Poor physical fitness and performance as predictors of mortality in normal populations and patients with rheumatic and other diseases

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ABSTRACT

Poor physical function and low muscle strength are significant predictors of mortality in rheumatoid arthritis, other chronic diseases, ageing individuals, and the general population. Poor physical function predicts earlier mortality in diseased and normal populations at levels of significance similar to or greater than most known biomedical predictors such as laboratory tests. This chapter summarizes data concerning the prediction of premature mortality by poor physical fitness and musculoskeletal function, according to performance and self-report measures. The data support recommendations for regular exercise in all individuals whether or not they have a disease, to promote health and longevity.

Introduction

A long and healthy life is a universal goal from the perspective of both the individual and the society. Acute and chronic diseases challenge this goal as they increase the likelihood of early mortality. The health professional attempts to follow the Hippocratic oath and to reduce or eliminate possible premature death in people with a disease.

In contemporary medicine, physicians focus on a single organ in efforts to reduce or prevent unfavorable outcomes of a specific disease, according to a "biomedical model," the dominant paradigm of modern medicine (1). In this model, laboratory tests and imaging data are regarded as the sources of the most valuable information about a patient and the basis of therapies. Survival and mortality are thought to depend primarily, if not almost exclusively, on actions of health professionals, rather than on actions of individuals themselves, whether or not they may have a disease.

The biomedical model has been and remains spectacularly successful in acute diseases in an inpatient hospital, the setting of most medical education, training and research. Laboratory tests and imaging data do provide the best information for effective therapies in acute diseases. Health professionals write "orders" for appropriate tests and therapies, and the patient has almost no role in the outcome over a short period.

Most contemporary medical care is concerned with chronic rather than acute diseases. In chronic diseases, the value of laboratory tests and imaging data often may be considerably more limited than in acute disease. For example, in patients with rheumatoid arthritis (RA), these data have limited value in the prognosis of outcomes such as work disability or mortality, while adding substantially to costs.

An example of the importance of patient actions in health and the course of chronic disease is seen in studies of exercise and physical activity. Poor performance on tests to quantify physical fitness and functional capacity predicts mortality in normal populations and in patients with cardiac, neoplastic, renal, pulmonary and rheumatic diseases. However, the importance of musculoskeletal function as a major predictor of mortality in specific diseases and on a population level is not widely recognized. Indeed, a focus on specific organs in health and disease in contemporary sub-specialized medical care of chronic diseases may neglect exercise and physical function, and other important aspects of the whole person. This chapter summarizes considerable evidence concerning quantitative indicators of poor physical fitness and functional capacity in the prediction of mortality, in people with chronic diseases and the general population.

Cardio-respiratory fitness and mortality

Physical fitness is a dynamic state of energy and vitality that enables an individual to carry out daily tasks, engage in active leisure-time pursuits and meet unforeseen emergencies effectively. Both cardiovascular and muscular fitness have a central role in physical performance, ranging from elite sports to independent function in daily life. Physical fitness can be assessed using tests that are designed to measure physical strength, agility, and endurance, as well as by self-report.

Performance measures of physical fitness range from a standardized treadmill test to assess aerobic fitness as an indicator of physical fitness and general health, to simple tests of specific muscles or muscle groups such as grip strength. Information concerning overall function may also be obtained from self-report questionnaires (2), again with a range from extensive physical exercise to simple activities of daily living (ADL), as well as self-rated global health.

Physical activity level is one of the most important determinants of cardio-respiratory fitness in healthy people (3-6). Deconditioning as a result of prolonged inactivity in healthy individuals (7), or chronic diseases such as heart failure (8), negatively affect aerobic capacity. Regardless of the level of intensity of the physical activity measured, poorer physical performance is invariably associated with a higher risk of death.

Extensive studies concerning physical fitness and mortality have been conducted at the Cooper Institute of Aerobics Research in Dallas, TX, USA (9). In one study, baseline physical fitness was measured in 10,224 men and 3,120 women according to a maximal treadmill exercise test. A follow-up analysis was conducted 8 years later according to quintiles of baseline values. The age-adjusted all-cause mortality rate over 8 years was 64.0 per 10,000 person-years in the quintile of men who were least fit at baseline, and declined across quintiles to 18.6 per 10,000 person-years in the most-fit men. Among women, the mortality rate was 39.5 per 10,000 person-years in the least-fit compared to 8.5 per 10,000 person-years in the most-fit quintile. Associations of poor fitness and high mortality remained statistically significant after adjustment for age, smoking, cholesterol level, systolic blood pressure, fasting blood glucose level, parental history of coronary heart disease, and follow-up interval (9).

