Progress in Cardiovascular Diseases 62 (2019) 327–333

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Review

Obesity, risk of diabetes and role of physical activity, exercise training and cardiorespiratory fitness

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ARTICLE INFO

Article history:
Received 14 August 2019
Accepted 14 August 2019

Keywords:
Obesity
Diabetes
Cardiorespiratory fitness
Physical activity
Exercise training
Sedentary behaviors

ABSTRACT

The epidemic of obesity contributes to the burden of type 2 diabetes mellitus (T2DM) in the United States and worldwide. Importantly, obesity is not only preventable but can be treated, particularly with lifestyle modifications to forestall T2DM in those with excess adiposity. The mechanisms linking obesity to T2DM are numerous and involve adipose tissue remodeling as a result of unhealthy behaviors, including unhealthy diet, reduced physical activity (PA) and exercise training (ET), and increased sedentary behaviors. Taken together, these factors markedly reduce cardiorespiratory fitness (CRF), one of the strongest predictors for cardiovascular outcomes and all-cause mortality in the general population, but also in those with T2DM.

In this review we describe the mechanisms leading to adipose tissue remodeling resulting in obesity, as well as the mechanisms linking excess adiposity to insulin resistance and, in turn, T2DM. We then present the therapeutic strategies that can be implemented in obesity to prevent T2DM, with a brief discussion on weight loss, and greater emphasis on PA and ET. We finally present the evidence to support the beneficial effects of such strategies in patients with established T2DM and discuss the importance of achieving improvements in CRF in this population to potentially improve clinical outcomes.

Contents

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CRF, cardiorespiratory fitness; CV, cardiovascular; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; ET, exercise training; FFA, free-fatty acids; FM, fat mass; GLUT4, glucose-transporter type 4; HbA1c, glycated hemoglobin; IL, interleukin; MET, metabolic equivalent of tasks; NLRP3, Nod-like receptor pyrin domain-containing protein; PA, physical activity; SB, sedentary behavior; T2DM, type 2 diabetes mellitus; VO_2, oxygen consumption; WC, waist circumference.

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Overweight and obesity are defined as excess adiposity that impairs health,[1] and together they affect over two thirds of the population in the United States, with obesity alone having a prevalence of 39.6% (41.1% in women and 37.9% in men), and severe obesity of 7.7% (9.7% in women and 5.6% in men).[2] The observed increase of obesity in the last decades is concerning due to the increased metabolic and cardiovascular (CV) disease (CVD) risk associated with the increased adiposity,[3] resulting in unacceptably high healthcare costs and reduced quality of life.[3,4]

Obesity is highly associated with perturbation of glucose metabolism, resulting in the development of type 2 diabetes mellitus

https://doi.org/10.1016/j.pcad.2019.08.004
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(T2DM).[5,6] Importantly, several non-pharmacologic, pharmacologic and surgical interventions are effective in preventing the development of T2DM in overweight or obese individuals, highlighting the importance of early interventions in this population. Obesity alone, even in absence of T2DM, strongly associates with greater CVD risk, and reducing excess adipose tissue serves as a therapeutic means to prevent the development of CVD.[3] Of note, both obesity and T2DM are associated with a significant reduction in cardiorespiratory fitness (CRF).[7,8] Considering that greater CRF is associated with overall improved survival, therapies aimed at increasing CRF, such as increased physical activity (PA), exercise training (ET) and potentially reduced sedentary behaviors (SB), have been proposed as therapeutic strategies.[9–11]

In this review we will describe the role of obesity, and particularly of body composition (i.e., fat mass [FM]), on the risk for T2DM. We will also discuss the non-pharmacologic interventions, with a focus on lifestyle modifications (i.e., diet, PA and ET) to prevent and treat the several cardiometabolic abnormalities associated with obesity and T2DM.

Obesity and adipose tissue remodeling

Obesity is a multifactorial chronic disease, in which environmental and genetic factors, as well as abnormalities of energy metabolism regulation, which may be caused by the use of medications that induce weight gain as a side effect, contribute to weight gain. Monogenic forms of obesity, mainly resulting from dysregulation of energy homeostasis, also exist.[12] Although environmental factors (i.e., unhealthy diet, physical inactivity and SB) are considered the major causes for obesity, the fact that individuals exposed to a similar environment and lifestyle may not necessarily gain the same degree of body weight and develop obesity, suggests a strong influence of genetic factors.[13] This is supported by early twin and adoption studies that observed strong heritability of body mass index (BMI; kg/m^2).[14]

Excess adiposity is typically accumulated over a long period of time, resulting from a chronic positive energy balance, with daily caloric intake exceeding energy expenditure. Although the positive chronic energy balance has been often thought to be exclusively the results of hypercaloric diet characteristic of the Western countries,[15–17] the overall caloric intake has not changed as dramatically over the years as one may think,[18] suggesting that other factors responsible for the overall reduction of energy expenditure may be responsible, and in fact may be the major contributors, for the current obesity epidemic. In support to this concept, occupation-related PA[19] as well as household management energy expenditure[20] have declined significantly over the past 50 years, providing evidence that reduced PA may play a major role in determining a chronic positive energy balance.

Based on these assumptions, increased PA and reduced caloric intake should result in a chronic negative energy balance, finally resulting in weight loss. However, maintenance of body weight resulting from disruption of energy balance, for instance during caloric restriction-induced weight loss, remains challenging due to several innate, compensatory mechanisms that return body weight to a 'set-point'.[21–24] This complex regulation of energy homeostasis involving a large number of peripheral and central pathways may explain the lack of curative measures of obesity, which typically target one or only few of them.[21–24] For these reasons, as recently largely described in a state-of-the-art review,[3] we believe that preventing obesity may represent a much more powerful and long-lasting tool to ultimately prevent the numerous cardiometabolic abnormalities associated with it.

