

**Instituting Moderate Physical Activity for Those at
High Cardiometabolic Risk: Just Get Your Patients to Move**

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ABSTRACT

Moderate levels of weekly physical activity (1000-1500 kcal/wk) is most often insufficient to significantly reduce body weight and LDL-cholesterol. Still, those who transition from very little or no daily physical activity to moderate levels, e.g., 120-150 minutes per week, do have clinically meaningful reductions in cardiometabolic risk and this fact is supported by scores of controlled trials. All physical activity is good and can help reduce cardiometabolic risk via biologic mechanisms that are not entirely dependent on body weight or BMI reduction. There is increasing research support for those who have prediabetes and/or the metabolic syndrome who consistently increase their physical activity levels but with little or no weight loss. These individuals should be given credit for any and all physical activity principally through objective measures of changes in physical activity. Health care providers have distinct options to better score physical activity outcomes and become more practical in instructing patients on strategies to increase weekly energy expenditure.

KEY WORDS

Moderate exercise, cardiometabolic risk, exercise pleiotropy, AMPK, metabolic syndrome, prediabetes, weight loss

Cardiometabolic risk (CMR) is defined by traditional cardiovascular and metabolic disease risk factors. One of the best clinical characterizations CMR is the metabolic syndrome for which the prevalence in adults in the U.S. is 34% according to a 2009 report (1). Some ethnicities require more immediate attention, e.g., American Indians, where the age-adjusted prevalence of the metabolic syndrome was 49.8% among 4,457 participants aged 18 to 88 years (2). One of the key benefits of managing the metabolic syndrome is type 2 diabetes prevention for which the metabolic syndrome is a significant predictor even more so than cardiovascular disease (3,4). Therapeutic lifestyle intervention particularly physical activity programming is one of the key components of cardiometabolic risk management.

Patient noncompliance and ambivalence with increasing their physical activity levels is, sadly, among the most telling issues in preventive endocrinology and cardiology. This is an issue both for the provider and the patient. For example - many clinicians will submit that their patients either will not or cannot increase their physical activity levels to levels required for weight reduction and/or decreased blood lipid levels. True, the volume of weekly exercise generally require to reduce body weight in obese individuals is quite substantial ($\geq 2,000$ kcal/week) (5). A Similar volume of weekly exercise is also required for clinically meaningful reductions in blood lipid and lipoprotein levels, e.g., TG <150 and LDL-C <100 mg/dl (5). Another conundrum for lifestyle conscious health care providers is the influence of conflicting if not misleading prescription drug promotional advertising campaigns. Many current patient-targeted statin print and TV ads more or less read or imply “When diet and exercise fail - meet another candidate for lipid lowering therapy (a statin)”. Indeed, exercise programs often fail to achieve more aggressive laboratory lipoprotein goals – but most often do not fail to reduce cardiometabolic risk, i.e. risk of diabetes and cardiovascular disease. The advent of six classes of obesity drugs and seven classes of drug therapies to manage dyslipidemia has for many providers created a convenient defense for spending less time on more thorough teaching of therapeutic lifestyle changes particularly getting patients to move more. This is not to say that these drug classes are not evidence-based and have not produced clinically important outcomes – especially with regard to statin therapy. But there are less-costly options for many patients.

If we look at physical activity program outcomes with regard to CMR reduction, particularly reduction in diabetes risk, there are a plethora of very beneficial physiological changes which occur with or without significant changes in LDL-cholesterol or body weight. The point is that small incremental increases in physical activity are clinically quite beneficial and this *frame-of-reference* on the provider’s part has been lost merely because the patient’s modest lifestyle changes are not perceived to be sufficient to reach laboratory-driven targets. This in no way is intended to disregard more aggressive and commitment to higher volume exercise programs for those who are motivationally ready to change however there are options for those who are more ambivalent and otherwise not ready for committing to >200 minutes of exercise per week.

Question: Is it not our overall clinical (and public health) mission to reduce the risk of cardiometabolic disease? And if so, are there not metabolic mechanisms by which lifestyle

changes, particularly physical activity intervention, interact to do just this – many of which are not uniquely married to blood lipid or even body weight changes?

We long since have been aware of the most impressive lifestyle study in the last two decades – the Diabetes Prevention Program (DPP) (6). Yet the DPP's 58% reduction in new onset diabetes occurred with a mere 5% weight loss despite the 7% targeted goal at the beginning of the study. These outcomes were achieved with very modest dietary intervention and approximately 1000 kcal of exercise a week. The figure of 150 minutes per week to reduce diabetes incidence is often misquoted when stating the DPP outcomes as 150 minutes per week was the goal which was not met by the average DPP study participant. The more recent DPP Outcomes Study reinforced the success of the DPP at 10 years of follow up sustaining a 34% decreased incidence of diabetes compared with controls (7). The Da Qing Chinese Diabetes Prevention Study compared the effects of exercise alone, diet alone, and exercise plus diet on the risk of development of type 2 diabetes and found that exercise with or without changes in dietary habits was more effective than diet alone in preventing diabetes. A recent 20-year follow-up analysis of the Da Qing Study using therapeutic lifestyle changes (TLC) to manage diabetes risk indicated that the TLC group had a 51% lower incidence of diabetes during the active intervention period and a 43% lower incidence controlled for age (8). These results were attained with very modest changes in blood lipids and body weight. More importantly, exercise with or without changes in dietary habits was more effective than diet alone in preventing diabetes.