In an extension of this study, 9,777 men from the original cohort had a second maximal treadmill exercise test 5 years after baseline (10). Five years after the second test (10 years after baseline), the lowest death rate was seen in men who were physically fit at both examinations. Men who improved from "unfit" to "fit" between the first and second examinations had a reduction in mortality risk of 44% relative to men who remained unfit at both examinations. Improvement in fitness was associated with lower death rates after adjusting for age, health status, and other risk factors for premature mortality (10).

Additional Cooper Institute studies of more than 25,000 men and 7,000 women indicated further that the least fit individuals in a maximal exercise test were at a highest risk for cardiovascular mortality. These studies also showed that good cardio-respiratory fitness protected against cardiovascular mortality, even in the presence of recognized cardiovascular risk factors such as high cholesterol, hypertension, and smoking (11-13). Similar results have been seen in numerous other studies in the general population and in patients with various diseases such as cardiovascular diseases, diabetes, hypertension, metabolic syndrome, and cancer (14-22) indicating that poor physical fitness is an important risk factor for mortality.

Muscle strength and mortality

Muscle strength is reduced seriously by most diseases as well as by aging, due to atrophy, deterioration of mechanical properties, and motor unit loss. Disease-related and age-related changes in body composition often remain unnoticed, in part because the loss of lean body tissue (sarcopenia/cachexia) is often accompanied by increased fat mass, and body weight remains unchanged despite changing body composition (23, 24). Loss of muscle strength varies from person to person and varies in different muscle groups.

Grip strength test, a simple measure to estimate overall muscle strength, is a significant predictor of mortality in patients with RA (25, 26), in geriatric patients (27) and in general populations (28-37). In the Women's Health and Aging Study, the unadjusted relative risk (95% CI) for mortality over 5 years was 2.4 (1.8 to 3.2) in the lowest and 1.7 (1.2 to 2.4) in the middle, compared to 1.0 in the highest baseline tertile for grip strength in 919 moderately or severely disabled women >65 years old. Cardiovascular mortality relative risk was 3.2 (2.0 to 5.1) in the lowest and 1.9 (1.1 to 3.2) in the middle, compared to 1.0 in the highest baseline tertile of grip strength. The grip strength test remained a significant independent predictor of cause-specific and total mortality, when adjusted for demographic and life-style variables and various serologic markers of inflammation (38, 39).

Measurement of grip strength is one of the simplest methods to assess muscular fitness in large studies, and therefore most often used. Grip strength is correlated with the strength of other muscles such as elbow flexors and knee and trunk extensors and thus provides an approximation of total body muscle strength (40). A strong association between low muscle strength and high risk of mortality has been confirmed in studies in which other muscle groups such as quadriceps were tested for strength (35, 41, 42), including among elderly populations (43). In patients with chronic obstructive pulmonary disease, quadriceps strength predicted mortality at higher levels of significance than pulmonary-specific measures (44).

Global scales scored by a health professional and the risk of mortality

Early efforts to assess patient functional status can be seen in global scales, assigned by a clinician, developed to quantify physical function in many types of diseases. In patients with cardiac disease, the New York Heart Association (NYHA) classification was reported initially in 1928 (45), based on

a clinician-assigned 1-4 score according to the extent to which breathlessness limited patient physical activity. In patients with cancer, the Karnofsky Performance Scale was introduced in 1949 (46) to evaluate functional status numerically, ranging from 0 to 100 (0 = dead; 60 = requires occasional assistance but is able to care for most personal needs; 90 = able to carry on normal activity, with minor signs or symptoms), based on a clinician's knowledge of a patient's capacities in daily activities. In patients with rheumatic diseases, the Steinbrocker classification for clinician-assessed global patient functional status of 1 to 4 was initially reported in 1949 (47).

Self-report global health and the risk of mortality

Patient self-report of global health is prognostic for poor outcomes and mortality. Mossey and Shapiro (48) reported in 1982 that self-reported poor health is a strong predictor of costs of medical care and mortality in the elderly, an observation that has been confirmed in several studies.