In the presence of a chronic positive energy balance, the adipocytes, the primary cells of adipose tissue, can grow in numbers (i.e., hyperplasia) and in size (i.e., hypertrophy).[22,25] In the initial phase of weight gain, the size of the adipocytes increases, however, when the size of the hypertrophic adipocytes reaches the limit of expansion for nutrients storage, preadipocytes can differentiate into more mature adipocytes.[25] Such events ultimately result in the typical obesity phenotype characterized by both hypertrophy and hyperplasia of adipocytes. Of note, therapies aimed at reducing body fat, such as caloric restriction, are associated with an improvement in adipocytes hypertrophy, but not of hyperplasia, making weight regain more likely to occur if energy balance returns to a positive state.[22] Additionally, adipocytes can be divided into subtypes, based on their color, from white to brown, with a more recently proposed brown-like beige adipocyte, with characteristics of both white and brown adipose tissue.[26] The distinction between white and brown adipose tissue is of utmost importance, particularly after the discovery a decade ago of active brown adipose tissue in adult humans.[27] While white adipocytes are considered the most common adipocytes responsible for the expansion of the adipose tissue (both visceral and subcutaneous), brown adipocytes are present in very small amounts, and their most well-known role is their ability to control thermogenesis.[28] As such, therapeutics currently under investigation are aimed at increasing brown adipose tissue amount or activity, or beigeing of white adipose tissue, and simulating its effects to increase daily energy expenditure, even in absence of increased PA, to promote a greater energy deficit to treat obesity and prevent the obesity-related metabolic abnormalities.[29–32]

Mechanisms leading obesity to T2DM: contributions of insulin resistance and chronic low-grade systemic inflammation

With respect to the risk of metabolic diseases, obesity remains perhaps the strongest modifiable risk factor for the development of insulin resistance, ultimately resulting in T2DM.[33] Hyperplasia and hypertrophy of the adipocytes can, in fact, occur in different locations within the body, including insulin-dependent tissues, like skeletal muscle, liver, and the adipose tissue itself.[34] In addition to accumulation of excess fat within the adipose tissue, skeletal muscle and liver, ectopic fat can accumulate around and within most organs, such as the heart, liver, pancreas and kidney (Fig. 1),[34] resulting in a number of abnormalities which can ultimately result in cardiometabolic chronic diseases. The excess adiposity characteristic of obesity may be responsible for the insulin resistance of the skeletal muscle and the liver, but also within the adipose tissue itself.[34–37]

Although the exact mechanisms linking obesity to insulin resistance are still being explored, preclinical data suggest that obesity alters the intracellular insulin signaling in insulin-sensitive tissues and downregulates the expression of the insulin-responsive glucose transporters exposed on the cell membrane that allows the flux of glucose inside the cells.[38,39] Furthermore, because insulin has antilipolytic effects, the deterioration of its signaling caused by insulin resistance is associated with a reduced suppression of lipolysis, resulting in a greater and constant release of free fatty acids (FFA) in the circulation. The release of FFA by the adipose tissue contributes to a vicious cycle, often referred as lipotoxicity, in which FFA can, in turn, increase hepatic and skeletal muscle insulin resistance, and at later stages, impair insulin secretion in predisposed individuals.[40,41] Particularly, hepatic insulin resistance results in an increased activation of the gluconeogenesis, promoting fasting and postprandial hyperglycemia.[41]

In normal conditions and in a fed state, the increased level of circulating insulin binds to the dedicated receptor located on the membrane of the adipocytes, which in turn stimulates the translocation of glucose-transporter type 4 (GLUT4) from the cytosol to the cell membrane, allowing the glucose to enter the cell.[42] In mice, the deletion of adipose tissue-specific GLUT4 induces insulin resistance in the skeletal muscle and the liver.[38] These data suggest that therapeutics improving insulin receptor signaling resulting in augmented translocation of GLUT4, such as drugs targeting the AMP-activated protein kinase, may improve insulin sensitivity and perhaps reduce the associated risk for T2DM. In fact, obesity, particularly increased abdominal adiposity, is associated with a markedly increased risk of T2DM.[5,6,43,44] In the Health Professionals Follow-Up Study, 27,270 men were followed for 13 years in a prospective cohort study, to investigate the effects of BMI, but also of waist circumference (WC), a surrogate for visceral fat, on the risk for