More recently, Saito found a 44% reduction in diabetes incidence versus controls in 641 Japanese with IFG after a 36-month dietary and moderate physical activity intervention program (9). Here the intervention group reduced body weight by only 3.4% (163 to 158 lbs). Systematic walking program interventions have supported this finding. In a similar study, Yates and co-workers increased walking steps by 5000-9000 steps per day versus standard physical activity counseling in 87 adults (67% male) with impaired glucose tolerance and demonstrated significant reductions in fasting glucose and 2-hour post-challenge glucose in favor of the increased walking group (10). These results were in the absence of changes in body weight or BMI. Collectively, the results of these trials underscore the fact that exercise employs metabolic mechanisms to reduce CMR other than those wedded only to body weight changes.

Key point: If a patient is only able to add 10 or 11 miles of walking a week (~1.5 miles/day) to their weekly activity they have essentially expended the same weekly energy expenditure on average as those who completed the DPP and other diabetes prevention studies with very favorable results.

Modest Time Investments in Daily Physical Activity are Beneficial

Jacob Sattelmair and others at the Harvard School of Public Health recently performed a meta-analysis of 33 epidemiological studies investigating physical activity and primary prevention of coronary heart disease (CHD) and found that even walking briskly for 15 minutes a day was associated with a significant reduction in CHD although more was better (11). Indeed, in a

prospective cohort study of 416,175 adults in Taiwan Wen and coworkers found that compared with individuals in the inactive group, those in the low-volume activity group, who exercised for an average of 92 min per week or 15 min a day, had a 14% reduced risk of all-cause mortality, and had a 3 year longer life expectancy (12). Kirk at Southern Illinois University showed that 6 months of 3 days a week for 11 minutes per session of resistance training (one set, 9 exercises at 3-6 repetition maximum) in 39 overweight adults significantly increased fat oxidation and 24-hour energy expenditure by 120 kcal (13). Even breaking up long periods of sedentary time, e.g., prolonged sitting at a work station, into short walking breaks has been shown to be associated with reduced waist circumference, BMI, triglycerides, and 2-hour plasma glucose (14). Other studies evaluating multiple daily short exercise bouts, e.g. walking, of 5 or 6 minutes have been shown to improve fitness and reduce blood pressure and body fat (15,16). These findings exhibiting benefit from short exercise bouts in no way should be translated to mean that these are optimal exercise durations or energy expenditure but compared to near complete inactivity – some activity is worth something.

Moderate Level Exercise, Alternative Lipoprotein Measures, and Arterial Changes

Exercise is not generally considered primary therapy for managing dyslipidemia particularly in the current era of lipid-altering drug therapy. This is unfortunate, because physical activity of appropriate quality and quantity can clearly reduce cardiometabolic risk through alternative lipoprotein assays. Exercise can also induce significant favorable changes in the lipoprotein profile only marginally related to changes in adiposity. Kraus was among the first to show in a well-controlled trial comparing various weekly volumes and intensities of exercise on lipids and lipoproteins in 84 sedentary overweight men and women that regular exercise with minimal weight change has broad beneficial effects on the lipoprotein profile – even without changes in total cholesterol and conventional Friedewald predicted LDL-C (17). Kraus found that moderate volumes and intensities (walking ~12 miles per week at 40-55% of aerobic capacity) can significantly reduce nuclear magnetic resonance spectrometry (NMR)-measured LDL-particle number when total cholesterol and Friedewald-predicted LDL-C remained essentially unchanged. Such patients on a return clinic visit would be considered unresponsive to exercise therapy when a conventional lipid profile was used to score the patient's progress. NMR measured LDL-particle number has gained much clinical trial support in recent years as a better predictor of cardiovascular events than LDL-cholesterol (18).

Improved arterial endothelial function is thought to be one of the primary mechanisms responsible for reduced CVD morbidity and mortality as transient impairment in endothelial function may well play a key role in the atherosclerotic disease process (19). Numerous trials have demonstrated improvements in arterial endothelial function with moderate levels of exercise training including cycling and walking (20,21,22). Postprandial lipemia (i.e., elevated post meal triglycerides) adversely affects arterial function particularly after a high fat meal (22). When postprandial triglyceride-rich lipoproteins are significantly elevated, especially after a fat-rich meal, arterial walls are exposed to a variety of atherogenic lipoproteins (e.g., intermediate density lipoproteins, remnant lipoproteins) and there is a transient reduction in arterial endothelial function. Single 30-minute moderate-paced exercise sessions, for example a 30

minute moderate pace walk, can significantly reduce postprandial triglyceride levels (23). Reductions in high fat meal-induced postprandial hypertriglyceridemia has also been observed with moderate levels of resistance training, e.g., 10 sets of 8 repetitions of 10 exercises at 50% of 1 repetition maximum (24,25).

The Pleiotropic Effects of Moderate Physical Activity: A Brief Look at The Evidence

The concept of exercise pleiotropy is one that principally looks at the secondary physiological responses to exercise and exercise training beyond conventional outcomes such as weight loss and blood lipid changes. Many of these “secondary” effects may serve as primary mechanisms in CMR reduction. **Table 1** depicts some of the core mechanisms by which positive changes in physical activity behavior can improve cardiometabolic health including but not limited to anthropometric and blood lipid changes.

Carey and others recently reviewed a host of trials justifying exercise with or without weight loss via a variety of cardiometabolic mechanisms (26). While the best-known effects of regular exercise energy expenditure are body weight control it is not necessary for overweight individuals to decrease body or adipose tissue mass to improve metabolic homeostasis. Accordingly, regular exercise results in adaptations including: 1) increased skeletal muscle oxidative capacity; (2) alterations in intracellular proteins and lipids involved in cellular signaling; 3) cardiovascular adaptations that result in improved muscle and whole body insulin sensitivity, fuel partitioning and cardiovascular function, and 4) decreased resting blood pressure. All of these mechanisms play a role in cardiometabolic disease prevention.

