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REVIEW

May the force be with you: why resistance training is essential for subjects with type 2 diabetes mellitus without complications

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Abstract

Physical activity, together with diet and pharmacological therapy, represents one of the three cornerstones in type 2 diabetes mellitus treatment and care. The therapeutic appeal of regular physical activity stems from: (i) its non-pharmacological nature; (ii) its beneficial effects on the metabolic risk factors associated with diabetes complications; (iii) its low costs. Evidence accumulated in the last years suggests that aerobic training—endurance training—constitutes a safe modality of intervention, achievable, and effective in diabetes treatment, whenever it is not limited by comorbidities. Aerobic training exerts insulin-mimetic effects and has been shown to lower mortality risk too. Anaerobic, intense physical activity, such as that of strength or power sports disciplines, is not univocally recognized as safe and simple to realize, however, it is important in stimulating energy and glucose metabolism. According to recent evidence, high-intensity training may be prescribed even in the face of cardiovascular diseases, peripheral vascular disease, or osteoarthritis. Some studies have shown resistance training to be more efficient than aerobic exercise in improving glycemic control. This review explores the most up-to-date indications emerging from literature in support of the beneficial effects of strength stimulation and resistance training in patients with type 2 diabetes without complications.

Keywords Resistance training · Strength · Type 2 diabetes · Glycemic control

Abbreviations

ACSM	American College of Sports Medicine
ADA	American Diabetes Association
AE	aerobic exercise
AMPK	phosphorylated adenosine monophosphate-activated protein kinase
ATP	adenosine triphosphate
AKT	protein kinase B
CaMKII	calmodulin-dependent protein kinase II
BMI	body mass index
DSME	diabetes self-management education
ECG	electrocardiogram
ESSA	Exercise and Sport Science Australia
GLP-1	glucagon-like peptide
GLUT4	glucose transporter 4
GSK3β	glycogen synthase kinase 3β
HbA1c	glycosylated hemoglobin
HDACs	histone deacetylases
HRM	maximum heart rate
IDF	International Diabetes Federation
Ig	immunoglobuline
IL	interleukin
LPS	lipopolysaccharide
MEF2	myocite enhancer factor 2
mTOR	mammalian target of rapamycin
NAFLD	nonalcoholic fatty liver disease
PI3K	phosphatidylinositol 3 kinase
PGC-1α	peroxisome proliferator-activated receptor-gamma coactivator 1α
PRT	progressive resistance training
1RM	one repetition maximum
RT	resistance training
T1D	type 1 diabetes
T2D	type 2 diabetes
TCA	tricarboxylic acid
TNF	tumor necrosis factor
TPE	therapeutic patient education
WHO	World Health Organization

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Background: the ascertained need of exercise in the management of diabetes

Diabetes mellitus represents a group of metabolism alterations characterized by chronic hyperglycemia due to defective secretion and/or insulin action, including abnormalities in fat and protein metabolism. When the cause is a regulatory disorder of the immune system (autoimmunity), pancreas either produces low insulin, or insulin is not produced at all; that is type 1 diabetes mellitus (T1D), which comprises 95% of all pediatric cases. In type 2 diabetes mellitus (T2D), the insulin action, i.e., the response of peripheral tissues to this hormone, is deficient within an insulin resistance context and/or inappropriate insulin secretion.

Often, both problems coexist in the same patient aggravating the syndromic clinical picture.

Diabetes results therefore as a chronic-degenerative metabolic disease that has reached pandemic proportions, mainly because of the increasing incidence and prevalence of T2D. According to the International Federation of Diabetes (IDF, 2017), 425 millions of people suffer from diabetes in the world and these may rise to 629 million in 2045 [1]. About 95% of known cases of diabetes and virtually all the cases of unknown diabetes are classifiable as T2D. Approximately 5% of the known cases of diabetes are classifiable as T1D.

