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Muscular Strength in Risk Factors for Cardiovascular Disease and Mortality: A Narrative Review

REVIEW

ABSTRACT

Cardiovascular disease is the leading cause of death globally, accounting for approximately 32% of all deaths in 2019. There has been increasing interest in understanding the role of low muscular strength as a risk factor for cardiovascular disease, given its association with other cardiovascular risk factors such as hypertension, diabetes mellitus, and metabolic syndrome. An inverse association between muscle strength, chronic disease, all-cause mortality, and cardiovascular-related death has been reported. Recent clinical trials have consistently shown that resistance exercise, which increases strength, and potentially muscle mass, significantly improves the control of known cardiovascular disease risk factors and reduces the risk of all-cause death and cardiovascular mortality. In the present article, we review the growing body of evidence that supports the need for future research to evaluate the potential of handgrip strength as a screening tool for cardiovascular disease and its risk factors in the clinical medical setting, as part of routine care using an affordable handgrip strength device. Moreover, it is crucial to devise large-scale interventions driven by governmental health policies to educate the general population and healthcare professionals about the importance of muscular strengthening activities and to promote access to these activities to improve cardiometabolic health and reduce incidence of cardiovascular disease and mortality.

Keywords: Muscular strength, hand grip, cardiovascular disease, cardiovascular risk factors, chronic diseases, mortality, hypertension, predictors, prevention, diabetes mellitus, hypertension

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally, accounting for approximately 32% of all deaths in 2019, 1/3 of which occurred prematurely (before age 70).[1] Although the prevalence of CVD is rising globally, developing regions have both a higher incidence rate and cardiovascular (CV) mortality. In low- and middle-income countries (LICs and MICs, respectively), CVDs are contributing to poverty due to catastrophic health expenses borne by patients and premature deaths during their most productive years, with wide-scale effects on the economy.[1]

Large-scale prospective cohort studies have shown that about 70% of CVD cases can be attributed to a small cluster of individual modifiable risk factors, among which hypertension, high non-high-density lipoprotein (HDL) cholesterol, low education, tobacco use, household air pollution, and poor diet have the biggest population attributable fractions (PAFs).[2]

Due to its largely preventable nature, the development and implementation of early predictive risk markers are of paramount importance in efforts to decrease the economic, social, and healthcare-related burdens attributable to CVD.

In recent years, the role of muscular strength in health and disease has been increasingly recognized, not only as a component of physical fitness but also as a strong predictor of all-cause mortality and as a key intervention point for the prevention of chronic illnesses. Furthermore, several observational studies have shown that low muscular strength is a strong predictor for cardiovascular death

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and a prognostic factor for CVD itself.[3] The inverse association between muscle strength, CVD risk factors, and poor cardiovascular outcomes has been demonstrated in initially healthy individuals of all age groups, beginning as early as the neonatal period and persisting throughout childhood, adolescence, and adulthood[2-5] and in those with existing disease.[6,7] Therefore, the main objective of this article is to review the associations of low muscular strength with metabolic alterations, all-cause mortality, and CVD-related death. In addition, we will explore the benefits derived from resistance training (RT) interventions aimed at developing muscular strength, according to the current available evidence.

Muscular Strength and All-Cause and Cardiovascular Mortality

Several prospective analyses in large samples have revealed that handgrip strength (HGS), an indirect measure for global muscle strength,[8] is inversely associated with all-cause mortality, cardiovascular-associated death, and higher fatality rates after an acute illness independently of demographic, anthropometric, or classic cardiovascular risk factors.[2,3,9-11]

The multinational Prospective Urban Rural Epidemiology (PURE) study (n = 139 691) reported that in adults aged 35-70 years followed up for 4 years, for every 5-kg reduction in HGS, there was a significant increase in all-cause mortality (hazard ratio = 1.16) and cardiovascular mortality (hazard ratio = 1.17) (all $P < .001$).[3] After 9 years of follow-up, low HGS was ranked the third strongest risk factor with the most PAF for all-cause mortality and CVD-related death across all income countries, only surpassed by low education and tobacco use.[2] The PAF indicates the proportional reduction of a disease or outcome in a population that would occur if exposure to a specific factor was eliminated; in this case, the reduction in overall or CVD-associated mortality that would happen if low grip strength was eradicated (Table 1).

The UK biobank study, which included 502 628 adults aged 40-69 years followed for 7.1 years, showed that for every 5-kg reduction in HGS, there was a significant increase in all-cause mortality (hazard ratio of 1.20 and 1.16) and death from CVD (hazard ratio of 1.19 and 1.22) for both women and men, respectively (all $P < .001$) after adjusting for multiple confounding factors. Both associations were slightly stronger in women than men and greater in younger members of the cohort in comparison to older individuals.[11] In addition, muscle weakness (defined as a grip strength ≤26.0 kg for men and ≤16.0 kg for women) was also found to be significantly associated with an increased risk of all-cause mortality, CVD-related death, and mortality due to all types of cancer and death due to respiratory causes.

The inverse association between HGS, all-cause mortality, and CV mortality seen in the UK Biobank study is of a similar magnitude to findings reported previously by the PURE analysis.

Both studies found that HGS is a stronger predictor of mortality than traditional CVD risk factors such as hypertension and low physical activity.[3]

The UK biobank analysis is one of the few studies that has evaluated the utility of HGS as a predictor of CVD, all-cause mortality, and CVD-related death when added to an established office-based risk score (including age, sex, diagnosed diabetes, BMI, systolic blood pressure, and smoking). Their results indicated that HGS improves the prediction ability of the aforementioned model to the same degree as the addition of HDL and N-terminal proB-type natriuretic peptide.

Additionally, a very large meta-analysis including adults from diverse ethnic groups (n = 1 907 580, average follow-up 11.5 years, ages 19-84.9 years) reported that high muscular strength in adults (using HGS) was associated with a reduction of 31% in all-cause mortality (hazard ratio = 0.69), in comparison to the "lower strength group" in the cohort. This association was slightly stronger in women (40% relative risk reduction) than men (31% relative risk reduction) ($P < .001$).[10]

Resistance Training, Mortality, and Cardiovascular Diseases

Data from studies assessing the efficacy of RT have shown beneficial effects in reducing overall mortality, cardiovascular-related death, and CVD incidence, independently of aerobic exercise and after adjusting for physical activity and body mass index (BMI).[12,13] Resistance training is a mode of exercise that increases muscle strength, and potentially muscle mass, as it involves exertion against resistance.[14] Resistance training has the capacity to change body composition by increasing lean body mass, can lead to significant improvement of metabolic parameters.[14,15]

A large meta-analysis (n = 370 256) reported that in adults aged 18-75 years (followed-up on average 8.85 years), performing RT at any frequency was associated with a significant reduction in overall mortality of 21%. The combination of RT and aerobic training resulted in additional benefits, including a reduction in overall mortality of about approximately 40%.[12] However, subgroup analysis revealed that the inverse association between mortality and RT only exists if the training frequency does not exceed a certain limit.