Patient self-report of global health predicted mortality in patients who had significant coronary artery disease diagnosed at heart catheterization. Among 2885 patients, those who reported "poor" health were 3.6 times more likely to die compared to patients who reported "very good" health (mean follow-up 3.5 years), after adjustment for all available cardiovascular-specific risk factors for death (49). In critically ill patients who entered an intensive care unit, who could not complete a self-report questionnaire, a one-item general health question completed by a relative was as predictive of mortality as the Acute Physiology and Chronic Health Evaluation (APACHE) score (50).

The Evergreen Project was begun in 1989 in Jyvaskyla, Finland, as a longitudinal study of elderly individuals to identify predictive factors for subsequent functional status and mortality. All individuals over age 75 were invited to join the study through a baseline home visit which included questionnaires, an interview, a medical examination, and extensive physical tests; 355 of 388 eligible individuals agreed to participate. Self-reported health was queried at baseline and follow-up 5 years later, with a question "At the moment would you say your health in general is very good /good / average / poor / very poor?" Poor self-report health was associated with higher 5-year mortality in men and with a higher 5- and 10-year mortality in women (51). Associations of poor self-reported health and higher mortality were independent of other health indicators, including chronic conditions and biomarkers, in this and other studies among elderly populations (52-67).

Self-report physical function and the risk of mortality

Although global scales are prognostic of premature mortality (68, 69), 4-point scales are relatively insensitive to changes in clinical status, and therefore limited to assess whether a medical intervention may favorably (or unfavorably) affect status from one visit to the next. Therefore, more detailed methods have been developed for assessment of functional status. Patient self-report questionnaires have become increasingly prominent, particularly with recognition that they provide scores that are as reliable (reproducible), or more reliable, compared to scores by health professionals (70). Furthermore, self-report questionnaire data are significant in the prognosis of long-term outcomes, including mortality (26).

Patient self-report questionnaires concerning physical function and global health are correlated with physical measures of function (71) and muscle strength (72). Patient questionnaires are more feasible than physical tests to estimate functional status in population studies and in clinical settings, at greatly reduced costs. Therefore, patient self-report questionnaires have been used in clinical settings as well as in population studies to monitor clinical status and to assess information prognostic of mortality.

In musculoskeletal conditions such as RA, poor physical function is an expected consequence of the disease. Patient self-report of functional capacity on the HAQ (70) and MHAQ (73) have been found to predict premature mortality in RA (26, 74) as well as functional declines (26) and work disability (75). Indeed, the HAQ (70) and MHAQ (73) are almost always superior to any joint count, radiographic or laboratory measures in the prognosis of mortality (76) in patients with RA.

Functional status has been found to be prognostic of premature mortality in many cohorts of patients with RA, even when extensive laboratory data and detailed radiographic scores are available, as reviewed in chapter B-1, page S35 of this Supplement (77). Self-report functional status data have also been found to be significant in the prediction of mortality in cardiac, neoplastic, renal and other diseases, as well as in elderly individuals who do not have a specific disease, independent of traditional laboratory and radiographic data, as summarized below.

In cardiology, poor self-report scores for function predicted 3 year hospitalization and mortality significantly, independent of age, treatments, ejection fraction, and NYHA classification (78). Low functional status by self-report predicted mortality after cardiac surgery (79). In an outcomes study of coronary artery bypass surgery in 1992-96 at 14 Fourteen US Veterans Affairs hospitals (80), 2480 patients completed a self-report short form 36 (SF-36) questionnaire before surgery. The mortality risk over the next 6 months rose by 39% for each 10 points worsening in the physical function score, adjusted for age, smoking history, diuretic use, creatinine level, prior heart surgery, myocardial infarction at surgery, 3-vessel disease, and left ventricular ejection fraction.

In nephrology, the Institute of Medicine recommended in 1997 that providers of care to patients with end-stage renal disease measure patient function and well-being at regular intervals (81). This recommendation was also included in guidelines for chronic kidney diseases in 2002 (82). The multinational Dialysis Outcomes and Practice Patterns Study (DOPPS) found that poor scores on physical, mental and kidney-specific subscales on a modified short-form 36 (SF-36) questionnaire in patients in the US, Japan and Europe predicted mortality. Indeed, poor scores

for physical function predicted mortality more significantly than low serum albumin levels (83). In 13,952 dialysis patients who were served by Fresenius Medical Care North America, both the physical and mental components of the modified SF-36 were significant predictors of mortality over 6 months, also after adjustment for clinical measures (84). Similar results are available from other studies of patients with end-stage kidney disease (85).

