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

Exercise and Cardiovascular Risk among Masters Athletes with Type 2 Diabetes

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Abstract

Purpose of Review

This review was designed to provide a scientific and clinical framework for the care of physically active men and women with an emphasis on the management of T2DM.

Recent Findings

The preventative and therapeutic benefits of physical activity (PA) on adult onset or Type 2 Diabetes Mellitus (T2DM) are well established. Individuals diagnosed with or are at risk for T2DM should be counseled and maximally supported to pursue an active or athletic lifestyle. Optimally, this translates into the adoption of an athletic lifestyle. "Masters athletes", men and women above the age of 35 who regularly train for and/or participate in competitive sport, represent a rapidly growing segment of the population. Although the high level of exercise characteristic of this population has numerous health benefits, it does not confer immunity from T2DM or cardiovascular (CV) disease.

Summary

Providing effective care for men and women above the age of 35 who regularly train for and/or participate in competitive sport requires an understanding of the interplay between basic exercise physiology and the pathogenesis of insulin resistance.

Keywords Exercise · Masters athletes · Lifestyle modifications · Cardiovascular disease · Diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a major cause of morbidity and mortality in the United States and other developed countries worldwide. The 2017 Center for Disease Control and Prevention National Diabetes Statistics Report estimates 30.2 million American adults, aged 18 years and older, have T2DM and an additional 84.1 million have prediabetes. [1] Furthermore, an estimated 1.5 million cases of T2DM were diagnosed in the year 2015 alone, solidifying its claim as one of the major public health concerns and economic burdens of the modern era [1]. Effective prevention and management of T2DM is best accomplished through a multi-tiered approach to lifestyle modification with particular emphasis on physical activity (PA) and dietary intake coupled with the addition of stepwise pharmacotherapy as dictated by disease severity. The preventative and therapeutic benefits of PA on T2DM are numerous, and individuals diagnosed with or are at risk for T2DM should be counseled and maximally supported to pursue an active or athletic lifestyle. "Masters athletes", men and women above the age of 35 who regularly train for and/or participate in competitive sport, represent a rapidly growing segment of the population [2]. Although the high level of exercise characteristic of this population has numerous health benefits, it does not confer immunity from T2DM or cardiovascular (CV) disease. This paper is designed to provide a review of basic exercise physiology with emphasis on the

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impact of habitual PA on T2DM and cardiovascular (CV) risk with a clinical focus on the implementation of individualized, patient-centered PA strategies among masters athletes.

Relevant Basic Exercise Physiology

PA is an energy intensive process that requires adequate substrate delivery and utilization. The CV system is responsible for substrate delivery and the interested reader is referred elsewhere for detailed discussion [3–6]. Briefly, the heart and systemic arterial vasculature deliver oxygenated blood and macro-molecules serving as substrates for energy production to active skeletal muscle beds, needed to propagate the dynamic cycling of muscle between contracted and relaxed states characteristic for exercise. This process of nutrient delivery can be quantified by measurement of cardiac output, the product of left ventricular stroke volume and heart rate. Among adults without significant CV disease, cardiac output ranges between 3 to 5 l per minute under resting conditions and may increase to as much as 30 l per minute among trained athletes during maximal effort exercise. Cardiac output augmentation during exercise is tightly linked to increases in work, which can be quantified by external metrics (watts of power on a cycle-ergometer, speed and incline on a treadmill, etc.) and internal or physiologic (oxygen consumption (VO_2)) metrics. Increases in external work necessitate matched increases in VO_2 and cardiac output. The relationship between VO_2 and cardiac output is defined by the Fick equation in which VO_2 equals the product of cardiac output and the arteriovenous oxygen difference, a metric that reflects the magnitude of oxygen extraction during the transit of fully oxygenated blood from the left ventricle to the return of variably deoxygenated blood to the right ventricle. Thus, impairments in ventricular function and/or key determinants of oxygen transport (i.e. the availability and functional quality of hemoglobin) result in reductions in maximally obtainable VO_2 and thereby exercise limitation. Failure of the CV system to meet the needs of the skeletal muscle is the hallmark pathophysiology of CV diseases that result in impairments in exercise capacity.