Within this epidemiological perspective, diabetes emerges as one of the main metabolic diseases with substantial costs for the European and worldwide sanitary system. Prevention is one of the major international challenges and therapies can luckily leverage on two modifiable risk factors: overnutrition (which leads to obesity) and physical inactivity. The major international medical agencies have claimed physical activity being fundamental against the diffusion of diabetes. According to American Diabetes Association (ADA) and American College of Sports Medicine (ACSM): "Physical exercise performs a primary role in the prevention and control of insulin-resistance, prediabetes, gestational diabetes mellitus, T2D and its complications" [2]. Physical exercise, in fact, is capable to activate acutely glucose metabolism. Ad hoc training programs are effective on stimulating insulin action in the organism of insulin resistant patients, in toto. Uncountable studies show how physical exercise increases glucose uptake at peripheral and systemic level, improves insulin sensitivity, and permits to positively ride the known hyperbolic curve of glucose tolerance [3]. While weight loss and improvement of insulin sensitivity have been positively associated to endurance training [2, 4, 5] owing to the insulin-mimetics effects of aerobic exercise (AE) in T2D patients, strength exercise and muscular conditioning have been always debated with controversy, mostly in reference to the acute stressors inducing an overload to vascular system, potentially already challenged by long-term hyperglycemic conditions. Recent literature, however, has confirmed the need to integrate training programs with force stimulation, in subjects with T2D, as addressed by several seminal studies—randomized controlled trials—whereby resistance training (RT) resulted to be beneficial under many aspects, even in a single-bout session [6].

Materials and methods

Literature search strategy

A systematic literature search was carried out in the Cochrane Library and MEDLINE databases for studies published in English (January 1998 to December 2017) combining the terms "resistance training," "type 2 diabetes," "strength," and "force." We examined reference lists in original articles, reviews, and trials. Study search was performed both electronically and by following up references quoted in relevant paper. Case reports were excluded.

Study selection

The articles were screened, extracted, and read. The relative findings were classified by: (i) resistance training effects on glycemic control; (ii) resistance training effects on insulin sensitivity; (iii) resistance training effects on cardiometabolic health, including body composition, in healthy, diabetic, and obese subjects; (iv) resistance training effects compared to other modalities of training.

Periods of data collections ranged from 1998 to 2017, obtaining outcomes mostly from human models. A synoptic table of the relevant studies analyzed is offered (Table 1).

Benefits of RT

Progressive resistance training (PRT) procures improvements in body composition mainly via an increase in lean body mass—that is the metabolic active mass capable to remove glucose from the blood stream, using the glucose substrate to produce energy. PRT has been shown to improve insulin resistance and glycemic control, with a reduction of glycosylated hemoglobin (HbA1c), an increase in muscle mass and/or reducing fat mass [7]. Importantly, these findings are even more impressive when considering that similar reduction of HbA1c was found only in combined pharmacological therapies; in particular when a sulphonylurea (secretagogue) was added to metformin (biguanide). Aerobic activity hardly brings to such increase of lean body mass, and often its practice results