HIGHLIGHTS

- Adequate muscular strength is associated with lower levels of classic cardiovascular risk factors and reduced risk of all-cause mortality and cardiovascular-related death.
- Muscular strength is conditioned by a genetic component that overlaps with longevity and health and an acquired component that reflects the cumulative incidence of lifelong stressors and changes in muscle mass and function due to physical activity and exercise patterns.
- A growing body of evidence supports the need for future research to evaluate the potential of handgrip strength as a screening tool for CVD and its risk factors in the clinical medical setting, as a part of routine care, using an affordable handgrip strength device.

Table 1. Rank Order for the Top 10 Risk Factors for Major CVD and All-Cause Mortality Across the Globe.

Rank	CVD Overall PAF (95% CI)	Mortality Overall PAF (95% CI)
1	Hypertension 22.3 (17.4-27.2)	Low education 12.5 (10.7-14.3)
2	High non-HDL cholesterol 8.1 (3.1-13.2)	Tobacco use 11.3 (8.1-14.5)
3	Household air pollution 6.9 (4.7-7.6)	Low grip strength 11.6 (7.3-16.0)
4	Tobacco use 6.1 (4.5-7.6)	Poor diet 11.1 (7.7-14.6)
5	Poor diet 6.1 (2.8-8.8)	Hypertension 8.8 (7.6-9.9)
6	Low education 5.8 (2.8-8.8)	Household air pollution 6.6 (4.7-8.5)
7	Abdominal obesity 5.7 (1.7-9.8)	Diabetes 5.5 (4.2-6.8)
8	Diabetes 5.1 (2.9-7.4)	Abdominal obesity 2.8 (1.3-4.3)
9	Low grip strength 3.3 (0.9-5.7)	Depression 2.2 (1.4-3.0)
10	Low physical activity 1.5 (0.3-2.7)	Low physical activity 2.2 (1.0-3.3)

CVD, cardiovascular disease, HDL, high-density lipoprotein, PAF, population attributable fraction.
Source: Yusuf et al[2] 2020, p. 26.

Data from the National Health and Nutritional Examination Survey 2003-2006 (NHANES) showed that in adults, performing 8-14 sessions of muscle-strengthening activities monthly was associated with a lower overall mortality and CVD-related mortality.[16] Increased muscular strength, rather than the associated behaviors, was the most important factor mediating the improvement in all-cause mortality.[16]

However, both studies demonstrated that the association between RT and decreased mortality risk is nonlinear, as it loses significance if training frequency exceeds a certain threshold.[13,16] This could potentially be explained by a lower long-term adherence to RT seen at higher training frequencies.[13,16]

The mechanism by which muscular strength exerts a protective effect against mortality is not completely understood. To a certain extent, it results in improved survival by improving CVD risk factors (e.g., dyslipidemia and diabetes) and thus reducing risk of CVD itself.[13] Muscle strength may also attenuate the risk of death due to acute stressful events (e.g., pneumonia or trauma), as it correlates with muscle mass, which constitutes the biggest reservoir of amino acids in the body, needed for tissue repair and healing after an injury.[8,17] Often, patients with low muscle strength are older, physically inactive, dependent, and prone to accidents such as injurious falls, which increases their mortality risk.[8,17]

However, it is important to note that evidence for the protective effects of adequate muscle strength is based on age- and sex-adjusted definition of low muscle strength—such that low strength within a category represents a risk, rather than it being attributed to an age-related loss per se.

Nonetheless, some authors have questioned if the association between mortality and HGS is mediated by confounding factors, such as underlying systemic diseases, which could result in both the loss of muscular strength (dynapenia) and eventually death.[17] Yet, longitudinal studies have shown that the association between HGS and mortality exists in young healthy individuals[4,9] long before the appearance of disease and that low muscle strength is associated with mortality independently of underlying diseases and many other factors such as inflammation, physical activity,[13] and cardiorespiratory fitness.[17] This indicates that muscular fitness/function is somehow involved in the preservation of health, and low strength is an early prognostic marker for death and future illness.[17]

In a cohort of exceptionally long-living individuals from the Hawaiian population (n=2239 men from the Honolulu Heart Program/Honolulu–Asia Aging Study, followed up for 44 years), midlife HGS, lifestyle habits, and parents' longevity were shown to be predictors of length of life and of becoming a centenarian. In addition, infants of long-living mothers had, in their later life, better HGS and less chronic diseases than offspring of mothers with average life span.[18] This finding suggests that the protective mechanism associated with higher muscle strength probably overlaps with the genetic component of both inherited longevity and innate health characteristics (e.g., the tendency to be healthy or not and depending on an individual's "physiological reserve" that confers protection from chronic disease as the person ages).[18] Although up to 60% of HGS is determined by genetic variants, it also reflects acquired modifications of body composition (e.g. variations in lean body mass and percentage of body fat) and fitness, the aging processes, chronic diseases, and lifelong stressors; all of which form a net of complex interactions, ultimately determining the overall health of an individual.[11,17,18]

Muscular Strength and Hypertension

The global prevalence of hypertension is around 34%, and it is expected to increase as the population progressively ages, leading to mounting health-care costs and increasing CVD.[19] Robust evidence from observational and interventional studies produces an inverse correlation between muscle strength and blood pressure (BP) across all ages.[20-24] In fact, in children and adolescents from different ethnicities, low HGS correlates with higher blood pressure (either systolic and diastolic or both), after controlling for BMI and other confounding factors.[4,5] Handgrip strength and BP are inversely correlated in healthy pre-hypertensive adults, suggesting

that muscle strength could act as a protective factor against hypertension.[20]