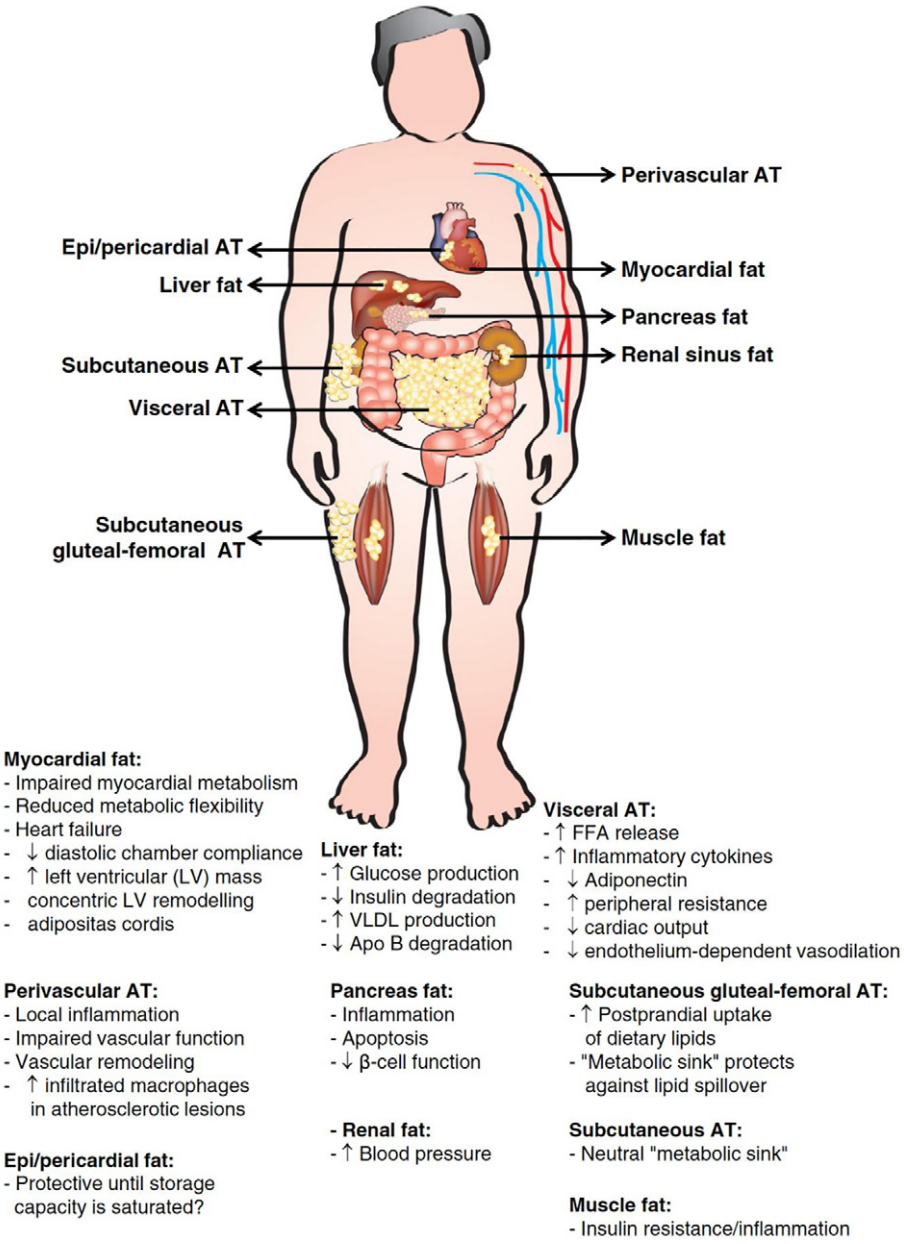

Fig. 1. Accumulation of visceral and ectopic adipose tissue in the body and cardiometabolic abnormalities. Apo, apolipoprotein; FFA: free fatty acids; AT, adipose tissue; VLDL, very-low-density lipoprotein. Modified with permission from Bastien et al.[34]

T2DM.[45] A BMI between 27.2 and 54.2 kg/m^2, representing the highest quintile in the study, was associated with an 8-fold increased risk to develop T2DM compared to those with a BMI < 22.8 kg/m^2. Those in the highest quintile for WC (101.6–157.5 cm), however, presented an even greater risk for T2DM, by about a 12- fold increased risk.[45] These results suggest that the location of adipose tissue within the body may play a more important role than overall adiposity. Nevertheless, an increased BMI remains a risk factor for T2DM in absence of more accurate measures of body fat distribution. Similarly, data from another prospective cohort study, The Nurses' Health Study, in 74,419 women, found that increased BMI was also associated with a greater risk for T2DM, however, the study also highlighted the different risk based on race and ethnicities, with a greater risk for T2DM at a given BMI in Asians, Hispanics and blacks compared to whites.[43] In fact, for each 5-unit increment of BMI, the relative risks for T2DM compared to whites were 1.43 for Asians, 1.76 for Hispanics, and 2.18 for blacks, respectively.[43]

Another hypothesis which may drive obesity to insulin resistance and ultimately T2DM is the inflammatory hypothesis.[46] The adipose tissue is an endocrine organ able to produce several adipokines and cytokines, the latter being recently targeted in an attempt to prevent T2DM.[47] In the setting of adipose tissue expansion, activated adipose tissue macrophages can be recruited by chemokines and release proinflammatory cytokines, which can increase lipolysis, which further contributes to the increased release of FFA in the circulation (i.e., lipotoxicity), further worsening insulin signaling activity in adipose tissue, liver and skeletal muscle.[41]

Despite the clear increased risk of T2DM at greater levels of BMI, whether increased BMI causes T2DM requires additional investigations. In the Diabetes Prevention Program (DPP), individuals with a mean BMI of 34.0 kg/m^2 receiving intensive lifestyle intervention aimed at achieving at least 7% weight loss through dietary modifications, in addition to 150 min per week of PA, presented a significant 58% reduction of the incidence of T2DM compared to those in the control group receiving standard lifestyle recommendations[48]; these marked benefits occurred despite the fact that average weight loss and PA were much less that anticipated. The strongest predictor for T2DM prevention was, however,

weight loss. For each kg of weight loss, individuals experienced a greater than16% relative risk reduction in the development of T2DM, even after adjustments for diet and PA.[49] These results suggested that excess body weight, likely as result of excess adiposity, may not be just a marker, but, in fact, a cause of T2DM.

Increased markers of chronic low-grade systemic inflammation in obesity are associated with incidence of T2DM[46,50–52] and preclinical data suggest that the resolution of such inflammation could prevent the development of T2DM in obesity and prediabetes. This hypothesis was substantiated by preclinical animal data, in which the deletion of the macromolecular complex NLRP3 inflammasome, responsible for the production of the pro-inflammatory cytokines interleukin [IL]-1β and IL-18, resulted in improved insulin sensitivity.[53] The hypothesis that the NLRP3 inflammasome may drive the insulin resistance state induced by obesity was partially recently tested in over 4000 patients with prediabetes and increased C-reactive protein (i.e., ≥2 mg/L) using a targeted anti-inflammatory strategy (i.e., canakinumab: IL-1β monoclonal antibody).[47] Canakinumab failed to prevent T2DM,[47] despite reducing major CVD events.[54] We cannot exclude, however, that additional proinflammatory cytokines are involved in the development of T2DM in individuals at risk. NLRP3 inflammasome also produces another major proinflammatory cytokine, namely IL-18, which has been involved in obesity-induced inflammation and insulin resistance.[55–59] In a preclinical study of high-saturated fat and high-sugar diet (i.e., Western diet)-induced metabolic abnormalities and cardiac dysfunction,[60] an oral inhibitor of the NLRP3 inflammasome was associated with improved cardiac function; but glucose metabolism abnormalities were not improved.[61] Taken together, these data do not support the role of the inhibition of the NLRP3 inflammasome in improving glucose metabolism and preventing the onset of T2DM in individuals with obesity, however, it suggests that such a strategy may still prevent or even treat the CV abnormalities induced by obesity and perhaps T2DM.