During PA, skeletal muscle cells continuously cycle through the contracted and relaxed states for the purpose of activity-specific force generation. Skeletal muscle function is largely supported by the transfer of energy from adenosine-triphosphate (ATP) during its conversion to adenosine-diphosphate (ADP). Skeletal muscle cells have the capacity to store only enough ATP to facilitate several contraction / relaxation cycles. Once basal ATP supplies are depleted, creatinine phosphate within the myoplasm transfers a high-potential phosphoryl group to ADP in order to regenerate additional ATP [7]. However, the total amount of ATP available from basal stores and subsequent contributions from the creatine phosphate pathway remains limited with the net capacity of providing adequate energy supply for approximately 5–6 s of PA thereby necessitating alternative energy sources for sustained PA [7]. During early phase exercise (i.e. the first 5 min), glycogen stored within skeletal muscle undergoes rapid glycogenolysis, yielding glucose as the end product, and thus provides the bulk of energy substrate needed during PA. Liberated molecules of glucose enter the glycolytic pathway after which their fate is determined by the availability of oxygen within the skeletal muscle mitochondria. Under oxygen-replete conditions, glucose, in conjunction with acetyl-CoA generated by the β-oxidation of free fatty acids, fuels the mitochondrial Krebs cycle which results in a relatively high energy yield of ATP (36 mM ATP per glucose molecule consumed). This "aerobic" metabolism is responsible for the vast majority of energy production during low to moderate intensity endurance exercises such as walking, jogging, swimming, or cycling. Under oxygen-deplete conditions, glucose is shunted to "anaerobic" pathways, most importantly towards lactate generation. The generation of ATP during lactate formation within the myoplasm occurs very rapidly but provides far less ATP (2 mM ATP per glucose molecule consumed) than aerobic glucose utilization. Anaerobic metabolism, given its rapidity and oxygen independence, facilitates short intense burst of PA and contributes to total ATP generation when the intensity of sustained exercise requires more ATP than can be provided by aerobic metabolism.

As skeletal muscle glycogen stores begin to diminish, muscles rely on the uptake of circulating glucose and FFA from the adjacent capillaries leading to reductions in blood glucose concentrations [8–10]. Skeletal myocyte contraction relies heavily on the use of carbohydrates and free fatty acids and to a less degree amino acids [8, 11, 12]. The type, intensity, and duration of the exercise determines which substrates are utilized. For example, FFAs are used almost exclusively to maintain resting muscle tone with increasing reliance on carbohydrate during increasing intensity of PA. Importantly, any amount of PA results shifts metabolic reliance away from FFA and towards the utilization of alternative substrates including blood glucose, muscle glycogen, and to a lesser degree amino acids [8, 11]. As PA continues, reductions in the concentration of circulating blood glucose stimulate the coordinated integration of endocrine and nervous systems, which function to liberate adequate amounts of energy containing substrate to maintain energy homeostasis. The complex process of ensuring adequate energy availability relies on multiple hormonal regulators, including insulin, glucagon, glucocorticoids, and catecholamines as well as other molecular regulators within the liver and skeletal muscles [13]. Perhaps most notably, insulin facilitates a shift from hepatic glycogenolysis to hepatic gluconeogenesis as the dependence on carbohydrates for energy substrate increases with the intensity and duration of PA [14, 15].

There are two separate and complementary pathways which exist to facilitate skeletal muscle glucose uptake: insulin-dependent and insulin-independent, [16–18]. Both pathways involve glucose uptake via GLUT protein transporters (particularly the GLUT4 isoform) which are stored within intracellular micro-vesicles and recruited to the myocyte plasma membrane when needed. Increases in circulating insulin, the normal and near immediate response to food intake, is a potent stimulus for GLUT transporter translocation and serves to facilitate the transfer of glucose from the blood stream into storage tissues including fat, muscle, and hepatic cells. Insulin-mediated GLUT activation is non-discriminatory and would be disadvantageous during exercise as skeletal muscle glucose uptake may be compromised by competition from alternative tissue types. In addition, exercise is not an effective stimulus for pancreatic β-cell insulin secretion and is consequently a state of relative hypoinsulinemia. Thus, GLUT translocation during exercise is facilitated mainly by insulin-independent mechanisms. While the mechanistic details of this process remain incompletely understood, skeletal muscle contraction with accompanying increases in cytosolic calcium concentration and subsequent activation of the calcium-dependent protein kinase C appear to be involved in this process. Given the fundamental teleologic importance of sustained moderate intensity exercise, redundant and perhaps synergistic mechanisms are likely to exist. While insulin-dependent glucose uptake is of limited importance during exercise, skeletal muscle demonstrates marked increases in insulin sensitivity following exercise [19]. Insulin-mediated maintenance of plasma membrane based-GLUT following an acute bout of exercise facilitates the replenishment of intracellular glycogen stores thereby preparing for subsequent bouts of exercise. Mechanisms for persistent post-exercise skeletal muscle insulin sensitivity remain incompletely understood with speculated contributions from cellular adenosine receptors and local tissue hypoxia [20].

