exercise and DASH with reduced energy intake improves insulin sensitivity [31], (3) the association of refined carbohydrates, sugared beverages, and processed foods (i.e., high glycemic load)—and *not* all higher fat foods—with weight gain, while many foods featured in DASH (e.g., fruits and vegetables, whole grains, nuts) are associated with weight stabilization or loss [32, 33], and (4) traditional reduced calorie, lower fat, and higher carbohydrate weight loss diets can result in reduced resting energy expenditure (REE) and total energy expenditure (TEE), setting the stage for weight regain [7, 11]. Studies indicate that the amount of initial weight loss often is not affected by the macronutrient content of the dietary plan, but a higher protein diet may limit weight regain [7, 8, 11, 34, 35]. However, the types of foods and meal patterns for DASH are quite

different from how most US adults eat [36], raising issues of feasibility and adherence. Recent studies (below), though, show the efficacy of targeting specific foods with a *cumulative series* of accomplishable smaller changes with DASH-compatible goals. In addition, nutritional, for example, higher protein goals are achievable within DASH principally by adding more servings of lower fat dairy, associated with reduced risk of T2D [37], e.g., adding ‘Greek yogurt’ (16–20 g of protein per 100 kcal nonfat serving), or even adding lean beef [30]. Both of these additions are nutrient-rich protein sources, contributing to high-quality protein distributed during the day. These additions to DASH can be accommodated for by modestly reducing other foods higher in calories.

MUSCLE PROTEIN SYNTHESIS, ANABOLIC RESISTANCE, AND IMPROVING TREATMENT

The anabolic processes of muscle protein synthesis (MPS) in response to food consumption are somewhat blunted (‘anabolic resistance’ [38]) in middle-aged to older physically inactive adults. Current RDAs for protein consumption for middle-aged and older adults (0.8 g/kg bodyweight) and following a *usual care* low-fat, low-calorie, moderate-protein diet appear inadequate for retention of skeletal muscle mass [39]. Studies suggest that the retention of skeletal muscle mass in middle-aged and older adults may require 1.2 g of protein per kilogram per day (or more) with regular daily meals containing 20–30 g of protein with 8–9 g of essential amino acids with meals distributed and consumed several times per day to optimize the stimulation of MPS [21, 40, 41]. Higher protein consumption but still within the acceptable macronutrient ranges accepted as healthy and within the context of an overall healthful nutrition pattern appears to decrease disease risk [12, 20, 39], and a recent meta-analysis showed that additional dietary protein improved strength and muscle hypertrophy adaptations to RT in middle-aged and older adults [42]. The acute rise in MPS also is somewhat blunted in older adults in response to the powerful stimulus from RT. However, recent research has focused on the synergistic benefits of the nutrition/exercise pattern of consuming protein-rich meals before RT and distributed during recovery over the next 24 h as a vehicle to enhance signaling mechanisms for MPS, an acute adaptive response to RT for chronic muscle hypertrophy. Studies show that ordinary, *readily available* and *inexpensive* lower fat milk or yogurt as additions to an already healthful dietary pattern, such as DASH, appear sufficient to enhance MPS after RT [40, 41]. DASH can be accommodated to meet 1.2–1.5 g of protein per kilogram of bodyweight per day [29], which then may be sufficient to lessen anabolic resistance [38, 39]. The additional lower fat milk or yogurt is a recommended food in DASH, and their consumption is inversely associated with T2D risk [37].

SIMPLE RESISTANCE TRAINING AS A CORE COMPONENT OF TREATMENT

Compelling evidence [43] shows that relatively simple, brief, lower volume RT protocols performed two to three times a week and focused on exercise movements that affect multiple muscle groups can provide an adequate stimulus to promote strength and hypertrophy and increase REE for 72 h post training by ~100 kcal/day [44]. Perhaps what is less known is that strength, independent of CRF, is inversely associated with many disease risk factors and premature death [26]. Research by Phillips and colleagues is particularly germane to middle-aged and older adults by showing that an effective RT stimulus is not dependent, as assumed within the current, century-old RT paradigm, upon the use of heavy load, i.e., an *extrinsic* model with the focus on the external resistance. Instead, muscle hypertrophy and strength can be fostered by simply working with lighter loads but ensuring fatigue. In such a paradigm, the stimulus that elicits a large MPS response and leads to strength gains is the *degree of effort* and fatigue at the end of a set of repetitions of a properly performed RT exercise [45, 46], findings consistent with the correct interpretation of the *size principle* [47, 48]. A high degree of effort and a high level of MPS can be achieved with the use of *light-to-moderate* resistance when an exercise set ends with a high, but manageable, degree of effort (‘failure at the end of the set’), with this approach both enhancing hypertrophy and strength. This *intrinsic* model, itself a paradigm shift from the extrinsic weightlifting model, focuses on proper form and degree of effort as opposed to merely trying to lift progressively heavier weights. In practice, middle-aged to older adults can, in this manner, more safely perform RT two to three times a week with whole-body routines taking about 35–40 min; however, as suggested above, the overall outcomes for RT may be *lessened* in the absence of adequate nutrition.

