Is weight loss the optimal target for obesity-related cardiovascular disease risk reduction?

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R Ross, PM Janiszewski. Is weight loss the optimal target for obesity-related cardiovascular disease risk reduction? Can J Cardiol 2008;24(Suppl D):25D-31D.

In the present review, it is argued that while weight loss is associated with substantial reduction in obesity-related cardiovascular disease risk and remains a desired outcome of relevant treatment strategies, increasing physical activity is associated with marked reduction in waist circumference, visceral fat and cardiometabolic risk factors, concurrent with an increase in cardiorespiratory fitness despite minimal or no change in body weight. Failure to recognize the benefits of exercise independent of weight loss masks opportunities to counsel and educate patients whose sole criteria for gauging obesity reduction success is the bathroom scale.

Key Words: *Cardiorespiratory fitness; Exercise; Physical activity; Visceral fat; Waist circumference*

La perte de poids est-elle l'objectif optimal de réduction du risque de maladie cardiovasculaire reliée à l'obésité ?

Dans la présente analyse, on postule que même si la perte de poids s'associe à une importante réduction du risque de maladie cardiovasculaire reliée à l'obésité et qu'elle demeure une issue souhaitée des stratégies de traitement pertinentes, l'accroissement de l'activité physique s'associe à une diminution marquée du tour de taille, de la graisse viscérale et des facteurs de risque cardiométaboliques, conjointement avec une augmentation de la capacité aérobique, malgré une perte de poids minime ou même l'absence de perte de poids. Le fait de ne pas reconnaître les bienfaits de l'exercice qui n'entraîne pas de perte de poids enlève la possibilité de conseiller et d'éduquer les patients qui se fient seulement au pèse-personne pour évaluer la réussite de leur réduction d'obésité.

Obesity and its attendant diseases represent a threat to public health and a major challenge to the allied health care profession. Clinicians remain a cornerstone of health care delivery in North America and, given that one in two Canadians are overweight (1), are often faced with the burden of educating overweight and obese persons on the associated health risks of obesity and appropriate strategies for its reduction. Counselling begins with accurate identification of those at risk, which is traditionally determined using the body mass index (BMI). BMI remains a well-established marker of health risk, and race-specific cutpoints for determination of overweight and obese individuals have been established (2). Given the strong association between BMI and cardiovascular disease (CVD), it follows that strategies designed to reduce obesity and CVD would identify weight loss as a primary end point for treatment success. It is now apparent, however, that obesity is a heterogeneous condition and that excess accumulation of abdominal fat presents the greatest health risk (3). Waist circumference (WC) is a simple marker of abdominal obesity, and is a strong predictor of morbidity and mortality independent of BMI (4-6). Although the causal link between WC and CVD is not firmly established, mounting evidence suggests that intra-abdominal or visceral fat is the depot that best explains the association between abdominal obesity and CVD (7). These observations suggest that both WC and visceral fat should be primary targets for strategies designed to reduce obesity-related CVD.

Consistent with the argument that weight loss is the primary end point for obesity reduction, leading health authorities suggest that the utility of exercise as a strategy for obesity reduction depends in large measure on body weight reduction (8). Although exercise-induced weight loss is associated with attenuated CVD risk, several lines of evidence suggest that weight loss is not absolutely necessary to observe substantial benefit. First, it is well established that increasing physical activity and associated improvements in cardiorespiratory fitness (CRF) are associated with profound reductions in coronary artery disease and CVD mortality, independent of weight or BMI (9,10). Second, acute and chronic exercise is associated with substantial reductions in several cardiometabolic risk factors despite minimal or no change in body weight (11-13). Third, while WC and visceral fat are reduced consequent to weight loss (14-16), it is also true that both variables are substantively reduced in response to exercise with minimal or no weight loss (14,15). These observations bring one to question whether weight loss is the optimal outcome for determining the efficacy of treatment strategies designed to reduce obesity and related comorbidities.

