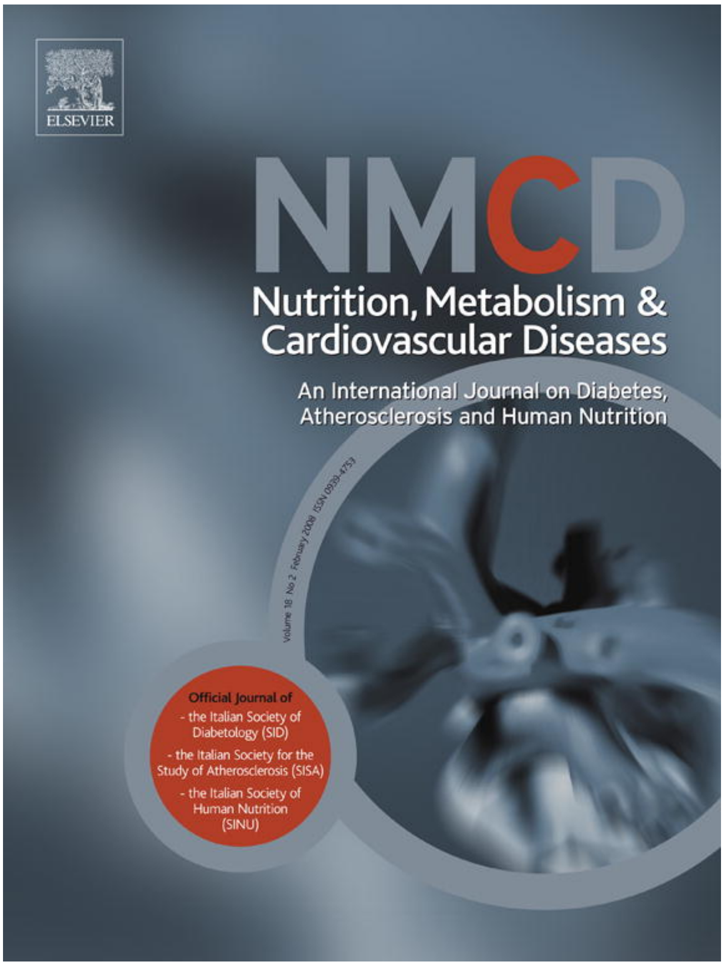
ELSEVIER
NMCD
Nutrition, Metabolism & Cardiovascular Diseases
An International Journal on Diabetes, Atherosclerosis and Human Nutrition
Volume 18 No 2 February 2008 ISSN 0939-4753
Official Journal of
- the Italian Society of Diabetology (SID)
- the Italian Society for the Study of Atherosclerosis (SISA)
- the Italian Society of Human Nutrition (SINU)

Nutrition, Metabolism & Cardiovascular Diseases (2008) **18**, 142—151

ELSEVIER

Nutrition, Metabolism & Cardiovascular Diseases

www.elsevier.com/locate/nmcd

Long-term cardiac rehabilitation and exercise training programs improve metabolic parameters in metabolic syndrome patients with and without coronary heart disease

Mathieu Gayda [a], Carlos Brun [a], Martin Juneau [a], Sylvie Levesque [b], Anil Nigam [a,*]

[a] *Medicine Department, Research Center, Centre de médecine préventive et d'activité physique (ÉPIC), Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada*
[b] *Montreal Heart Institute Coordinating center (MHICC), 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada*

Received 10 March 2006; received in revised form 27 June 2006; accepted 12 July 2006

KEYWORDS
Cardiac rehabilitation;
Exercise training;
Metabolic syndrome;
Coronary heart disease

Abstract *Background and aims:* The effectiveness of long-term cardiac rehabilitation and exercise training programs on metabolic parameters was evaluated in metabolic syndrome subjects with and without coronary heart disease (CHD).
Methods and results: Fifty-nine CHD and 81 non-coronary patients with metabolic syndrome (59 ± 8 vs 56 ± 9 years) were identified retrospectively at entry into identical cardiac rehabilitation and exercise-training programs. Metabolic syndrome was defined using modified Adult Treatment Panel III criteria. Exercise training occurred approximately twice per week. Metabolic and exercise testing data were collected at baseline and after 12 months during the course of the program. Mean duration of cardiac rehabilitation and exercise training programs was over one year in both coronary and non-coronary patients (366 ± 111 vs 414 ± 102 days for CHD and non-coronary CHD cohorts respectively, $p < 0.01$). Significant improvements in bodyweight, body mass index, blood lipids, triglyceride/HDL ratio and exercise tolerance were noted in both cohorts. At the end of follow-up, 31% of CHD and 20% of non-CHD subjects no longer possessed diagnostic criteria for metabolic syndrome ($p < 0.0001$ and $p < 0.001$ respectively).

* Corresponding author. Tel.: +1 514 376 3330x4033; fax: +1 514 376 1355.
E-mail address: anil.nigam@icm-mhi.org (A. Nigam).

0939-4753/$ - see front matter
doi:10.1016/j.numecd.2006.07.003

Conclusions: A long-term cardiac rehabilitation program reduces metabolic syndrome prevalence in CHD patients and results in a similar improvement in risk factor control for metabolic syndrome patients without CHD.