To this regard, despite significant improvements made in the treatment of T2DM in the last decades, patients with T2DM still present an unacceptably high risk for CVD, which remains the leading cause of death in this population. This highlights the need for greater efforts of clinicians and researchers to develop effective strategies to reduce the burden of CVD in T2DM. We believe that such therapies should be developed and implemented even in absence of improvements in typical T2DM-related endpoints, such as improved glycemic control, which, to date, have not consistently been shown to reduce major CVD events, but rather microvascular complications.[62,63]

PA and ET to improve body weight and CRF to prevent T2DM

As discussed at length elsewhere, intentional weight loss induced by caloric restriction, but also pharmacologic and surgical interventions, in the setting of a comprehensive lifestyle modification program, remains the cornerstone therapy to improve insulin sensitivity and in some circumstances to prevent the incidence of T2DM in individuals with obesity and prediabetes.[64] The amount of weight loss required to result in clinically significant improvements can vary, but even small improvements in body weight of the magnitude of 2.6 kg to 5 kg have been associated with reduced incident T2DM.[48] Those with lower FM before the interventions seem to present greater benefits in terms of weight loss.[48] Of note, in addition to caloric restriction, improvements in quality of diet, such as an increase in dietary unsaturated fatty acids consumption, may also prevent T2DM, even in absence of weight loss.[65–67]

Most clinical trials investigating the effects of weight loss in preventing T2DM in individuals with overweight/obesity and prediabetes typically involve a multidisciplinary comprehensive approach, including dietary changes, such as improvements in quality of diet, with or without caloric restriction, but also strategies to increase daily PA and/or ET, making it difficult to differentiate whether the benefits on metabolic outcomes are the result of dietary modifications, PA/ET or a combination of those. As described above, the degree of weight loss seems to be an independent predictor for the remission of T2DM, even after adjustments for diet and PA,[49] however, in the DPP, in those not achieving the weight loss goal of 7% at 1 year, meeting the recommended level of PA of 150 min per week was still associated with a 44% reduction of T2DM, even after adjustments for changes in body weight.[49] Furthermore, an increase in PA of 5 metabolic equivalent of tasks (METs) after 3 years was also associated with a small, although statistically significant, reduction in body weight of 0.43 kg.[49] In addition to the potential contribution to weight loss, increased levels of PA are typically associated with an improved CRF,[10,68–70] which is one of the strongest predictors for reduced CVD and all-cause mortality in the general population as well as those with chronic diseases, including T2DM.[10,71–76]

In a prospective study of 7804 men without T2DM followed for a period of over 20 years,[77] greater CRF defined as the highest quartile of peak oxygen consumption (VO_2) (49.8 mL•kg^{-1}•min^{-1}), the gold standard assessment of CRF,[78,79] presented a 42% reduced risk for incidence of T2DM compared to those in the lowest quartile. Of note, although the highest quartile presented the greatest associated reduction with incident T2DM, also quartile 2 (36.4 mL•kg^{-1}•min^{-1}) and quartile 3 (41.5 mL•kg^{-1}•min^{-1}) were associated with a greater likelihood to prevent T2DM, suggesting that any improvements in CRF would be desirable.[77] Similarly, in a 17-year follow-up study in women without T2DM at baseline, CRF lower than 7 MET (1 MET = 3.5 mL•kg^{-1}•min^{-1}) measured with a treadmill exercise test was associated with a 3-fold increased risk for T2DM compared to those with CRF ≥ 10 MET.[80] Of note, these associations were only true in the overweight and obesity groups, while in those women with a body weight within normal range, the unfit women did not present a significantly greater risk for T2DM compared to the fit ones.[80] A recent meta-analysis of 13 studies, including 1,601,490 patients, has shown that after controlling for adiposity, each increase in CRF by 1 MET was associated with a linear 8% reduction in future T2DM (Fig. 2).[81]

PA and ET to increase CRF in T2DM

In addition to the strong association between improved CRF and reduced risk for T2DM, the role of CRF has been also investigated in those with established disease. In a recent analysis of 150 patients with T2DM, CRF (i.e., peak VO_2) was found to be markedly reduced, even after adjustments for fat-free mass,[8] which has been proposed to be a better assessment of CRF,[82] particularly in individuals with overweight and obesity, in which the use of CRF adjusted by total body weight may result in an underestimated CRF.[83–85] These data confirmed what was previously described in a larger analysis of 5145 individuals with T2DM.[86]

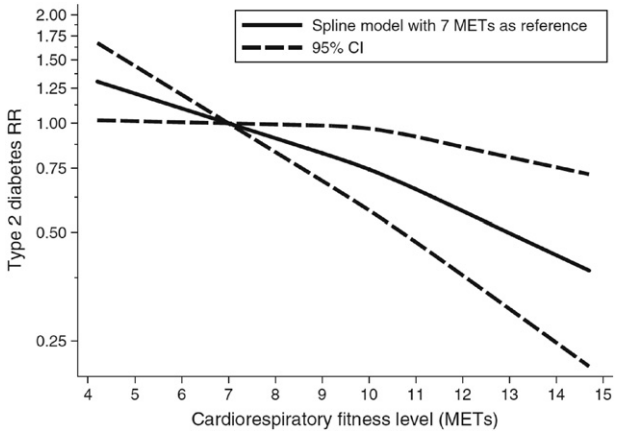

Fig. 2. Linear association between improvement in cardiorespiratory fitness and reduced risk for type 2 diabetes mellitus. RR, relative risk. Modified with permission from Tarp et al.[81]