VERY BRIEF AEROBIC TRAINING TO IMPROVE TREATMENT

Recent exercise science studies have shown that higher intensity interval training protocols *safely* produce, even for people with prominent risk factors, improved health-related outcomes versus typical low to moderate intensity protocols with the same energy expenditure [49–56]. However, those interval protocols have multiple repeats, raising the question of translatability [49, 50, 52–54]. The threshold model [51] postulates, though, that the stimulus can be brief if it is at a proper threshold of *intensity*. Research with the Graded Exercise Protocol [55] showed that after a graded warm-up to a 4-min work segment at ~75 % $\text{VO}_{2\text{max}}$ with twice-a-week training produced about the same increase in CRF as much as longer duration training at the same intensity. Very similar outcomes including favorable changes in glucose metabolism and blood pressure (BP) with a single, harder 3–4 min workpiece have

been found by a prominent Norwegian research group [56] and Gibala's group in Canada [52]. Collectively, these data from different investigators point toward the efficacy of very brief, moderately hard AT that can be an important component of multiple health behavior interventions and replace the arduous, traditional long duration, lower to moderate intensity endurance training. Further, such brief training would allow an entire session that also includes RT to only require about 45 min. It is important to note that recent studies such as STRRIDE AT/RT [57–59], while showing superior effects for long duration AT vs. RT on ectopic fat, may have found (as the authors noted) an effect from caloric expenditure and deficit that in a new multiple health behavior protocol would be produced from PA and quality nutrition without extended AT.

PHYSICAL ACTIVITY AS A TREATMENT COMPONENT

Within the age groups of 40–49 and 50–69 years old in the USA, it has recently been found that they have mean steps of only about 6,000 and 4,700 steps per day, respectively [60]. Studies using accelerometers suggest that only 5 % of adults meet the physical activity guidelines [61], and occupational physical activity has appreciably declined [62]. Lower step counts are associated with higher BMI and more hours of sitting which has recently been shown to be associated with morbidity and premature mortality [63–67]. Therefore, meaningfully increasing PA, to a significant extent, remains an important component in a program for prediabetes and central obesity and related disorders, and in a multiple health behavior program, a simple pedometer step count program which follows 'best practices' to promote increases, remains important [67].

THEORY-BASED, LONG-TERM BEHAVIOR CHANGE AS CENTRAL TO TREATMENT AND POLICY CHANGES

Recent research has shown the effectiveness of face-to-face counseling especially combined with *continuous supervised exercise training* [68, 69] for previously untrained people with T2D diabetes. A strong case has been made for counseling with supervised exercise training as empirically validated treatments *essential for meaningful health behavior changes* that have *public health viability* and should be supported by insurance payers [70]. However, a caveat is that these recent studies have not yet shown that people will reliably *maintain* exercise training in concert with other health behaviors such as healthful nutrition without continuous supervision. A stronger case can be made for insurance payment for supervised exercise training in conjunction with other health behaviors if theory-based programs that clearly operate through their theoretical constructs and provide a replicable set of maintenance procedures *within an extended care model* [71] *consistently* lead to efficacious outcomes *after supervision ends*.

FEASIBILITY AND EVIDENCE: SCT-BASED INTERVENTIONS

Questions of feasibility, efficacy, and translatability become paramount when a new approach is proposed. We therefore briefly provide supportive data from one research program with social cognitive theory (SCT)-based secondary prevention programs with extended, though faded, contacts after a more intensive treatment phase [72, 73].

