Original paper

Chronic Respiratory Disease

Chronic Respiratory Disease
2018, Vol. 15(2) 173–181

DOI: 10.1177/1479972317736294
journals.sagepub.com/home/crd
SAGE

Obesity and metabolic syndrome in COPD: Is exercise the answer?

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Abstract

Approximately half of all patients with chronic obstructive pulmonary disease (COPD) attending pulmonary rehabilitation (PR) programmes are overweight or obese which negatively impacts upon dyspnoea and exercise tolerance particularly when walking. Within the obese population (without COPD), the observed heterogeneity in prognosis is in part explained by the variability in the risk of developing cardiovascular disease or diabetes (cardiometabolic risk) leading to the description of metabolic syndrome. In obesity alone, high-intensity aerobic training can support healthy weight loss and improve the constituent components of metabolic syndrome. Those with COPD, obesity and/or metabolic syndrome undergoing PR appear to do as well in traditional outcomes as their normal-weight metabolically healthy peers in terms of improvement of symptoms, health-related quality of life and exercise performance, and should therefore not be excluded. To broaden the benefit of PR, for this complex population, we should learn from the extensive literature examining the effects of exercise in obesity and metabolic syndrome discussed in this review and optimize the exercise strategy to improve these co-morbid conditions. Standard PR outcomes could be expanded to include cardiometabolic risk reduction to lower future morbidity and mortality; to this end exercise may well be the answer.

Keywords

COPD, obesity, metabolic syndrome, exercise, pulmonary rehabilitation

Date received: 12 April 2017; accepted: 11 August 2017

Prevalence of obesity in COPD

The effect of body composition upon clinical outcomes in individuals with chronic obstructive pulmonary disease (COPD) has been a focus for researchers and clinicians for decades. However, the lower end of the body mass index (BMI) spectrum and cachexia have predominated and justified by the associated poor prognosis[1] of this habitus. Towards the 21st century, the obesity epidemic encompassed patients with COPD where the prevalence of obesity (BMI > 30 m kg^{-2})[2] is reported to be between 10% and 30% depending on the country of origin and severity of disease.[3–5] The majority of patients with COPD in typical pulmonary rehabilitation (PR)

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populations[6] and in large randomized controlled trials of pharmacological therapy are overweight.[7] Conflicting results remain regarding the prevalence of obesity between those with and without COPD from epidemiological studies with similar, higher and lower prevalence all reported for those with COPD.[3,8,9]

Obesity and mortality

In non-COPD populations, the relationship between BMI and mortality has been described by a 'J-shaped curve', but the magnitude of the increased risk of death per increase in BMI is unknown. Furthermore, reduced functional status, frequency and type of co-morbid conditions have a greater association with mortality than a high BMI alone.[10,11] Physical inactivity is implicated as a factor in the development of obesity inferring a negative impact upon clinical outcomes. In addition, individuals with obesity, who are fit, do better than their lean unfit counterparts.[12] Studies exploring the obesity 'paradox' have subcategorized individuals with obesity into metabolically healthy or unhealthy[13] with an increase in coronary artery disease reported in those who are metabolically 'unhealthy' (or have the metabolic syndrome).[14] The concept of 'metabolically healthy' obesity is still being debated as this group appears to sustain more cardiovascular events compared with the people of normal weight.[13]

BMI and prognosis in individuals with COPD

In populations with COPD, a paradox is described whereby patients with a higher BMI live longer than those with either a low or normal index particularly in those with severe disease.[15] The severity of COPD is predominantly assessed by the degree of airflow impairment so one explanation may be that the severity of COPD is overestimated by the physiological reduction in lung volumes in obese individuals. Furthermore, when carbon dioxide levels, muscle mass (measured by thigh cross-sectional area) and exercise capacity are included, the obesity paradox appears to disappear.[16] Physical inactivity and co-morbid conditions both negatively impact survival in individuals with COPD,[17,18] similar to the obese individuals without COPD. An increased risk of heart failure, diabetes and hypertension is seen in COPD associated with increased systemic inflammation[18]; metabolic disturbances may be implicated as part of the pathophysiological mechanisms.