Furthermore, improvements in CRF are also typically associated with improved cardiometabolic risk factors in patients with T2DM. In a sub-analysis of 3942 patients of The Action for Health in Diabetes Study (Look AHEAD),[87] one of the largest multicenter clinical trials ever performed investigating the effects of intensive lifestyle interventions on CVD events in T2DM,[88] improvements in CRF (i.e., MET) were associated with a greater reduction in glycated hemoglobin (HbA1c). Another analysis of this study of 4408 patients showed that increased CRF was associated with improved cardiometabolic risk factor, such as glucose, high-density lipoprotein cholesterol, triglycerides and diastolic blood pressure, even after adjustments for the degree of weight loss.[89] In a study of 4156 veterans with T2DM, each increase in 1 MET was associated with a 12% lower risk for all-cause mortality.[90] Importantly, those individuals with a CRF > 5 MET had a marked reduction in all-cause mortality, ranging from 35% to 55%, compared with those with lower CRF[90]

As mentioned above, PA and ET remain the strongest tools to improve CRF,[10,73,74] which may in turn result in improved clinical outcomes. Approaches aimed at increasing PA and at reducing SB are effective strategies to improve CRF in the general population, however, their effects in individuals with T2DM with "have not been explored extensively until very recently. Nevertheless the American Diabetes Association (ADA) recommends that most adults with T2DM should engage in 150 min or more of moderate-to-vigorous PA per week or 75 min of vigorous PA in younger individuals, with no >2 consecutive days without PA.[91] Such recommendations are similar to what is recommended in the general population.[92]

In the randomized Italian Diabetes and Exercise Study 2 (IDES_2), 300 physically inactive patients with T2DM were assigned and followed for a median follow-up of 3 years to a behavioral intervention to increase PA and reduce SB (1 individual theoretical counseling session and 8 individual biweekly theoretical and practical counseling sessions per year), or to a control group receiving standard therapy following the ADA guidelines.[93] The study resulted in a significant improvement in objectively measured PA with an accelerometer by 3.3 MET-hour/day compared to the control group, reflected in a significant increase in both light-intensity PA and moderate-to-vigorous intensity PA.[93] The patients assigned to the behavioral intervention also presented a significantly lower sedentary time by 0.8-h/day compared to the control group.[93] Importantly, the improvements in PA and SB also resulted in impressive improvements in CRF (+ 2.6 mL•kg^{-1}•min^{-1}), also associated with a greater lower body strength, whereas upper body strength was unchanged.[93] Interestingly, no improvements in HbA1c nor lipids were reported, while there were significant reductions in fasting glycemia (−9.15 mg/dL) and systolic blood pressure (−2.88 mmHg).[93]

With regards to ET, in a meta-analysis including 266 individuals with T2DM, a mean ET of 49-min session, 3.4 times per week for 20 weeks, was associated with an almost 12% increase in peak VO_2, with greater benefits found at greater intensity of ET.[94] Even shorter duration of ET can, however, result in improvements in CRF. In a small pilot study of 16 individuals with T2DM, an 8-week combined ET program of aerobic ET and resistance ET was associated with a significant improvement of 1.7 mL•kg^{-1}•min^{-1} in peak VO_2, in addition to improvements in muscle strength, FM, HbA1c and fasting glycemia.[95] In a larger randomized controlled trial of 262 sedentary individuals with T2DM, the role of aerobic ET and resistance ET alone or combined was investigated in a 9-month program.[96] Importantly, aerobic ET and resistance ET alone did not result in a significant improvement in CRF compared to the control group, however, the combined ET program resulted in a significant 1.0 mL•kg^{-1}•min^{-1} increase in peak VO_2.[96] The individual ET groups only improved exercise time and estimated METs, which were, however, still lower that what was found in the combined ET group.[96]

The beneficial effects of PA and ET are numerous and have been recently reviewed elsewhere.[10] Briefly, improvements in mitochondrial functionality, skeletal muscle, cardiac muscle and endothelial function have been reported in both clinical and preclinical data (Fig. 3).

Conclusions

Chronic positive caloric balance from unhealthy dietary habits, reduced PA and increased SB result in increased adiposity, eventually leading to adipose tissue remodeling and obesity. This excess adiposity, in turn, markedly increases the risk for cardiometabolic disease, particularly T2DM. Importantly, in patients with obesity, T2DM can be prevented by implementing lifestyle behavior modifications, including improvements in diet, increased PA, ET and perhaps SB, ultimately