Exercise and T2DM

T2DM is a heterogeneous metabolic syndrome characterized by relative hypoinsulinemia resulting from blunted insulin secretion, blunted peripheral tissue insulin sensitivity, and in most cases, a combination of both abnormalities. Regardless, T2DM results in impaired glycemic regulation and eventual hyperglycemia with corollary metabolic abnormalities and eventual CV pathology. The principal inciting pathology of T2DM is the failure of typically insulin-responsive organs, including myocytes, adipocytes, and hepatocytes, to appropriately respond to insulin. The mechanistic underpinnings of reduced tissue insulin sensitivity remain incompletely understood; however, several pathophysiologic processes, more commonly associated as being risk factors including: chronic physical inactivity, obesity, long term exposure to highly processed diets, and underlying genetic predisposition have been proposed [21–24].

Unifying the various pathways towards disease development is the onset of declining tissue insulin sensitivity leads to post-prandial elevations in blood glucose. Pancreatic β-cells initially compensate by increasing insulin secretion with a resultant state of hyperinsulinemia early on in the disease course. In advancing stages of T2DM, β-cell insulin secretion eventually fails to maintain homeostatic euglycemia resulting in chronic and persistent hyperglycemia [21, 25]. The combination of chronic hyperinsulinemia and chronic hyperglycemia underlie the development of the myriad of well-establish micro- and macrovascular complications that account for the majority of morbidity and mortality associated with T2DM [26].

Habitual PA, including structured exercise, is among the most effective ways to both prevent and treat T2DM. Numerous large-scale cohort studies have demonstrated the impact of PA on the prevention of T2DM [27, 28].PA serves as an effective preventative strategy by facilitating weight loss and maintaining lean body mass [29–31], increasing and maintaining cardiopulmonary fitness [32, 33], and promoting euglycemia through enhanced insulin action and increased fatty acid oxidation [19, 34]. Similarly, PA serves as a cornerstone treatment modality for established T2DM, with efficacy comparable to pharmacologic strategies [35]. Among patients with established T2DM, acute bouts of exercise stimulate durable (4 to 72 h) increases in skeletal muscle, hepatic, and adipose insulin sensitivity which promote efflux of blood glucose for subsequent storage [36–39]. Thus, patients with T2DM typically experience optimal glucose control in the immediate few hours following exercise.

T2DM and CV DISEASE

The association between T2DM and morbidity and mortality attributable to CV disease is well established [40–42], and T2DM alone serves as an independent risk factor for incident CV disease in both men and woman [43, 44]. In fact, 65% of all causes of death for individuals with diabetes are attributed to CV diseases [45]. Chronic hyperglycemia has a direct pathogenic effect on the systemic vasculature leading to common micro- and macrovascular complications of clinically appreciable CV pathology including epicardial atherosclerotic coronary disease, cerebrovascular disease, and renovascular disease [43, 46–50]. To date, trials such as the UKPDS [51], ACCORD [52], VADT [53], and ADVANCE [54] which have investigated the effect of stricter glycemic control on CV outcomes have been mixed, and thus target glycemic levels remain controversial. However, other factors outside of chronic hyperglycemia, most importantly physical inactivity, as well

as obesity, genetics, gender, and advanced age, predispose one to T2DM by synergistically increasing the risk of CV disease through complex mechanisms that can also be independent of glycemic control [55, 56]. Therefore, while some of the aforementioned are non-modifiable, optimizing one's alterable risk factors, specifically physical activity, can prevent or delay the onset of CV disease [57, 58]. Furthermore, the "major" independent CV disease risk factors including: dyslipidemia [59–62], systemic hypertension [63, 64], and arterial stiffening [65, 66], are positively impacted by PA and exacerbated by inadequate PA. Thus, PA exerts its preventative and therapeutic effects on T2DM through both glucose-dependent and glucose-independent mechanisms and is a vital preventative and therapeutic intervention.