Metabolic syndrome and COPD

Metabolic syndrome: an evolving definition

The co-existence of several metabolic disturbances, namely obesity, dyslipidaemia, hypertension and hyperglycaemia, has been increasingly observed over the last century and led to the description of a 'metabolic syndrome'.[19] Originally defined by Reaven as 'Syndrome X' through identifying the relationship between insulin resistance, hyperinsulinemia, hypertension, coronary artery disease and noninsulin-dependent diabetes mellitus.[20] In 1998, the World Health Organization was the first to formalize the definition of a metabolic syndrome creating a working definition[3]: 'the occurrence of "glucose intolerance, impaired glucose tolerance or diabetes mellitus and/or insulin resistance together with two or more of the components below":

1. Raised arterial pressure > 160/90 mmHg
2. Raised plasma triglycerides (>1.7 mmol L^{-1}; 150 mg dL^{-1}) and/or low high-density lipoprotein-cholesterol (<0.9 mmol L^{-1}; 35 mg dL^{-1} men; <1.0 mmol L^{-1}; 39 mg dL^{-1} women)
3. Central obesity (males: waist to hip ratio > 0.90; females: waist to hip ratio > 0.85) and/or BMI > 30 kg m^{-2}
4. Microalbuminuria (urinary albumin excretion rate > 20 μg min^{-1} or albumin: creatinine ratio > 20 mg g^{-1})'

The term metabolic syndrome or 'cardiometabolic syndrome' is commonly used today to describe the interaction between cardiovascular, renal, metabolic, prothrombotic and inflammatory abnormalities leading to increased morbidity and mortality.[21] The development of metabolic syndrome is thought to be closely associated with physical inactivity leading to the accumulation of visceral fat, which activates pro-inflammatory pathways leading to type II diabetes mellitus and cardiovascular disease.[12]

Whilst the common features of metabolic syndrome are generally accepted, the precise definition is continuing to be refined; probably the most universally accepted is the 2009 joint consensus definition,[22] which is slightly modified from that proposed by the International Diabetes Federation in 2006[23] (Table 1).

Table 1. Definition of metabolic syndrome.

2009 Consensus definition criteria for the clinical diagnosis of the metabolic syndrome: present if any three of the criteria are might shown below:	
2006 IDF definition criteria for the diagnosis of the metabolic syndrome present if central obesity (defined as waist circumference with ethnicity specific values, or assumed if BMI is greater than 30 kg m^{-2}) is present plus any two of the following four factors:	
Measure	Categorical cut points
Elevated waist circumference[a]	Population and country-specific definitions
Elevated triglycerides (or drug treatment for this disturbance)	$\geq$150 mg dL^{-1} (1.7 mmol L^{-1})
Reduced HDL (or drug treatment for this disturbance)	<40 mg dL^{-1} (1.0 mmol L^{-1}) in males; <50 mg dL^{-1} (1.3 mmol L^{-1}) in females
Elevated blood pressure (or drug treatment for this disturbance or previous hypertension diagnosis)	Systolic $\geq$ 130 and/or diastolic $\geq$ 85 mm Hg
Elevated fasting glucose (or drug treatment for this disturbance)	$\geq$100 mg dL^{-1}

IDF: International Diabetes Federation; BMI: body mass index; HDL: high-density lipoprotein.
[a]Has to be present for the 2009 definition.

Prevalence of metabolic syndrome in COPD

Data from the 2003 to 2012 National Health and Nutrition Examination Survey collected in the United States concluded the prevalence of metabolic syndrome was 33%, with a significantly higher prevalence in women than men (35.6% vs. 30.3%, respectively).[24] The prevalence of metabolic syndrome among those with COPD is reported to be anywhere between 21% and 58% depending on disease severity, geographic location, definition utilized and the assessments made.[25] There is a suggestion that metabolic syndrome is more prevalent in those with milder airflow obstruction,[25,26] but this may in part reflect the weight loss observed in the severe stages of COPD. Single studies have reported a higher prevalence of metabolic syndrome than age- and gender-matched individuals without COPD.[27] However, pooled estimates of 10 studies reported similar (32% vs. 30%) prevalence of metabolic syndrome between COPD and healthy controls.[25] In contrast, a prospective study, where the components of the metabolic syndrome were objectively assessed, reported a prevalence of 57% in 228 participants, which was significantly higher than healthy controls (40%).[28] The results from this study suggested that the presence of metabolic syndrome did not impact the functional outcomes in those with COPD.

Cardiovascular disease and diabetes are significant causes of morbidity and mortality for patients with COPD, and their prevalence is significantly higher than in matched-controls. This association likely relates to several pathophysiological mechanisms, including systemic inflammation, physical inactivity and oxidative stress.[26,29] International COPD guidelines recommend 'the proactive identification and treatment of comorbidities',[30] yet often this is routinely performed in clinical practice. Whether earlier identification and management of metabolic syndrome in patients with COPD would lower the risk of developing cardiovascular disease and improve long-term clinical outcomes is unclear.

There is also intriguing evidence that diabetes mellitus and metabolic syndrome through an inflammatory mechanism result in airflow obstruction[31,32] rather than metabolic derangement occurring in COPD as a co-morbidity. Whether effective metabolic management may slow the progression of airflow limitation in patients with COPD is yet unknown.

Obesity and metabolic syndrome are common in patients with COPD who are symptomatic and referred for PR.[6,27] Despite the association between obesity in COPD and a reduced exercise performance compared to normal-weight individuals, obese individuals gain similar improvements with PR in terms of exercise capacity and health-related quality of life as patients who are normal weight.[6] However, weight loss is not often a specific goal of PR and not achieved by most standard PR programmes.