Introduction

The metabolic syndrome refers to a constellation of coronary heart disease (CHD) risk factors including obesity and abdominal fat distribution, disorders of glucose and lipid metabolism, and hypertension. While each of these risk factors individually has been shown to increase cardiovascular risk [1—5], the metabolic syndrome itself has been shown to increase cardiovascular and all-cause mortality in subjects without known heart disease [6—8]. Additionally, patients with metabolic syndrome and CHD are at increased risk of death compared to CHD patients without metabolic syndrome [9]. The prevalence of obesity continues to rise at epidemic proportions in both North America and Europe, with estimates suggesting that over 50% of adults above the age of 50 in the United States have the metabolic syndrome [10]. Currently, there is need to develop efficacious and effective lifestyle strategies to reduce the prevalence of the metabolic syndrome and its associated health risks, as this syndrome is often unrecognized and untreated [11—17]. Exercise training has been shown to reduce individual components of metabolic syndrome including hypertension, elevated plasma triglycerides, elevated blood glucose and low HDL-cholesterol [16]. Several randomized, controlled exercise-training studies have shown positive effects on metabolic parameters and exercise tolerance in metabolic syndrome subjects without coronary heart disease [11,15,18,19]. Only one brief report has evaluated the effects of short-term phase II cardiac rehabilitation on metabolic syndrome parameters in CHD patients following an acute coronary syndrome [20]. No data however are available regarding the effects of a more long-term exercise-training program on exercise tolerance and metabolic risk factors in metabolic syndrome subjects with coronary heart disease. The aim of this study was therefore to assess the effect of a long-term (≥6 months) exercise-training program on exercise tolerance and metabolic risk factors in metabolic syndrome patients with stable CHD enrolling in a cardiac rehabilitation and exercise-training program with therapeutic lifestyle change.

Methods

Patients

This retrospective chart review study was conducted at the cardiovascular prevention center of the Montreal Heart Institute. Our center provides a multiphase, multidisciplinary approach to cardiac rehabilitation as well as providing exercise and risk factor control programs in the primary prevention setting [21]. Data were examined from a cohort of metabolic syndrome patients with and without coronary heart disease enrolled into identical cardiac rehabilitation and exercise-training programs. All patients included in our retrospective analysis were required to have had a diagnosis of metabolic syndrome at their first evaluation, have undergone a physical examination with measurement of height and weight, an initial symptom-limited exercise stress test, fasting blood glucose and lipid profile, and have participated in a long-term cardiac rehabilitation and exercise-training program lasting ≥6 months. Consecutive attendees of the program fitting the study criteria and with complete data were identified from our center's database from 1988 to 2004. Their data are included in the present study. Coronary heart disease was defined as the presence of documented prior myocardial infarction, prior coronary revascularization, or documented myocardial ischemia on myocardial scintigraphy. Hypertension was defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, or use of anti-hypertensive therapy. Presence of dyslipidemia was defined as a medical history of dyslipidemia, use of lipid-lowering therapy or an LDL-cholesterol >2.5 mmol/l and total/HDL-cholesterol ratio >4 mmol/l in patients not receiving statins [22]. Medication was checked on each patient's medical chart.

Metabolic syndrome definition

Metabolic syndrome was defined according to National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria: presence of ≥three of five criteria, namely abdominal obesity (waist circumference >102 cm in men and >88 cm in women), triglycerides ≥1.70 mmol/l, decreased

HDL-cholesterol (<1.0 mmol/l in men and <1.3 mmol/l in women), systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, and FPG ≥6.1 mmol/l [13]. Because waist circumference was not systematically available for all patients, a body-mass index (BMI) >27 kg/m^2 cut-point was chosen as our criterion for abdominal obesity [19,23]. Patients receiving pharmacological therapy for either diabetes or hypertension were not excluded from our analyses.

Cardiac rehabilitation, exercise training and risk factor intervention

Both CHD and non-CHD metabolic syndrome subjects underwent the same aerobic training program at an exercise intensity corresponding to 65—90% of their maximal heart rate (Borg scale level 11—14) based upon the initial and subsequent exercise stress tests [21]. Exercise prescription and intensity were gradually increased (from Borg scale level 11 to 14) during the training program according to each patient's progress. Supervised exercise training according to recent recommendations [24] was performed two times per week for 40 min per session (5-min warm-up, 30-min aerobic exercise and 5-min cool down) in different activities such as walking, stationary cycling and rowing [21]. In addition, subjects were told to perform 1 to 2 more aerobic exercise sessions such as walking and/or cycling (30—45 min duration) outside the center on a weekly basis. Physicians and/or nurses provided patients with recommendations regarding a low-fat, low-cholesterol diet and smoking cessation, generally on a yearly basis. In addition, formal dietary and psychological counseling, and a smoking cessation program were available for subjects if deemed necessary [21].

Patient follow-up, exercise stress testing and risk factor analysis

During the follow-up period, patients were reevaluated every 6—12 months by a physician with repeat measurement of weight and height, fasting glycemia and lipid profile, and completion of an exercise stress test. Treadmill exercise testing was performed using a symptom-limited ramp protocol [24]. During the tests, the subject's electrocardiogram and blood pressure were monitored continuously. The electrocardiogram was recorded at 30-s intervals. Maximal exercise tolerance was defined as the highest level of metabolic equivalent units estimated from maximal treadmill speed and grade during the treadmill test according to the American College of Sports Medicine guidelines for cardiac patients [25]. At the end of the test, each patient had a 5-min passive recovery period. All patients were instructed to take their usual medications prior to exercise testing.

