HIGHLIGHTED TOPIC | Physiology and Pathophysiology of Physical Inactivity

Understanding multi-organ pathology from insufficient exercise

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Knowledge that physical inactivity is detrimental to human health can be traced back two millennia. Sushruta, an ancient Indian surgeon (~650 BC), observed that sedentary lifestyle and excess weight were associated with Type 2 diabetes (12). Hippocrates (~450 BC) stated that the body falls sick when exercise is deficient. Similar conclusions have been drawn from two recent U.S. governmental epidemiological surveys. Hahn et al. (6) from the U.S. Centers for Disease and Prevention attributed 23.3% of U.S. deaths in 1986 to no regular exercise. The 2008 Committee Report for the U.S. Physical Activity Guidelines to the U.S. Department of Health and Human Services concluded, “...the data very strongly support an inverse association between physical activity and all-cause mortality. Active individuals—both men and women—have approximately a 30% lower risk of dying during follow-up, compared with inactive individuals” (13). Thus, in our opinion, lack of sufficient daily physical activity is a major contributor to increased chronic disease and premature death.

A series highlighting the physiological and pathophysiological bases and consequences of physical inactivity was originally proposed by the Journal of Applied Physiology Editor Jerome Dempsey. The plan was to present a survey of a number of the organ systems/functions/diseases (blood vessels, central circulatory function, cognitive function, death, metabolism, nonalcoholic fatty liver disease, and skeletal muscle) that are affected by physical inactivity. Bed rest, reduced daily stepping, and a sedentary, inactive lifestyle were highlighted as experimental models. The aim was to provide insights into biological mechanisms by which physical inactivity leads to dysfunction and negative health consequences.

Thijssen, Green, and Hopman (10) review the alterations in vascular structure and function with physical inactivity and question the common assumption that physical inactivity is merely the reverse of exercise training. For example, in resistance vessels, physical inactivity results in upregulation of vasoconstrictor pathways, rather than affecting vasodilator function. This contrasts with the well described effects of exercise training on vasodilator pathways.

Voss et al. (14) conclude that ample evidence exists to support aerobic and resistance exercise as the most effective strategy to improve mental and physical health, without the side effects of many pharmacological treatments. As often stated (3, 4), we believe the reference group should be one with physical activity levels similar to those present when genes were selected during evolution. Voss et al.’s (14) reference group is reversed by our interpretation. Thus, compared with a physically active group, an inactive lifestyle limits attainment of optimal cognitive and brain health.

Thyfault and Krogh-Madsen (11) cite studies providing evidence that a 2-wk transition period, from an ambulatory lifestyle without structured exercise training to inactivity, results in reduced insulin sensitivity and increased central adiposity in both animal and human subjects. They contend that, if extended, chronic inactivity provides a permissive environment for pathogenesis of obesity and Type 2 diabetes. A second review extends the duration of inactivity to periods of 4–6 mo. Patel et al. (8) concluded from these clinical trials that chronic physically inactive lifestyles resulted in progressive deterioration of 13 cardiometabolic parameters related to an increased prevalence of chronic diseases [Table 1 in Patel et al. (8)]. Patel et al. state, “While the degree of metabolic deterioration attributable to continued physical inactivity over years remains unclear, the progressive metabolic deterioration associated with continued physical inactivity in the short and medium terms (in the order of weeks and months, respectively) is clear.” Taken together, data in this review strongly support the proposition that physical inactivity is a major, if not the primary, cause of the increased prevalence of chronic diseases in our modern, largely sedentary society.

Kelley and Mandarino’s (7) original definition for metabolic inflexibility was “skeletal muscle in insulin resistance is accompanied by increased, rather than decreased, muscle glucose oxidation under basal conditions and decreased glucose oxidation under insulin-stimulated circumstances, producing a state of ‘metabolic inflexibility’”. Bergouignan et al. (2) cite 60 yr of bed rest research to propose a sequence of events that explain how physical inactivity can progress to metabolic inflexibility. One important component of the metabolic syndrome is liver dysfunction. Nonalcoholic fatty liver disease (NAFLD) is a chronic, progressive liver disease that affects >90 million Americans. Rector and Thyfault (9) conclude that physical inactivity is an actual cause of NAFLD, and most cases of NAFLD can be primarily prevented by sufficient physical activity.

Thirty percent of U.S. deaths are attributable to physical inactivity, according to the National Physical Activity Guidelines Advisory Report commissioned by the Secretary of the U.S. Department of Health and Human Services. Thirty percent translates to 720,000 preventable deaths in the U.S., making physical inactivity the number one cause of death in the U.S. Accelerated secondary aging of specific physiological functions contributes to premature mortality and is described by Booth et al. (5).

The reviews also highlight areas for further examination. The role and importance of hemodynamic stimuli that result in vascular adaptations during deconditioning require elucidation (10). More studies are needed to 1) explicitly examine the...
effect of exercise type and intensity on cognition, the brain, and clinically significant outcomes; 2) use human neuroimaging in a more unified multi-modal framework; and 3) compare the results of studies on exercise effects on brain and cognition across the life span in human and animal models (14). More research on how reduced levels of daily ambulatory activity connect the acute responses to the chronic changes is required, along with investigation of underlying mechanisms. The wider scientific and medical community must also be convinced of the primary role that inactivity has in the development of obesity and Type 2 diabetes (11). Future mechanistic studies are needed to separate the peripheral adaptations from the direct molecular and biochemical alterations occurring in the liver in response to physical inactivity (9). The physical activity level threshold below which metabolic inflexibility develops needs to be identified to refine the physical activity recommendations for the general population (2). An improved understanding of how an individual’s diet, nonexercise physical activity patterns, genetic profile, and medications influence an individual’s physical activity requirements is required to advance the field and inform the development of more personalized physical activity recommendations (8).

The current Highlighted Topic series in the Journal of Applied Physiology is a microcosm of exciting work that attempts to understand the mechanisms and processes that are activated in response to chronic physical inactivity. Since physical inactivity is an actual cause of atherosclerosis, low maximal cardiac output and maximal oxygen uptake, Type 2 diabetes, breast and colon cancers, obesity, osteoporosis, attenuated learning, nonalcoholic liver disease, some secondary aging, and premature death, an understanding of the local and systemic signals that result from inactivity is a significant challenge. The public and other scientists underappreciate the biological complexity of inactivity research and they fail to accept it as the actual cause of dysfunction and pathophysiology in many conditions. As a result of the lack of knowledge about the fundamental importance of avoiding physical inactivity and its unhealthy consequences, funding for this important area is a fraction of what is needed to accelerate progress and move the public toward prevention of further escalation in health care costs (1). One of the biggest impediments for exercise scientists is earning respect of the scientific community and the public for their quality research and effective outreach (1). To paraphrase an earlier Highlighted Topic editorial (1), only then will physical inactivity science take its rightful place in the research effort to prevent and manage noncommunicable diseases.

REFERENCES