If co-morbidities such as obesity and metabolic syndrome are to be addressed in the personalization of PR delivery, it is important to understand the current recommendations for exercise therapy for both of these conditions when COPD is not present.

Obesity and exercise interventions

Obesity is considered the result of a complex interplay of individual and environmental factors; therefore, its

management demands a comprehensive approach.[33] Exercise is an important component of this approach, the goals of which include improvements in general health and reduction in risk of comorbid disease in addition to weight loss.[33,34]

Weight loss requires a shift in energy balance of which exercise forms a negative component of the equation.[35] As such sufficient quantities of exercise must be achieved without compensatory behaviours such as increased calorie intake. The absolute quantity of exercise or activity appears to be more important than the type or intensity; individuals exercising at lower intensity can achieve similar weight changes by increasing duration, and greater improvements in weight reduction are seen with increasing overall amount.[36,37] Results from the studies of a targeted risk reduction intervention through defined exercise (STRRIDE) study, a randomized control study investigating the effects of exercise duration and intensity in overweight and obese adults, suggest that an equivalent volume above 6–7 miles a week may be required in order to achieve weight loss. Going further, a 14-week daily exercise program where obese women were asked to expend approximately 500 kcal resulted in an average body weight reduction of 6.5%.[38] A similar study in obese men where daily expenditure was approximately 700 kcal resulted in an 8% reduction over 3 months. Studies have tended to focus on aerobic exercise interventions for weight loss employing a range of modalities, including walking, stationary cycling and elliptical cross trainers, and the evidence seems to support this approach.[36–38] There may be additional gains and other benefits, for example, on body composition, muscle strength and cardiovascular fitness, through the addition of high intensity or resistance exercise.[36,39,40]

Weight loss alone has the potential to impact several of the adverse health risk factors, which are highly prevalent in obesity, such as hypertension, dyslipidaemia and insulin resistance.[41–46] However, exercise may deliver improvements in these elements above that achieved through weight reduction and even when weight remains stable.[35,38,47]

Where studies have specifically examined the effects of exercise in overweight and obese individuals, improvements in blood pressure, lipid profiles, glucose, glycosylated haemoglobin (HbA1c) and insulin sensitivity[46–49] have been described. Again the overall volume of exercise appears to be more important than exercise modality for most of these risk factors, and modification has been demonstrated with even small increases in weekly exercise although larger volumes of moderate exercise appear to result in greater effects on lipid and glycaemic profiles.[48,50–54] In those with established type II diabetes, a meta-analysis demonstrated improvements in levels of HbA1c through either aerobic, resistance or combined exercise, and such improvements have also been seen in obese groups.[55,56]

In addition to the effects on risk factor modification, exercise can enhance cardiovascular fitness, which is also related to a lower all-cause and cardiovascular mortality, and improve social engagement and measures of well-being.[57–59]

How these elements are combined to form the optimal exercise prescription to achieve both increased energy expenditure to aid healthy weight loss and evoke an important cardiovascular stimulus is still unknown. Clinicians and researchers often quote that weight supported exercise should be the initial modality. In a direct comparison of weight supported and unsupported (cycling versus treadmill walking) exercise at 60% and 80% VO_2 peak, treadmill walking was associated with the greatest energy expenditure and with a higher cardiovascular stimulus in obese individuals.[60] However, whether this translates to a more effective training regime with the additional factors of comfort, tolerance and compliance remains unknown.

Uncertainty exists around the translation of research to the prescription for an individual. Individual barriers, such as time, physical discomfort, and embarrassment as well as physical mobility and equipment weight limitations, are important to address.[61] Adherence can be an issue, with many trials demonstrating a significant drop-out rate in the exercise intervention group.[33,36,37] Therefore, individual tailoring, focusing on meaningful and realistic goals with adequate support, is a proposed strategy.[33,34,36]

The effects of obesity on exercise in individuals with COPD

Obesity can impair exercise capacity due to the increased mechanical load from carrying the extra weight, altered economy due to gait alterations and joint and spine discomfort. In COPD, the addition of obesity further impairs walking performance independent of the degree of airflow limitation. An interesting phenomenon has been demonstrated, whereby, in individuals with COPD and obesity, the development

of dynamic hyperinflation during cycling is lower in obese individuals compared to normal weight.[62] Furthermore, the relationship between the progression of breathlessness with increasing ventilation is similar between walking and cycling in obese individuals with COPD,[63] whereas in obese individuals without COPD, there is a greater progression of breathlessness with cycling compared to treadmill walking and earlier termination of exercise.[60]