Table 1 Synopsis of the RT intervention studies in T2D and metabolism

Authors	Model	Type of exercise	Results
Honkola et al. [12]	T2D	CWT vs control (2 d/wk for 5 mo) moderate intensity	↔HbA1C ↔BMI, ↓LDL, ↓TC, ↓TG, ↑HDL in control
Dunstan et al. [52]	T2D	CWT vs control (3 d/wk for 8 mo) 50–55% 1RM	↔HbA1C, ↓insulin AUC, ↓glucose AUC, ↔BMI, ↔FBG, ↔FI
Ishii et al. [53]	T2D	RT vs control (5 d/wk for 4–6 wk) 40–50% 1RM	↑glucose disposal rate, ↔HbA1C, ↔BMI, ↔VO_2peak
Castaneda et al. [49]	T2D	RT vs control (3 d/wk for 16 wk) 60–80% 1RM	↑muscle glycogen, ↓HbA1C, ↑lean mass, ↓sBP, ↔BMI, ↔FBG, ↔TG
Baldi et al. [86]	T2D	RT vs control (3 d/wk for 10 wk) 10RM upper body, 15RM lower body	↓HbA1C, ↓FBG, ↓FI, ↑FFM
Balducci et al. [13]	T2D	RT, CT, AE, control (2 d/wk for 1 year)	↓HbA1C, ↑strength, ↑aerobic fitness, ↓sBP
Bacchi et al. [54]	T2D, NAFLD	RT, AE, control (3 d/wk for 4mo)	↓hepatic fat content, ↓IS, ↓VAT, ↓SAT, ↓HbA1C
Phillips et al. [41]	Elderly	RT vs control, (3 d/wk for 10 wk)	↓IL–6, ↓TNF–α
Balducci et al. [87]	T2D and metabolic syndrome	RT + AE vs AE vs control (2 d/wk for 52 wk)	↑AD, ↓LP, ↓CRP, ↓IL–6, ↓TNF–α, ↑IS
Cuff et al. [88]	Obesity and T2D	RT + AE vs AE vs control (3 d/wk for 16 wk)	↓VAT, ↓SAT, ↑IS
Janssen et al. [89]	Humans, obesity (women)	RT + CR vs AE + CR vs CR (3 d/wk for 16 wk)	↓VAT, ↓SAT, ↓FI, ↓insulin AUC
Rice et al. [90]	Obesity (men)	RT + CR vs AE + CR vs CR (3 d/wk for 16 wk)	↓VAT, ↓SAT, ↓FI, ↓insulin AUC
Riechman et al. [91]	Healthy. Muscular physiology	RT (3 d/wk at 75% 1RM, for 10 wk)	↑IL–15 after acute RT, but not chronically
Nielsen et al. [92]	Healthy, physically active subjects. Muscular physiology	RE acute protocol	↑IL–15mRNA
Sparks et al. [57]	T2D	RT, CT, AE, control (AE,150 min/wk RT, 3 d/wk for 9 mo)	↑mitochondrial content, ↑enzyme activity, ↓HbA1C, ↑VO_2max
Umpierre et al. [45]	T2D	RT, CT, AE, control (2–4 d/wk for ≥ 12 wk)	↓HbA1c

↑ significant increase, ↓ significant decrease, ↔ unchanged, *AE* aerobic exercise, *AD* adiponectin, *AUC* area under the curve, *BMI* body mass index, *sBP* systolic blood pressure, *CR* caloric restriction, *CRP* C reactive protein, *CT* combined training, *CWT* circuit weight training, *d* day, *FBG* fasting blood glucose, *FFM* fat–free mass, *FI* fasting insulin, *HbA1c* glycosylated hemoglobin, *HR* heart rate, *HDL* high density lipoprotein, *IgA* immunoglobulin A, *IL* interleukin, *IS* insulin sensitivity, *LDL* low density lipoprotein, *LP* leptin, *min* minutes, *mo* month, *NAFLD* nonalcoholic fatty liver disease, *NS* not significant, *PA* physical activity, *1RM* repetition maximum, *RT* resistance training, *SAT* subcutaneous adipose tissue, *T2D* type 2 diabetes, *TC* total cholesterol, *TG* triglycerides, *TNF* tumor necrosis factor, *VAT* visceral adipose tissue, VO_2 oxygen uptake, *wk* week

incompatible with several common clinical conditions of people with T2D, aggravated by comorbidities such as obesity, osteoarthritis, peripheral vascular disorders, and other physical disabilities. Paradoxically, in case of these comorbidities, exercise intensity becomes an issue in performing AE far more than RT. For these subjects, 20–30 min walking can be difficult, harsh, or even painful [8]. In contrast, lifting small weights and anaerobic muscle stimulation, can appear as a valid alternative, leading to metabolic gains that are essential in the management of T2D.

Summarizing, the major benefits documented with RT in subjects with T2D are: (i) increase of insulin sensitivity and glycemic control [9–11]; (ii) improvement of blood cholesterol profiles [12]; (iii) blood pressure decrease [13]; (iv) improvement of cardiac performance; (v) increase in strength and muscular power [14, 15]; (vi) increase of lean body mass [16]; (vii) increase in bone mineral density (with preventive effect on sarcopenia and osteoporosis) [17, 18]; (viii) increase of daily energy expenditure [19, 20], and (ix) quality of life [21].