A cohort study in the United Kingdom (n=2677, adults aged 59-73 years) reported that a decrease in 1 standard deviation (SD) of HGS was significantly associated with higher BP (odds ratio (OR)=1.13, $P < .05$).[21] Data from the NHANES 2011-2012 showed that in adults from the United States with normal BMIs and no history of CVD, the mean HGS was lower among individuals with undiagnosed and diagnosed hypertension compared with individuals without HTN.[22]

Moreover, the PURE China study (n=39 862, adults aged 35-70 years, followed up for 8.9 years) demonstrated that hypertensive individuals with low HGS had a higher CVD incidence, cardiovascular mortality, and all-cause mortality ($P < .001$), in comparison to hypertensive subjects with greater HGS.[7]

As a proxy of whole-body strength, isometric HGS can be used unadjusted (raw or absolute HG, the recorded value from the dynamometer) or it can be adjusted by bodyweight/BMI or other anthropometric indicators of mass, or body size—referred to as relative HGS. Due to the direct relationship between body mass (in kilograms and BMI) and muscle strength,[23] in overweight individuals, the associations between absolute HGS and cardiometabolic abnormalities (e.g., hyperglycemia, hypertension, and metabolic syndrome) may be confounded by the large contribution of adiposity to additional mass (at least in non-athletic populations). The latter adds to the inflammatory burden, therefore attenuating the underlying positive association between high muscle strength and cardiometabolic health and explaining the lack of positive association between low HGS and hypertension in some populations. For example, a cross-sectional study based on data from the NHANES 2011-2012 and 2013-2014 (n=4597, survey participants aged ≥18 years old, US population) reported that HGS was positively related to higher diastolic blood pressure (DBP). Specifically, in obese and overweight men, increased HGS was associated with a higher risk of hypertension (OR=1.31, $P < .05$).[25] In addition, some cross-sectional studies in Chinese individuals showed a positive association between HGS and higher BP, in both children and adults.[26,27] However, in these studies, there was positive association between HGS and BP before adjusting for BMI, suggesting that overweight individuals have a variable HGS according to their body composition, which in turn determines their metabolic risk. Neither BMI nor body mass discriminates between mass from lean or fat components of body composition, confounding the analysis of associations between strength and cardiometabolic health.

Conversely, the Korean Longitudinal Study of Ageing (n=3383 aged >65 years, followed up for 10 years) reported that the risk of hypertension significantly decreased across groups of increasing relative HGS (adjusted by bodyweight). This study also compared the predictive value of raw HGS versus relative HGS as a predictor of HTN, concluding that the latter correlates better with the risk of hypertension in adults.[23] Moreover, a longitudinal study in China (n=8480, age >40 years, followed up for 6 years) showed that the risk of hypertension was inversely correlated to quartiles of increasing weight-adjusted HGS.[24]

These findings highlight that relative HG, rather than absolute HGS, is more consistently associated with BP values and the risk of hypertension. Aligning with this, Chun et al[28] showed that low HGS was only predictive of metabolic syndrome (MetS) after adjusting it by bodyweight or BMI. The lack of adjustment of HGS might explain the positive associations between HGS and HTN in the aforementioned Chinese studies and in the NHANES analysis.[25-27]

Currently, the strongest evidence supporting a protective effect of muscle strength/function against hypertension comes from a number of clinical trials assessing the effects of RT on BP. These studies demonstrated that RT results in significant reductions of BP,[29,30] but the magnitude of the effect differed substantially according to the specific training mode—isometric RT being the most effective.[30] A meta-analysis (n=5223, adults aged >18 years) which compared the effects of 4 different types of training on BP concluded that endurance exercise and dynamic and isometric RT all produced significant reductions in systolic blood pressure (SBP) and DBP. However, reductions in SBP and DBP were larger after isometric training (mean reduction of BP: −10.9/−6.2 mm Hg), more than double the effect obtained by aerobic exercise (repeated submaximal contractions of large skeletal muscle groups), dynamic resistance exercise (concentric, isometric, and eccentric muscle contractions), and the combination of both[30] (Figure 1).

Isometric exercise was superior regardless of age, sex, characteristics of exercise sessions (e.g., frequency and duration) and BP classification, with benefits more pronounced in hypertensive individuals. Furthermore, another meta-analysis (n=122, adults >18 years) demonstrated that despite its short duration (less than 20 minutes a session, 3 times a week for a total time of less than 1 hour weekly), isometric exercise is more effective than longer sessions of combined endurance plus RT, diet, and even pharmacological interventions for BP control.[29] These findings are promising because they represent an efficient alternative to aerobic and dynamic resistance exercise, potentially improving adherence in many hypertensive patients, especially in those with comorbidities that render endurance training difficult to tolerate, such as arthritis.

Several mechanisms that link low HGS with hypertension and other chronic diseases have been proposed. First of all, it is believed that obesity and age-related changes in body composition constitute the starting point for inflammation.[31,32] With aging and obesity, visceral fat increases parallel to a marked loss of skeletal muscle mass (aging leads to reduced size and number of type II muscle fibers, motor neurons, satellite cells, and mesenchymal progenitor cells, partly due to hypogonadic states), and an infiltration of fatty tissue.[31] Obesity is associated with increased leptin concentrations, which promote ectopic fat deposition in the muscle, due to a lack of fatty acid oxidation as a source of energy.[31]