Exercise-induced insulin sensitization is one of the principal metabolic benefits of acute bouts of exercise as well as long-term training. Duncan was among the first to show that 30 minutes of walking, 5-6 times per week for 6 months, significantly improved insulin sensitivity in the absence of weight loss (27). Nassissab also demonstrated similar increases in insulin sensitivity without weight loss after 12 months of moderate-level aerobic exercise training in overweight and obese young girls (28). These changes have also been observed in patients with type 2 diabetes. Hansen reported that when matched for energy cost, prolonged continuous low- to moderate-intensity endurance type exercise training is equally effective as continuous moderate- to high-intensity training in lowering blood glycated hemoglobin and increasing whole body and skeletal muscle oxidative capacity in 50 obese type 2 male diabetic patients (29). It is also worth understanding that the volume of weekly exercise to improve glucose tolerance (especially in type 2 diabetes) and weight loss is much less than that required for weight loss (30,31).

Similar Metabolic Mechanisms as The Biquanides and Thiazolidinediones (without side-effects)

Both moderate and intensive exercise bouts utilize similar metabolic mechanisms as several diabetes drug classes, the Biquanides (Metformin) and Thiazolidinediones (e.g., pioglitazone, rosiglitazone) but without many of the adverse side-effects, e.g., fluid retention of the glitazones. The value of brief acute bouts of physical activity, e.g. 2-5 minute intentional bouts of physical

activity at moderate intensities activate AMP kinase, glucose transport mechanisms, and insulin signaling. Each intentional walking step is an AMP kinase activator (AMP-activated protein kinase is an enzyme that works as a fuel gauge which becomes activated during physical activity) which works similarly to glucophage and the PPAR γ (peroxisome proliferator-activated receptor-gamma) activating diabetes drugs (32). See **Figure 1** which illustrates muscle contraction mediated AMPK activation. In 2006 we conducted a trial of exercise training versus pioglitazone administration in 39 obese insulin resistant nondiabetic men and women (33). We employed 19 weeks of 1200 kcal/week of moderate intensity aerobic exercise and a modest decrease in energy intake in 37 overweight insulin resistant patients. The exercise training group showed significantly greater efficacy in improving insulin sensitivity, LDL-cholesterol particle number, and triglycerides compared to 30 mg/day of pioglitazone. The pioglitazone group increased body weight by 2.7kg whereas the exercise group lost 11.8 kg. Pioglitazone increased DEXA-assessed fat stores predominantly in the legs whereas the exercise group lost fat in the visceral and femoral regions. Pioglitazone (trade name: Actos) is widely used in diabetes medicine and similar to exercise stimulates PPAR- γ and muscle AMPK signaling and increases the expression of genes involved in adiponectin signaling, mitochondrial function and fat oxidation. The lesson here is that for adult overweight patients with prediabetes (impaired fasting glucose and/or impaired glucose tolerance) exercise is the preferred option over thiazolidinedione therapy particularly with regard to improvements in fat weight loss, insulin sensitization, LDL-C particle number, and of course aerobic capacity.

Butcher at Cardiff University in the UK showed how walking 10,000 steps three days a week at self-selected speeds on a treadmill in 34 sedentary adults stimulated PPAR γ and reduced LDL-C 16 mg/dL and triglycerides 21 mg/dL (34). They concluded that low-intensity exercise (30-40% of V02 max) regulates lipid and lipoprotein levels but has no effect on anthropometric outcomes. Both aerobic and resistance exercise training improve insulin sensitivity and glucose transport mechanisms which help to improve cardiometabolic health and are involved in deterring diabetes in prediabetic subjects. Well engineered step-filtered pedometers can reliably measure these insulin sensitizing muscular contractions by registering walking step counts.

Perhaps the most interesting of the metabolic mechanisms physical activity has to offer is the ability to upregulate PPAR δ (delta) nuclear receptors in skeletal muscle which can occur with low or moderate intensity physical activity (35,36). PPAR δ receptors are intimately involved in fatty acid transport, inflammation, and increased HDL-C – essentially improving multiple aspects of the metabolic syndrome. Future development of diabetes drugs will target PPAR δ essentially mimicking the many benefits of exercise. There is also emerging evidence from investigators here at Duke University that exercise training can reverse skeletal muscle mitochondrial abnormalities from lipid overload induced by high fat load diets and inactivity (37).

Is It The Weight Loss or Physical Activity Itself ?

In one of the most elegant clinical exercise science reviews published in the last decade Richard Telford, physiologist at the University of Melbourne, revealed that the scientific literature

indicates consistent findings of strong associations of physical activity (PA) with mortality and with morbidity associated with type 2 diabetes, after controlling for obesity and other potentially confounding factors (38). Collectively, these findings indicate that low PA is not just a predictor, but a direct cause of metabolic dysfunction and the morbidity and mortality associated with diabetes. Considering the many cellular mechanisms that can help explain this - this finding is not difficult to justify. By contrast, Telford argues, there is little evidence that overfatness and obesity (adjusting for any effect of reduced PA) actually cause diabetes. Observational studies suggest that obesity, including viscerally sited obesity, is most appropriately categorized as a marker or predictive (noncausal) risk factor for T2D, although, in contrast to PA, several studies were not able to detect any significant correlation after controlling for PA. The findings are consistent with the premise that PA is of direct benefit, perhaps even essential to preventive and curative medicine in relation to insulin resistance and T2D. In support of Telford's argument Church's investigation of 2316 men with diabetes over 16 yr which found that low-fit individuals were at 2.7 times the risk of dying of CV disease compared with the normal-weight men of high fitness, irrespective of whether they were of normal weight, overweight, or obese (39). Studies on Pima Indians corroborated this trend of observing a reduction in new onset diabetes with physical activity intervention with some independence of changes in BMI or body weight (40).

