EXERCISE IS AS EFFECTIVE AS DRUGS FOR MOST CARDIO-METABOLIC DISEASES

SO WHY DON'T MEDICAL PRACTITIONERS PRESCRIBE IT?

– Written by Ian Gillam, Australia

Exercise elicits a wide range of health benefits, but can also be designed to produce specific clinical outcomes that improve the health and well-being of individuals with chronic disease[1]. In an editorial in the *Canadian Family Physician*, Pimlott[2] described the 'exercise pill' as a miracle drug that has the ability to increase the capacity of almost every organ system. The wide-ranging actions of exercise cannot be matched by any prescription drug; a product designed with specific indications. As a result, multiple medications are required for patients with numerous chronic conditions. An additional benefit of exercise is that it has very few contraindications or adverse effects and there is increasing evidence that the more of the exercise pill you take, the healthier you will be[3].

Regular exercise has been shown to be as effective as most medically prescribed drugs in reducing the death rate from the major cardiovascular diseases, including coronary heart disease, heart failure, stroke as well as the prevention of diabetes[3]. This study concluded that "exercise interventions should therefore be considered as a viable alternative to or alongside drug therapy" and recommended that "the 'exercise pill' should be prescribed as a preventative strategy to reduce morbidity and mortality" from the major cardio-metabolic diseases.

If the results of that study could be replicated and perhaps extended to include the other major chronic diseases such as cancer, mental illness and degenerative musculoskeletal conditions, the implications would be profound. Similar findings would challenge and potentially change the priorities within current medical practice, such that exercise would become a primary treatment for the management of chronic disease. Could drugs be considered as an adjunct therapy to exercise? This four-part article develops the evidence base for exercise as a primary treatment for chronic disease management, questions the purpose of recent research on the development of a 'pseudo-exercise pill', examines some important adverse interactions between exercise and

Table 1: Exercise compared with drug efficacy

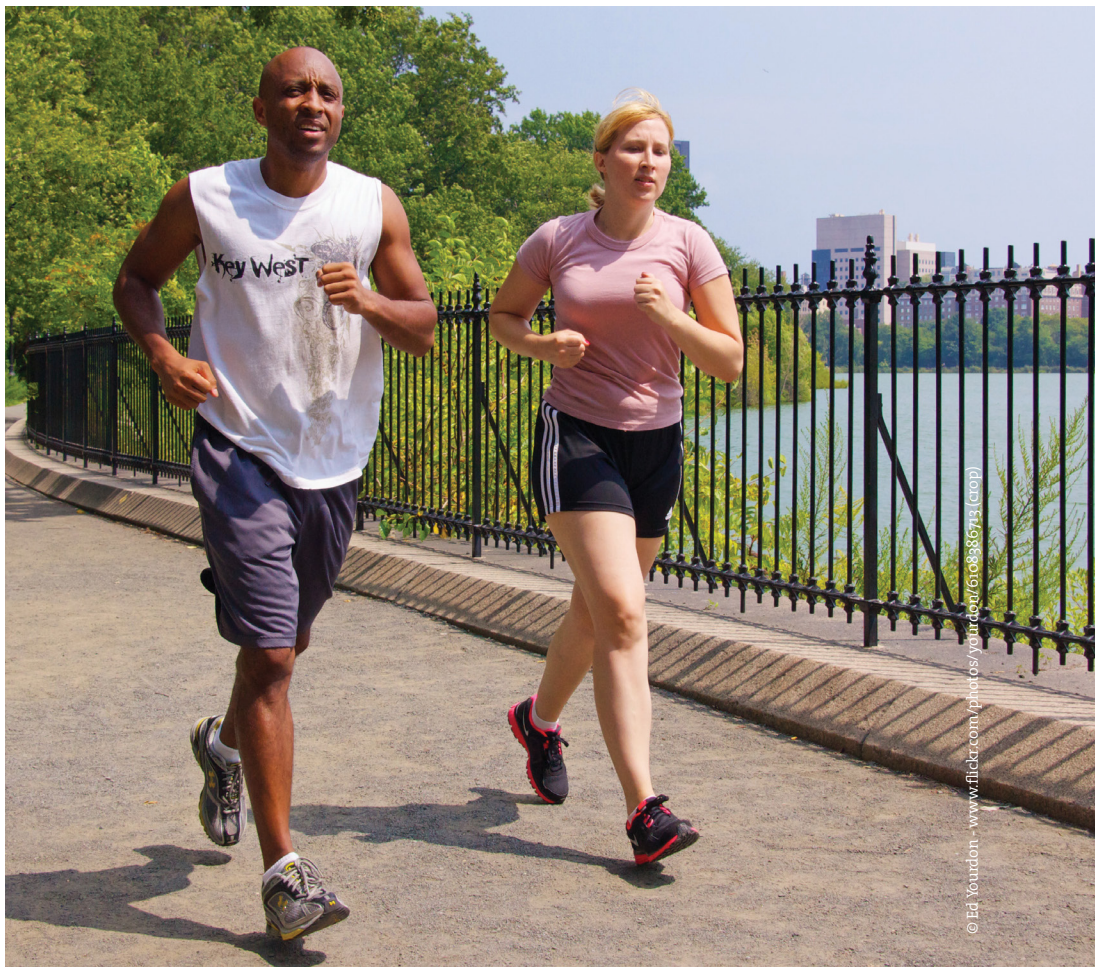
Disease type	Intervention	Mean OR (95% confidence interval)
Coronary heart disease	Exercise	0.89 (0.76-1.04)
	Statin medication	0.82 (0.75-0.90)
	Beta-blockers	0.85 (0.78-0.92)
	ACE inhibitors	0.83 (0.72-0.96)
	Anti-platelet medication	0.83 (0.74-0.93)
Heart disease and specifically heart failure.	Exercise	0.79 (0.59-1.00)
	Diuretics	0.19 (0.03-0.66)
	Beta-blockers	0.71 (0.61-0.80)
	ACE inhibitors	0.88 (0.69-1.16)
	Angiotensin receptor blockers	0.92 (0.74-1.09)
Stroke	Exercise	0.09 (0.01-0.72)
	Anti-coagulant therapy	1.03 (0.93-1.12)
	Anti-platelet therapy	0.93 (0.85-1.01)
Pre-diabetes	Exercise	0.67 (0.22-1.27)
	Biguanides (including metformin)	0.25 (0.02-1.46)
	Alpha-glucosidase inhibitors	3.03 (0.51-34.87)