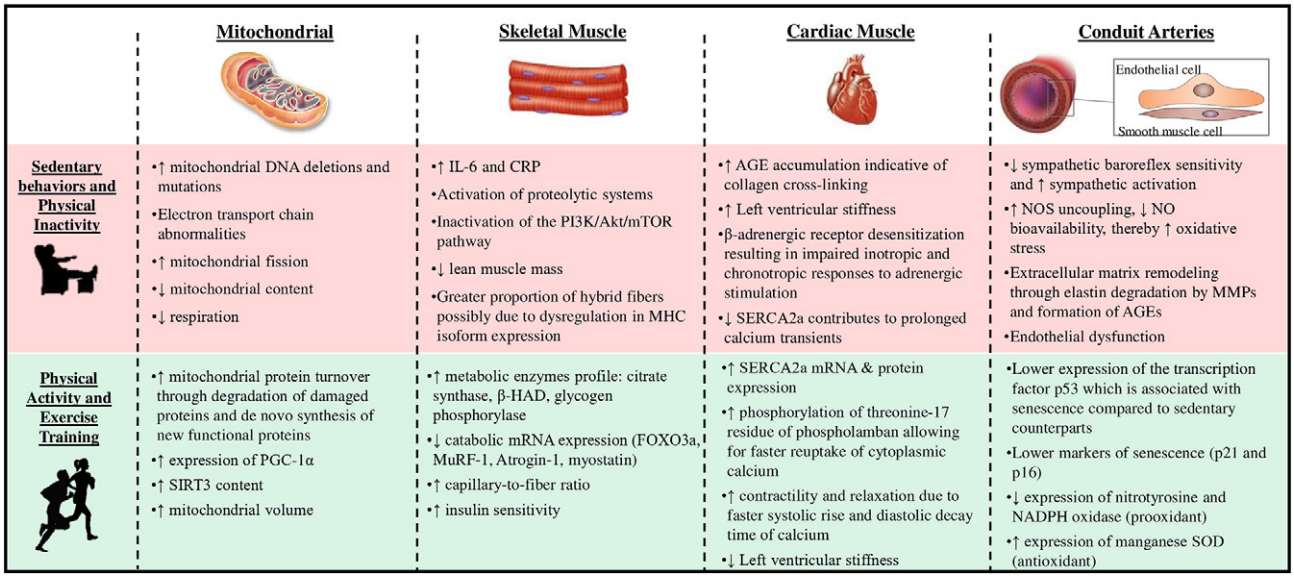

Fig. 3. Detrimental effects of sedentary behavior and physical inactivity and the beneficial effects of physical activity and exercise training in mitochondria, skeletal muscle, myocardium, and conduit arteries. AGE, advanced glycation end products; Akt, protein kinase B; β-HAD, beta-hydroxyacyl CoA dehydrogenase; CRP, C-reactive protein; FOXO3a, forkhead box O3; DNA, deoxyribonucleic acid; IL-6, interleukin-6; MHC, myosin heavy chain; mRNA, messenger ribonucleic acid; MuRF-1, muscle RING-finger protein-1; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; SERCA2a, sarcoplasmic reticulum calcium adenosine triphosphatase; SIRT3; nicotinamide adenine dinucleotide dependent deacetylase sirtuin-3 SOD. Modified with permission from Lavie et al.[10]

leading to improved CRF. Clearly, greater CRF is, in fact, associated with reduced risk for CVD events and mortality and all-cause mortality. Certainly, the prevention of obesity in the first place would be desirable, however, in those with established disease, we believe that clinicians should put forth a greater effort to implement lifestyle modifications to improve patients' quality of life and to reduce the unacceptably high healthcare costs associated with obesity, T2DM and their related complications, especially from CVD.

Funding support

Salvatore Carbone is supported by a Career Development Award 19CDA34660318 from the American Heart Association.

Declaration of competing interest

None.