Waller and coworkers provided provocative recent support for the independent nature of physical activity to reduce diabetes by following 8,182 complete twin pairs physical activity patterns for nearly 30 years (41). They found that in twins sufficient leisure time physical activity significantly reduces the risk for type 2 diabetes when controlled for genetic predisposition and childhood home environment. This was seen in the pairwise analyses among both monozygotic and dizygotic pairs, including those using BMI-adjusted data. It can therefore be assumed that physical activity independently protects against diabetes, as many unmeasured confounding factors (both genetic and environmental) are controlled for by the twin design.

Exercise without weight loss has also been shown to be a useful method in both men and women for reducing total and abdominal fat and preventing further increases in obesity (42-44). It has been reported that as little as 20 minutes of moderate-intensity daily physical activity with an energy expenditure of <1,500 kcal/week is generally associated with modest reductions (5-10%) in abdominal visceral fat (45,46). Findings from studies in type 2 diabetic subjects also suggest that ~2-3 months of regular moderate-intensity aerobic exercise is associated with substantive reductions in visceral fat (-27 to -45%) despite little or no change in weight (47-49). **Figure 2** illustrates much of the research support for this phenomenon of body fat reduction's disconnect from body weight reduction including Ekelund's large prospective cohort study EPIC (European Prospective Investigation into Cancer and Nutrition) where 84,511 men and 203,987 women were followed for 5.1 years (50). They concluded that a higher level of physical activity reduces abdominal adiposity independent of baseline and changes in body weight and is thus a useful strategy for preventing chronic diseases and premature deaths.

Key point: Without the employment of alternative measures of adiposity, e.g., waist circumference or select skinfold assessment, many patients who consistently increase their physical activity will be considered lifestyle "failures" because they did not lose weight or decrease BMI.

Lastly, Lopez-Soriano and colleagues in Spain and France who have focused nearly all of their experimental work on exercise induced PPAR nuclear receptor activation in both muscle and adipose tissue, cogently argue that physical activity is afforded little attention in recent studies and reviews evaluating the link between insulin resistance, inflammation and obesity (51). They insist that physical activity is a potentially confounding factor which has been overlooked by many attempting to understand the role of obesity. They submit that to the same extent as adipose tissue, skeletal muscle is the source of many metabolic signals, i.e., myokines (e.g., myostatin, TNF, and IL-6) not only with autocrine effects, but also with direct and specific effects in other tissues such as adipose tissue and liver. The “adipocentric” point of view generated in the last decade tries to explain this interrelationship by a unidirectional flow of messengers from the “endocrine” adipose tissue to a rather “passive” muscle, but this explanation seems inadequate to explain such a complex situation and some of the findings discussed thus far in this paper. Muscle contractions – at any level, influence many important cardiometabolic processes and are therefore worthy of independent assessment and documentation.

Key Points: Physical activity helps reduce risk by reducing body fat and curbing weight regain after weight loss but the more important message here is that PA operates through metabolic mechanisms which are not uniquely married to weight loss. Just get your patients to move!!

Increasing physical activity can significantly reduce abdominal adipose tissue (including waist circumference) and improve insulin sensitivity *without significant changes* in body weight and/or BMI.

Regaining Our Enthusiasm for Modest but Measurable Physical Activity Intervention

For those of us who have lost our *frame of reference* with respect to the value of moderate levels of physical activity – particularly for our patients but also for ourselves – transitioning from a relatively sedentary lifestyle to 1000-1500 kcal per week is clearly helpful particularly with regard to reducing the risk of cardiometabolic disease and perhaps most importantly delaying the onset of type 2 diabetes. There is encouraging evidence that patients who are at higher CMR risk, e.g., who have prediabetes, benefit more from exercise training than normoglycemic individuals. Jenkins demonstrated significant reductions in post-glucose and insulin responses in 47 prediabetic men compared to normal glycemic controls after 6 months of standardized moderate-vigorous level endurance training (walking, cycling, rowing) (52).

Table 2 depicts thresholds for what would be considered moderate levels of activity. Note that when discussing “moderate” physical activity we are not only addressing exercise intensity but also *total energy expenditure and duration*. Once again, this is not meant to disregard the recommendation for higher volumes of weekly exercise that can infer even greater cardiometabolic benefit – for those who are motivationally ready to embark upon 150 - 300 minutes of week of exercise. Patients who do not achieve these higher exercise volumes but who consistently improve their physical activity patterns are not failures. Serial clinical outcomes on

return patient visits should record objective measures of physical activity as tier 1 outcomes commensurate with BMI and LDL-C (see recommendations below).

Jim Hill of the University of Colorado Health Sciences Center in Denver and a well-respected investigator and authority on exercise and obesity analyzed the U.S. Longitudinal (CARDIA study) data and cross-sectional (NHANES) data sets to determine the distribution of weight gain over time (53). Hill and his team estimated the degree of change in the daily energy balance point (the absolute energy intake and expenditure at which balance is reached) required for success in body weight goals. For primary obesity prevention, Hill estimates that the “energy gap” in the U.S. to be less than 100 kcal/day for 90% of the population, meaning that relatively small changes in energy intake and expenditure adding up to 100 kcal/day could arrest excess weight gain in most people. This physical activity volume is quite consonant with the theme of this paper – modest changes go a long way.

