Exercise is Medicine

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Abstract Physical inactivity is the most significant lifestyle risk factor of the 21st century. It is associated with increased morbidity affecting every major organ system, increased mortality risk, and significant economic cost. Exercise has clear benefit in certain conditions, both for disease prevention and disease treatment. In this paper, we review the recent evidence of the effect exercise has on various organ systems, osteoarthritis and low back pain, cancers, and mortality, and also propose strategy for implementing actionable plans toward healthier living through exercise.

Keywords Lifestyle medicine · Exercise · Metabolic syndrome

Introduction

The National Institute of Health identifies physical inactivity as one of the most significant lifestyle risk factors for worldwide morbidity and mortality [1]. Physical inactivity is associated with hypertension (HTN), cardiovascular disease (CVD), coronary heart disease (CAD), diabetes, obesity, and cerebral vascular accidents (CVA) [2–5]. Persons with low cardiorespiratory fitness (CRF) have 1.5 times higher relative risk of developing HTN compared to highly fit individuals [6, 7], resulting in: 18–21 % elevated cardiovascular mortality, 30–42 % increased stroke risk, and 14–23 % increased CAD risk [8]. Overweight and obesity can lead to multiple metabolic derangements including insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, and HTN. These derangements together are known as the metabolic syndrome [9, 10], which is associated with further cardiovascular morbidity and mortality worldwide [11]. Dyslipidemia and low CRF are associated with increased CVD risk, even after adjusting for age, smoking status, family history and BMI [12]. Diabetes is the leading cause of chronic kidney disease, which leads to a nearly two-fold increase in all-cause mortality rate compared to non-CKD patients [13, 14]. Lastly, obesity is one of the most significant risk factors for developing musculoskeletal disorders such as osteoarthritis (OA) in weight-bearing joints and chronic low back pain (CLBP), both of which are major causes of disability in the world [15, 16].

The economic consequence of physical inactivity is staggering. Chronic illnesses accounts for 60 % of all deaths annually worldwide and 80 % of these deaths occur in low- and middle-income countries [1]. A report by The Milken Institute in 2007 estimated that while the cost of the common chronic illnesses in the USA in 2003 for non-

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institutionalized adults was \$277 billion through direct medical expenditure, the economic cost through loss of productivity was nearly 3.8 times the medical cost at \$1.064 trillion. If left unchecked, these figures are projected to increase to \$790 billion for direct medical expenditures and \$3.4 trillion for indirect impact cost, for a total economic cost of \$4.2 trillion. The report concluded that increasing physical activity levels is one of the most important health behavior changes we can make [17].

The purpose of this paper is to review the scientific evidence showing that exercise has a major role to play in the reduction of morbidity and mortality, address the current epidemic of chronic disease, and propose strategy for implementing actionable plans toward healthier living through exercise.

Cardiovascular Disease

Cardiovascular disease (CVD) affects nearly one-third of US adults and is associated with one-third of all deaths before the age of 75. About 150,000 deaths in the US were attributed to CAD in 2008. Each year, an estimated 785,000 Americans have new myocardial infarctions (MI), and 470,000 will have recurrent MI. More than 795,000 people experience stroke each year, accounting for nearly one in every 18 deaths in the US in 2008. More than one of every nine deaths certificates mentions heart failure [18].

HTN is a major risk factor for CVD. Even at high-normal blood pressure range, there is a risk-factor-adjusted hazard ratio for CVD of 2.5 in women and 1.6 in men [19]. This finding supported establishing the pre-hypertension class in the Joint National Committee (JNC 7) for individuals with systolic blood pressure of 120–139 mmHg and diastolic blood pressure of 80–90 mmHg as a means to identify and designate individuals at elevated risk of developing HTN [20]. Controlling HTN is the central tenant of moderating risks for CVD morbidity and mortality.

Exercise is an effective treatment for HTN. Barone et al. [21] reported that after 6 months of supervised aerobic and strength training, adults who were sedentary before the study achieved a 7 mmHg drop in BP regardless of their baseline HTN stage. Those with stage 3 and stage 4 achieved the most significant reductions, with the added benefit of reduction of waist circumference and improved peak oxygen uptake (VO₂). Review of a meta-analysis in the ACSM Position Stands on Exercise and Hypertension concluded that both resistance training and dynamic aerobic training reduces resting blood pressure [22].