WC, VISCERAL OBESITY AND CARDIOMETABOLIC RISK

Since the seminal work of Jean Vague (17) more than 50 years ago, numerous investigators have confirmed that abdominal obesity, as measured by WC, conveys a substantial health risk, and that WC explains morbidity and mortality risk beyond that explained by BMI (18). The recently published findings of the International Day for Evaluation of Abdominal Obesity (IDEA) (19) provide compelling evidence that WC explains both diabetes and CVD risk beyond that explained by BMI alone. The IDEA study involved 6407 randomly chosen primary care physicians in 63 countries, who evaluated 168,159 patients aged 18 to 80 years. The authors observed a graded increase in the frequency of CVD and diabetes mellitus with both BMI and WC; there was a stronger relationship for WC than for BMI across regions for both sexes. Extending these observations is the recent report from Janiszewski et al (5) demonstrating that WC predicts diabetes risk beyond BMI and other commonly measured

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Received for publication March 24, 2008. Accepted March 26, 2008

TABLE 1
Changes in body composition, fitness and metabolic parameters in exercise groups with nonsignificant change in weight from randomized and nonrandomized trials (1997–2007)

Reference	Experimental design	Subjects, description	Exercise time, type	Study length (weeks)	Weight Δ (kg)	Waist circumference Δ (cm)	ASAT Δ (%)	VAT Δ (%)	VO_2 max Δ (mL/kg/min)	Metabolic improvement	
Mourier et al, 1997 (31)	RCT	11 T2D (45 y)	112 min/wk, AE	8	–1.5	–1.0	–17.9*	–48.5*	+9.3*	√	IS
Owens et al, 1999 (73)	RCT	35 M/F (10 y)	160 min/wk, AE	16	+1.1		–1.0	+0.5*		√	TG†
Wilmore et al, 1999 (74)	Non-RCT	250 M (17-65 y)	150 min/wk, AE	20	–2.4	–1.0	–4.8	–7.1*		√	HDL, TG†
Wilmore et al, 1999 (74)	Non-RCT	252 F (17-65 y)	150 min/wk, AE	20	–0.1	–0.9	–2.9	–4.6*		√	HDL
Boudou et al, 2000 (30)	RCT	8 T2D M (45 y)	115 min/wk, AE	8	–1.9		–18.1*	–44.7*	+9.4*	√	TG, IS
Eliakim et al, 2000‡ (75)	RCT	22 M (16 y)	540 min/wk, AE	5	+0.8		–7.6*	–0.2		√	HDL
Poehlman et al, 2000‡ (76)	RCT	14 F (29 y)	99 min/wk, AE	24	0.0		–0.5	+2.5	+10.2*	√	IS
Poehlman et al, 2000‡ (76)	RCT	17 F (28 y)	81 set/wk, RE	24	+2.0		0	0	+1.1		
Ross et al, 2000 (14)	RCT	14 M (45 y)	443 min/wk, AE	12	–0.5	–1.8		–11.8*	+7.4*		
Thomas et al, 2000 (32)	Non-RCT	17 F (25-45 y)	120 min/wk, AE	24	–0.6		–6.6	–23.5*	+3.9*	√	HDL
Gan et al, 2003 (53)	Non-RCT	18 M (37 y)	164 min/wk, AE	9.7	–1.3	–2.0*	–4.6*	–5.4	+5.2*	√	Chol, TG, IS
Short et al, 2003‡ (77)	RCT	65 M/F (22-87 y)	160 min/wk, AE	16	–0.8	–4.1	–6.5	–6.0	+2.7	√	TG, IS
Green et al, 2004 (78)	Non-RCT	30 F (56 y)	150 min/wk, AE	20	+0.1	–0.9	–1.2	+3.1	+4.3*		
Green et al, 2004 (78)	Non-RCT	18 F (52 y)	150 min/wk, AE	20	+0.5	–0.1	+1.6	–6.7	+4.8*	√	LDL
Ross et al, 2004 (15)	RCT	12 F (41 y)	441 min/wk, AE	14	–0.5	–3.1*	–4.9*	–18.2*	+5.9*		
Giannopoulou et al, 2005 (29)	Non-RCT	11 T2D F (56 y)	150 min/wk, AE	14	–1.7	–3.0*	–5.3*	–10.2*	+3.2*	√	IS
Ibanez et al, 2005 (79)	Non-RCT	9 T2D M (67 y)	105 min/wk, RE	16	–0.5		–13.3*	–9.6*		√	F Glu, IS
Lee et al, 2005 (12)	Non-RCT	8 M (48 y)	300 min/wk, AE	13	–0.4	–2.7*		–10.0*	+10.5*		
Lee et al, 2005 (12)	Non-RCT	8 M (47 y)	300 min/wk, AE	13	–0.4	–2.6*		–15.0*	+6.6*		
Lee et al, 2005 (12)	Non-RCT	7 T2D M (51 y)	300 min/wk, AE	13	–0.8	–2.7*		–23.7*	+11.3*		
O'Donovan et al, 2005 (80)	RCT	14 M (41 y)		24	–1.1	–1.0			+4.9*		
O'Donovan et al, 2005 (80)	RCT	13 M (41 y)		24	–0.5	–2.0*			+7.1*	√	Chol, LDL
Dolan et al, 2006 (81)	Non-RCT	20 HIV F (43 y)	90 min/wk, AE	16	+0.4§	–1.0	+0.8	–1.4	+1.5*		
Church et al, 2007 (82)	RCT	155 F (58 y)	72 min/wk, AE	24	–0.4	–1.9*			+0.7*¶		
Church et al, 2007 (82)	RCT	104 F (57 y)	136 min/wk, AE	24	–2.2	–2.9*			+1.5*¶		
Church et al, 2007 (82)	RCT	103 F (57 y)	191 min/wk, AE	24	–0.6	–1.4*			+0.8*¶		
Ramalho et al, 2006 (83)	Non-RCT	7 T1D M/F (13-30 y)	120 min/wk, AE	12	+0.05§	–1.9*			+2.0	√	HbA1c
Ramalho et al, 2006 (83)	Non-RCT	6 T1D M/F (13-30 y)	120 min/wk, RE	12	+0.0§	+0.9			+5.1		
Shojaee-Moradie et al, 2007 (33)	RCT	10 M (50 y)	60 min/wk, AE	6	+0.2		–3.0	–18.0	+7.0*		