It should now be clear that moderate levels of exercise including utilitarian forms of physical activity can reduce cardiometabolic disease risk with or without dramatic changes in LDL-C or reduced body weight. This has important implications for diabetes prevention, cardiac rehabilitation, and employee and community CMR management programs that otherwise tend to give insufficient credit for those who become more physically active but fall short of reaching laboratory and anthropometric goals. Get your patients to move then give them credit.

Recommendations for Providers Counseling Patients to Become More Physically Active *

1. Give your patients credit for each and every step they take irrespective of laboratory measures or body weight changes. Prescribe walking programs through the systematic use of clinical pedometry (systematic prescription of walking stepcounts with reliable clinical-grade pedometers). Clinical-grade pedometers have 6-12-month memories and step-filters which filter out spontaneous movements and which permit the patient to accurately record steps over a longer period of time without inadvertently resetting. Have patient record baseline weekly stepcount and then “titrate” and increase in daily and weekly stepcount from there. At the patient’s return visit chart and give credit for each and every recordable step much as you would for charting their glucophage or statin compliance. Each intentional walking step (i.e., muscle contraction) is an AMPK and PPAR activator working very similar to many of the antidiabetic agents. The stepcount should be the principle outcome measure – versus the estimated distance or caloric expenditure.

Stepcount Rx example: add at least 1000 kcal of exercise per week to existing weekly activity pattern. This would be the equivalent of adding approximately 10 miles of walking a week or ~20,000 stepcounts on a reliable pedometer for most adults. Ideally, graduating to at least 1500 kcal week over time would be near optimal (~15 miles/wk or ~30,000 steps) depending on goals. *Pedometer trekking* programs are also a creative and effective way to prescribe variable-terrain walking programs. Variable-terrain walking increases energy expenditure for a given walking speed and distance. A variety of

walking/hiking treks ranging from 0.5 to 5 miles (1000-10,000 steps) can be prescribed based on local geography and public access. *Clinical Pedometry Recommendations and Instructions for Providers* and *Pedometer Trekking Protocols* are available from the author on request (rlaforge@nc.rr.com).

2. Many patients actually reduce total body adiposity without changes in body weight owing to small increases in lean muscle weight as a result of a new exercise program (especially true with resistance exercise training programs). Employ more objective measures of body fat changes beyond body weight measurement. Use Gulick tape measures to more reliably measure waist circumference. A Gulick is a tape measure with a tension sensing device to ensure reproducible measurements. Select skinfold measures can also be helpful in demonstrating reduced body fat – e.g., the subscapular and/or tricep skinfolds are particularly sensitive to changes in total body fat – as are others. If you use skinfold calipers use only professional clinical quality calipers, e.g. Lange or Harpenden calipers. *Clinical Anthropometric Assessment Instructions for Cardiometabolic Risk Reduction Programs* are available on request by emailing the author: rlaforge@nc.rr.com.
3. Fasting triglycerides and non HDL-Cholesterol are perhaps the most sensitive laboratory measures of changes in physical activity. Triglyceride-rich lipoproteins are a large component of nonHDL-C and respond quite well to increases in weekly energy expenditure compared to LDL-C. LDL-particle number as measured by nuclear magnetic resonance imaging (LipoScience Laboratories, Raleigh NC) is also a reliable measure of increased physical activity compared to Friedewald predicted LDL-C (the laboratory LDL-C assay in a standard lipid profile).
4. Write exercise instructions/prescriptions as combination therapy. Clinicians need to quantify and prescribe physical activity (in terms of kcal/day or /week or stepcount/week) as prescribed combination therapy with drug therapy when applicable (see **Figure 3**). For example, 1500 kcal of weekly exercise, ~13-15 miles of walking, when added to omega 3 fatty acid therapy would further reduce triglycerides and VLDL-cholesterol knowing that 1500 kcal of energy expenditure at moderate exercise intensities will oxidize intramuscular and adipose tissue stores of triglycerides and fatty acids.
5. Systematize household/domestic chores into a circuit of short utilitarian activities such that the patient expends 150-350 kcal during one household/domestic circuit session. This would provide a sense of accomplishing both household/yard/community tasks as well as generating increased daily energy expenditure. **Figure 4** depicts a patient household circuit prescription form for which the patient rotates between 6-8 domestic activity stations with each station requiring 6-10+ minutes of activity. Instructions for domestic circuit activities: *Systematic Domestic Activity Exercise for Adults: Systematic Domestic Circuit Training Instruction Guide* and prescription form is available from the author by request: rlaforge@nc.rr.com.

*Many of these strategies are depicted graphically and narratively on the U.S. Indian Health Service Diabetes Treatment and Prevention Website website under the new *Quick Guide Cards* link and then under Physical Activity and Anthropometry (<http://www.ihs.gov/medicalprograms/diabetes/index.cfm?module=toolsQuickGuides>).