Exercise and physical activity also has protective effects on other cardiac conditions. For example, many patients with lower extremity peripheral artery disease (PAD)

experience rapid functional impairment and decline [23]. However, patients with higher levels of physical activity had less annual decline in objectively measured functional performance measures over a 4-year tracking period [24]. Furthermore, exercise has additive benefit in PAD patients undergoing endovascular therapy for treatments of intermittent claudication. When comparing the outcome of endovascular and non-invasive therapies for PAD, a meta-analysis by Ahimastos et al. [25•] found that supervised exercise therapy has equivalent efficacy to endovascular therapy. Moreover, the efficacy of supervised exercise therapy with endovascular therapy is superior to that of endovascular therapy alone.

Exercise is also beneficial for patients with atrial fibrillation (AF). AF patients have a high prevalence of reduced quality of life due to increased fatigue, dyspnea, and palpitation. A randomized controlled trial assessing the effect of exercise on functional capacity showed improved muscle strength, exercise capacity, 6-minute walk test, and quality of life for subjects who received 12 weeks of supervised cross training compared those who did not [26].

Additionally, exercise plays a significant role in improving the morbidity and the mortality of CAD. A meta-analysis of exercise-based rehabilitation for CAD by Heran et al. examined 47 studies including 10,794 patients with MI and angina pectoris comparing exercise-based cardiac rehabilitation to usual medical care. They found that the medium-term and long-term overall and cardiovascular mortality were reduced in the exercise-based programs [RR 0.87 (95 % CI 0.75, 0.99) and 0.74 (95 % CI 0.63, 0.87)], respectively [27]. Exercise also has clear benefit over coronary angiography. The Exercise Training Intervention after Coronary Angioplasty (ETICA) trial randomly assigned 118 patients to an exercise training group and a control group for 6 months. The trial found that while there was no difference between the two groups in angiographic restenosis, the exercise group demonstrated significant increase in peak VO₂ and quality of life compared to the control group. There were less cardiac events during the 33 ± 7-month follow-up period and less hospital readmission in the exercise group [28]. Exercise therapy is therefore an equivalent alternative for patients who are unsuitable for aggressive coronary revascularization procedures.

Metabolic Syndrome and Obesity

In 2009–2010, more than 33 % of US adults and nearly 17 % of US children under 18 years old were classified as obese, and their likelihood of being overweight or obese generally increases with age [29]. Although the prevalence has not increased significantly compared to the previous

years, it is still short from The Healthy People 2010 goal of 15 % obesity among adults and 5 % obesity among children [30].

Research has consistently demonstrated the remarkable positive effect that exercise can have on improving obesity and other metabolic syndrome-related biomarkers. Supervised aerobic exercise training can improve HDL in participants without CAD [31]. A systematic review by Curioni et al. [32] on long-term weight loss showed that the combination of dieting and exercise could produce the greatest initial and sustained weight loss after one year. After systematically evaluating 43 similar studies involving 3,476 participants, Shaw et al. [33] showed that integrating an exercise program with dieting improves the success rate for long-term weight loss, with the added benefits in reduction of serum lipids, blood pressure, and fasting glucose. A meta-analysis by Boulé et al. [34] evaluating the effect of aerobic exercise and resistive exercise treatment without medications for adults with type 2 diabetes found that while there was no significant body weight change, exercise played a significant role in reducing HbA1c by 0.66 %. This level of reduction is almost equivalent to patients receiving intense pharmacological treatment in the United Kingdom Prospective Diabetes Study. Considering that the decrease of 1 % in HbA1c is associated with 15–21 % decrease in major cardiovascular events, a 14 % decrease for MI, and a 37 % decrease in microvascular complications, this finding validates that exercise reduces CVD risk with efficacy comparable to pharmacological treatments [35, 36].

Exercise also has protective effects against the onset of type 2 diabetes mellitus (T2DM). A large prospective observational cohort study of 32,002 men from 1990 to 2008 tracked the weekly time spent on exercise through questionnaires, the authors found a dose–response correlation between time spent doing exercise and the risk of developing T2DM. They concluded that subjects who engaged in at least 150 min per week of mixed aerobic exercise and weight training lowered their risk of developing T2DM by 59 % [37].

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the world. While worldwide prevalence of COPD varies widely across countries and populations with estimation anywhere from 0.2 to 37 %, COPD consistently ranks in the top five causes of death in persons from 55 to 74 years of age [38]. Including exercise as part of pulmonary rehabilitation is one of the most effective treatments for patients with COPD. A literature review by Ries et al. [39] showed that

pulmonary rehabilitation programs comprised of endurance training using large muscle groups, dyspnea compensatory techniques, ambulatory training, and strength training at high and moderate intensity produce marked improvement in dyspnea symptoms, psychological well being, and health-related quality of life while reducing COPD-related hospitalization.