Program attendance

Data on program attendance was obtained from medical charts. In addition, data was obtained from an electronic entry system which automatically records patient attendance since 1999 for patients who began their training programs at this time or afterwards.

Statistical analysis

All data are expressed as mean value ± standard deviation and/or in number and percentage. For continuous variables, statistical differences between groups and time were evaluated by a two-way analysis of variance with one repeated measure (time) and by a generalized estimating equation (GEE) for categorical variables. Differences in the prevalence of metabolic syndrome and medication prescription before and after training were tested using chi-square analysis. Univariate logistic regression analysis was used to identify which baseline variables were significantly associated with being a non-responder (continuing to possess ATP III criteria for metabolic syndrome at the end of the treatment period) to our long-term exercise-training interventions. Due to the small number of non-responder patients, a multivariate logistic regression model was performed including the four baseline variables that showed the strongest association with being a non-responder in the univariate analyses. All analyses were performed using SAS 8.2 (SAS Institute Inc., Cary, NY, USA) and Statview 5.0 (SAS Institute Inc., Cary, NY, USA). A p-value ≤0.05 was considered statistically significant.

Results

Subject characteristics

Table 1 describes the clinical characteristics of both metabolic syndrome cohorts at baseline. The mean duration of exercise training was slightly less in CHD patients with metabolic syndrome relative to non-coronary subjects ($p < 0.01$). Program attendance was similar in both groups. Statin use increased significantly ($p < 0.001$) over time in both groups (Table 1).

Table 1 Characteristics of metabolic syndrome patients with and without coronary heart disease and medication at first and last evaluation

	MS patients without CHD ($n = 81$)		MS patients with CHD ($n = 59$)	
Age (years)	56 ± 9		59 ± 8	
Duration of cardiac rehabilitation (days)	414 ± 102		366 ± 111†	
Median program attendance (sessions/week)	1.83 ± 0.5		1.83 ± 0.6	
Female sex	13 (16%)		0 (0%)	
Smoking	13 (16%)		7 (12%)	
Hypertension[a]	59 (72%)		42 (71%)	
Abnormal glucose metabolism[b]	40 (49%)		33 (55%)	
History of dyslipidemia	64 (79%)		50 (85%)	
Obesity[c]	64 (79%)		44 (74%)	
Prior MI	0 (0%)		26 (45%)	
Prior PCI	0 (0%)		28 (49%)	
Prior CABG	0 (0%)		25 (44%)	
Medication	Pre	Post	Pre	Post
Beta-blockers	16 (17%)	17 (18%)	37 (58%)	40 (63%)
ACE inhibitors	10 (10%)	10 (10%)	21 (33%)	24 (38%)
Antiplatelet agents	14 (15%)	15 (15%)	56 (95%)	56 (95%)
Angiotensin receptor blockers	8 (8%)	12 (12%)	6 (9%)	8 (12%)
Statin therapy	12 (12%)	18 (19%)‡	34 (53%)	44 (69%)‡
Calcium channel blockers	9 (9%)	13 (13%)	16 (25%)	13 (20%)
Diuretics	11 (11%)	10 (10%)	8 (12%)	7 (11%)
Nitrates	1 (1%)	1 (1%)	5 (7%)	7 (11%)
Digitalis	0 (0%)	0 (0%)	2 (3%)	2 (3%)
Hypoglycemic agents	7 (7%)	8 (8%)	14(22%)	15(23%)
Insulin therapy	1 (1%)	1 (1%)	0 (0%)	1 (1%)
Fibrates	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Niacin	0 (0%)	0 (0%)	0 (0%)	0 (0%)

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting surgery; CHD, coronary heart disease; MI, myocardial infarction; MS, metabolic syndrome; PCI, percutaneous coronary intervention. †$p < 0.01$. ‡ = $p < 0.001$ for pre vs. post medication.
[a] Rest SBP ≥130 mmHg.
[b] Glucose ≥6.1 mmol/l.
[c] BMI >27 kg/m^2.

Coronary risk factors

Table 2 describes the metabolic coronary risk factors of both metabolic syndrome cohorts before and after training. Approximately 75% of patients at baseline suffered from abdominal obesity as defined by a BMI >27 kg/m^2 [19,23]. Total cholesterol and LDL-cholesterol were significantly lower in metabolic syndrome patients with coronary heart disease at baseline and LDL-cholesterol decreased significantly with exercise training in this same cohort. Weight, BMI, total cholesterol, LDL-cholesterol, triglycerides and triglyceride/HDL ratio decreased significantly over time in both cohorts. Similarly, HDL-cholesterol increased significantly over time in both cohorts with exercise training. Although waist circumference data was incomplete, BMI was highly correlated to waist circumference in the entire cohort ($r = 0.85$, $p < 0.0001$).

We also performed secondary analyses on metabolic parameters excluding 16 patients (6 non-CHD and 10 CHD patients) who initiated statin therapy during the course of the study. These analyses provided similar results to the ones reported herein (data not shown).