References

1. Ervin RB. Prevalence of Metabolic Syndrome Among Adults 20 Years of Age and Over, by Sex, Age, Race and Ethnicity, and Body Mass Index: United States, 2003–2006. *National Health Statistics Reports*. 2009;13(May).
2. Sinclair K, Bogart A, Buchwald D et.al. The prevalence of metabolic syndrome and associated risk factors in Northern Plains and Southwest American Indians. *Diabetes Care* doi:10.2337/dc10-022, Sept 23, 2010. .
3. Wannamethee SG, Shaper AG, Lennon L et.al Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus.. *Arch Int Med*. 2005;165(22):2644-50.
4. Lorenzo C, Williams K, Hunt KJ, Haffner SM: The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007;30:8-13.
5. American College of Sports Medicine. ACSM’s Guidelines for Exercise Testing and Prescription. (8th ed., Whaley MH senior editor) (2009). Philadelphia: Lipincott Williams & Wilkins.
6. Knowler WC et.al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*.346:393–403, 2002.
7. Diabetes Prevention Program Research Group. 10-year follow up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 374:1677-1688, 2009.
8. Guangwi L, Zhang P, Wang J. et.al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet*. 371:1783-1789, 2008.
9. Saito T, Watanbe M, Nishida J et.al. Lifestyle Modification and Prevention of Type 2 Diabetes in Overweight Japanese With Impaired Fasting Glucose Levels: A Randomized Controlled Trial. *Arch Int Med*. 2011;171:1352-1360.
10. Yates T, Davis M, Gorely T. et.al. Effectiveness of a Pragmatic Education Program Designed to Promote Walking Activity in Individuals With Impaired Glucose Tolerance A randomized controlled trial *Diabetes Care* 32:1404–1410, 2009.
11. Sattelmair J, Pertman J, Ding EL, Kohl HW et.al. Dose Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis. *Circulation*. 2011;124:789-795.

12. Wen PC, Jackson PMW, Tsai KM, et.al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *The Lancet*, 2011;378:1244 – 1253.
13. Kirk EP, Donnelly JE, Honas J. et.al. Minimal resistance training improves daily energy expenditure and fat oxidation. *Med Sci Sports Ex.* 2009;41(5):1122-1129.
14. Healy GN, Dunstan DW, Salmon JO, et.al. Breaks in Sedentary Time: Beneficial associations with metabolic risk. *Diabetes Care* 2008;31:661–666, 2008.
15. Coleman KJ, Raynor HR, Mueller DM, et al. Providing sedentary adults with choices for meeting their walking goals. *Prev Med* 1999; 28: 510-519.
16. Macfarlane DJ, Taylor LH, Cuddihy TF. Very short intermittent vs continuous bouts of activity in sedentary adults. *Prev Med* 2006; 43: 332-336.
17. Kraus WE, Houmard JA, Duscha B et.al. The effects of the amount and intensity of exercise on plasma lipoproteins. *NEJM.* 2002;347:1483-1492.
18. Rosenson RS, Davidson MH, Pourfarzib R. Underappreciated opportunities for low-density lipoprotein management in patients with cardiometabolic residual. *Atherosclerosis.* 2010;213(1):1-7, 2010.
19. Esper RJ, Nordaby R, Vilarino JO et.al. Endothelial dysfunction: a comprehensive appraisal. *Cardiovascular Diabetology.* 5:1-18, 2006.
20. Sonne MP, Scheede-Bergdahl C, Olsen DB et.al. Effects of physical training on endothelial function and limb blood flow in type 2 diabetes. *Appl Physiol Nutr Metab.* 32:936-941, 2007.
21. Seligman BG, Polanczyk CA, Santos AS, et.al. Intensive practical lifestyle intervention improves endothelial function in metabolic syndrome independent of weight loss: a randomized controlled trial. *Metabolism.* 2011;60(12):1736-40
22. Gill JM, Al-Mamari A, Ferrell WR, et al. Effects of prior moderate exercise on postprandial metabolism and vascular function in lean and centrally obese men. *J Am Coll Cardiol.* 2004;44:2375–82.
23. Hashimoto S, Ootani K, Hayshi S, et.al., Acute Effects of Shortly Pre- Versus Postprandial Aerobic Exercise on Postprandial Lipoprotein Metabolism in Healthy but Sedentary Young Women. *J Atherosclerosis and Thromb.* 2011;18(10):891-900.
24. Ho S, Dhaliwal SS, Hills A, et.al. Acute exercise improves post prandial cardiovascular risk factors in overweight and obese individuals. *Atherosclerosis.* 2011;214(1):178-184. 2011
25. Singhal A, Trilk J, Jenkins N, et.al. Effect of intensity of resistance exercise on postprandial lipemia. *J Appl Physiol* 2009;106: 823-829.
26. Carey AL and Kingwell BA. Novel pharmacological approaches to combat obesity and insulin resistance: targeting skeletal muscle with ‘exercise mimetics’. *Diabetologia* 2009; 52(10):2015-26.
27. Duncan GE, Perri MG, Theriaque DW, et.al. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care.* 2003;26:557-562.
28. Nassisab GP, Papantakou K, Skenderi K, et.al. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metab. Clin&Exper.* 2005;54:1472-1479.
29. Hansen D, Dendale P, Jonkers RAM et al (2009) Continuous low to moderate-intensity exercise is equally as effective as moderate to high-intensity exercise training to lower