Clinical Considerations

Clinical Assessment of Habitual PA Contemporary PA recommendations for adults suggest at least 150 to 300 min of moderate-intensity or 75 to 150 min of vigorous-intensity aerobic activity coupled with at least two sessions of major muscle group strengthening activity weekly [67]. While these recommendations are based largely on all-cause mortality data, the independent and potentially synergistic impacts of both aerobic and strength exercise have been demonstrated in the setting of T2DM prevention and therapy [68, 69]. Maximizing patient adherence to these recommendations begins with the determination of the individual patient's baseline. PA habits should be assessed during all routine clinical encounters and some have advocated that PA be considered a "vital sign" [70••]. The assessment of habitual PA permits clinicians to categorize patients into one of three groups as function of adherence to contemporary PA guidelines: 1) patient routinely not meeting PA guidelines, 2) patient routinely meeting PA guidelines, and 3) patient routinely exceeding PA guidelines (FIG. 1). As previously delineated, the subsequent conversation about the risks, benefits, and logistics of optimizing differs substantially as a function of these designations [70••].

Patients Who Fail to Meet PA Guidelines Unfortunately, the majority of adults in developed countries fail to meet contemporary PA recommendations [71], harboring the highest risk of present and future T2DM and represent the greatest opportunity for clinical impact. Identifying this as an intervenable public health issue globally, the World Health Organization has targeted a reduction of 10% in the prevalence of insufficient PA by 2020 [72]. While this goal is noble and important at the public health level, there remains some uncertainty as to how best to achieve this. Recognition of inadequate habitual PA may be best addressed determining individual patient barriers including disease-imposed limitations, iatrogenic limitations resulting from pharmacotherapy or surgical intervention, and perceived limitations conferred by lifestyle choice. The identification of individualized patient-centered limitations to exercise sets the stage for the patient and clinician to engage in a bidirectional problem-solving approach to overcome both real and perceived barriers to performing sufficient PA. Exercise science professionals and other members of the allied health team may play invaluable roles in this process [70••]. The use of traditional hospital-based rehabilitation programs and/or structured community-based exercise facility programs improve adherence to recommendations and should be accessed whenever possible [73, 74].

Patients Who Meet PA Guidelines Individuals who meet – but do not exceed - PA recommendations are likely to derive some health benefits from increasing their amount of routine PA [75, 76•]. Therefore, we recommend these individuals be provided positive reinforcement and keys to success should be discussed and documented. Certain health issues including insulin insensitivity and maintenance of ideal body weight may require more than 150 min of weekly aerobic activity [77]. In addition, many active patients meet recommendations for aerobic exercise at the expense of strength building exercise and vice versa. Focusing on the specific dose-response relationship between exercise and factors that are most relevant to the individual patient provides opportunities to further leverage the preventative and therapeutic impact of PA.

Patients Who Exceed PA Guidelines - Masters Athletes Patients, who routinely exceed PA guidelines in our experience, most commonly self-identify as athletes. Historically, T2DM was considered to be an extremely rare entity among competitive athletes. This perspective was based on the relatively late life emergence of clinically appreciable T2DM coupled with the historically narrow age definition of a competitive athlete as someone in the first three decades of life. In contemporary clinical practice, "masters athletes", men and women older than 35 years of age who participate in high-intensity and/or high-volume exercise with ambitions of competition, are encountered with increasing frequency [2]. The increasing popularity and accessibility of organized competitive sports opportunities including marathon running, triathlons, and facility-based exercise options (i.e. CrossFit™) coupled with increasing recognition of the substantial physical, emotional, and psychological benefits of exercise have led to explosive growth of this population. While engagement in such activities typically results in improved metrics of health, including improved glucose handling among people with or at risk for T2DM, no amount exercise confers complete immunity from T2DM and diseases of the CV system. In addition, patients identified as having insulin insensitivity may elect to adopt an athletic lifestyle to avoid disease progression; thereby, increasing the prevalence of aging athletes with or at risk for T2DM, and thus necessitating clinicians to optimize the