Exercise stress testing data

Exercise testing data are shown in Table 3. Exercise tolerance, resting heart rate, maximal heart rate and maximal rate-pressure product were lower in metabolic syndrome patients with CHD. Functional capacity increased to a similar degree

Table 2 Metabolic risk factors in metabolic syndrome patients with and without coronary heart disease before and after cardiac rehabilitation program

	MS patients without CHD ($n = 81$)		MS patients with CHD ($n = 59$)		p
	Pre	Post	Pre	Post	
Bodyweight (kg)	89 ± 15	87 ± 15	87 ± 12	86 ± 12	b§
BMI (kg/m^2)	30.4 ± 4.3	29.7 ± 4.2	29.4 ± 3.7	29.0 ± 3.8	b§
Rest SBP (mmHg)	136 ± 16	136 ± 17	139 ± 20	130 ± 17	c*
Rest DBP (mmHg)	82 ± 10	82 ± 8	81 ± 9	79 ± 8	a*
Fasting glucose (mmol/l)	6.42 ± 1.62	6.26 ± 1.42	6.62 ± 1.59	6.44 ± 1.6	ns
Total cholesterol (mmol/l)	5.74 ± 1.15	5.39 ± 1.11	5.33 ± 1.32	4.86 ± 1.12	a*, b§
HDL-cholesterol (mmol/l)	0.91 ± 0.17	0.99 ± 0.18	0.88 ± 0.15	0.94 ± 0.16	b§
LDL-cholesterol (mmol/l)	3.43 ± 1.06	3.31 ± 1.05	3.17 ± 1.26	2.88 ± 1.02	a*, b*
Total Chol/HDL-cholesterol	5.87 ± 1.20	4.94 ± 1.40	5.44 ± 1.57	4.83 ± 1.56	b§
Triglycerides (mmol/l)	2.98 ± 1.35	2.45 ± 1.11	3.05 ± 1.61	2.46 ± 1.60	b*
Triglycerides/HDL	3.56 ± 2.2	2.62 ± 1.57	3.67 ± 2.29	2.66 ± 1.81	b§

a, CHD vs non-CHD patients; b, pre vs post; c, interaction group × time; BMI, body-mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; MS, metabolic syndrome; ns, not significant; SBP, systolic blood pressure. * = $p < 0.05$. § = $p < 0.0001$.

in both metabolic syndrome cohorts although patients without coronary disease had better exercise tolerance.

Evolution of metabolic risk factors and prevalence of metabolic syndrome

Table 4 describes the evolution of patients fitting the modified ATP III metabolic syndrome criteria before and after training. The prevalence of elevated fasting glycemia ($p < 0.01$), low HDL-cholesterol ($p < 0.0001$), high triglycerides ($p < 0.0001$) and hypertension ($p < 0.05$) decreased in both cohorts after exercise training. In general, there was reduction in the prevalence of individuals possessing multiple MS components at the end of the follow-up period (Figs. 1a, b). After the intervention, 20% of non-CHD ($p < 0.001$) patients and 31% of CHD patients ($p < 0.0001$) were no longer classified as having metabolic syndrome (Figs. 1a,b). Even among subjects considered ''non-responders'' (continuing to possess ATP III diagnostic criteria for metabolic syndrome), we noted significant improvements in HDL-cholesterol ($p = 0.021$), triglycerides ($p = 0.0014$), BMI ($p = 0.0009$) and systolic blood pressure ($p = 0.044$). Fasting glucose and diastolic blood pressure were unchanged in non-responders (data not shown).

Predictors of being non-responders to cardiac rehabilitation and exercise training

Among the entire cohort of 140 subjects, we identified 106 individuals who were considered ''non-responders'' and continued to possess ATP III diagnostic criteria for metabolic syndrome at the end of the study. Table 5 describes the baseline univariate predictors of being a non-responder. Higher weight, BMI, systolic and diastolic blood pressure and triglyceride levels were all significant predictors of being a non-responder, as were lower HDL-cholesterol levels and exercise tolerance. Statin use had a protective effect.

Table 3 Exercise parameters in metabolic syndrome patients with and without coronary heart disease before and after cardiac rehabilitation program

	MS patients without CHD ($n = 81$)		MS patients with CHD ($n = 59$)		p
	Pre	Post	Pre	Post	
Exercise capacity in METs	8.22 ± 1.91	9.30 ± 2.06	7.59 ± 1.45	8.39 ± 1.76	a*, b§
Rest HR (beats/min)	76 ± 15	72 ± 13	70 ± 12	65 ± 12	a†, b§
Max HR (beats/min)	151 ± 24	152 ± 23	135 ± 23	135 ± 23	a§
Max RPP (HR × SBP)/100	293 ± 64	299 ± 59	249 ± 70	247 ± 65	a§

a, CHD vs non-CHD patients; b, pre vs post; CHD, coronary heart disease; METs, metabolic equivalent units; HR, heart rate; MS, metabolic syndrome; RPP, rate-pressure product; SBP, systolic blood pressure. * = $p < 0.05$. † = $p < 0.01$. § = $p < 0.0001$.