Table 1: Comparison of the effects of an exercise intervention to common prescription drug treatments on mortality for selected cardio-metabolic diseases, based on the meta-analysis by Naci et al[3]. Data are presented as the mean Odds Ratio (OR) and its 95% confidence interval (CI) for each treatment. An OR of less than 1.0 favours the intervention as this associated with a lower risk of death and an OR of greater than 1.0 indicates a greater risk of death. The 95% CI (+/- 2 standard devaitions) estimates the precision of the OR with a large CI indicating a poor level of precision.

drug therapy and finally discusses why many medical professionals often fail to recommend exercise as integral part of every medical consultation. In Australia, the services provided by accredited exercise physiologists have now been recognised for rebates from the national Medicare system and as experts in prescription of exercise for individuals with chronic conditions. There is now increasing pressure in a number of countries to provide similar recognition for the allied health services provided by the 'clinical exercise physiologist' (or equivalent) and this paper argues that this is important in a contemporary health care system.

HOW DOES EXERCISE COMPARE WITH PRESCRIPTION DRUG TREATMENT TO PREVENT DEATH FROM CHRONIC CARDIO-METABOLIC DISEASE?

Naci et al[3] analysed the data from 16 meta-analyses (12 drug and four exercise interventional studies) to calculate the mean odds ratio (OR including its 95% confidence interval) to compare the effect of exercise and common drug interventions and their effect on mortality (the outcome measure). The OR data are shown in Table 1. For patients with coronary heart disease, exercise was at least as effective as statin medication, beta-blockers, ACE (angiostensin-converting-enzyme) inhibitors and anti-platelet medication in reducing the risk of death. For heart failure patients, only diuretics were more effective than exercise, with beta-blockers only marginally more effective and angiotensin receptor blockers and ACE inhibitors being less effective. For death from stroke, exercise was 90% more effective in reducing motality than the two most commonly prescribed drug interventions; anti-coagulants and anti-platelet therapy. Finally, for patients with pre-diabetes, only biguanides (which included metformin and its derivatives) were more effective than exercise, with alpha-glucosidase inhibitors and other anti-diabetic medications being less effective than exercise. The wide confidence interval in this group of patients was due to the few studies available for comparison. The exercise intervention data in this comparative meta-analysis should be considered with caution. One limitation was that the exercise interventions were considered as uniform treatments and there was no attempt to determine if exercise type or the dose of the exercise intervention (duration, intensity, frequency or progressive overload) was influential when evaluating its effect on the clinical outcomes. Indeed, it was not specified if the exercise intervention



met the minimum dose requirements to achieve the required clinical outcomes for reducing the risk cardio-metabolic disease. The authors acknowledge that a stricter control of the exercise specificity and dose of the intervention may have reduced the confidence interval for the exercise interventions, thus improving the ability to make comparisons between the interventions. It is important that future studies compare the efficacy of exercise and drug interventions, that there is an attempt to ensure that exercise interventions meet the recommended minimum dose requirement, treatment compliance rates are assessed and that exercise type is specific to the desired clinical outcomes. While a comparison of the mortality rates for these two interventions is important, an attempt should also be made to assess the effect of the treatments on the patient's quality of life.