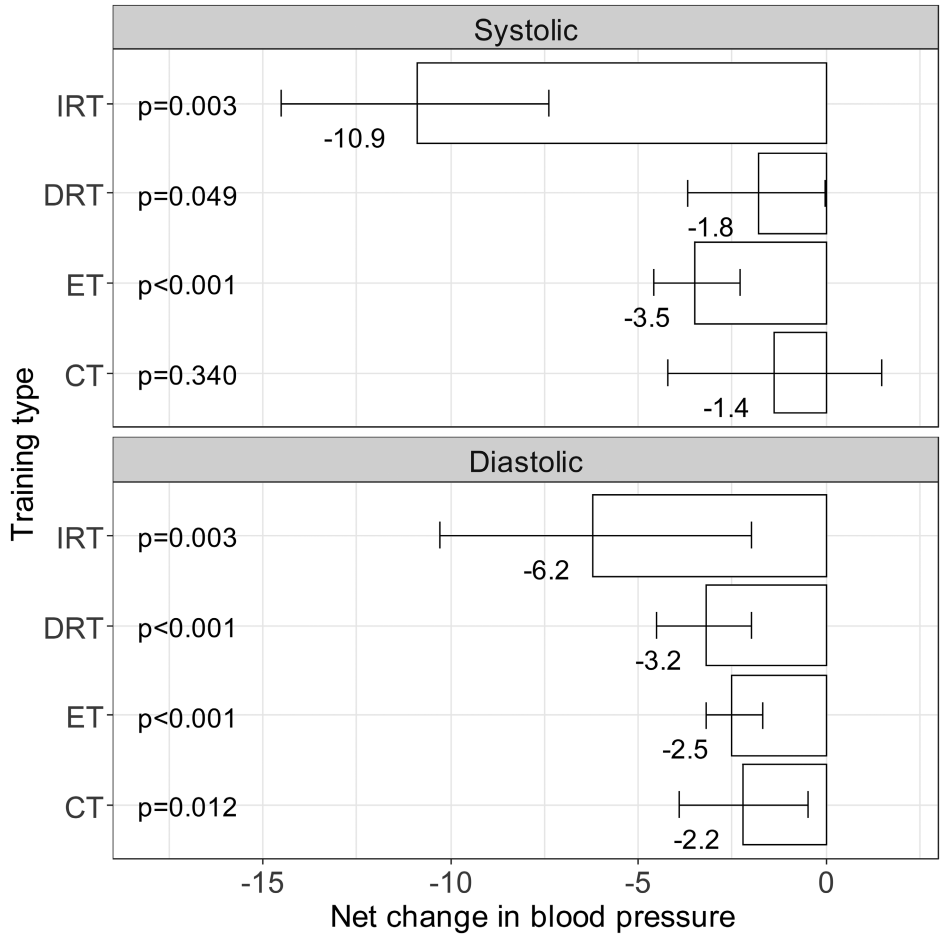

Figure 1. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) following different types of exercise training. Net mean change in mm Hg, adjusted for control data (95% confidence limits). Adapted from: Cornelissen et al[30] 2013.
IRT, isometric resistance training; ET, endurance training; DRT, dynamic resistance training; CT, combined endurance and dynamic resistance training

Lipid infiltration in the muscle decreases its quality (lower muscle quality is a direct precursor of sarcopenia) and strength, adversely affecting focal insulin signaling and mitochondrial function/concentration, both of which constitute pivotal points for the development of metabolic derangements.[22] Impairment of mitochondrial function leads to significant changes in cellular metabolism. Fatty acid oxidation decreases significantly, resulting in disrupted healing processes, reduced myocyte oxidation capacity and muscular power (reduced contractile function and lower force generation). Increased reactive oxygen species produced by fatty tissue, which exert a direct toxic effect over myocytes, favor the differentiation of mesenchymal cells into adipocytes. In turn, all of these events lead to fibrosis after an injurious insult, which is worsened by the dwindling number of mesenchymal progenitor cells associated with aging, ultimately resulting in decreased muscle mass.[31]

Moreover, visceral adipocytes act as an endocrine organ, activating immune cells (which infiltrate adipose tissue) and producing pro-inflammatory cytokines (including leptin), that in turn stimulate the secretion of acute phase reactants in the liver (e.g., C-reactive protein, fibrinogen, and sialic acid) and have a direct oxidative (lypotoxic) effect over myocytes.[31,32] This results in chronic low-degree inflammation, which leads to insulin resistance (IR) and lower muscle quality (reducing strength/function per unit of mass) partly due to increased muscle catabolism and impaired growth.[31,33] In addition, individuals with IR, obesity, or diabetes type 2 have a lower concentration of cytokines with anti-inflammatory properties such as adiponectin, which has vasodilatory, antithrombotic, and antiatherogenic effects. This results in an increased risk of CVD, coronary atherosclerosis, left ventricular hypertrophy (associated with diastolic dysfunction), and worse cardiovascular outcomes. Research has demonstrated that coronary atherosclerosis is distinctively associated with an increased leptin/adiponectin ratio, which is observed in obese individuals.[34] In contrast, the release of anti-inflammatory myokines from muscular tissue, such as irisin, counteracts the inflammatory effect of adipose tissue.[35]

Inflammation also results in hypertension, due to endothelial dysfunction compromising blood vessel relaxation and NO synthase expression. Chronic inflammation, obesity (which causes an upregulation of the renin–angiotensin system, increasing BP), and IR are independent risk factors for hypertension.[22,31] Lower levels of adiponectin are

also associated with a decreased response to acetylcholine and increased vasoconstriction in response to angiotensin II (Ang II), contributing to a further increase in BP.[35] In turn, endothelial dysfunction and hypertension result in the formation of atheroma plaques and consequently, acute thrombotic complications that are directly linked to chronic low-grade inflammation.[35] Other possible mechanisms that link low HGS to HTN include an impaired autonomic regulation of BP and HR, seen in patients with low muscle strength.[24]

To summarize, visceral fat accumulation results in microinflammation, which is directly responsible for muscle fitness decline (loss of mass and strength). It is the starting point for many chronic diseases, such as diabetes and hypertension, as it affects cellular metabolism and energy expenditure (decreased fatty acid oxidation due to downregulation of lipoprotein lipase and impaired mitochondrial function). It also has multiple systemic effects (e.g., in the endothelium) that contribute to the development of clinically relevant disorders and ultimately cardiovascular disease.

Muscular Strength and Diabetes

The prevalence and incidence of type 2 diabetes (T2DM) continue to increase worldwide, and more rapidly in low- and middle-income countries (LMIC) than in high-income countries (HIC).[36] Mounting evidence indicates that there is an independent, inverse association between low muscle strength and T2DM incidence, prevalence, and risk, allowing low muscle strength to serve as a possible early marker for disease and a therapeutic target.[37-40]

The inverse association between low muscular strength and T2DM, or alternatively dysglycemia, has been demonstrated in both cross-sectional and longitudinal studies using different parameters that quantify muscle strength, such as HGS, muscle fitness scores (which comprise measures of strength, power, and muscular endurance), back muscle endurance, key pinch-power in the dominant hand, or leg press and bench press strength.[5,21,22,37-40] These associations were significant after adjusting for anthropometric, demographic, and social factors, as well as cardiorespiratory fitness in some analyses. A large meta-analysis (n = 1 713 468 US adults aged 45-64 years) showed that each SD increase in HGS, decreased the risk of T2DM by 13% in both men and women, after adjusting for anthropometric markers of adiposity.[37]