We have shown the efficacy at *16-month follow-up* of a targeted, *cumulative small change* approach to nutrition similar to DASH and PA (step counts) within a large church-based health behavior trial ($N \sim 1,000$) [74], and more recently, a completely automated (*Guide to Health* (GTH)) [75], entirely Internet-based health behavior intervention that demonstrated the prevention of weight gain in overweight and obese adults. These SCT-based interventions focused on changes similar to DASH including increasing consumption of fruits, vegetables, whole grains, and lower fat dairy products and decreasing energy-dense nutrient poor refined carbohydrate sources from soft drinks, candy, and other snacks. Participants iteratively tracked and reported to our website their progress on consuming targeted foods, increasing step counts, and maintaining or reducing body weight; made specific plans for physical activity, exercise, and targeted food choices; and received tailored positive and corrective feedback and goals. The most sedentary participants sufficiently increased their steps per day to meet minimal, national PA guidelines. The Internet GTH nutrition, PA, and prevention of weight gain program showed a several percent weight loss at the 16-month follow-up point in participants with higher BMI at baseline and demonstrated the ability to maintain nutrition and physical activity behaviors with an entirely electronic extended care. The small change, GTH approach for nutrition and PA, was adapted in an early efficacy study for people with prehypertension using one initial instruction session by a registered dietitian on consuming foods with the DASH dietary pattern, instruction on the pedometer-based step count program, plus our electronic approach for monitoring, planning, and setting goals, reporting, and receiving tailored feedback on DASH and PA [76]. Participants increased their steps per day by $\sim 3,000$, decreased weight by 4.8 kg (5 %), and decreased systolic BP by 15 mmHg.

The *Resist-Diabetes* project involves inactive, overweight, and obese people, 50–69 years old with prediabetes, and the aim is to assess the short- and long-term effects of RT on strength, fasting glucose, and glucose tolerance. Our 'whole body' intrinsic RT program involves 12 exercises performed with moderate resistance with good form for eight to ten repetitions and training with a high degree of effort (to voluntary fatigue). At this point, about 4,000 training sessions in the supervised initiation phase ($N=143$) have been conducted with *no* lasting serious adverse events [77]. About 91 % of the scheduled training sessions were completed, strength increased by about 25 %, and glucose tolerance was significantly improved. In a still-ongoing SCT-based extended contact phase, there is

brief, faded personal contact, and electronic contact is maintained through the project website also available as a *smartphone app*. At this point, participants have reported about 85 % of their workouts in detail and received individualized feedback, and depending upon reported data, they were presented, used, and provided subsequent feedback on strategies for specific problems encountered [78].

A critical point noted at the outset is that people often engage in multiple risk behaviors pointing toward the need for multiple health behavior interventions. The multiple health behavior ASPIRE intervention was developed for overweight and obese weight status middle-aged, inactive adults with central obesity (WC, mean=105 cm) [55]. Nutrition and physical activity counseling plus initial supervised RT and AT, emphasizing mastery experiences and self-regulation, were all fitted into two 1-h sessions per week. Relevant points included (1) a targeted 'small changes' healthful nutrition plan similar to DASH (not drastic calorie restriction 'dieting', but rather 'shaping' nutrition changes through a cumulative series of *prescriptive but acceptable changes*, e.g., adding one fruit as a snack and dropping one soft drink per day [79] to produce a small (5–7 %) clinically relevant and, importantly, sustainable weight loss; (2) a pedometer step count program with specific graduated goals to increase physical activity; (3) brief RT, a forerunner of the intrinsic model, using moderate resistance, controlled repetitions but higher effort; (4) brief AT, the graded exercise protocol as described above; and (5) a hands-on approach for transitioning people to continued exercise training in various facilities or at home. Study results showed after a 4-month intervention followed by a no-contact, 3-month follow-up that ASPIRE participants *maintained* all changes from post-intervention including (1) increasing PA by ~4,500 steps per day to reach ~10,000 steps per day, (2) increasing strength by ~50 %, (3) increasing CRF by ~1.5 METs, (4) reducing weight by 5–6 %, (5) demonstrated effective body composition change by a reduced WC of ~8 cm while (6) maintaining lean body mass, and (7) increasing consumption of fruits and vegetables and decreased refined carbohydrates, e.g., from soft drinks and candy. A study with similar components was conducted by Dr. Stuart Phillips' group at McMaster University. Their IDEAL trial found that with additional dietary protein in the form of low-fat dairy products, participants not only lost weight and body fat, but also *gained* lean body mass [80] which would be advantageous given the high potential for a sarcopenic obese phenotype in aging persons with multiple poor health behaviors.

These secondary prevention trials using a range of intervention modalities demonstrate the feasibility and efficacy of intervention components as well as multiple health behavior interventions representing a new treatment paradigm for disease prevention and healthy aging. The next stage of research needs to focus on improving the components and overall

approach including the long-term maintenance of changes; systematic applications to other diseases and conditions such as with people who have survived cancers and where attention needs to be directed to safely and efficiently improve nutrition patterns, strength, lean body mass, and CRF [81]; the relative cost-effectiveness and benefits compared to current standard practices that can make the approach attractive to health care insurers; and strategies for translation into practice [82].

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