*Age is presented as mean or range. *Significant improvement (P<0.05); †Metabolic variables from the Wilmore et al (74) are reported in reference 52; ‡Only within-group difference reported; §Change in body mass index (kg/m²); ¶Peak maximal oxygen consumption (VO_2 max). Δ Change in; AE Aerobic exercise; ASAT Abdominal subcutaneous adipose tissue; Chol Total cholesterol; F Glu Fasting glucose; F Female; HbA1c Glycosylated hemoglobin; HDL High-density lipoprotein; IS Insulin sensitivity; LDL Low-density lipoprotein; M Male; RCT Randomized controlled trial; RE Resistance exercise; T1D Type 1 diabetes; T2D Type 2 diabetes; TG Triglycerides; VAT Visceral adipose tissue; wk Week; y Year*

cardiometabolic risk factors, such as smoking, dyslipidemia and blood pressure. Together, these observations underscore the importance of WC as a routine measure in clinical practice to help to identify the high-risk, abdominally obese patient. Accordingly, these observations support the notion that WC should be a primary treatment target for strategies designed to reduce obesity-related CVD risk.

Overwhelming evidence suggests that, of the two abdominal fat depots (subcutaneous and visceral), visceral fat is the depot that best explains the association between abdominal obesity and CVD risk (please see Després et al in the present issue, pages 7D-12D). Indeed, independent of subcutaneous fat, visceral fat is a strong predictor of dyslipidemia (20,21), glucose tolerance (22,23), insulin resistance (24) and systemic inflammation (25), as well as incidence of hypertension (26), CVD (7), type 2 diabetes (27) and all-cause mortality (28). These observations underscore the notion that both WC and visceral fat should be primary targets for strategies designed to reduce obesity and related CVD risk. While it is clear that diet- or exercise-induced weight loss is associated with substantial reductions in both WC and visceral fat (14-16), increasing evidence supports the view that both WC and visceral fat are substantially reduced in response to exercise with minimal or no weight loss (14,15,29).