In addition, longitudinal studies demonstrate that HGS is a predictor of mortality and CVD among patients with T2DM or hyperglycemia. The multinational Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial (n = 12 537 participants aged >50 years, followed up for 6.2 years) showed that in adults with impaired fasting glucose (12%) or T2DM (88%), an increase of 1 SD of HGS resulted in a significantly lower incidence of CVD, all-cause death (hazard ratio: 0.70 for women and 0.87 for men), and CV-related mortality (hazard ratio: 0.88 for men, 0.70 for women) (all $P < .001$).[6]

Available evidence suggests that the lack of muscular fitness is involved in the progression from normoglycemia to prediabetes and finally T2DM, as low HGS is not only associated with the outcome itself (T2DM) but also with all of the metabolic alterations that precede it, such as IR, beta cell dysfunction, and hyperglycemia in premorbid populations.[5,21,22,37-40]

For instance, The European Youth Heart Study (n = 317) showed that both HGS and cardiorespiratory fitness measured during adolescence were inversely correlated with fasting insulin levels, homeostatic model assessment for insulin resistance (HOMA-IR) (which is a proxy for insulin resistance), and B-cell function (measured with HOMA-B model) at a 12-year follow up.[39] For each 1-SD increase in HGS, fasting insulin, HOMA-IR, and HOMA-B decreased by 11.3%, 12.2%, and 8.9%, respectively. These associations remained significant after adjusting for waist circumference (WC), suggesting that muscle strength could act as a protective factor against metabolic derangements even in the presence of central obesity and increased adiposity. Another study in adults (n = 2677) aged 59-73 years indicated that a 1-SD decrease in HGS was associated with a significant elevation of HOMA-IR (0.07 SD unit increase) and peripheral glycemia 2 hours after ingesting 75 g of glucose (0.05 SD unit increase).[21] Handgrip strength is also inversely associated with the risk of prediabetes even in normal-weight adults, and it is estimated that an increase of 1-SD could potentially prevent up to 52% of cases of T2DM in men and 62% in women (all $P < .01$).[40] Overall, these studies suggest that poor muscular fitness is involved in the development of dysglycemia and ultimately clinically relevant disorders such as T2DM.[5,21,22,37-40]

Resistance Training, Type 2 Diabetes Mellitus, and Insulin Sensitivity

Recent clinical trials have shown that RT, either alone or in combination with aerobic exercise, can potentially prevent new cases of diabetes and improve glycemic control (HBA1C) in subjects already diagnosed with T2DM, while increasing functional capacity, muscle strength, and lean body mass and ameliorating the patient's metabolic profile.[41-47]

A sub-analysis of the Women's Health Study which followed 35,754 healthy women for 10.7 ± 3.7 years reported that compared to women who reported no engagement in strength training, women who performed any RT had 30% lower risk (hazard ratio: 0.70, 95% CI: 0.6-0.80) of incident type 2 diabetes. In addition, RT can prevent up to 26% of incident CVD cases, experiencing the greatest benefit at a training frequency of 60-120 minutes weekly. Both of these associations were independent of other covariates such as aerobic exercise, changes in dietary intake, age, smoking status, and alcohol consumption. Besides, engagement in both resistance and endurance exercise was associated with additional risk reductions for both T2DM and cardiovascular disease compared with participation in aerobic activity only.[42]

To the present, trials evaluating the effects of RT over glycemic control (determined by HBA1C) in patients with T2DM have shown divergent results.

Some studies assessing the effects of moderate-intensity, high-volume RT such as performed 5 times a week for 4-6 weeks in middle-aged adults with T2DM, failed to show an improvement in HBA1c, although insulin levels and plasma

glucose decreased significantly.[43] In contrast, a meta-analysis reported that HBA1c improved after all types of RT, but the magnitude of the effect was greater at a higher intensity. Also, insulin levels were significantly decreased with high-intensity RT, but not with low-to-moderate intensity exercise.[41] Another meta-analysis revealed that high-intensity and lengthy RT (duration of 12 weeks or more) improved HOMA-IR in healthy older adults. On the other hand, moderate-intensity RT for shorter less than 12 weeks improved HbA1c in old people with or without T2DM. Exercise programs that were longer and/or more intense did not result in significant improvements in glycemic control (HbA1C).[46] In this meta-analysis, exercise intensity was defined according to the "American's College of Sports Medicine" classification of RT, which is based on the maximum weight that an individual can lift during one single repetition of a given excercise (1RM). In this case, lifting a weight lower or equal to 50% of 1RM qualifies as "light exertion" 51%-69% is considered "moderate," and finally, 70% or higher is classified as high-intensity exercise. Other studies, in overweight, sedentary older adults (aged 60-80 years) reported that high-intensity (75%-80% of total capacity) RT is not only safe but also leads to a significant improvement in HbA1c and lean body mass even in the absence of weight loss, independently of changes in WC, age, sex, duration of diabetes, use of oral hypoglycemic medication, medication changes, and baseline HbA1c levels.[45,47] Although the results of the aforementioned trials vary, they suggest that higher-volume and higher-intensity protocols may yield greater metabolic benefits compared with lower-volume and lower-intensity exercise programs, depending on the population being considered.[45] Also, research has shown that moderate- and high-intensity RT results in significant increase in adiponectin concentrations, which ameliorates insulin sensitivity and affects carbohydrate and lipid metabolism. Resistance training intensity is correlated with adiponectin levels after the intervention has ceased, suggesting that high-intensity protocols might yield a greater long-term benefit over IR and ultimately glucose disposal.[46]

Various studies have shown that there is a strong correlation between the increase in lean body mass, post-training muscle cross-sectional area, and improvement of both glycemic control and insulin sensitivity in diabetic patients (with or without changes in adiposity).[45] Differences in the magnitude of muscle size and fat-free mass changes after each exercise program could potentially explain the discordant results in many of the available trials. However, a number of studies have also reported that IR can improve in the absence of lean body mass changes after RT, possibly due to improvements in muscle quality and upregulation of GLUT4 glucose cotransporters, insulin receptors, and enhanced enzymatic activity of protein kinase B-α/β and glycogen synthase (which leads to increased glycogen storage in the muscle, reducing blood glucose by utilizing it in glycogen synthesis).[45] Further research is needed to understand the mechanisms by which RT ameliorates hyperglycemia and insulin sensitivity and also to determine which RT parameters yield the greatest benefit for different groups of patients (e.g., healthy adults and older adults) as their response to exercise seems to differ according to their baseline characteristics. It is possible that older adults with T2DM may require higher intensity and/or longer interventions than younger and healthier subjects, in order to experience significant changes in glycemic control and basal insulin sensitivity, due to extensive β-cell damage.[46] Differences in the exercise protocols used by each study make comparisons the relative benefits of aerobic exercise versus RT over glycemic control difficult.[44] Further research evaluating frequent RT versus aerobic training is required to establish solid conclusions regarding the potential superiority of either of these modes of exercise in improving glycemic control.