References

1. World Health O. Obesity and overweight fact sheet. WHO Media centre 2016.
2. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. JAMA 2018;319:1723-1725.
3. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC health promotion series. J Am Coll Cardiol 2018;72:1506-1531.
4. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. J Health Econ 2012;31:219-230.
5. Koh-Banerjee P, Wang Y, Hu FB, Spiegelman D, Willett WC, Rimm EB. Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. Am J Epidemiol 2004;159:1150-1159.
6. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961-969.
7. Gallagher MJ, Franklin BA, Ehrman JK, et al. Comparative impact of morbid obesity vs heart failure on cardiorespiratory fitness. Chest 2005;127:2197-2203.
8. Jarvie JL, Pandey A, Ayers CR, et al. Aerobic fitness and adherence to guideline-recommended minimum physical activity among ambulatory patients with type 2 diabetes mellitus. Diabetes Care 2019;42:1333-1339.
9. van der Velde J, Schaper NC, Stehouwer CDA, et al. Which is more important for cardiometabolic health: sedentary time, higher intensity physical activity or cardiorespiratory fitness? The Maastricht Study Diabetologia 2018;61:2561-2569.
10. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary behavior, exercise, and cardiovascular health. Circ Res 2019;124:799-815.
11. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting physical activity and exercise: JACC health promotion series. J Am Coll Cardiol 2018;72:1622-1639.
12. Pigeyre M, Yazdi FT, Kaur Y, Meyre D. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci (Lond) 2016;130:943-986.
13. Brandkvist M, Bjorngaard JH, Odegard RA, Asvold BO, Sund ER, Vie GA. Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT study. Bmj 2019;366:l4067.
14. Bray MS, Loos RJ, McCaffery JM, et al. NIH working group report-using genomic information to guide weight management: from universal to precision treatment. Obesity (Silver Spring) 2016;24:14-22.
15. Popkin BM, Hawkes C. Sweetening of the global diet, particularly beverages: patterns, trends, and policy responses. Lancet Diabetes Endocrinol 2016;4:174-186.
16. Katan MB, Ludwig DS. Extra calories cause weight gain—but how much? JAMA 2019;303:65-66.
17. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? Science 2003;299:853-855.
18. Rehm CD, Penalvo JL, Afshin A, Mozaffarian D. Dietary intake among US adults, 1999-2012. Jama 2016;315:2542-2553.
19. Church TS, Thomas DM, Tudor-Locke C, Katzmarzyk PT, Earnest CP, Rodarte RQ, Martin CK, Blair SN and Bouchard C. Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. *PLoS One*. 2011;6:e19657.
20. Archer E, Shook RP, Thomas DM, et al. 45-year trends in women's use of time and household management energy expenditure. PLoS One 2013;8, e56620.
21. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and Management of Obesity. N Engl J Med 2017;376:254-266.
22. MacLean PS, Higgins JA, Giles ED, Sherk VD, Jackman MR. The role for adipose tissue in weight regain after weight loss. Obes Rev 2015;16:45-54.
23. Leibel RL, Seeley RJ, Darsow T, Berg EG, Smith SR, Ratner R. Biologic responses to weight loss and weight regain: report from an American Diabetes Association research symposium. Diabetes 2015;64:2299-2309.
24. Ochner CN, Tsai AG, Kushner RF, Wadden TA. Treating obesity seriously: when recommendations for lifestyle change confront biological adaptations. Lancet Diabetes Endocrinol 2015;3:232-234.
25. Rutkowski JM, Stern JH, Scherer PE. The cell biology of fat expansion. J Cell Biol 2015;208:501-512.
26. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med 2013;19:1252-1263.
27. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509-1517.
28. Celi FS. Brown adipose tissue–when it pays to be inefficient. N Engl J Med 2009;360:1553-1556.
29. Cypess AM, Weiner LS, Roberts-Toler C, et al. Activation of human brown adipose tissue by a beta3-adrenergic receptor agonist. Cell Metab 2015;21:33-38.
30. Mirbolooki MR, Upadhyay SK, Constantinescu CC, Pan ML, Mukherjee J. Adrenergic pathway activation enhances brown adipose tissue metabolism: a [(1)(8)F]FDG PET/CT study in mice. Nucl Med Biol 2014;41:10-16.
31. Mirbolooki MR, Constantinescu CC, Pan ML, Mukherjee J. Targeting presynaptic norepinephrine transporter in brown adipose tissue: a novel imaging approach and potential treatment for diabetes and obesity. Synapse 2013;67:79-93.
32. Ruiz JR, Martinez-Tellez B, Sanchez-Delgado G, Osuna-Prieto FJ, Rensen PCN, Boon MR. Role of human brown fat in obesity, metabolism and cardiovascular disease: strategies to turn up the heat. Prog Cardiovasc Dis 2018;61:232-245.
33. Chobot A, Gorowska-Kowolik K, Sokolowska M, Jarosz-Chobot P. Obesity and diabetes-not only a simple link between two epidemics. Diabetes Metab Res Rev 2018;34, e3042.
34. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis 2014;56:369-381.
35. Piche ME, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity and body fat distribution to cardiovascular disease: an update. Prog Cardiovasc Dis 2018;61:103-113.
36. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013;93:359-404.
37. Muller MJ, Lagerpusch M, Enderle J, Schautz B, Heller M, Bosy-Westphal A. Beyond the body mass index: tracking body composition in the pathogenesis of obesity and the metabolic syndrome. Obes Rev 2012;13(suppl 2):6-13.
38. Abel ED, Peroni O, Kim JK, et al. Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature 2001;409:729-733.
39. Shepherd PR, Kahn BB. Glucose transporters and insulin action–implications for insulin resistance and diabetes mellitus. N Engl J Med 1999;341:248-257.
40. Belfort R, Mandarino L, Kashyap S, et al. Dose-response effect of elevated plasma free fatty acid on insulin signaling. Diabetes 2005;54:1640-1648.
41. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest 2016;126:12-22.
42. Kahn BB, Cushman SW. Subcellular translocation of glucose transporters: role in insulin action and its perturbation in altered metabolic states. Diabetes Metab Rev 1985;1:203-227.
43. Shai I, Jiang R, Manson JE, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 2006;29:1585-1590.
44. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers 2015;1:15019.
45. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr 2005;81:555-563.
46. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 2014;105:141-150.
47. Everett BM, Donath MY, Pradhan AD, et al. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. J Am Coll Cardiol 2018;71:2392-2401.
48. Knowler WC. Barrett-Connor E, fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM and diabetes prevention program research G. reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
49. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006;29:2102-2107.
50. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Jama 2001;286:327-334.
51. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes 2004;53:693-700.
52. Spranger J, Kroke A, Mohlig M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European prospective investigation into Cancer and nutrition (EPIC)-Potsdam study. Diabetes 2003;52:812-817.
53. Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 2011;17:179-188.
54. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-1131.
55. Leick L, Lindegaard B, Stensvold D, Plomgaard P, Saltin B, Pilegaard H. Adipose tissue interleukin-18 mRNA and plasma interleukin-18: effect of obesity and exercise. Obesity (Silver Spring) 2007;15:356-363.
56. Bruun JM, Stallknecht B, Helge JW, Richelsen B. Interleukin-18 in plasma and adipose tissue: effects of obesity, insulin resistance, and weight loss. Eur J Endocrinol 2007;157:465-471.
57. Fischer CP, Perstrup LB, Berntsen A, Eskildsen P, Pedersen BK. Elevated plasma interleukin-18 is a marker of insulin-resistance in type 2 diabetic and non-diabetic humans. Clin Immunol 2005;117:152-160.
58. Hung J, McQuillan BM, Chapman CM, Thompson PL, Beilby JP. Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. Arterioscler Thromb Vasc Biol 2005;25:1268-1273.