Exercise-induced reduction in WC with minimal or no weight loss

Table 1 reveals that short-term, regular, physical activity is associated with a marked reduction in WC, independent of sex or age, despite no statistically significant change in body mass. In these

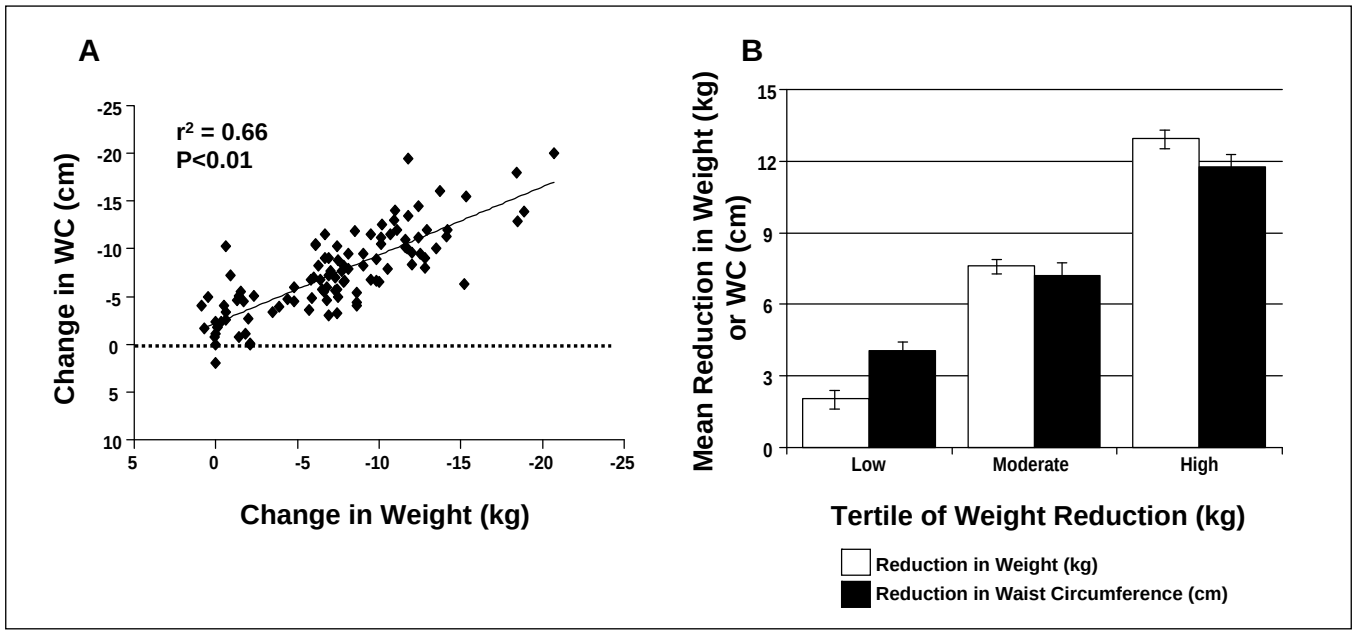

Figure 1) *Relationship between changes in body weight and waist circumference (WC).* **A** *Data are taken from prior publications (14,15,71,72) and illustrate the relationship between change in weight (kg) and change in WC (cm) in a sample of 105 men and women combined.* **B** *Based on the same subjects in Panel A, the data were separated into tertiles of weight reduction (<6.1 kg, 6.2 kg to 9.8 kg, and 9.9 kg to 20.7 kg). Each tertile of weight and WC reduction was significantly different from the other two tertiles (P<0.05)*

studies, the negative energy balance was induced by the increase in physical activity, because all participants were instructed not to reduce caloric intake. It is also noteworthy that in the majority of studies, the reduction in WC without significant weight loss was associated with significant reductions in cardiometabolic risk factors. These are encouraging findings and suggest that reliance on BMI alone to determine the utility of strategies to reduce obesity and related cardiometabolic risk factors are misguided.