COPD often leads to physical inactivity and metabolic syndrome through two general patterns: emphysema, which leads to wasting, low BMI, and osteoporosis; and chronic bronchitis, which leads to high BMI, obstructive sleep apnea, and diabetes mellitus [40]. The presence of obesity and metabolic syndrome is increasingly becoming a recognized issue in COPD patients. Metabolic syndrome has a higher prevalence in COPD patient populations. Marquis et al. found that the incidence of metabolic syndrome in COPD population is at 61 % compared to a 25–32 % prevalence rate in other populations [41, 42]. While research that specifically addresses the impact of obesity on COPD rehabilitation is limited, a study by Sava et al. [43] suggests that obesity can impact ambulatory function negatively despite more favorable airflow obstruction and peak VO₂. However, additional studies are needed to further elucidate the specific impact exercise has on COPD and obesity-associated comorbidities.

Cancer

The economic and societal burden of cancer is significant. In 2003, \$48 billion was spent in cancer direct care, second only to heart disease. More than \$271 billion was lost due to loss of productivity, the highest of all chronic diseases [17]. In addition to the health and economic hardship, many cancer survivors also experience significant decrease in their quality of life due to increased fatigue, depression, anxiety, physical inactivity, and weight gain [44]. Weight gain and associated metabolic syndrome are negatively linked to the cancer treatment success rate and survival probability. Research by Goodwin et al. [45] showed that in women diagnosed with early-stage breast cancer, those with increased levels of fasting insulin, insulin-like growth factor (IGF-1), and low physical activity have higher risks of breast cancer recurrence, poorer surgical prognosis, and three-fold increased risk for all-cause mortality, even if they have no previous diagnosis of diabetes.

Increased BMI is linked to increased cancer risk and subsequent cancer mortality. Studies showed that obesity is linked to increased incidence of colorectal, pancreas, and breast cancer in postmenopausal women; and of hepatic cancer in patients with prior history of hepatitis C virus infection [46–49]. Calle et al. [50] tracked more than 900,000 initially cancer-free adults prospectively for over

16 years and found that the cohort with the highest BMI had a combined 52 % higher cancer and mortality risk compared to the cohort with normal BMI in certain types of cancers. The authors conclude that the current pattern of obesity in the US accounts for 14 % of all deaths from cancer in men and 20 % in women; a reduced prevalence of obesity thus could have prevented these deaths.

Osteoarthritis and Low Back Pain

Osteoarthritis (OA) and chronic low back pain (CLBP) are common musculoskeletal disorders associated with inactivity and obesity. Approximately 46 million adults ages 18 years and older have OA, and its prevalence is expected to increase to more than 67 million by 2030 [51, 52]. An estimated 3 % of elderly Americans have symptomatic hip OA [53].

Current theory suggests muscle weakness and obesity are important causes of OA. Relative muscle weakness leads to relative loss of shock attenuation, thus altering the load rate of the joints and causing abnormal and accelerated joint wear [54]. Increased proportional body weight is associated with both increased joint load and malalignment in knee OA, particularly for individuals with genu varum [55]. Exercise treatment therefore focuses on the strengthening of the prime movers for the joints and reducing obesity. Despite marked variability across the included studies in participants recruited, symptom duration, exercise interventions assessed (e.g. quadriceps muscle strengthening, aerobic walking programs), and study methodology, meta-analyses and reviews have consistently found that exercise has clinically significant positive effects for pain reduction in OA, comparable to the pharmacological effects of acetaminophen or NSAIDs. Exercise also has additional benefits such as improvements in strength, cardiorespiratory capacity, physical function, and quality of life that are not seen with pharmacological treatment [56–60].

The effect of therapeutic exercise treatment for hip OA was mostly extrapolated from studies for knee OA, and was designated as expert opinion due to the absence of hip-specific data [61, 62]. However, the meta-analysis by Hernández-Molina et al. found that exercise treatment leads to a small to moderate pain improvement in patients with hip OA comparable to the effect of pharmacological treatment such as acetaminophen or NSAIDs. Treatments that incorporated specialized supervised exercise training and elements of strengthening are particularly effective for hip OA but with much fewer side effects compared to pharmacological treatments [57, 59]. These findings show the effect of therapeutic exercise for hip OA is equivalent to that of knee OA, although additional studies designed to

evaluate hip OA and therapeutic exercise are needed to further evaluate this question.