Nevertheless, differently from aerobic activity (e.g., walking), resistance exercises can require a competent, skilled supervision, the proper execution of training techniques, and handling with a specific equipment.

In this perspective, it is desirable that RT becomes a concrete way, valuable, feasible, and economic, in order to successfully train subjects with T2D. On the other hand, training studies are highly advocated to demonstrate the efficacy of these modalities of intervention, focusing on uncertain factors like intensity and genetic variability for training responsiveness. The ultimate goal would be, for instance, to regulate glucose homeostasis favorably.

Future research strategies and areas should be implemented for an increasingly high number of RT practitioners, giving the great potential of physical activity against the epidemic rising of chronic diseases associated with sedentarism.

International guidelines: recommendations

Over 60% of diabetic people do not practice regular physical activity [22]. ADA recommended to subjects with type 2 diabetes at least 150 min per week of moderate aerobic activity, or 90 min per week of relevant intensity aerobic activity [23] (Table 2). The Exercise and Sport Science Australia increased previous goals to 210 min per week of moderate activity or 125 min per week of strenuous activity, inclusive of two or more RT sessions [24]. Unfortunately, only 28% of subjects with T2D meet ADA recommendations [25]. Despite a lifestyle modification of such small entity would significantly impact on cardiometabolic health

Table 2 Major exercise guidelines for patients with type 2 diabetes

Agency	Type	Frequency	Duration	Intensity
ADA American Diabetes Association	AE, RT, CT, FLEX	≥5 d/wk	≥150 min/wk	Moderate
EASD European Foundation for the Study of Diabetes	AE, RT, CT, FLEX	n.r.	≥150 min/wk	Moderate Moderate– vigorous
CDA Canadian Diabetes Guidelines	AE, RT, CT	≥5 d/wk	≥150 min/wk	Moderate Moderate–vigorous
ESSA Exercise and Sport Science Australia	AE RT	No more than 2 consecutive days w/out exercising ≥2 d/wk	125 min/wk 210 min/wk 60 min/wk	Vigorous Moderate Moderate–vigorous
FDS Francophone Diabetes Society	AE, RT, FLEX	≥3 d/wk	≥150 min/wk	Moderate Moderate–vigorous
SID Società Italiana di Diabetologia	AE, RT, FLEX	≥3 d/wk	≥150 min/wk	Moderate
UK Diabetes UK	AE	3–5 d/wk	15–60 min/session	Moderate
DDG German Diabetes Association	AE, RT, CT	6–7 d/wk	≥180 min/wk	Moderate

AE aerobic exercise, *CT* combined training, *d* days, *FLEX* flexibility training, *RT* resistance training, *min* minutes, *n.r.* no recommendation, *wk* week

of the population, unfortunately it is unreal that sedentary subjects would be able to respect these guidelines. Thus, it becomes urgent to conceive a training modality practicable for people with T2D.

The ADA and ACSM joint position stand encourages diabetic people to perform RT 2–3 times per week, in non-consecutive days, focusing on all major (eight) muscle groups [26]. Patients should perform from 5 to 10 exercises including squat, push-up, abdominals, lifts on the ankles, so that all the principal muscle groups would be involved. The ACSM calls to execute 2–3 sets per exercise, from 8 to 10 repetitions each, with a reasonable workload (75–80% of one repetition maximum, 1RM). Sessions should be anticipated by 5 min of warm up, as well as should be followed by a final step of cool down at lower intensity. Untrained subjects could span the work during the day in multiple sessions of shorter duration, in order to reach the predetermined goal with lower fatigue. As to this latter, it would be useful to monitor and quantify the perceived effort with a Borg scale (Borg Rate of Perceived Exertion) [27]. Several devices are also available to manage the cardiovascular intensity, ranging from modern heart rate monitors to smartphone applications, to theoretical algorithms (maximum heart rate, HRM: 220 – age). Moderate intensity should be set as 50–70% HRM, while vigorous intensity between 70 and 85% HRM [28]. Obviously, subjects with known cardiovascular problems, autonomic neuropathy, or under beta-blocker regimen, should cautiously modulate and regulate training intensity on predetermined cardiovascular parameters. Abstaining is reasonable, as well as consulting a specialist. An ad hoc visit with diabetologist or sports physician for anamnesis, physical examination, and functional evaluation (resting and exercise electrocardiogram, ECG-test) are therefore strongly recommended before engaging in any physical activity practice [26].