In different types of cancers, scores for physical function predicted survival significantly in univariate models (86), and in multivariate models were independent of the extent of the disease and other available clinical prognostic factors (87). Physical function was an independent predictor of mortality among 2,864 HIV-patients, independent of sociodemographic and clinical data, including CD4 counts and stage of HIV infection (88), confirming observations of a previous study (89).

In patients with type-2 diabetes, poor self-report scores for physical function predicted 6-year mortality, independent of traditional risk factors such as age, sex, smoking, body mass index, blood pressure, cholesterol, diabetes duration, A1C, renal function, and macrovascular complications (90).

In the Nurses' Health Study, reflecting non-diseased normal populations, self-reported health data of 40,337 healthy women more than 45 years old at baseline in 1992 and after four years predicted all-cause mortality, monitored over 12 years through 2004. Women with poor scores at baseline or 4 years later on physical and mental dimensions had significantly higher mortality than women with stable or improved scores (91).

Low functional status by self-report also predicts mortality in the elderly (55, 57, 60, 92-97), although, in the general population, effects of aging on function in activities of daily living is generally not seen until the age of 70 (98).

Self-report of physical exercise and mortality

The frequency and intensity of physical activity can be captured by high-technology equipment such as accelerometry, but can also be estimated from patient self-report questionnaires (2). Regular physical activity is associated with better physical and mental health, and lower risk of mortality (22). The risk of all-cause mortality may be reduced by up to 30% in those who report that they participate in regular physical activities compared to those who have an inactive life style (99-107).

It has been estimated that physical activity increases life expectancy by 10-20 years at age 65 (108). In addition, regular physical activity is associated with prevention of cardiovascular diseases and stroke, diabetes, certain cancers, falls and injuries. Self-report of a physically inactive life-style and poor physical function have been shown to be independent predictors of mortality in every population of normal and diseased individuals in which they have been studied.

Discussion

Patient self-report of global health, functional status, and frequency/intensity of exercise provide feasible measures that should be included in visits of all patients with rheumatic diseases. Poor perceived global health, low functional status, and especially the absence of physical exercise provide potentially modifiable risk factors that can be discussed and addressed to improve patient health, as well as possibly improve survival.

These observations suggest that a biomedical model – which holds that the most important measures in clinical care are derived from a health professional, laboratory tests and imaging results – may be supplemented with a simple one-page patient self-report questionnaire. The one-page questionnaire can provide global and detailed information concerning functional status and exercise activity, important predictors of mortality in healthy, aging and diseased populations (92). In rheumatology, simple patient self-report questionnaires have been available since the early 1980s for research and routine care, and are in regular use in certain rheumatology clinics.

Patient self-report questionnaires for clinical care differ substantially from questionnaires for clinical research. Questionnaires designed for clinical care must be easily completed by patients and scored by physicians. Such questionnaires add information to patient care, and save time for a health professional (109). By contrast, research questionnaires are thorough but may be time-consuming, with complicated scoring that cannot be performed during a patient visit. Research questionnaires cannot be interpreted during the visit, and therefore do not add to a clinical visit. Indeed, questionnaires used in clinical trials are forwarded to a data center without any review by a health professional.

Quality of life (QOL) questionnaires such as SF-36 are excellent research questionnaires, but are not easily scored and therefore not feasible for usual clinical care. The physical function component among 8 components of the SF-36 appears adequate for prediction of mortality in all reviewed studies, but cannot be implemented as part of routine clinical care, for reasons listed above. Therefore, a simple one-page questionnaire which includes a measure of functional status, global status, and the frequency and intensity of exercise can capture vital information that is easily collected in usual rheumatology care, and in other settings in which patients with chronic disease receive medical care.

Given the importance of physical performance in activities of daily living, efforts to increase and maintain higher levels of cardiovascular fitness and muscle strength would likely improve the capacity of an individual to live independently with better health and reduce mortality. Therefore, attention to the whole patient, from global status to simple activities to vigorous exercise, should be increased in modern medical care, to improve patient health and survival.

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