Table 4 Metabolic risk factors in metabolic syndrome patients with and without coronary heart disease before and after a long-term exercise training program

	MS patients without CHD ($n = 81$)		MS patients with CHD ($n = 59$)		p
	Pre	Post	Pre	Post	
Glucose (≥6.1 mmol/l)	39 (53%)	30 (41%)	30 (60%)	23 (46%)	a†
HDL-cholesterol (<1.04 mmol/l)	72 (90%)	52 (65%)	50 (86%)	40 (69%)	a§
Triglycerides (≥1.69 mmol/l)	76 (94%)	61 (75%)	53 (89%)	39 (66%)	a§
BMI (>27 kg/m^2)	64 (79%)	62 (77%)	44 (75%)	40 (68%)	ns
Rest SBP (≥130 mmHg)	59 (73%)	57 (70%)	42 (71%)	32 (54%)	a*
Rest DBP (≥85 mmHg)	34 (42%)	33 (41%)	23 (39%)	16 (27%)	ns

a, pre vs post; MS, metabolic syndrome; CHD, coronary heart disease; BMI, body-mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ns, not significant. * = $p < 0.05$. † = $p < 0.01$. § = $p < 0.0001$.

Cohort (CHD vs non-CHD) was not a predictor of response to our long-term interventions.

We created a multivariate logistic regression model containing the four baseline variables most closely associated with being a non-responder in the univariate analyses (Table 6). Elevated BMI and systolic blood pressure, low HDL-cholesterol and statin use (presence vs absence) all remained significant predictors of continuing to possess diagnostic criteria for MS at the end of the follow-up period.

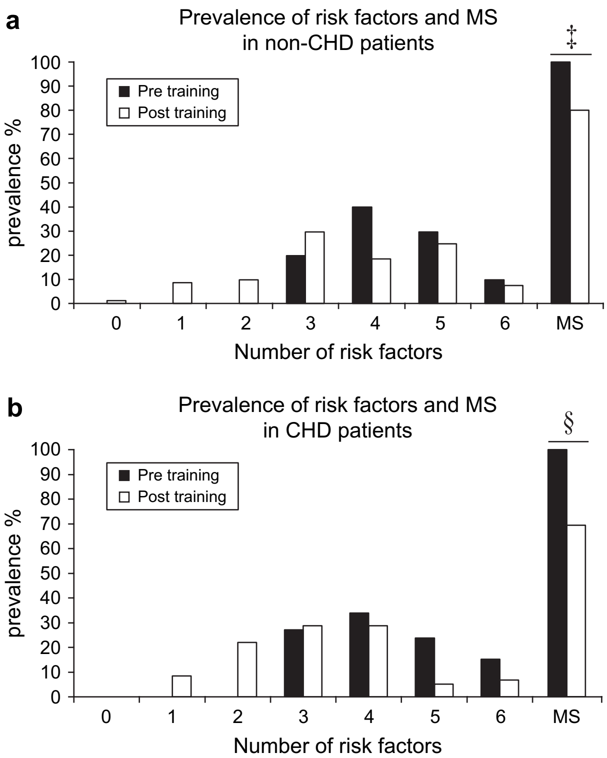

Figure 1 Frequency distribution of the number of risk factors (NCEP III criteria) before and after cardiac rehabilitation and exercise training programs in: (a) non-CHD patients with metabolic syndrome; and (b) CHD patients with metabolic syndrome. MS, metabolic syndrome. ‡ = $p < 0.001$, § = $p < 0.0001$.

Discussion

Our results demonstrate that a long-term cardiac rehabilitation and exercise-training program of approximately one-year duration can be effective in reducing the prevalence of metabolic syndrome and its individual components and leads to an improvement in exercise tolerance in both subjects with and without CHD. In particular we noted improvements in bodyweight, BMI, triglyceride and HDL-cholesterol levels and insulin resistance as evaluated using the triglyceride/HDL-cholesterol ratio.

To our knowledge, this is the first study to document the effect of a long-term exercise-training program on metabolic syndrome parameters in coronary heart disease patients. Milani et al. [20] evaluated the effect of 3-month phase II cardiac rehabilitation on metabolic parameters in subjects following an acute coronary syndrome. In contrast to our study, their results did not demonstrate any significant improvements in lipid parameters or BMI in coronary subjects with the metabolic syndrome. Both our study and Milani's revealed an improvement in insulin resistance based upon the triglyceride/HDL ratio. These data suggest that while a short-term exercise-training program is beneficial, a longer program provides incremental improvements in metabolic parameters and presumably further reduces the risk of subsequent clinical events.

The baseline metabolic profile of our metabolic syndrome patients was similar to that of metabolic syndrome patients in previous studies of exercise training [11,15,19,20,26]. Long-term exercise

Table 5 Univariate baseline predictors of being a non-responder* to cardiac rehabilitation and exercise-training programs in the entire metabolic syndrome cohort

Variables	Odds Ratio†	95% CI	*P*-value
Weight	1.06	1.02–1.10	0.003
BMI	1.24	1.10–1.40	0.0005
Cohort (CHD vs non-CHD)	0.56	0.26–1.22	0.145
Resting SBP	1.04	1.01–1.07	0.003
Resting DBP	1.05	1.01–1.10	0.022
Max SBP	1.02	1.00–1.03	0.047
Max DBP	1.02	0.98–1.05	0.409
Exercise capacity in METs	0.78	0.61–0.98	0.035
Fasting Glucose	1.42	0.98–2.07	0.061
Total Cholesterol	1.47	1.04–2.07	0.028
LDL-Cholesterol	1.21	0.85–1.71	0.285
HDL-Cholesterol	0.03	0.002–0.51	0.015
Triglycerides	1.46	1.03–2.05	0.032
Total Cholesterol/HDL	1.62	1.08–2.44	0.020
Triglycerides/HDL	1.35	1.04–1.75	0.025
Beta Blockers	0.40	0.18–0.87	0.022
Calcium Channel Blockers	1.02	0.37–2.80	0.971
ACE inhibitors	0.76	0.30–1.92	0.555
Angiotensin receptor blockers	0.47	0.14–1.56	0.219
Statins	0.29	0.13–0.65	0.003
Hypoglycemic agents	3.27	0.72–14.89	0.125

*Non-responders were defined as subjects continuing to possess diagnostic criteria for metabolic syndrome at the end of the intervention; †Odds ratio per 1 unit increase for continuous variables or presence versus absence for categorical variables. CI indicates confidence interval; BMI, body-mass index; CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; METs, metabolic equivalent units; ACE, angiotensin-converting enzyme.