The mechanisms that link T2DM and low muscular strength are not completely understood. As with hypertension, it is believed that aging, obesity, and consequent chronic inflammation play a key role in the development of IR and later T2DM.[31,32] As previously discussed, lipid infiltration of skeletal muscle directly causes the loss of lean body mass, subsequently resulting in lower muscular quality and strength, adversely affecting insulin signaling and mitochondrial function.[21,22,31] Myolipid infiltration also inhibits the synthesis of structural muscle proteins such as myosin heavy chain, eventually leading to myocyte apoptosis and muscle atrophy, which are enhanced by mitochondrial dysfunction and IR.[21,22,31-33] In turn, apoptosis of myocytes leads to a decreased expression of glucose cotransporters (GLUT4) at the muscle plasma membrane, as it is proportional to fiber volume, resulting in a decreased muscular uptake of glucose and consequent hyperglycemia.[21,22] High intracellular glucose concentrations alter muscle function due to molecular changes in structural proteins, negatively affecting strength and power.[22] Damaged proteins are difficult to dispose of due to age-related reductions in proteasome activity, deficiencies in ubiquitylation, and autophagy and impairments in removing degraded proteins and end products, contributing to lower muscular fitness.[31] Ultimately, the cells enter a vicious cycle in which hyperglycemia potentiates myocyte apoptosis and vice versa, until finally diabetes ensues. Nonetheless, myokines released during exercise can counteract the effects of inflammation and help improve metabolic homeostasis.[35] In addition, diabetic hand syndrome (characterized by limited joint mobility or diabetic cheiroarthropaty) and Dupuytren's disease, which are common among patients with T2DM, might also contribute to low Hand Grip (HG) measured with a dynamometer.[22] Peripheral neuropathy affecting the upper or lower limbs can also affect different muscle strength measurements (e.g., handgrip and knee extensor strength).

Muscular Strength, Obesity, Metabolic Syndrome

In recent decades, the global prevalence of obesity has increased in response to the adoption of unhealthy lifestyles, such as lack of exercise, increased sedentarism, and hypercaloric diets.[33] Significantly, obesity is strongly associated with CVD and increased morbidity and mortality, affecting predominately LMIC.

Research has shown that both obese and dynapenic individuals have abnormally high levels of pro-inflammatory cytokines, which are associated with the

development of chronic diseases, and decreased levels of chemokines with anti-inflammatory properties such as adiponectin.[5,31,32,34,48] Furthermore, numerous studies in both adolescents and adults have revealed an inverse association between muscular strength (particularly if adjusted for BMI or weight) and MetS, as defined by the International Diabetes Federation (IDF) or National Cholesterol Education Program Adult Treatment Panel III (ATP III), or alternatively its individual components, after controlling for multiple confounding factors including smoking, alcohol intake, metabolic syndrome risk factors at baseline, family history of chronic diseases (diabetes, hypertension, and premature coronary disease) as well as cardiorespiratory fitness in some analysis.[4,5,21,26,49] This association probably stems from the fact that obese and dynapenic patients have chronic low-grade inflammation and IR, alterations linked to MetS.[5,31,32] Indeed, this group demonstrated that lower levels of adiponectin, especially an increased leptin/adiponectin ratio (reflecting the imbalance between pro-inflammatory and anti-inflammatory cytokines), positively correlate with the individual components of metabolic syndrome, including triglycerides level, fasting plasma glucose, and BP levels and negatively with HDL-C levels in T2DM patients.[34] Interestingly, both low muscular strength and increased adiposity seem to have an additive effect on metabolic risk. In adults from Colombia (n = 5026, 64% women; mean age 51.2 years), a MIC in South America, we showed that the joint evaluation of WC and relative HG is a better predictor of MetS than either of those variables alone.[49]

The prevalence of metabolic syndrome varies between 15% and 40% globally and is higher in the populations of developing countries.[34] Though obesity rates are increasing rapidly in LIC and MIC, maternal undernutrition remains a significant public health problem in these regions, in contrast to HIC. The greater prevalence of maternal malnourishment, leading to fetal exposure to an adverse nutritional in-utero environment, could explain the higher prevalence of MetS in LIC in comparison to richer nations within the same region.[33] An association between low birthweight (LBW), as a result of maternal malnutrition and altered fetal programming,[33] and later chronic disease (including MetS), higher level of pro-inflammatory markers, and lower levels of muscle mass and strength has been proposed.[33]

To test this proposal, we evaluated the impact on muscle strength, aerobic fitness, and body composition by replacing the physical education (PE) class of Colombian adolescents with resistance or aerobic training. One hundred twenty tanner stage 3 adolescents attending a state school were randomized to RT, aerobic training, or a control group who continued to attend a weekly 2-hour PE class for 16 weeks. The RT and aerobic training groups participated in twice-weekly supervised after-school exercise sessions of <1 hour instead of their PE class. Sum of skinfolds, lean body mass (bioelectrical impedance analysis), muscular strength (6 RM) (bench press, lateral pulldown and leg press), and estimated cardiorespiratory fitness (multistage 20-m shuttle run) were assessed at pre- and post-intervention. Resistance training attenuated increases in sum of skinfolds compared with controls ($d = 0.27$, [0.09-0.36]). We found no significant effect on lean body mass. Resistance training produced a positive effect on muscle strength compared with both controls ($d = 0.66$ [0.49-0.86]) and aerobic training ($d = 0.55$ [0.28-0.67]). There was a positive effect of RT on cardiorespiratory fitness compared with controls ($d = 0.04$ [−0.10 to 0.12]) but not compared with aerobic training ($d = 0.24$ [0.10-0.36]). Thus, replacing a 2-hour PE class with two 1-hour RT sessions attenuated gains in subcutaneous adiposity and enhanced muscle strength and aerobic fitness development.[50] In addition, we assessed the efficacy of the supervised in-school combined resistance and aerobic training program according to birthweight. We compared changes within lower (<3000 g) and normal birthweight intervention and PE control subgroups. Within the intervention group, improvements in all fitness measures were larger in lower birthweight ($g = 0.53$-0.94) than in normal birthweight girls ($g = 0.02$-0.39).[51] These findings suggest an enhanced adaptive response to training in participants with lower birthweight which warrants further investigation.