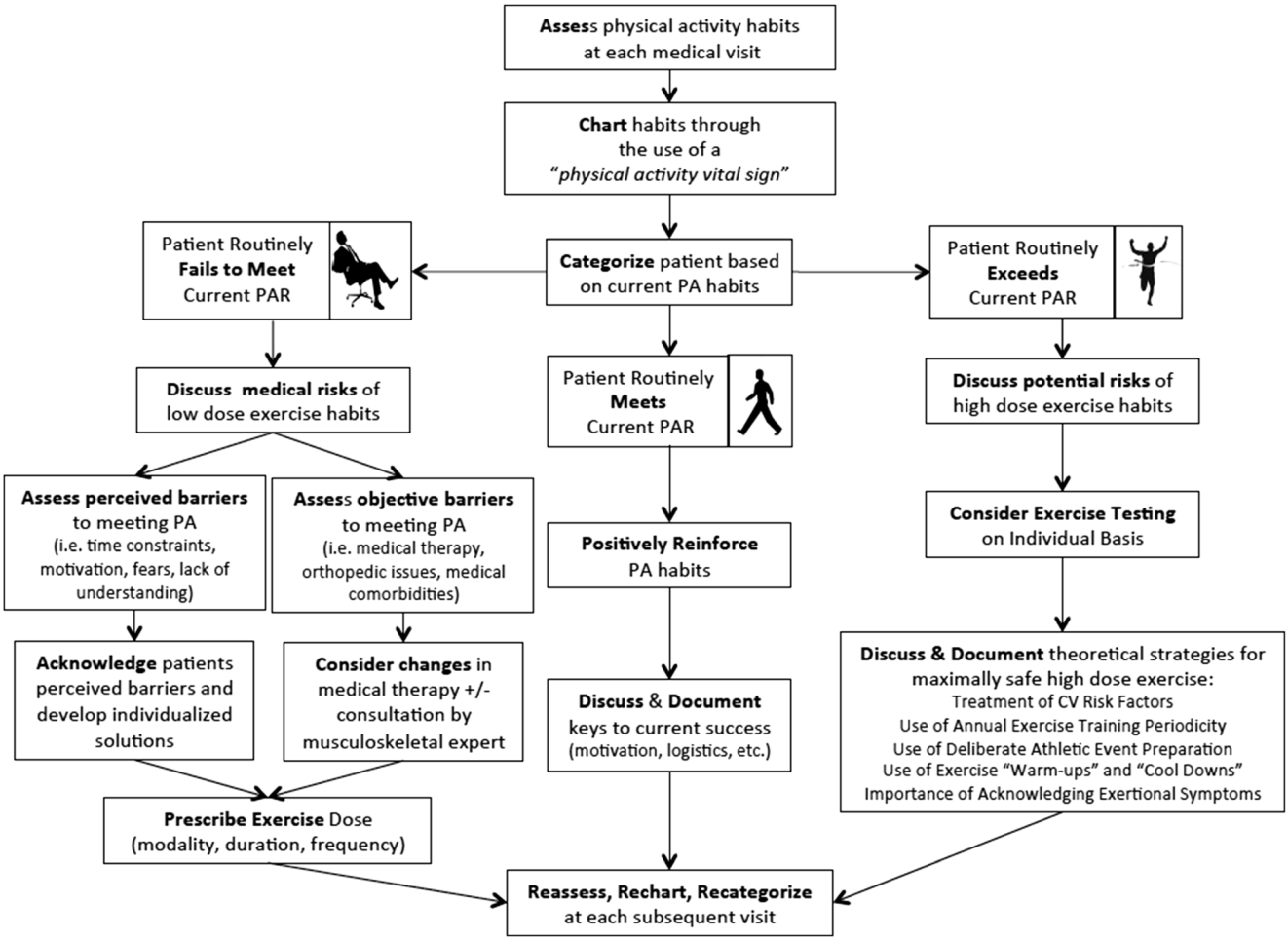

Fig. 1 Algorithm for the assessment and management of habitual physical activity in clinical practice. (Reproduced from: Wasfy MM, Baggish AL. Circulation. 2016;133(23):2297–313, with permission from Wolters Kluwer Health Inc.) [70••]

care of this population by developing a familiarity with key several issues.