- blood HbA1c content in obese, type 2 diabetes patients. *Diabetologia*. 2009;52(9): 1789–1797.
30. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001;286(10):1218–27.
 31. Colberg SR, Sigal RJ, Fernhall B, et.al. Exercise and Type 2 Diabetes: The American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care* 2010;33:e147–e167.
 32. Schimmack G, DeFronzo RA, & Musi N. AMP-activated protein kinase: role in metabolism and therapeutic implications. *Diabetes, Obes. & Metab.* 2006;8:591-602.
 33. Shadid S, La Forge R, Otvos JD, Jensen M. Treatment of obesity with diet/exercise versus pioglitazone has distinct effects on lipoprotein particle size. *Atherosclerosis*. 2006;188:370-376.
 34. Butcher LR, Thomas A, Backx K et.al., Low-Intensity Exercise Exerts Beneficial Effects on Plasma Lipids via PPAR γ . *Medicine & Science in Sports & Exercise* 2008;40:1263-1270.
 35. Fritz T, Kramer D, Karlsson H et.al. Low intensity exercise increases skeletal muscle protein expression of PPAR δ and UCP3 in type 2 diabetic patients. *Diabetes/Metabolism Research and Reviews*. 2006;22:492-498.
 36. Narkar V, Evans R. et.al. AMPK and PPAR δ Agonists Are Exercise Mimetics. *Cell*. 2008;134:405-415.
 37. Muoio DM & Koves TR. Skeletal muscle adaptation to fatty acid depends on coordinated actions of the PPARs and PGC1 α : implications for metabolic disease. *Appl Physiol Nut Metab*. 2007;32:874-883.
 38. Telford RD. Low Physical Activity and Obesity: Causes of Chronic Disease or Simply Predictors? *Med & Science in Sports & Ex*. 2007;39:1233-1240.
 39. Church T, LaMonte M, Barlow C, & Blair SN. Cardiorespiratory Fitness and Body Mass Index as Predictors of Cardiovascular Disease Mortality Among Men With Diabetes *Arch. Intern. Med.* 2005;165:2114-2120.
 40. Kriska AM, et.al. Physical Activity, Obesity, and the Incidence of Type 2 Diabetes in a High-Risk Population. *Am J Epidemiol* 2003;158:669–675.
 41. Waller K, Kaprio J, Lehtovirta M, Silventoinen K, Koskenvuo M, Kujala UM. Leisure-time physical activity and type 2 diabetes during a 28 year follow-up in twins. *Diabetologia*. 2010;53(12):2531-7.
 42. Ross R, Ian Janssen I, Dawson J et.al. Exercise-Induced Reduction in Obesity and Insulin Resistance in Women: a Randomized Controlled Trial. *Obes Res*. 2004; 12:789 – 798.
 43. Ross R, Damon D, Jones PJ et.al. Reduction in Obesity and Related Comorbid Conditions after Diet-Induced Weight Loss or Exercise-Induced Weight Loss in Men. *Ann Intern Med*.. 2000;133:92-103.
 44. Janiszewski PM, Ross R. The Utility of Physical Activity in the Management of Global Cardiometabolic Risk. *Obesity* 2009;17(3):S3-14.
 45. Irwin ML, Yasui Y, Ulrich CM *et al*. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. *JAMA* 2003;289:323–330.

46. Giannopoulou I, Ploutz-Snyder LL, Carhart R *et al.* Exercise is required for visceral fat loss in postmenopausal women with type 2 diabetes. *J Clin Endocrinol Metab* 2005;90:1511–1518.
47. Boudou P, Sobngwi E, Mauvais-Jarvis F, Vexiau P, Gautier JF. Absence of exercise-induced variations in adiponectin levels despite decreased abdominal adiposity and improved insulin sensitivity in type 2 diabetic men. *Eur J Endocrinol* 2003;149:421–424.
48. Mourier A, Gautier JF, De Kerviler E *et al.* Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM. Effects of branched-chain amino acid supplements. *Diabetes Care* 1997;20:385–391.
49. Lee S, Kuk JL, Davidson LE *et al.* Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type 2 diabetes. *J Appl Physiol* 2005;99:1220–1225.
50. Ekelund U, Besson H, Luan J. *et.al.* Physical activity and gain in abdominal adiposity and body weight:prospective cohort study in 288,498 men and women. *Am J Clin Nutr* 2011;93:826–35.
51. Lopez-Soriano J, Chiellini C, Margherita M *et.al.* Roles of skeletal muscle and PPARs in the development and treatment of obesity. *Endocrine Reviews* 2006;27:318–329.
52. Jenkins NT and Hagberg HM. Aerobic Training Effects on Glucose Tolerance in Prediabetic and Normoglycemic Humans. *Med & Science in Sports & Exercise*. 2011;43(12):2231-2240.
53. Hill JO, Peters JC, and Wyatt HR. Using the Energy Gap to Address Obesity: A Commentary *J Am Diet Assoc*. 2009;109(11):1848–1853.

Table 1

Exercise Training and Select Pleiotropic Mechanisms

Decrease in LDL particle number

Body composition changes (e.g., increased lean muscle mass, decreased fat mass)

Insulinemic changes and GLUT 4 gene expression & insulin sensitization

Decreased fasting plasma glucose and glycated hemoglobin

AMP kinase activation

PPAR gamma/delta activation

Increased skeletal muscle mitochondrial biogenesis

Increased adiponectin levels

Blood pressure reduction

Increased arterial endothelial function

Reduced platelet adhesiveness

Reduced inflammatory cytokines (e.g., IL-6, CRP)

Reduced oxidative stress

Increased ventricular dysrhythmia threshold

Psychobiologic changes (reduced response to stress)

Post prandial lipemia reduction (decreased triglycerides, VLDL, IDL)

Table references

American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. (8th ed., Whaley MH senior editor) (2009). Philadelphia: Lipincott Williams & Wilkins

Hawley JA and Holloszy JO. Exercise: it's the real thing! *Nutrition Review*. 2009;67(3):172–178

Table 2
Moderate Physical Activity

INTENSITY: 40-60% of aerobic capacity or effort max
or 3-6 MET's

WEEKLY VOLUME (amount): *

~1000-1500 kcal

120-150 minutes

20,000 - 30,000 walking steps

*over and above sedentary living habits

Reference: Adapted from ACSM Guidelines for Exercise Testing and
Prescription, 8th Ed., 2009