In addition, in school children (n = 669, aged 8-14 years, 47% female), we showed a significant inverse correlation between relative HGS and composite metabolic risk, an association which was greater in the low birthweight school children (<2800 g at full-term) than in those with normal birthweight (>2800 g at full term).[5] Moreover, we observed that in the children with LBW, there was a stronger inverse association between HGS and metabolic risk score: $r = -0.599$, $P = .002$ compared to $r = -0.383$, $P < .001$, in the normal birthweight school children. Overall, these findings support the fetal programming hypothesis mentioned earlier.

The association between low HGS, inflammation, and MetS has been supported by recent clinical trials which showed that RT leads to increased muscle mass, strength, and lower concentrations of pro-inflammatory biomarkers, independent of weight loss, age, and baseline disease.[33,52]

CONCLUSIONS

Adequate muscular strength is associated with lower levels of classic cardiovascular risk factors and reduced risk of all-cause mortality and cardiovascular-related death, although the mechanism by which muscular strength improves health and decreases mortality is not completely understood. Furthermore, muscular strength is conditioned by a genetic component that overlaps with longevity and health and reflects the cumulative incidence of lifelong stressors, beginning in the gestational period. These findings strongly support the need for future research to evaluate the potential for introducing the assessment of HGS in the clinical medical setting as part of routine care using an affordable device, in order to identify individuals with low strength, and as part of office-based models to predict CVD. Moreover, it is crucial to devise large-scale interventions, such as governmental health policies, to promote muscular strengthening activities in the general population, in order to reduce incidence of CVD and mortality.

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REFERENCES

1. World Health Organizarion [internet]. Cardiovascular diseases (CVDs) Fact sheet; 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds); Cited 2022 March 4.
2. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;395(10226):795-808. [CrossRef]
3. Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet*. 2015;386(9990):266-273. [CrossRef]
4. Grøntved A, Ried-Larsen M, Møller NC, et al. Muscle strength in youth and cardiovascular risk in young adulthood (the European Youth Heart Study). *Br J Sports Med*. 2015;49(2):90-94. [CrossRef]
5. Cohen DD, Gómez-Arbeláez D, Camacho PA, et al. Low muscle strength is associated with metabolic risk factors in Colombian children: the ACFIES study. *PLoS ONE*. 2014;9(4):e93150. [CrossRef]
6. Lopez-Jaramillo P, Cohen DD, Gómez-Arbeláez D, et al. Association of handgrip strength to cardiovascular mortality in prediabetic and diabetic patients: a subanalysis of the ORIGIN trial. *Int J Cardiol*. 2014;174(2):458-461. [CrossRef]
7. Liu W, Leong DP, Hu B, et al. The association of grip strength with cardiovascular diseases and all-cause mortality in people with hypertension: findings from the Prospective Urban Rural Epidemiology China Study. *J Sport Health Sci*. 2021;10(6):629-636. [CrossRef]
8. Wind AE, Takken T, Helders PJ, Engelbert RH. Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults? *Eur J Pediatr*. 2010;169(3):281-287. [CrossRef]
9. Soysal P, Hurst C, Demurtas J, et al. Handgrip strength and health outcomes: umbrella review of systematic reviews with meta-analyses of observational studies. *J Sport Health Sci*. 2021;10(3):290-295. [CrossRef]
10. García-Hermoso A, Cavero-Redondo I, Ramírez-Vélez R, et al. Muscular strength as a predictor of all-cause mortality in an apparently healthy population: a systematic review and meta-analysis of data from approximately 2 million men and women. *Arch Phys Med Rehabil*. 2018;99(10):2100-2113.e5. [CrossRef]
11. Celis-Morales CA, Welsh P, Lyall DM, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ*. 2018;361:k1651. [CrossRef]
12. Saeidifard F, Medina-Inojosa JR, West CP, et al. The association of resistance training with mortality: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2019;26(15):1647-1665. [CrossRef]
13. Kamada M, Shiroma EJ, Buring JE, Miyachi M, Lee IM. Strength training and all-cause, cardiovascular disease, and cancer mortality in older women: a cohort study. *J Am Heart Assoc*. 2017;6(11):e007677. [CrossRef]
14. Westcott WL. Resistance training is medicine: effects of strength training on health. *Curr Sports Med Rep*. 2012;11(4):209-216. [CrossRef]
15. Hunter GR, Bryan DR, Wetzstein CJ, Zuckerman PA, Bamman MM. Resistance training and intra-abdominal adipose tissue in older men and women. *Med Sci Sports Exerc*. 2002;34(6):1023-1028. [CrossRef]
16. Dankel SJ, Loenneke JP, Loprinzi PD. Determining the importance of meeting muscle-strengthening activity guidelines: is the behavior or the outcome of the behavior (strength) a more important determinant of all-cause mortality? *Mayo Clin Proc*. 2016;91(2):166-174. [CrossRef]
17. Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc*. 2003;51(5):636-641. [CrossRef]
18. Rantanen T, Masaki K, He Q, Ross GW, Willcox BJ, White L. Midlife muscle strength and human longevity up to age 100 years: a 44-year prospective study among a decedent cohort. *Age (Dordr)*. 2012;34(3):563-570. [CrossRef]
19. Poulter NR, Borghi C, Damasceno A, et al. May Measurement Month 2019: results of blood pressure screening from 47 countries. *Eur Heart J Suppl*. 2021;23(Suppl B):B1-B5. [CrossRef]
20. Maslow AL, Sui X, Colabianchi N, Hussey J, Blair SN. Muscular strength and incident hypertension in normotensive and prehypertensive men. *Med Sci Sports Exerc*. 2010;42(2):288-295. [CrossRef]
21. Sayer AA, Syddall HE, Dennison EM, et al. Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. *Qjm*. 2007;100(11):707-713. [CrossRef]
22. Mainous AG, 3rd, Tanner RJ, Anton SD, Jo A. Grip strength as a marker of hypertension and diabetes in healthy weight adults. *Am J Prev Med*. 2015;49(6):850-858. [CrossRef]
23. Chon D, Shin J, Kim JH. Consideration of body mass index (BMI) in the association between hand grip strength and hypertension: Korean Longitudinal Study of Ageing (KLoSA). *PLoS ONE*. 2020;15(10):e0241360. [CrossRef]
24. Gu Y, Dong J, Meng G, et al. Handgrip strength as a predictor of incident hypertension in the middle-aged and older population: the TCLSIH cohort study. *Maturitas*. 2021;150:7-13. [CrossRef]
25. Ji C, Zheng L, Zhang R, Wu Q, Zhao Y. Handgrip strength is positively related to blood pressure and hypertension risk: results from the National Health and nutrition examination survey. *Lipids Health Dis*. 2018;17(1):86. [CrossRef]
26. Mallah MA, Liu M, Liu Y, et al. Association of handgrip strength with the prevalence of hypertension in a Chinese Han population. *Chronic Dis Transl Med*. 2019;5(2):113-121. [CrossRef]
27. Dong B, Wang Z, Arnold L, Song Y, Wang HJ, Ma J. The association between blood pressure and grip strength in adolescents: does body mass index matter? *Hypertens Res*. 2016;39(12):919-925. [CrossRef]
28. Chun SW, Kim W, Choi KH. Comparison between grip strength and grip strength divided by body weight in their relationship with metabolic syndrome and quality of life in the elderly. *PLoS ONE*. 2019;14(9):e0222040. [CrossRef]
29. Owen A, Wiles J, Swaine I. Effect of isometric exercise on resting blood pressure: a meta analysis. *J Hum Hypertens*. 2010;24(12):796-800. [CrossRef]

30. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2(1):e004473. [CrossRef]
31. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol*. 2018;14(9):513-537. [CrossRef]
32. 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(2):141-150. [CrossRef]
33. Lopez-Lopez J, Lopez-Jaramillo P, Camacho PA, Gomez-Arbelaez D, Cohen DD. The link between fetal programming, inflammation, muscular strength, and blood pressure. *Mediators Inflamm*. 2015;2015:710613. [CrossRef]
34. López-Jaramillo P, Gómez-Arbeláez D, López-López J, et al. The role of leptin-adiponectin ratio in metabolic syndrome and diabetes. *Horm Mol Biol Clin Investig*. 2014;18(1):37-45. [CrossRef]
35. So B, Kim HJ, Kim J, Song W. Exercise-induced myokines in health and metabolic diseases. *Integr Med Res*. 2014;3(4):172-179. [CrossRef]
36. International Diabetes Federation. *IDF Diabetes Atlas*. 10th ed. [internet]; 2021. Available at: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf. Accessed 2022 Mar 04.
37. Tarp J, Støle AP, Blond K, Grøntved A. Cardiorespiratory fitness, muscular strength and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetologia*. 2019;62(7):1129-1142. [CrossRef]
38. Wang Y, Lee DC, Brellenthin AG, et al. Association of muscular strength and incidence of type 2 diabetes. *Mayo Clin Proc*. 2019;94(4):643-651. [CrossRef]
39. Grøntved A, Ried-Larsen M, Ekelund U, Froberg K, Brage S, Andersen LB. Independent and combined association of muscle strength and cardiorespiratory fitness in youth with insulin resistance and beta-cell function in young adulthood: the European Youth Heart Study. *Diabetes Care*. 2013;36(9):2575-2581. [CrossRef]
40. Hu S, Gu Y, Lu Z, et al. Relationship Between grip strength and prediabetes in a large-scale adult population. *Am J Prev Med*. 2019;56(6):844-851. [CrossRef]
41. Liu Y, Ye W, Chen Q, Zhang Y, Kuo CH, Korivi M. Resistance exercise intensity is correlated with attenuation of HbA1c and insulin in patients with type 2 diabetes: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2019;16(1):140. [CrossRef]
42. Shiroma EJ, Cook NR, Manson JE, et al. Strength training and the risk of type 2 diabetes and cardiovascular disease. *Med Sci Sports Exerc*. 2017;49(1):40-46. [CrossRef]
43. Ishii T, Yamakita T, Sato T, Tanaka S, Fujii S. Resistance training improves insulin sensitivity in NIDDM subjects without altering maximal oxygen uptake. *Diabetes Care*. 1998;21(8):1353-1355. [CrossRef]
44. Yang Z, Scott CA, Mao C, Tang J, Farmer AJ. Resistance exercise versus aerobic exercise for type 2 diabetes: a systematic review and meta-analysis. *Sports Med*. 2014;44(4):487-499. [CrossRef]
45. Eves ND, Plotnikoff RC. Resistance training and type 2 diabetes: considerations for implementation at the population level. *Diabetes Care*. 2006;29(8):1933-1941. [CrossRef]
46. Jiahao L, Jiajin L, Yifan L. Effects of resistance training on insulin sensitivity in the elderly: a meta-analysis of randomized controlled trials. *J Exerc Sci Fit*. 2021;19(4):241-251. [CrossRef]
47. Dunstan DW, Daly RM, Owen N, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care*. 2002;25(10):1729-1736. [CrossRef]
48. Lopez-Lopez JP, Cohen DD, Ney-Salazar D, et al. The prediction of Metabolic Syndrome alterations is improved by combining waist circumference and handgrip strength measurements compared to either alone. *Cardiovasc Diabetol*. 2021;20(1):68. [CrossRef]
49. Jurca R, LaMonte MJ, Barlow CE, Kampert JB, Church TS, Blair SN. Association of muscular strength with incidence of metabolic syndrome in men. *Med Sci Sports Exerc*. 2005;37(11):1849-1855. [CrossRef]
50. Cohen DD, Sandercock GR, Camacho PA, et al. The SIMAC study: a randomized controlled trial to compare the effects of resistance training and aerobic training on the fitness and body composition of Colombian adolescents. *PLoS ONE*. 2021;16(4):e0248110. [CrossRef]
51. Cohen DD, Carreño J, Camacho PA, et al. Fitness changes in adolescent girls following in-school combined aerobic and resistance exercise: interaction with birthweight. *Pediatr Exerc Sci*. 2021:1-8. [CrossRef]
52. Olson TP, Dengel DR, Leon AS, Schmitz KH. Changes in inflammatory biomarkers following one-year of moderate resistance training in overweight women. *Int J Obes (Lond)*. 2007;31(6):996-1003. [CrossRef]