While it has been shown that performing competitive endurance and team-based sports early in life has a legacy effect leading to increased longevity [78–80], reductions in incident T2DM [11, 76•, 81], and reduced overall healthcare utilization [82, 83], literature documenting health outcomes among masters athletes is essentially non-existent. Thus, we offer several considerations based on extensive clinical experience and as means to identify necessary areas of future work. First, dietary intake among masters athletes may be counterproductive in the setting of desired improvements in blood glucose control. Typical "athletic" diets are rich in carbohydrates and may include large quantities of simple sugars delivered in sports drinks and energy supplements. Such dietary intake may overwhelm the beneficial effects of PA, and in some cases anti-hyperglycemic pharmacotherapy, on blood glucose levels. We therefore routinely query masters athletes with T2DM about macro-nutrient choices and often engage qualified sports nutrition experts in an attempt to strike the best balance between a diet that emphasizes sport performance and one that focuses on optimizing glucose control. Second, masters athletes with or at risk for T2DM commonly have other established CV risk factors [84, 85]. Despite the fact that they are indeed physically fit and "look" healthy, they can harbor significant hypertension and dyslipidemia. The common misconception that exercise negates the risk of such issues may lead to under diagnosis and under treatment by clinicians, and medication non-compliance by patients. Third, though not well studied, some common pharmaceutical agents used in the management of T2DM may confer risk in the setting of high-intensity or high duration exercise. As a first principle, it is vital that masters athletes with T2DM, controlled with pharmaceuticals perform frequent serial blood glucose checks before and after exercise, particularly in the setting of significant changes in exercise volume, intensity, or duration. Masters athletes with T2DM, who require exogenous insulin therapy, are relatively rare but are at highest risk for intra- and post-exercise hypoglycemia. Such patients can be guided through athletic cycles (i.e. 18 to 20-week marathon training blocks) in an individualized fashion and often require insulin dose modification before long training runs and races. We routinely advise the temporary

discontinuation of metformin and sulfonylureas, for 48 h prior to moderate or high-intensity sporting events in excess of two hours to avoid theoretical concerns of profound lactic acidosis and hypoglycemia respectively. Finally, several forms of CV disease including atrial fibrillation [86], non-ischemic myocardial fibrosis [87, 88], and proximal coronary artery calcification [89–91] appear to be uniquely enriched among masters athletes. To what degree subclinical dysregulation of glucose homeostasis contributes the development of these entities is an intriguing question that has yet to be studied with any rigor.

Pre-Exercise Clinical Evaluation The CV abnormalities that accompany T2DM may increase risk of adverse outcomes during exercise. Accordingly, an exercise or PA recommendation for such patients should be coupled by a consideration of the role of additional risk stratification. The American College of Sports Medicine (ACSM) in conjunction with the American Heart Association (AHA) and the American Diabetes Association (ADA) have individually prepared consensus clinical recommendations for this purpose [92–94]. This ACSM/AHA algorithm refers to "metabolic disease", not differentiating between type 1 and T2DM, and suggests that both sedentary patients with metabolic disease who plan to engage in any form of structured exercise and habitually active patients with metabolic disease who wish to engage in vigorous exercise should be referred to a clinician for medical clearance. In contrast, the ADA assumes a more conservative approach and suggests that adults with T2DM planning to exercise at higher intensities than currently undertaken or who are at elevated risk for cardiovascular disease based on risk factor assessment (e.g., have elevated blood cholesterol, smoke, have a strong family history, etc.) obtain a pre-exercise examination from a health-care provider. Discrepancies between the professional organizations exist due to the paucity of data defining adverse event rates among patients with T2DM. The more conservative approach, endorsed by the ADA and routinely recommend among clinicians, advises maximal-effort limited exercise testing among patients with T2DM and other CV risk factors that wish to or who have been counseled to engage in moderate to vigorous intensity exercise.

Conclusion

The therapeutic and prophylactic effects of PA on T2DM are expansive and well-accepted. However, in spite of this ever-growing body of evidence, most US citizens are not meeting contemporary PA requirements and thus are not only missing out on the health benefits PA confers, but also putting themselves at risk of developing chronic disease with high-risk implications such as T2DM. A reversal of this trend is imperative and may be accomplished by the development of more pragmatic, accessible, and sustainable models in order to promote PA for our patients. As clinicians, we must continue to stress the critical importance of lifestyle modifications including nutritional therapy and attaining the appropriate physical activity recommendations. Recognizing that the healthcare delivery is a complex multidisciplinary and multifaceted institution, other key players including patients, healthcare providers, community managers, and insurance corporations, must become invested if we as a nation are to succeed in this endeavor.

Furthermore, future research identifying the impact of PA on other forms of DM, alternatives to the classic aerobic PA, such as high-interval training, which may allow for more individuals to meet exercise recommendations, and a more definitive answer regarding exercise's effect on cholesterol and triglycerides is warranted.

Compliance with Ethical Standards

Conflict of Interest Erika J. Parisi and Aaron L. Baggish 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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