Figure 1

Walking Muscle Contraction and AMPK Activation

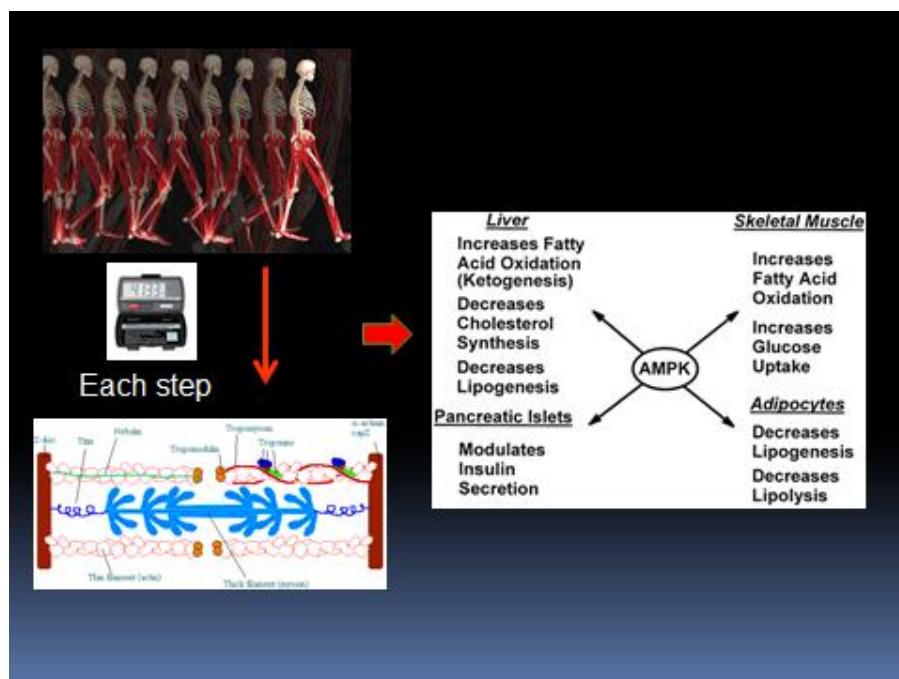


Figure 2

The Body Fat and Body Weight Disconnect

✓ Increasing physical activity can significantly reduce abdominal adipose tissue (including waist circumference) and improve insulin sensitivity *without significant changes in body weight and/or BMI*

Ekkelund Am J Clin Nutr 2011;93:326-35.
Yates T et al. Diabetes Care 2009;32:1484.
Velthuis MJ et al. Menopause 2009;16:777
van der Heijden et al. J Clin Endo Met. 2009;94:4292
Carey AL et al. Exercise Mimetics, Diabetologia, 9/09
Hansen D Diabetologia 2009; 52:1789-1797
Brown R Med Sci Sports Ex 2009;41:497
Ribello ICD Med.Sci Spts Ex 2008;40:779
Despres JP SYNERGIE Trial EAS 2008
Misra A et al. , Diabetes Care 2008;31:1282-1287
Bell LM et al. J Clin Endo Met 2007;92:4230
Ekkelund, U et al. Diabetes Care 2007;30:2101
Dekker M Metabolism 2007;56:332
DiPietro L et. al. JAP 2006
Lee SJ & Ross JAP 2005;99:1220
Wong SL et al. Med Sci Sports Ex 2004;36:286
Duncan GE Diabetes Care 2003;26:557
Boudou P et al. Eur J Endocrinol 2003;149:421-424
Ross R et al. Obes Res. 2004;12:789-798.
Ross R et al. Relat Met Dis 2003;27:204
Ross R et al. Ann Intern Med 2000;133:92
Mourier A et al. Diabetes Care 1997;20:385

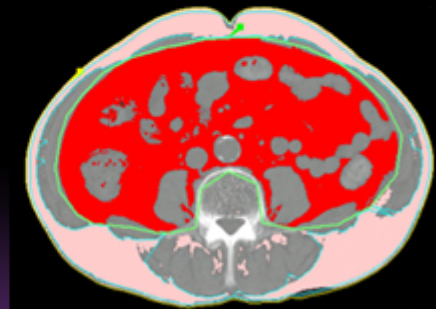


Figure 3

Exercise as Combination Therapy

R_x Physical Activity as Combination Therapy

1-2g n3 fatty acids
5 mg rosuvastatin,
10-20 mg atorvastatin
or simvastatin
10 mg ezetimibe
Metformin 1000 mg
15-30 mg pioglitazone
145 mg fenofibrate
1-1.5g nicotinic acid

+ **1000 – 2000 kcal of
added physical activity
(20-40K steps/wk)**

Figure 4
Household Circuit Activity Rx Form

The diagram illustrates a circular circuit for household domestic chores. A central yellow circle contains instructions. Surrounding this circle are eight rectangular boxes, each representing a work station. Arrows indicate a clockwise flow from one station to the next. The top right station is labeled with a duration of 20 - 90 minutes/circuit. The background is dark blue with a subtle wave pattern.

Household-Domestic Chore Circuit Rx

20 - 90 minutes/circuit

- Each work station, rectangles, should be 6-10 minutes (start with simple tasks and insert more difficult tasks in the middle of the circuit)
- 2-minute rest/water break between stations
- Always start and end each circuit session with a short walk and relaxation exercise as prescribed
- Do not continue exercise or go the next station if you experience chest discomfort, palpitations, dizziness or unusual fatigue