HOW DOES EXERCISE MEDIATE ITS HEALTH BENEFITS?

Moderate intensity exercise causes profound cellular changes that are responsible for widespread improvements in health and longevity[4]. The most likely of these cellular events is an increase in AMP-activated protein kinase (AMPK), a fuel-sensing enzyme, which is activated by an increase in the intracellular AMP:ATP (adenosine monophosphate:adenosine triphosphate) ratio. The increase in AMPK only occurs when the exercise intensity exceeds 60% of maximal aerobic capacity[5]; a level that also corresponds to the known threshold for aerobic training adaptation. This increase in AMPK then sets off a cascade of intracellular events that includes activation of the protein, sirtuin 1 or SIRT1, which is often referred to as the Silent Information Regulator. Activation of AMPK counteracts many of the metabolic disturbances observed in metabolic syndrome including insulin resistance and angiogenesis, thus improving health and potentially increasing longevity. Interestingly, research has shown that the anti-diabetic drug metformin, which is used to treat insulin resistance, also activates AMPK, so potentially acts as a mimetic for exercise[4].

IS RESEARCH TO DEVELOP A PILL TO MIMIC THE EFFECTS OF EXERCISE WORTHWHILE?

In December 2013, David Sinclair from University of New South Wales in Sydney and his colleagues from the Harvard Medical School showed for the first time that injecting the compound nicotinamide mononucleotide (NMN) could reverse the ageing process[6]. NMN increases levels of cellular NAD+, a key cellular intermediate in the communication cascade between the nucleus and mitochondria that sets off the metabolic cascade that increases the NAD+ dependent deacetylase or SIRT1[6]. This confirmed previous work which had shown that increased levels of NAD+ slowed the progression of age-related metabolic dysfunction, such as diabetes[7]. Levels of NAD+ have been shown to decline by up to 50% as we age, which also parallels the decrease in total antioxidant capacity and increase in indices of oxidative damage to lipids, proteins and DNA damage, which are key characteristics of the ageing process[8]. Interestingly, NMN is claimed to 'mimic the effect of exercise and diet restriction', which are also known determinants of the ageing process. However, as the required dose of NMN is 500 mg/day/kg body weight, the cost to use this product to delay the ageing process is currently estimated to be an unacceptable $43,000/day for an 86 kg human! Providing advice and support for individuals to participate in a regular exercise programme and for those individuals at higher health risk, to be appropriately supervised by a health professional seems like better advice!

SOME ADVERSE EFFECTS AND INTERACTIONS BETWEEN EXERCISE AND PRESCRIPTION DRUGS AND THEIR EFFECT ON PHYSICAL PERFORMANCE – WHAT ARE THE IMPLICATIONS?

There is increasing evidence that some prescription drugs result in adverse side effects, including increased levels of muscle pain and fatigue or impaired exercise performance. Consider the mitochrondrial

membrane-bound antioxidant coenzyme Q10 (CoQ10). CoQ10 is an essential cofactor in the mitochondrial electron transport system, aerobic energy production and muscle performance[9]. The commonly used cholesterol-lowering medication simvastatin interferes with a precursor in the biosynthesis of CoQ10 and the regular use of this statin medication reduces levels of CoQ10 in skeletal muscle[9]. This has been shown to be a significant cause of mitochondrial dysfunction, statin-induced, myopathies and muscle pain, especially in older people, who appear to be at greater risk[9]. There is substantial evidence that increased oxy-radical production due to high intensity training will also deplete the serum and tissue levels of CoQ10[10]. This reduction in the serum CoQ10 levels can result in muscle fatigue and reduced endurance performance in highly trained endurance athletes[10,11]. It is recommended that serum CoQ10 levels are monitored in individuals taking statin medication and especially athletes undertaking high intensity training. If serum levels of CoQ10 are shown to be low, supplementation may be recommended to ameliorate fatigue[11-13].

