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

**Table 1** Human gene therapy studies with potential application to sport

| Model | Status |
|---|---|
| Muscular dystrophy | Using animals with muscular dystrophy caused by mutations in the dystrophin gene, it is possible with gene therapy to inject into muscle a functional dystrophin gene.[4] The effects observed include a reduction in contraction induced injury, and an increase in muscle bulk. |
| Muscular atrophy | The National Aeronautics and Space Administration (NASA) in the United States has shown that space travel can produce skeletal muscle atrophy. Experimental studies are now underway to determine the preventive effects of *IGF1* in a retroviral vector given regularly by intramuscular injection.[5] |
| Rheumatoid arthritis | Phase I studies show little toxicity when inflammatory molecules such as interleukin 1 are inhibited by intra-articular injection of gene therapy products.[6] |

are particularly useful for gene therapy, such as the capacity to permanently integrate introduced genetic sequences into the host cell genome.

Apart from viruses, there are numerous physicochemical methods for introducing DNA (or RNA) into somatic cells. The most relevant in the context of sport involves direct injection of DNA that has been formulated with a chemical carrier for more efficient uptake by cells. None of the physicochemical approaches has been successful in human trials, as the levels of gene transfer achieved are insufficient for therapeutic benefit.

The results in gene therapy have generally been disappointing despite over 1000 clinical trials since 1990.[1] Only two diseases have been successfully treated by gene therapy. Both are forms of severe combined immunodeficiency, SCID-X1 and ADA-deficiency.[2 3] Unfortunately, success has come at a cost, with three of 18 infants with SCID-X1 treated developing leukaemia. This has now been shown to have been caused by insertional mutagenesis, which had previously been considered a remote theoretical risk associated with the integrating gene transfer technology used.

At present, there are three limitations to gene therapy: (*a*) gene transfer technologies are not efficient enough for most applications; (*b*) therapeutically useful integrating gene transfer technologies carry unresolved risks; (*c*) there remains an inadequate understanding of the biology of therapeutically relevant target cell populations.

## GENE THERAPY AND SPORTING INJURIES

There are a number of models illustrating how gene therapy may at some future time be used to treat sporting injuries (table 1).

## GENE DOPING IN SPORT

Sports men and women and sporting administrators faced with the prospect of drug cheating and blood doping now need to consider gene doping.[7] Although therapeutic benefit from gene therapy is difficult to achieve, gene doping is paradoxically more feasible because a very large output from the introduced gene may not be required, and the desired effect need only be short term. Regular injections at the time of sporting events may suffice. Gene doping is further simplified as it would not be necessary to have the transferred gene regulated so that its output corresponds to specific cellular requirements as might be the case for treating disease.

Genes of relevance to doping such as growth hormone, insulin-like growth factor I, and erythropoietin have been cloned, and so are readily available. They could be used as an alternative way to produce a range of performance enhancing agents. The risks of taking these substances in the form of traditional chemicals are known, and so decisions about risk versus benefit are straightforward. The same cannot be said for gene doping, as there continue to be many unknowns in this form of cellular intervention. Effects cannot be predicted, and so the sportsperson taking this route for cheating does not have control of the product. Random integration of vector sequences, for example, could produce complications such as acute leukaemia or other forms of cancer. Finally, unlike taking a drug, gene transfer is not easy to reverse, and so any untoward effects may be long term. There is also a small risk of inadvertent gene transfer to germ cells with the potential for harm to be passed on to an athlete's children.

Today, the risks for gene doping are much greater than the taking of traditional chemical products. Those involved in sport should be sufficiently informed of the risks, as well as likely future benefits of gene therapy. As the technology improves, many of the complications may be avoided, and so ongoing assessment of the potential for gene doping will be necessary. Detecting gene doping cheats will be possible using the standard assays as well as through the identification of gene vectors or their products. The bypassing of various metabolic pathways through the insertion of genes may lead to changes in gene expression profiles, and this may open up another approach to detecting gene doping.

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