Table 6 Multivariate predictors of being a non-responder* to cardiac rehabilitation and exercise training programs in the entire metabolic syndrome cohort

Variables	Odds Ratio	95% CI	*P*-value
BMI	1.28	1.11–1.47	0.0008
Resting SBP	1.06	1.03–1.09	0.0003
HDL-cholesterol	0.01	<0.001–0.37	0.0107
Statin use (presence vs absence)	0.39	0.15–0.99	0.0494

*Non-responders were defined as subjects continuing to possess diagnostic criteria for metabolic syndrome at the end of the intervention; CI indicates confidence interval; BMI, body-mass index; SBP, systolic blood pressure.

training resulted in modest but significant reductions in both bodyweight and BMI in both metabolic syndrome cohorts, with improvements being somewhat greater in non-coronary heart disease patients. Additionally, lipid parameters also improved in both groups, including significant reductions in total cholesterol, triglycerides, LDL-cholesterol, triglyceride/HDL ratio and an increase in HDL-cholesterol. Previous studies in metabolic syndrome subjects without CHD have demonstrated similar results with respect to weight loss and lipid parameters [15,17–19,26]. Finally, although we did not witness a significant reduction in fasting blood glucose levels, insulin resistance as measured using the triglyceride/HDL-cholesterol ratio [27] did decrease significantly. None of the patients in our study were receiving fibrates or niacin therapy that could have potentially altered the triglyceride/HDL-cholesterol ratio to a significant extent. Two other studies have demonstrated a decrease in insulin resistance with exercise-training in metabolic syndrome patients [17,20].

Despite lower baseline exercise tolerance in CHD patients with metabolic syndrome, exercise training improved functional capacity to a similar degree in both cohorts (+1.1 metabolic equivalent units or 13%; +0.8 metabolic equivalent units or 10% for non-CHD and CHD patients respectively, $p < 0.0001$). Our results are consistent with those reported in other non-CHD cohorts [11,15,18]. We also demonstrate for the first time that a long-term cardiac rehabilitation and exercise-training program significantly increases functional capacity in stable coronary patients with metabolic syndrome. Finally, our intervention reduced the percentage of patients fulfilling the ATP III criteria for metabolic syndrome (Table 4). In both cohorts, there was a reduction in the prevalence of individuals containing multiple MS criteria (Figs. 1a,b). After training, 20% of the non-coronary heart disease cohort and 31% of the coronary heart disease cohort were no longer classified as having the metabolic syndrome (Figs. 1a,b).

As expected, more abnormal values of the various metabolic syndrome components at baseline were predictors of continuing to fulfill our ATP III criteria at the end of training and hence be categorized as ''non-responders'' to our exercise-training interventions. In addition, lower exercise tolerance was also a significant predictor of being a non-responder. Finally, statin use at baseline was predictive of a beneficial response to our cardiac rehabilitation and exercise training programs. Statins have modest but significant beneficial effects on both HDL-cholesterol and triglyceride levels, and their use at baseline appears to have facilitated the positive response to exercise training. This occurred despite the fact that HDL-cholesterol and triglyceride levels were similar in both cohorts at baseline even though considerably more CHD patients were receiving statin therapy compared to non-CHD patients. Due to a restricted sample size, we included in our multivariate model, the four variables most closely associated with being a non-responder based upon the univariate analyses. All four variables, namely elevated BMI and systolic blood pressure, low HDL-cholesterol and statin use (presence vs absence) remained significant predictors of being non-responders to our interventions.

It must also be emphasized that even among the non-responders, we noted a significant improvement in all the metabolic syndrome components except for fasting glucose and diastolic blood pressure. This data would indicate to us that the entire cohort benefited from the cardiac rehabilitation and exercise-training programs, and that classifying individuals according to the presence or absence of metabolic syndrome leads to an underestimation of the metabolic improvements achieved.

Unfortunately we did not possess a control group in our study due to its retrospective nature. However, previous studies of exercise training or cardiac rehabilitation programs in non-CHD and CHD patients with metabolic syndrome have failed to show improvements in metabolic parameters or exercise tolerance in their control groups. Watkins et al. [15] in a randomized trial of 6 months duration in 53 non-CHD metabolic syndrome patients, failed to show any improvement in exercise or metabolic parameters in the control group. Similarly, Christ et al. [19] in 52 metabolic syndrome subjects without CHD followed for 36 months in a risk reduction program, observed an increase in weight and BMI in the control group while exercise and lipid parameters remained unchanged. Finally, Milani et al. [20] in their study of metabolic syndrome patients entered into a phase II cardiac rehabilitation program following an acute coronary event, found that patients in the control group failed to show an improvement in lipid parameters and glycemia at the end of the study. Other studies by the same authors have also noted in control CHD populations, the lack of temporal improvements in their overall risk factor profiles [28,29]. Based upon the aforementioned studies, we believe it is unlikely that a control group would have shown a significant improvement in metabolic or exercise parameters.