Statin therapy may also impair usual exercise adaptations. In an exercise training study conducted over 12 weeks with overweight adults with two or more metabolic risk factors, patients who had been prescribed simvastatin (40 mg/day) failed to increase aerobic capacity and the activity of a key mitochondrial enzyme in skeletal muscle when compared to an identical placebo training group[14]. As exercise training is often prescribed in combination with statin therapy to manage patients with metabolic syndrome, the interaction between these two interventions needs to be further investigated and evaluated so appropriate clinical decisions can made for these clients. Further evidence of the interaction between statin therapy and aerobic fitness and their effects on mortality risk[16] was summarised in a letter to *The Lancet* by Kokkinos et al which stated that "physical activity should be regarded as the first step in cardiovascular disease prevention and that the addition of a statin should be considered only if it does not interfere with exercise"[17]. The adverse effects of statins on muscle metabolism and training have also been suggested as a factor leading to some patients not complying with their (statin) medication[15].

Strenuous exercise increases pro-inflammatory cytokines, which are balanced by an increase in the anti-inflammatory cytokine, IL-10[18]. These exercise-induced pro-inflammatory processes increase the synthesis of prostanoids, which play an important role in the anabolic signalling responsible for muscle protein synthesis and muscular adaptations to resistance training[19].

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to reduce and alleviate the pain associated with an increase in musculoskeletal inflammation due to hard physical exercise or underlying pathology, such as arthritis. However, since NSAIDs suppress the production of prostanoids, these drugs may interfere with adaptive responses to strength and exercise training[19]. Specifically, NSAIDs may inhibit the growth of muscle satellite cells, a myogenic precursor cell essential for muscle growth and hypertrophy after eccentric exercise or muscle injury[20,21]. While a single infused dose of NSAIDs does not appear to reduce myofibrillar or collagen protein synthesis in skeletal muscle[20], no studies have investigated the possible adverse effects of long term use of NSAIDs on muscle protein synthesis and recovery. As NSAIDs could potentially interfere with muscle recovery, growth and repair, this is an area under close investigation[19].

physical activity should be regarded as the first step in cardiovascular disease prevention and the addition of a statin should be considered only if it does not interfere with exercise

TREATMENT COMPLIANCE: EXERCISE VS DRUGS?

Some medical practitioners argue that prescribing exercise has limited health benefits because of poor patient compliance. Approximately 50% of individuals who start an aerobic exercise programme will stop within 6 months[22]. However, patient compliance to exercise programmes is highly variable and depends upon the type of exercise, the required exercise frequency and the behavioural support provided to the participants[23]. Multiple bouts of shorter duration exercise separated by short rest periods (or intermittent exercise) may improve a patient's exercise compliance. A walking programme conducted on a group of moderately obese women, which compared 30 minutes of continuous walking to intermittent walking, consisting of 2x 15-minute exercise bouts, showed that the attrition rate after 24 weeks was 38% and 16% respectively. However, the attrition rate after 72 weeks was 58%, which was the same for both groups[24].

Patient adherence to prescribed medications is often not optimal, with drug compliance rates similar to those for exercise interventions. When examining the adherence to prescribed anti-hypertension medications, approximately 50% of hypertensive patients stopped taking their medications after 1 year[25]. Drug compliance rates can vary from 40% to 83% depending on the definition of compliance, the type of medication prescribed, potential adverse effects of the medication and the method used to detect non-compliance[26]. As treatment compliance for exercise and drug interventions are similar, this should not be a factor either when recommending or determining the efficacy of these two interventions.

DO MEDICAL PRACTITIONERS RECOMMEND EXERCISE TO THEIR PATIENTS WITH CHRONIC DISEASE AND IF NOT, WHY NOT?

With the mounting level of evidence on the role of physical activity in reducing the incidence of chronic disease, disability and premature death[27-29] it is surprising that many general practitioners (GPs) still fail to recommend regular exercise as a primary intervention. Sallis[30] stressed the importance of recording physical inactivity as a modifiable, vital sign and a key component of all medical or clinical consultations. A client's record of physical inactivity can provide a rationale for recommending an exercise intervention to improve health, especially those with a chronic disease[30,31].

Patients regard advice on how to adopt a healthy lifestyle, including exercise, as important and they regard their medical practitioner as the best and most credible source for this advice[32]. Yet a survey of 23 medical practices in the United Kingdom in 1987 found that only 3 to 6% of patients had ever received exercise advice from their GP as part of their consultation[32]. A more recent study in the USA in 1999[33] showed that 48% had received exercise advice and two subsequent studies in Canada in 2007[34,35] showed that 70% to 85% of patients had received such advice from their family physician. These data indicate that the importance of physical activity as a contributor to health is now being recognised by family physicians as part of a routine medical consultation.