The lack of association between changes in body weight and WC in response to increases in physical activity are underscored in Figure 1. The data presented clearly show that change in body weight is a poor indicator of corresponding changes in WC on an individual basis, and perhaps more importantly, that the lack of association is greatest for the lowest tertile of change in weight and WC. This is not a trivial observation, because resistance to apparent weight loss often occurs during the early stage of initiating a program of obesity reduction. In other words, during the early phase of attempts to change behaviour (increase physical activity combined with a healthful diet) to reduce obesity, negligible changes in body weight may be discouraging to the participant to the point that they discontinue attempts to change behaviour. On the other hand, recognition that changes in WC are occurring in the absence of weight change would be extremely positive and empowering for the participant, and this presents the clinician with an excellent opportunity to acknowledge benefit.

Exercise-induced reduction in visceral fat with minimal or no weight loss

Consistent with the observation that exercise is associated with WC reduction despite minimal weight loss, it is also apparent that regular physical activity is associated with a marked reduction in visceral fat despite little or no change in weight (Table 1). Several studies have examined the effect of physical activity on visceral fat independent of weight loss by having study participants consume compensatory kilocalories equivalent to the amount expended during physical activity (12,14,15). The results suggest that in Caucasian lean and obese men and obese women, significant reductions in visceral fat (–10% to –19%) occur consequent to three months of regular physical activity (40 min/day to 60 min/day) despite no significant change in body weight. These observations are consistent with findings from studies in type 2 diabetic subjects suggesting that two to three months of moderate intensity aerobic exercise is associated with substantive reductions in visceral fat (–27% to –45%) despite little or no change in weight (12,30,31). Similar results have been documented in healthy, nonobese, premenopausal women (32) and middle-aged men (33).

These observations reinforce the long-standing notion that changes in body composition, rather than body weight, are more meaningful outcomes in response to physical activity (34). In fact, significant reductions in fat mass, especially visceral fat, often occur concurrent with equal increases in lean body mass in response to physical activity (15). These equal but opposite changes in fat mass and lean mass are not detected by alterations in body weight (15) but may be interpreted from changes in WC. Indeed, as illustrated by the data presented in Figure 2, while increases in lean mass offset corresponding changes in total fat or body weight, substantial reductions in WC are observed. Combined with the increase in CRF and insulin sensitivity (please see below), the reductions in WC offer the clinician a valuable opportunity to counsel the patient with respect to the benefits of exercise-induced reductions in abdominal obesity despite no change in scale weight.

It is important to emphasize, however, that the reductions in WC and visceral fat observed in exercisers who maintain body weight are substantially less than those observed in exercisers who lose weight (14,15). Thus, from a clinical perspective, those at obesity-related CVD risk should be advised that exercise-induced weight loss is likely associated with the greatest benefit. On the other hand, given the challenges associated with attaining substantial weight loss for many obese individuals, in particular, older adults – because of ingrained, lifelong habits – it is equally important to recognize that abdominal obesity and related health risk can be markedly reduced with minimal weight loss.

Exercise-induced reduction in cardiometabolic risk factors without weight loss

It is important to recall that significant improvements in a number of cardiometabolic risk factors are known to occur after only a single session of moderate-intensity aerobic exercise (11). For instance, insulin