Recent epidemiological studies have shown that men with metabolic syndrome and without CHD have higher rates of all-cause and cardiovascular mortality compared to healthy men [6,12,30]. Metabolic syndrome patients with CHD also have higher rates of all-cause and cardiovascular mortality relative to CHD patients without metabolic syndrome [9]. The risk of death in metabolic syndrome is greatly influenced by both the number of metabolic abnormalities [8] and cardiorespiratory fitness [12,30]. Greater cardiorespiratory fitness is protective against all-cause and cardiovascular mortality in obese men and those with metabolic syndrome [12,31]. Similarly, women who are obese but physically active appear to have better long-term outcomes relative to both obese and lean sedentary women [32]. Furthermore, 150 min a week of moderate intensity physical activity in obese subjects is sufficient to avoid the low-fitness category associated with higher all-cause mortality [31,33].

Whether a higher training frequency would have led to greater improvements in metabolic parameters in our metabolic syndrome sample remains a possibility. On average, subjects in both cohorts trained approximately twice per week. Current guidelines suggest a training frequency of 3–5 sessions per week [24], although a training frequency <3 sessions per week has been shown to improve exercise tolerance and lipid parameters in coronary patients [34,35]. In addition, patients in both of our cohorts were told to perform aerobic activities outside the center 1–2 times per week. Based upon this information, we believe that 2–3 sessions of aerobic activity on a weekly basis is the minimum training frequency required to improve metabolic parameters and exercise tolerance in subjects with metabolic syndrome although a higher training frequency presumably leads to even greater improvements.

A long-term cardiac rehabilitation and exercise-training program would appear to provide cardiovascular protective effects to metabolic syndrome patients through multiple mechanisms. These include a reduction in the prevalence of the individual metabolic abnormalities that define metabolic syndrome and hence their associated cardiovascular risk. Exercise also has significant beneficial effects on other factors including endothelial function [36], inflammation [37], autonomic nervous system function [38] and coagulation abnormalities [39], all of which have been shown to be abnormal in the metabolic syndrome [40–44].

There are several limitations inherent in the study design. Firstly, this was a non-randomized observational study and did not include a matched control population. However, as noted previously, prior studies in non-CHD and CHD samples evaluating the effectiveness of exercise-training programs in metabolic syndrome, have all failed to show significant improvements in metabolic parameters in the control groups [15,19,20]. At the same time, our intervention resulted in similar improvements in metabolic parameters in our CHD cohort as in those achieved in our non-coronary cohort. Our results also compare favorably to those achieved in previous prospective studies in the primary CHD prevention setting [11,15,18], and extend knowledge with respect to the utility of long-term cardiac rehabilitation in CHD patients. While our study represents the experience of one institution's efforts to provide a long-term cardiac rehabilitation and exercise-training program to patients at risk for cardiovascular events, we do believe that a long-term exercise-training program with a minimum training frequency of 2—3 sessions per week is both feasible and beneficial in metabolic syndrome patients with and without CHD and results in improvements in abdominal obesity, functional capacity, lipid parameters and insulin resistance index. Finally, most of our subjects were men, the effects of cardiac rehabilitation perhaps being different in non-CHD and CHD women with metabolic syndrome.

In conclusion, our results show the beneficial effects of a long-term cardiac rehabilitation and exercise-training program on metabolic parameters and exercise tolerance in coronary heart disease patients with metabolic syndrome. The results achievable in CHD patients are similar to those achievable in a non-coronary population undergoing a similar program. A training frequency of 2—3 sessions per week does improve metabolic parameters and exercise tolerance although a higher training frequency presumably provides incremental benefits. Prospective studies are now required to evaluate and enable us to generalize the benefits of exercise-training to metabolic syndrome patients with coronary heart disease and especially in women.

References

[1] McGill HC Jr, McMahan CA, Herderick EE, Zieske AW, Malcom GT, Tracy RE, et al. Obesity accelerates the progression of coronary atherosclerosis in young men. Circulation 2002;105:2712—8.

[2] The DECODE Study Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and non-cardiovascular diseases? Diabetes Care 2003;26:688—96.

[3] Eberly LE, Stamler J, Neaton JD, Multiple Risk Factor Intervention Trial Research Group. Relation of triglyceride levels, fasting and non-fasting, to fatal and non-fatal coronary heart disease. Arch Intern Med 2003;163:1077—83.

[4] Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, et al. Primary prevention of coronary heart disease: guidance from Framingham. A statement for healthcare professionals from the AHA task force on risk reduction. Circulation 1998;97:1876—87.

[5] Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:953—62.

[6] Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709—16.

[7] Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683—9.

[8] Trevisan M, Liu J, Bahsas FB, Menotti A. Syndrome X and mortality: a population-based study. Risk factor and life expectancy research group. Am J Epidemiol 1998;148: 958—66.

[9] Nigam A, Bourassa M, Fortier A, Guertin MC, Tardif JC. The metabolic syndrome and its components and the long-term risk of death in patients with coronary heart disease. Am Heart J 2006;151:514—21.

[10] Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. Adults. Diabetes Care 2004;27:2444—9.