The effects of exercise training upon the metabolic syndrome

A large randomized controlled trial confirmed the evidence from smaller trials demonstrating that a period of aerobic exercise training in otherwise healthy adults with metabolic syndrome achieves a reduction in some but not all of the constituent components. Markers of insulin resistance and systemic inflammation have also been seen to be reduced after three months of high-intensity exercise training in adults with type II diabetes mellitus and the metabolic syndrome[64] appearing to be related to gains in peak oxygen uptake (cardiorespiratory fitness) rather than weight loss. Similarly, a small study reported that high-intensity aerobic training (via an interval training regime) improved the constituent components of metabolic syndrome greater than moderate intensity training (via a continuous training regime).[65] Other modalities of exercise training have also been tested such as resistance training where the hypothesis is based around increasing muscle mass to reduce insulin resistance. However, the results to date have been inconsistent: a meta-analysis showed resistance training significantly reduced the levels of HbA1c in adults with abnormal glucose metabolism with a reduction in body fat mass and visceral adipose tissue.[66] The results of a large randomized trial were published a year later,[67] concluding resistance training alone did not improve any parameters of the metabolic syndrome, whereas aerobic training alone showed a reduction in metabolic syndrome although not significantly greater than combined aerobic and resistance training. The training period was over 8 months and included adults who were overweight with dyslipidaemia. Other research has concentrated on how the effects of exercise upon metabolic syndrome may be attenuated by age, race and gender.

Overall, it appears that there is a beneficial effect of high-intensity aerobic exercise training upon the components of metabolic syndrome in adults who are overweight or obese. Correspondingly, physically active individuals have lower rates of all-cause mortality, cardiovascular disease, hypertension and importantly the metabolic syndrome.[68] There is a convincing body of literature to support this and international guidelines promoting physical activity in all adults.[68] Physical activity is a complex construct involving intense (aerobic exercise), mild and moderate physical activities, and time being very inactive (sedentary). Although there is interest in promoting adults (particularly those with long-term conditions) to be less sedentary, prospective data showing a reduction in long-term risk compared with increasing moderate or intense physical activity are not yet available.[69]

Exercise training, COPD and metabolic syndrome

People with co-existing COPD and metabolic syndrome appear to benefit comparably from a course of PR as patients with COPD alone[70] in terms of health-related quality of life and exercise performance. Similarly, studies have investigated the effects of co-morbidities on the outcomes of PR,[71] but to date, there has been far less focus on the effects of PR on the underlying co-morbid conditions such as metabolic syndrome. A couple of studies have investigated the effects of PR in patients with COPD on cardiovascular risk by assessing systemic blood pressure, lipid levels and aortic stiffness but found differing results.[72,73]

There are surprisingly few studies examining the effects of standard rehabilitation on all the constituent parts of the metabolic syndrome or on different modalities. Although high-intensity aerobic training programmes have been found to improve metabolic syndrome in those without COPD, whether the relative rather than absolute high-intensity training achieved in people with COPD would be enough to improve metabolic syndrome, or whether strategies to increase the muscle-specific stimulus would be optimal remains unanswered.

Currently, the evidence base and data for cost-effectiveness of PR is derived from patients who have significant dyspnoea rendering them unable to walk at their own pace on the flat without stopping.[74] The aim, for this population, has been to reduce dyspnoea and improve the quality of life, which PR does very successfully.[75] However, perhaps the focus should also be to reduce cardiometabolic risk (the risk of

developing cardiovascular disease and/or diabetes) which may be even more relevant when designing exercise or physical activity interventions for those with milder disease. The duration of standard PR is typically 6–12 weeks and it is also unknown if this is sufficient to reduce cardiometabolic risk in the longer term. Even if some benefits were observed in the short term, it is likely that long-term behaviour change and healthy lifestyle adaptations would be necessary to impact upon long-term cardiometabolic risk.

In summary, co-morbid conditions of obesity and metabolic syndrome are common in COPD. In those without COPD, exercise and high-intensity physical activity can support healthy weight loss and improve the constituent components of the metabolic syndrome. Those with COPD, obesity and/or metabolic syndrome undergoing PR appear to do as well as their normal-weight metabolically healthy peers and should therefore not be excluded. To progress the benefit of PR for this complex population, we should learn from the extensive literature examining the effects of exercise in obesity and metabolic syndrome and target the exercise strategy to ameliorate these co-morbid conditions. Standard PR outcomes should be expanded to include cardiometabolic risk reduction in order to lower future morbidity and mortality; to this end, exercise may well be the answer.

Authors' note

Rachael A Evans holds an NIHR clinical scientist fellowship CS-2016-16-020. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Ruth E Trethewey is undertaking a PhD funded by Loughborough University. Amy V Jones is undertaking a PhD funded by Loughborough University.

Author contributions

BDJ, AVJ and RET contributed equally to the preparation and drafting of this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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