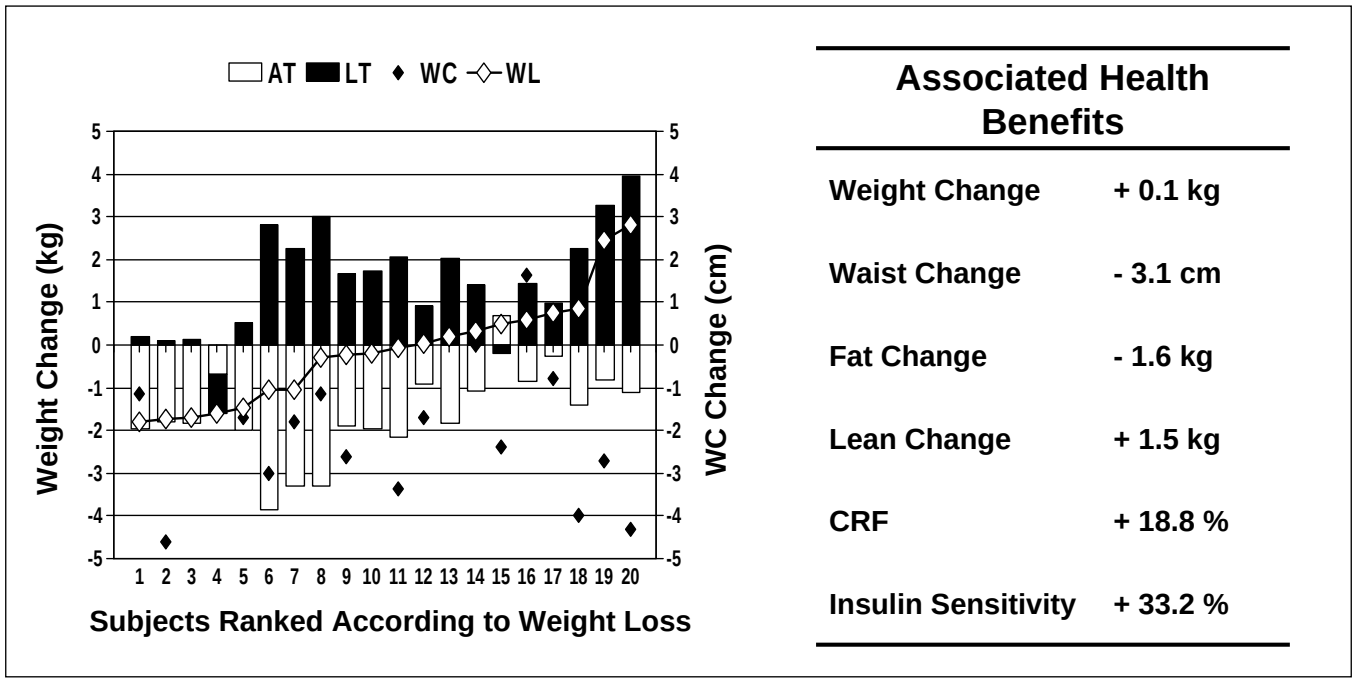

Figure 2) *Disassociation between changes in body weight, body composition and health risk. Individual body composition change data are shown for a sample of 20 obese men who participated in studies designed to reduce obesity by increasing exercise without changing caloric intake (14). AT Adipose tissue; CRF Cardiorespiratory fitness; LT Lean tissue; WC Waist circumference; WL Weight loss*

resistance is known to improve by approximately 20% after 1 h of aerobic exercise in healthy (35,36), insulin-resistant (37) and diabetic subjects (36,38) – improvements that are equivalent in magnitude to those achieved through chronic pharmacological intervention (39,40). The augmented insulin sensitivity is apparent immediately after exercise (36) and persists for 20 h to 48 h thereafter (35,37,38). It is also well established that a single bout of aerobic exercise results in 10% to 25% reductions in triglycerides (TGs) and 7% to 15% increases in high-density lipoprotein (HDL) cholesterol levels (11,41-43). These lipid changes become apparent between 24 h and 48 h after exercise in both untrained (41,42) and trained subjects (43) in response to caloric expenditures of 350 kcal to 500 kcal and 1000 kcal, respectively. Additionally, the blood pressure-lowering effect of acute aerobic exercise has been long established (44). This effect, termed postexercise hypotension, is especially pronounced among hypertensive individuals with maximal reductions in systolic and diastolic blood pressure of –11 mmHg and –6 mmHg, respectively (45,46). The onset of postexercise hypotension is immediate and can persist for up to 22 h after an acute bout of aerobic physical activity (47). Indeed, as little as 15 min of low-intensity (40% maximal oxygen consumption) aerobic exercise can induce marked postexercise hypotension that persists throughout the day (48). In unison, these encouraging results suggest that independent of any training effects, repeated bouts of aerobic exercise may be a viable treatment strategy for the treatment of insulin resistance, as well as dyslipidemia and hypertension.