Exercise has long been employed as one of the main tenants of treatment for CLBP, but the heterogeneous nature of CLBP and the multitude of treatment modalities complicate efforts to elucidate the effect of exercise on CLBP. Meta-analysis performed by Hayden et al. [63] showed that exercise therapy could lead to clinically significant pain improvement if the treatment plans include a higher dose exercise program, and combine exercise programs with conventional treatment. Stretching and muscle strengthening programs have the best evidence for improving pain and function.

Mortality

The constellation of chronic diseases associated with inactivity contributes to a significant portion of mortality. In 2006, 81.5 % of all deaths in the USA were due to factors considered to be the 15 leading causes, led by heart disease (number one), stroke (number three), chronic respiratory disease (number four), and diabetes (number six) [64]. All-cause mortality risk for patients with CKD is 56 % higher than non-CKD patients. Only 50 % of dialysis patients and 82 % of transplant patients are alive after three years of ESRD treatment, a mortality rate nearly twice of those in the general population with DM, CA, CHF, CVA/TIA, or MI [65].

Physical inactivity, low fitness, and increased BMI are all linked with increased mortality risk, particularly for patients with CVD, CKD, diabetes, and cancer [66]. Healthy individuals with increased BMI have a 20–300 % increased risk of all-cause mortality, even if they have no chronic illness [67]. Similarly, low CRF is associated with increased CVD mortality [12], and individuals with PAD and low CRF have mortality risks three times higher compared to those with high CRF [68].

Conversely, being physically active and maintaining good CRF are linked with reduced mortality risk. Shoenborn et al. [69•] compared the National Death Index with the 1997–2004 NHIS data to evaluate the relative mortality risk of individuals who met the 2008 physical activity guideline compared to those who did not. They found startling results. Meeting the aerobic physical activity guideline was associated with significant reduction of mortality risk, especially for individuals with at least one chronic disease. In addition, muscle strengthening may offer additional survival benefit for adults 45 years and older. Similar findings are reached in cancer survivors. A meta-analysis of 27 articles from 1950 to 2011 showed that physical activity is associated with lower all-cause and cancer-specific mortality risk in breast and colon cancer survivors [70].

Call to Action

Despite the mounting evidence supporting the positive health benefit of exercise, the epidemic of inactivity is staggering. The 1996 Report of the Surgeon General estimated that less than 20 % of Americans engage in regular physical activity [71]. The 2005–2006 National Health and Nutrition Examination Survey (NHANES) found an alarming correlation between age and the decline of physical activity. While 42 % of children between ages 6–11 meet the U.S. Department of Health and Human Services (USDHHS) recommendation for physical activity levels, the prevalence dropped to 8 % by age 12–15, and down to 3–5 % between ages 20–59 [72]. Only 9–26 % of adults age 60–69 and 6–10 % of adults age 70 or older met current USDHHS recommendation for physical activity [73]. Less than 12 % of adults age 65 or older in the USA engage in strength training [74, 75]. Average adults age 60 and older in the USA spent 8.5 h per day in sedentary behaviors [75]. Matheson and colleagues [76•] identified several key factors leading to the discrepancy between this knowledge and action. (1) The current healthcare delivery system is based on disease treatment instead of disease prevention, and medical providers are incentivized accordingly. (2) The current reductionistic medical paradigm fails at the multiple disciplinary approaches required for the treatment of chronic illness. (3) The existing medical education system is inadequate at training physicians in disease prevention, health promotion, and exercise prescription. (4) There is a lack of distribution channel of preventative healthcare services as the majority of healthcare delivery is focused on disease treatment than disease prevention. (5) Behavioral change in patients is generally motivated by the presence of immediate, unpleasant consequences of a disease, and rather than the gradual accumulation of the invisible benefit in disease prevention. Facing these challenges, systematic approach addressing them at every level is needed to overcome them.

Changes need to start from the highest level in order to have effect at the individual level. We need to start incorporating curriculum focusing on health promotion and exercise prescription in medical education so that individual physicians will have an understanding of how to use this knowledge in their treatment of patients. Such change will not come easily and will need the coordinated effort of those who already understand the benefit of health promotion. Specialists in the field of physical medicine and rehabilitations (PM&R) and sports medicine are already armed with the vast knowledge of functional-based treatment and should lead the charge. Individually, they can help foster the awareness for health promotion by exercise through their interactions with other physicians, and collectively, their perspective professional societies can help

generate the agenda at the national and international level to bring the much-needed attention to the reform of medical education curriculum. Through collaboration with other disciplines, we can develop a comprehensive curriculum that allows all disciplines to have a buy-in. Such collaboration can eventually lead to not only standardized curriculum but also certification criteria for physicians who may be specialized in this field.