59. Carbone S, Lee PJ, Mauro AG, et al. Interleukin-18 mediates cardiac dysfunction induced by western diet independent of obesity and hyperglycemia in the mouse. Nutr Diabetes 2017;7, e258.
60. Carbone S, Mauro AG, Mezzaroma E, et al. A high-sugar and high-fat diet impairs cardiac systolic and diastolic function in mice. Int J Cardiol 2015;198:66-69.
61. Carbone S, Mauro AG, Prestamburgo A, et al. An orally available NLRP3 inflammasome inhibitor prevents western diet-induced cardiac dysfunction in mice. J Cardiovasc Pharmacol 2018;72:303-307.
62. Carbone S, Dixon DL, Buckley LF, Abbate A. Glucose-lowering therapies for cardiovascular risk reduction in type 2 diabetes mellitus: state-of-the-art review. Mayo Clin Proc 2018;93:1629-1647.
63. Bonaventura A, Carbone S, Dixon DL, Abbate A, Montecucco F. Pharmacologic strategies to reduce cardiovascular disease in type 2 diabetes mellitus: focus on SGLT-2 inhibitors and GLP-1 receptor agonists. J Intern Med 2019;286:16-31.
64. Association AD. 3. Prevention or delay of type 2 diabetes: standards of medical Care in Diabetes-2019. Diabetes Care 2019;42:S29-s33.
65. Salas-Salvado J, Bullo M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med 2014;160:1-10.
66. Wu JHY, Marklund M, Imamura F, Tintle N, Ardisson Korat AV, de Goede J, Zhou X, Yang WS, de Oliveira Otto MC, Kroger J, Qureshi W, Virtanen JK, Bassett JK, Frazier-Wood AC, Lankinen M, Murphy RA, Rajaobelina K, Del Gobbo LC, Forouhi NG, Luben R, Khaw KT, Wareham N, Kalsbeek A, Veenstra J, Luo J, Hu FB, Lin HJ, Siscovick DS, Boeing H, Chen TA, Steffen B, Steffen LM, Hodge A, Eriksdottir G, Smith AV, Gudnason V, Harris TB, Brouwer IA, Berr C, Helmer C, Samieri C, Laakso M, Tsai MY, Giles GG, Nurmi T, Wagenknecht L, Schulze MB, Lemaitre RN, Chien KL, Soedamah-Muthu SS, Geleijnse JM, Sun Q, Harris WS, Lind L, Arnlov J, Riserus U, Micha R and Mozaffarian D. Omega-6 fatty acid biomarkers and incident type 2 diabetes: pooled analysis of individual-level data for 39 740 adults from 20 prospective cohort studies. Lancet Diabetes Endocrinol. 2017;5:965–974.
67. Billingsley HE, Carbone S, Lavie CJ. Dietary fats and chronic noncommunicable diseases. Nutrients 2018;10:1385.
68. Lynch J, Helmrich SP, Lakka TA, et al. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med 1996;156:1307-1314.
69. Katzmarzyk PT, Craig CL, Gauvin L. Adiposity, physical fitness and incident diabetes: the physical activity longitudinal study. Diabetologia 2007;50:538-544.
70. Ozemek C, Laddu DR, Lavie CJ, et al. An update on the role of cardiorespiratory fitness, structured exercise and lifestyle physical activity in preventing cardiovascular disease and health risk. Prog Cardiovasc Dis 2018;61:484-490.
71. Blair SN, Kohl 3rd HW, Barlow CE, Paffenbarger Jr RS, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. Jama 1995;273:1093-1098.
72. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics center longitudinal study. Circulation 2011;124:2483-2490.
73. Davidson T, Vainshelboim B, Kokkinos P, Myers J, Ross R. Cardiorespiratory fitness versus physical activity as predictors of all-cause mortality in men. Am Heart J 2018;196:156-162.
74. Lee DC, Sui X, Ortega FB, et al. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. Br J Sports Med 2011;45:504-510.
75. Kokkinos P, Faselis C, Narayan P, et al. Cardiorespiratory fitness and incidence of type 2 diabetes in United States veterans on statin therapy. Am J Med 2017;130:1192-1198.
76. Wang Y, Lee DC, Brellenthin AG, et al. Association of muscular strength and incidence of type 2 diabetes. Mayo Clin Proc 2019;94:643-651.
77. Kawakami R, Sawada SS, Lee IM, et al. Long-term impact of cardiorespiratory fitness on type 2 diabetes incidence: a cohort study of Japanese men. J Epidemiol 2018;28:266-273.
78. Del Buono MG, Arena R, Borlaug BA, et al. Exercise intolerance in patients with heart failure: JACC state-of-the-art review. J Am Coll Cardiol 2019;73:2209-2225.
79. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisloff U, American Heart Association Physical Activity Committee of the Council on L, Cardiometabolic H, Council on Clinical C, Council on E, Prevention, Council on C, Stroke N, Council on Functional G, Translational B and Stroke C. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e653-e699.
80. Sui X, Hooker SP, Lee IM, et al. A prospective study of cardiorespiratory fitness and risk of type 2 diabetes in women. Diabetes Care 2008;31:550-555.
81. Tarp J, Stole AP, Blond K, Grontved A. Cardiorespiratory fitness, muscular strength and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetologia 2019;62:1129-1142.
82. Osman AF, Mehra MR, Lavie CJ, Nunez E, Milani RV. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. J Am Coll Cardiol 2000;36:2126-2131.
83. Carbone S, Billingsley HE, Rodriguez-Miguelez P, et al. Lean mass abnormalities in heart failure: the role of sarcopenia, sarcopenic obesity, and cachexia. Curr Probl Cardiol 2019.
84. Carbone S, Popovic D, Lavie CJ, Arena R. Obesity, body composition and cardiorespiratory fitness in heart failure with preserved ejection fraction. Future Cardiol 2017;13. fca-2017-0023.
85. Konigstein K, Klenk C, Rossmeissl A, Baumann S, Infanger D, Hafner B, Hinrichs T, Hanssen H and Schmidt-Trucksass A. The obesity factor: how cardiorespiratory fitness is estimated more accurately in people with obesity. *Obesity (Silver Spring)*. 2018;26:291–298.
86. Ribisl PM, Lang W, Jaramillo SA, et al. Exercise capacity and cardiovascular/metabolic characteristics of overweight and obese individuals with type 2 diabetes: the look AHEAD clinical trial. Diabetes Care 2007;30:2679-2684.
87. Jakicic JM, Egan CM, Fabricatore AN, et al. Four-year change in cardiorespiratory fitness and influence on glycemic control in adults with type 2 diabetes in a randomized trial: the look AHEAD trial. Diabetes Care 2013;36:1297-1303.
88. Look ARG, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF and Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145–54.
89. Gibbs BB, Brancati FL, Chen H, et al. Effect of improved fitness beyond weight loss on cardiovascular risk factors in individuals with type 2 diabetes in the look AHEAD study. Eur J Prev Cardiol 2014;21:608-617.
90. Kokkinos P, Myers J, Faselis C, Doumas M, Kheirbek R, Nylen E. BMI-mortality paradox and fitness in African American and Caucasian men with type 2 diabetes. Diabetes Care 2012;35:1021-1027.
91. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2065-2079.
92. Committee PAGA. Physical activity guidelines advisory Committee scientific report. Washington, DC: US Department of Health and Human Services 2018;2018:2018.
93. Balducci S, D'Errico V, Haxhi J, et al. Effect of a behavioral intervention strategy on sustained change in physical activity and sedentary behavior in patients with type 2 diabetes: the IDES_2 randomized clinical trial. Jama 2019;321:880-890.
94. Boule NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. Diabetologia 2003;46:1071-1081.
95. Maiorana A, O'Driscoll G, Goodman C, Taylor R, Green D. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabetes Res Clin Pract 2002;56:115-123.
96. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. Jama 2010;304:2253-2262.