Chronic exercise training, or the summation of acute bouts of exercise, can lead to further improvements in cardiometabolic risk factors, even in the absence of clinically significant weight loss. Indeed, numerous studies have shown that improvements in insulin sensitivity through chronic exercise can occur in the absence of significant weight reduction (13,14,29,30). For example, three months of daily aerobic training in obese men, who consumed compensatory kilocalories equivalent to the amount expended during exercise, resulted in a 30% improvement in insulin sensitivity despite no change in weight (14). Furthermore, while improvements in HDL cholesterol and TGs are generally greater in those who lose weight, these improvements can be seen even when weight remains virtually unchanged (49-51). For example, a number of physical activity interventions that do not significantly alter body weight have documented 5% to 35% reductions in TG levels (52,53) and/or 3% to 5% increases in HDL values (32,52). Lastly, the blood pressure reductions induced through chronic exercise do not appear to be related to alterations in body weight or abdominal obesity (54). In fact, a large meta-analysis (54), which reported an overall beneficial effect of chronic exercise on blood pressure, found that the average weight loss across the reviewed trials was largely inconsequential (–1.2 kg). Nevertheless, some studies report that individuals who become active and also lose a significant amount of weight (–7.9 kg), in comparison with those who lose minimal weight (–1.8 kg), show greater reductions in systolic and diastolic blood pressure (–7 mmHg and –5 mmHg versus –4 mmHg and –4 mmHg, respectively) (55).

The improvement in insulin resistance through chronic physical activity independent of weight change likely involves changes in body composition – in particular, reductions in visceral fat (14), as well as augmented expression of GLUT-4 protein in skeletal muscle (56,57), and enhanced metabolic efficiency of muscle (58,59). The lipid improvements independent of significant weight reduction may also be mediated by improvements in body composition, such as reductions in visceral fat (60), but apparently are not due to improvements in CRF (51). Lastly, it appears that physical activity and weight loss may have independent effects on blood pressure, because reductions in blood pressure are significantly related to training-induced improvements in CRF (54), as well as the magnitude of weight loss (55).

Consistent with the effects of chronic exercise described above, prospective studies with long-term follow-up have demonstrated an inverse association between physical activity and fitness on the one hand, and morbidity and mortality on the other, independent of obesity status. For example, Helmrich et al (61) have previously shown, in a 14-year prospective study of approximetely 6000 men, that a high level of physical activity is associated with the lowest risk of diabetes irrespective of the level of obesity. Specifically, it was reported that for every 500 kcal/week increase in physical activity, the risk of diabetes

decreased by 6% (61). Results of other prospective studies in men and women further suggest that high levels of physical activity protect against the incidence of coronary artery disease, independent of BMI, as well as other factors such as age, smoking, diabetes and hypertension (62). Furthermore, prospective analyses from the Aerobics Center Longitudinal Study have consistently reported that CRF is a significant predictor of mortality from all causes (9,10,63,64), CVD (9,10) and type 2 diabetes (65) in men and women, independent of BMI or WC. These relationships have been confirmed in older adults (66) and Canadian women (67).

