it is our belief that this strategy may yield positive clinical results without exact knowledge of its mechanism. In this context, our complexity based approach may provide a tool to optimise rest inserted loading waveforms and to design strategies that compensate for potential variations associated with factors such as age or genetic background. With future optimisation, rest insertion holds the potential to enable more bone accretion with less exercise compared with current repetitive loading strategies. Whereas cyclic aerobic exercise undoubtedly confers numerous physiological and psychological benefits beyond the skeleton, a rest inserted exercise regimen, in our view, holds greatly enhanced potential for utilisation in a couch potato era of substantially diminished physical fitness.

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COMMENTARY

Dynamic mechanical loading has been shown to actively influence the adaptive activities of bone in many animal studies and clinical observations. This report reviews recent studies on rest insertion between loading events, which amplifies the response of bone to loading, and suggests that the adaptation of bone to mechanical loading may be triggered by specific mechanical stimuli, but not necessarily correlate with the "magnitude" per se. The authors further develop a model and examine the cellular signalling pathway to predict the signalling activity in the osteocytic networks. This is an interesting approach to explaining how bone is sensitive to novel mechanical intervention at the cellular level. The high anabolic response to rest insertion of loading may also be supported by the mechanotransduction pathway, in which rest insertion would improve the fluid saturation caused by continuous loading and enhance perfusion in bone. This work provides valuable insight into the mechanism of bone adaptation and potential design of therapeutic strategies for clinical applications.

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Exercise for chronic disease

Benefits of exercise therapy for chronic diseases

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Evidence on the benefits of exercise therapy for chronic diseases based on randomised controlled trials is accumulating

Regular physical activity is one means of decreasing disability and increasing the number of independently living elderly people, as well as decreasing the costs of the healthcare system. On the basis of a recent review of the results of randomised controlled trials (RCTs), there is accumulating evidence that, in patients with chronic disease, exercise therapy is effective in increasing fitness and correcting some risk factors for the development of disease complications.[1]

FROM PREVENTION TO TREATMENT

Traditionally physical activity has been regarded as a powerful tool in the prevention of certain chronic diseases, even though this has been confirmed in only a very few cases by RCTs.[2] When the strength of evidence for the use of exercise in health care is evaluated, data from epidemiological observational follow ups, studies on the mechanisms of disease, and controlled clinical trials are used. Observational follow up studies can be biased for many reasons, such as genetic selection bias and inability to control for all confounding lifestyle factors.[3] However, it has been widely accepted that an epidemiological observational study with supportive data from studies on disease mechanisms provides enough evidence for exercise recommendations in disease prevention. Conclusive evidence for the benefits of exercise in the treatment of patients with chronic disease using the limited resources of the healthcare system should optimally be based on well designed RCTs.[1] Recently, the number of RCTs evaluating the effects of physical exercise therapy for specific diseases has increased substantially, allowing disease specific systematic reviews including meta-analyses.

MAIN FINDINGS OF SYSTEMATIC REVIEWS BASED ON RCTS

The most consistent finding of the studies is that exercise capacity or muscle strength can be improved in patients with different diseases without having detrimental effects on disease progression.[1] Severe complications in the exercise trials were rare. In some diseases, such as osteoarthritis, pain symptoms may also be reduced. Most RCTs are too short to document disease progression. Studies on patients with coronary heart disease,[4] as well as studies on patients with heart failure,[5] show that exercise groups have a somewhat reduced all-cause mortality. The clinically very significant findings include that exercise therapy has beneficial effects on all metabolic syndrome components and is highly beneficial for patients with type 2 diabetes mellitus.[1 6]

STUDY QUALITY IS IMPORTANT

Before the results are considered, the methodological quality of the individual RCTs should be critically analysed.[7 8] Biased results from poorly designed and reported trials can mislead decision making. It should be taken into account that exercise trials cannot usually be properly blinded, which may lessen the reliability of the results. In addition to other quality criteria, we have to keep in mind that generalisability may be a problem as some RCTs include patients that are not representative of the general population of patients with regard to age and coexisting diseases. This is typically seen in RCTs on coronary heart disease and heart failure.

The fact that most trials are of short duration means that some benefits, such as increases in physical fitness, are reached within weeks or months. However, specific RCTs are usually too short to provide conclusive evidence on the effects of exercise therapy on the true progression of disease. RCTs on the effects of exercise on lipid risk factors, blood pressure levels, and glucose homoeostasis,[6] as well as sporadic long term follow ups of disease progression,[4 5] support the conclusion that exercise therapy may have a beneficial effect on the long term progression of specific diseases.[1] However, there is a need for RCTs with long term follow ups, including documentation, of such outcomes as survival rate, rate of hospital admission, and healthcare costs.

CLINICAL PRESCRIPTION OF EXERCISE

Doctors prescribing exercise therapy have to know the basics of exercise physiology and training principles. Also, tailoring of a programme depends on the disease and its stage, the baseline fitness level of the patient, and the goals of the programme set together with the patient.

The available RCTs include a large variety of effective training programmes. Most patients seem to benefit from low to moderate intensity aerobic exercise. Detailed conclusions on the dose-response of exercise therapy in the treatment of specific diseases cannot be drawn from the available RCTs. We have to remember that the beneficial results of exercise therapies for patients with chronic disease shown by RCTs are based on carefully planned and followed exercise interventions in patients whose clinical status has first been examined to take into account possible risks. Unlike the prevention of disease in young healthy people, the therapeutic range of physical activity for patients with chronic disease may be limited. In exercise therapy, long term adherence is a general problem. Exercise consultations face to face or by telephone can be used to maintain high physical activity levels.[9] Also, whereas we look for evidence of the benefits of exercise therapy from RCTs specifically investigating the effects of exercise, in clinical work we have to bear in mind that correction of other modifiable risk factors such as diet[10] and smoking[3] are also important, as is the optimal medication.

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Gene therapy

Gene therapy in sport

R J Trent, I E Alexander

The potential benefits of gene therapy for sports injuries are counterbalanced by the potential for gene doping

Human gene therapy involves the insertion of DNA (or RNA) into somatic cells to produce a therapeutic effect. Gene therapy was first envisaged as an approach to treating genetic disorders. In this scenario, missing or mutant genes could be replaced or repaired. Today, gene therapy has broader applications, with trials covering many clinical problems including genetic diseases, cancer, infections such as HIV, and degenerative diseases.

The transfer of genetic material into cells can be undertaken in many ways, most commonly using a viral vector. For this, viruses are genetically engineered to remove infectious potential while retaining the capacity to carry a therapeutic gene(s) into selected target cells. The inserted sequences can encode a missing or mutant product as might occur in the case of cancer, or alternatively could be used to inhibit a foreign protein as would be found in HIV infection. Viral vectors have been derived from a number of different viruses. Some, such as the adenovirus, are associated with relatively mild human infections, whereas others are associated with more serious disease, for example HIV. Certain viral properties