While 67% of family physicians were confident in prescribing exercise[34] only 16% provided their patients with written exercise prescriptions[35]. Most physicians stated that insufficient consultation time, a lack of the necessary knowledge and skills and inadequate reimbursement for the time required to conduct an exercise assessment or give exercise advice were significant barriers to providing this service[34]. A general lack of education in exercise physiology and practical skills in exercise assessment and prescription in many medical programmes globally, have also been identified as major barriers[35]. As a result, many medical practitioners now choose to refer their patients to sport and exercise physicians and university qualified exercise physiologists.

EXERCISE PHYSIOLOGISTS: ESSENTIAL PLAYERS IN INTER-DISCIPLINARY HEALTHCARE TEAMS FOR INDIVIDUALS WITH CHRONIC DISEASE

The medical referral of patients to exercise physiologists for exercise assessment and

prescription is increasingly being recognised as a best practice model across the western world. Exercise physiologists are required to have at least a university degree in exercise physiology, kinesiology or biokinetics, with most countries now requiring additional postgraduate studies in clinical exercise physiology to meet the requirements for registration or accreditation. In the USA, the American College of Sports Medicine (ACSM) has developed five levels of certification for exercise specialists; certified personal trainers that develop health and fitness programmes for healthy individuals, through to the most advanced level, the ACSM Registered Clinical Exercise Physiologist (RCEP). The RCEP is recognised as an allied health professional that is responsible for designing, implementing and supervising exercise interventions for individuals with diagnosed chronic disease[36]. The Canadian Society of Exercise Physiology also has similar certification programme for exercise physiologists (CSEP)[37] and the British Association of Sport and Exercise Science (BASES) has developed an interest group in clinical exercise physiology, but has yet to develop an accreditation or registration process[38].


© Maks Karochkin - www.flickr.com/photos/karochkin/5712957260 (crop)

In Australia, accredited exercise physiologists (AEP) are university-trained allied health professionals who are recognised as the most qualified to design and deliver clinical exercise interventions for high-risk clients with existing chronic and complex medical conditions and injuries[39]. In 2006, AEPs were granted eligibility for a Medicare Provider number as part of the Australian Federal Government's Medicare system. This enabled their clients to claim a healthcare rebate for up to five exercise physiology services per year. Since 2006, the number of referrals to AEPs has grown significantly; 80,000 services were delivered in 2010, increasing sevenfold to 620,000 services in 2013[40]. The ACSM and CSEP, representing exercise physiologists in North America, are also attempting to lobby their Government health departments to obtain medical rebates for exercise physiology services, similar to that in Australia.

The Medicare funding channel in Australia is triggered by a referral from the patient's general GP to the AEP, who then works as part of the interdisciplinary team to assist the client in the management of their chronic disease[41,42]. After conducting an initial physical assessment and risk stratification, the AEP then develops an exercise programme consistent with the clinical objectives outlined by the client's GP.

CONCLUSION

A truly inter-disciplinary system with cross-referral pathways to appropriate members of the inter-disciplinary healthcare team must be an important feature of any contemporary health system if we are to address a growing chronic disease epidemic. This must include exercise physiologists who can deliver the exercise 'pill'. The exercise 'pill' not only provides a modality to maintain health as we age, but also provides a multi-system treatment for the prevention and management of non-communicable diseases that dominate the burden of disease in both developed and middle/low income countries. It is important to also recognise the potential financial savings to the healthcare budget and productivity benefits that could be achieved through a fitter and healthier workforce[43].

In a letter to *The Lancet*, De Souto Barreto[44] stated that; "the prescription of exercise should be placed on par with drug prescription". A health industry that is focused on hospital-based care, costly government-subsidised pharmaceuticals and medical procedures is failing to address future health needs. The research on exercise as a primary treatment for the management of chronic disease, as an adjunct to drug therapy and any potential interactions between drug therapy and exercise adaptation has just begun.

References

Available at www.aspetar.com/journal

Ian Gillam B.Sc. (Hons), M.Sc., Ph.D., Dip. Phys. Ed., A.E.P., A.Sp.

Fellow, Exercise & Sports Science Australia

Fellow, Sports Medicine Australia

Accredited exercise physiologist and accredited sports scientist.

National Institute of Integrative Medicine

East Hawthorn, Melbourne, Australia

www.niim.com.au

Contact: drigillam@niim.com.au