Beyond weight loss as the only indicator of obesity treatment success

From the observations described in the present overview, it is apparent that the time has come to look beyond weight loss as the only criteria for successful obesity treatment. Indeed, decreases in WC combined with increases in skeletal muscle mass, improvements in cardiometabolic risk factors and CRF consequent to exercise, with little or no weight loss, underscore the recommendation that clinicians include WC as a routine measure in clinical practice and encourage their patients to monitor WC in addition to scale weight to gauge treatment success (Figure 3). However, as reviewed here, it is also clear that increasing physical activity is associated with marked attenuation in CVD risk factors, at least partly mediated by increased CRF independent of BMI or WC. Furthermore, it is reported that CRF is associated with a substantial reduction in cardiometabolic risk factors independent of visceral fat (68). These findings support the recommendation that CRF be assessed by clinicians as an objective measure of changes in physical activity level and associated reductions in CVD risk. Although the measurement of CRF in clinical practice may be difficult for pragmatic reasons, referral of patients to properly trained Certified Exercise Physiologists (69) working at commercial and/or public health facilities offers a reasonable alternative to practitioners.

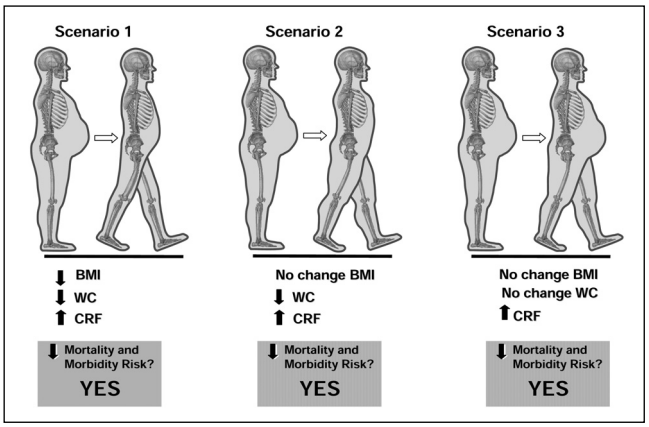

Figure 3) *Favourable effects of physical activity on obesity-related health risk: three possible scenarios. The scenarios presented represent three possible outcomes when increasing physical activity combined with a balanced (healthful) diet for the purpose of reducing obesity and related comorbid conditions. BMI Body mass index; CRF Cardiorespiratory fitness; WC Waist circumference*

SUMMARY AND RECOMMENDATIONS

In the present brief report, we propose the notion that, while weight loss is associated with marked reduction in obesity-related CVD risk and remains a desired outcome of strategies designed to reduce obesity-related CVD, increasing physical activity is often associated with a decrease in WC and cardiometabolic risk, as well as an increase in CRF, despite little or no change in body weight or BMI. These observations support the recommendation that clinicians look beyond weight loss as the only indicator of treatment success when targeting obesity-related CVD risk. Indeed, as illustrated in Figure 3, we propose three distinct scenarios for which an increase in physical activity is associated with substantial reduction in obesity-related CVD risk with or without weight loss. That all three scenarios described are associated with attenuated CVD risk is encouraging, and offers both the clinician and the patient treatment options. Indeed, recognition of the distinct benefits of exercise, combined with the consumption of a balanced diet, on CVD risk factors offers the clinician several unique opportunities to counsel and educate patients on the benefits of adopting healthy behaviours for the purpose of reducing obesity and related health risks despite possible resistance to weight loss. In this way, it is recommended that WC should be a routine measure in clinical practice for identifying the high-risk, abdominally obese patient, and that patients should be educated on the proper methods for self-measurement of WC (70). Finally, overwhelming evidence supports the recommendation that CRF be a routine measure in clinical practice. Although this may be impractical for many, if not most, clinicians, referral to appropriately trained personnel working at commercial or public health centres is a realistic option for both the clinician and the participant. Obesity is a multidimensional problem that requires a multidimensional response. Close collaboration among practitioners at all levels of health care is a small step toward the resolve of a major public health problem

DISCLOSURE: Dr Robert Ross is a speaker for GlaxoSmithKline and sanofi-aventis. He has received research funding from MARS Inc, Roche Pharmaceutical and sanofi-aventis; is on the advisory board for sanofi-aventis; has received consulting fees from GlaxoSmithKline, Roche Pharmaceutical, sanofi-aventis and Theratechnologies Inc; and receives royalties from Human Kinetics. Peter M Janiszewski is supported by a Doctoral Research Award from the Institutes of Health Research.

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