At the individual level, each physicians need to incorporate physical activity assessment and exercise prescription into their clinical practice. Inquiring and assessing a patient's physical activity level and providing an exercise prescription need to become a normal part of the clinical encounter. Given the quantifiable benefits exercise has on all major body organ systems, all clinicians should follow these recommendations to actively promote exercise, regardless of their specialties. Sadly, this is not common practice, partly due to physicians' lack of recognition of the importance of exercise and due to the lack of training in exercise prescription during medical education. Increased awareness and training are needed to overcome this deficit. Physicians also need to change their paradigm and to start considering physical activity evaluation and exercise prescription as essential parts of patient care. Exercise prescription needs to be as equally important as medication prescription. The 2008 Physical Activity Guideline by USDHHS [77] has developed recommended level of physical activity for various populations. While the optimal regimen of exercise treatment has yet to be established, the current guideline has been shown to be safe and applicable for the general population, serving as an excellent starting point for clinicians to counsel patients [22, 78]. Exercise treatment therapy should be individualized based on the patient's existing physical condition and comorbidities. Guidelines have been established for adults with chronic illness such as CVD, CHF, and COPD to provide detailed recommendations for these populations. Physicians need to work with their patients and members of the health care team closely to provide safe and individualized exercise prescription [79, 80].

Physicians can quickly assess the general physical activity levels by inquiring the recreational activities the patient engages in, or by tallying the number of hours and intensity of activities engaged in on a weekly basis. For more detailed and objective assessments, validated instruments are available to help clinicians to accurately quantify the level of physical activity for patients. Some examples include the Rapid Assessment of Physical Activity Among Older Adults (RAPA) and the Telephone Assessment of Physical Activity (TAPA). RAPA was developed to provide rapid, office-based assessment that covers a range of levels of physical activity from sedentary to regular to vigorous physical activity. RAPA can also assess the level

of strength training and flexibility training needed. The questions are accompanied by graphical depiction and the language is rated at a sixth-grade level, making it suitable even for adults with cognitive deficits [81]. TAPA is a validated assessment tool derived from RAPA to allow a telephone-based interview to facilitate community-level assessment [82]. Together, these instruments can help physicians measure the physical activity level of their patients accurately and objectively, allowing them to use these data to develop detailed exercise prescription.

Since primary care providers play a key role in offering health care for the majority of the population, Bauman et al. [83] developed a list of recommendations for them to promote health through exercise for their patients. They are to (1) become active role models by adopting active lifestyles themselves, (2) participate and advocate for community and local physical activity events (i.e. community runs, walkathon, etc.), (3) utilize popular mass events (i.e. the Olympic Games) to promote physical activity, and (4) actively encourage patients to participate in community events.

In order to have a population-level impact, a supportive public health policy is vital. This is where the organized national and international effort by professional societies must coordinate their effort. This must include investments in public infrastructure like green spaces and bike paths, youth programs such as school physical education and after-school programs to foster healthy active lifestyle behaviors. Further research on how to effectively promote and maintain an active lifestyle is needed. Finally, physical activity counseling intervention should be a reimbursable medical expenditure, not only to incentivize clinicians to take part in this important aspect of health care but also to recognize that exercise is as vital as any other legitimate medical therapy [78].

Conclusion

There are clear benefits of exercise in the primary and secondary prevention of cancer and various conditions such as cardiovascular, metabolic, pulmonary, and musculoskeletal disorders. Exercise treatment can lead to clinically meaningful improvements for pre-existing conditions and quality of life. To overcome the epidemic of inactivity and the associated chronic diseases, a change in paradigm is required for the public, clinicians, medical education, healthcare delivery model, and public health policies. Specialists in the PM&R and sports medicine fields have an important role to play individually and collectively through their professional societies to influence the healthcare delivery systems and the medical education system, in order to change the paradigm of healthcare system from

disease treatment to disease prevention. Every clinician has the unique role to inform and empower. Through educating patients and the public, clinicians can help patients make the right choice for their health. Equally important, they have a role to act as advocates of active lifestyle for the community, to influence health at the policy level, and to help bring awareness that an active lifestyle and exercise is every bit as vital as medicine. Exercise can play a central role to improve health and human conditions, but only if we recognize its importance and incorporate it into our tool set of medical treatments.

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