[11] Katzmarzyk PT, Leon AS, Wilmore JH, Skinner JS, Rao DC, Rankinen T, et al. Targeting the metabolic syndrome with exercise: evidence from the HERITAGE Family Study. Med Sci Sports Exerc 2003;35:1703—9.

[12] Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004;164:1092—7.

[13] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486—97.

[14] Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE family study. Aims, design, and measurement protocol. Med Sci Sports Exerc 1995;27:721—9.

[15] Watkins LL, Sherwood A, Feinglos M, Hinderliter A, Babyak M, Gullette E, et al. Effects of exercise and weight loss on cardiac risk factors associated with syndrome X. Arch Intern Med 2003;163:1889—95.

[16] Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388—9.

[17] Carroll S, Dudfield M. What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. Sports Med 2004;34:371—418.

[18] Couillard C, Despres JP, Lamarche B, Bergeron J, Gagnon J, Leon AS, et al. Effects of endurance exercise-training on plasma HDL-cholesterol levels depend on levels of triglycerides: evidence from men of the Health, Risk Factors, Exercise-Training and Genetics (HERITAGE) Family Study. Arterioscler Thromb Vasc Biol 2001;21:1226—32.

[19] Christ M, Iannello C, Iannello PG, Grimm W. Effects of a weight reduction program with and without aerobic exercise in the metabolic syndrome. Int J Cardiol 2004; 97:115—22.

[20] Milani RV, Lavie CJ. Prevalence and profile of metabolic syndrome in patients following acute coronary events and effects of therapeutic lifestyle change with cardiac rehabilitation. Am J Cardiol 2003;92:50—4.
[21] Gayda M, Juneau M, Lévesque S, Guertin MC, Nigam A. Effects of long-term and ongoing cardiac rehabilitation in elderly patients with coronary heart disease. Am J Geriatr Cardiol 2006;15(6):345—51.
[22] Genest J, Frohlich J, Fodor G, McPherson R, the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. CMAJ 2003;169:921—4.
[23] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356—9.
[24] Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 2001;104:1694—740.
[25] Pate R, Blair S, Durstine J. Metabolic calculations. In: American College of Sports Medicine, editor. ACSM's guidelines for exercise testing and prescription. Philadelphia: Lea & Febiger; 1991. p. 296.
[26] Banz WJ, Maher MA, Thompson WG, Bassett DR, Moore W, Ashraf M, et al. Effects of resistance vs aerobic training on coronary artery disease risk factors. Exp Biol Med (Maywood) 2003;228:434—40.
[27] Hawley JA. Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. Diabetes Metab Res Rev 2004;20:383—93.
[28] Milani RV, Lavie CJ. Prevalence and effects of non-pharmacologic treatment of ''isolated'' low-HDL cholesterol in patients with coronary artery disease. J Cardiopulm Rehabil 1995;15(6):439—44.
[29] Milani RV, Lavie CJ. Marked reduction in outpatient, impatient and total medical costs with comprehensive work-site primary prevention programs. J Am Coll Cardiol 1997;29:49A—50A.
[30] Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. Diabetes Care 2005;28:391—7.
[31] Blair SN, Church TS. The fitness, obesity, and health equation: is physical activity the common denominator? JAMA 2004;292:1232—4.
[32] Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004;351:2694—703.
[33] Blair SN, Brodney S. Effects of physical inactivity and obesity on morbidity and mortality: current evidence and research issues. Med Sci Sports Exerc 1999;31:S646—62.
[34] Kodis J, Smith KM, Arthur HM, Daniels C, Suskin N, McKelvie RS. Changes in exercise capacity and lipids after clinic versus home-based aerobic training in coronary artery bypass graft surgery patients. J Cardiopulm Rehabil 2001;21(1):31—6.
[35] Brochu M, Poehlman ET, Savage P, Fragnoli-Munn K, Ross S, Ades PA. Modest effects of exercise training alone on coronary risk factors and body composition in coronary patients. J Cardiopulm Rehabil 2000;20(3):180—8.
[36] Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care 2003;26:2119—25.
[37] Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol 2005;98:1154—62.
[38] Billman GE. Aerobic exercise conditioning: a non-pharmacological anti arrhythmic intervention. J Appl Physiol 2002;92:446—54.
[39] El-Sayed MS, El-Sayed Ali Z, Ahmadizad S. Exercise and training effects on blood haemostasis in health and disease: an update. Sports Med 2004;34:181—200.
[40] Fornoni A, Raij L. Metabolic syndrome and endothelial dysfunction. Curr Hypertens Rep 2005;7:88—95.
[41] Malik S, Wong ND, Franklin S, Pio J, Fairchild C, Chen R. Cardiovascular disease in U.S. patients with metabolic syndrome, diabetes, and elevated C-reactive protein. Diabetes Care 2005;28:690—3.
[42] Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14719 initially healthy American women. Circulation 2003;107:391—7.
[43] Huggett RJ, Burns J, Mackintosh AF, Mary DA. Sympathetic neural activation in non-diabetic metabolic syndrome and its further augmentation by hypertension. Hypertension 2004;44:847—52.
[44] Nieuwdorp M, Stroes ES, Meijers JC, Buller H. Hypercoagulability in the metabolic syndrome. Curr Opin Pharmacol 2005;5:55—9.

Available online at www.sciencedirect.com
ScienceDirect