Study outcomes and molecular mechanisms

In sedentary adults, muscle mass and strength decrease progressively with age, particularly after age of 45, with a more pronounced reduction following 60-year age [29, 30]. Skeletal muscle tissue—being the first site for glucose and triglycerides disposal—decreases by 3–8% every decade after the age of 30 [31], increasing the risk of glucose intolerance and T2D pathogenesis, considerably [32]. Diabetes is an independent risk factor for the low-muscular strength [33], and subjects with T2D in old age show an accelerated decline of strength and muscle mass compared with nondiabetic peers [34, 35]. Epidemiological studies confirm the inverse correlation between muscle strength and metabolic syndrome, and between muscular strength and all-cause mortality [36]. The deleterious loss in lean mass

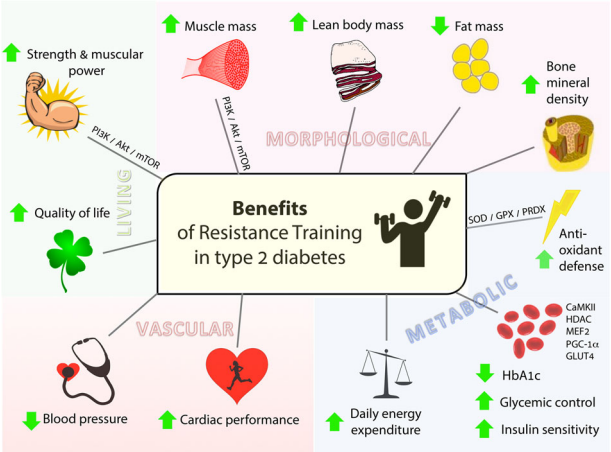

Fig. 1 Depicting overall beneficial adaptive responses of RT in T2D, mediated by peculiar transduction pathways

and muscular strength associated with aging can be exacerbated, in a vicious circle, by progressive physical inactivity. Carrying out activities of daily living (physical independence) and simple motor tasks become harsh, especially for elderly. The muscle of a subject with T2D may be threatened by insulin resistance, impaired glycogenesis, mitochondrial dysfunction, and lipid accumulation [37]. As said, aging per se, is responsible of lean mass loss, however, metabolic and functional disorders can be definitely hindered with strength exercises [38]. A widespread body of evidence points at RT to obtain positive physiological adaptations and unique benefits in T2D (Fig. 1).

In the Health Professional Follow-up Study [39], which monitored more than 32,000 subjects over 18 years, those who trained with RT for more than 150 min per week showed a 34% reduction in risk of T2D (normalized for body mass index (BMI) and aerobic activities) [40]. The protection offered by physical activity against T2D increased up to 60% when the analysis included obese people (BMI ≥ 30) performing RT with ≥150 min/week [40].

RT can represent an excellent adjuvant in T2D prevention and management by decreasing visceral fat and inflammatory markers [41]. A 3-month program of RT in obese teenagers determined a significant reduction of total and visceral fat, accompanied by an increase of insulin sensitivity compared with nonexercising controls [42]. Some studies have also demonstrated how RTs are effective in reducing abdominal fat in subjects with T2D, even without a weight loss [43]. In the study of Honkola et al. [12], 5 months of PRT in circuit were capable to significantly reduce LDL cholesterol and fasting triglycerides, compared to the control group.

Unanimously, HbA1c is accepted as the most indicative parameter for measuring long-term glycemic control, and is

strongly associated with diabetes risk, cardiovascular disease, and mortality [44]. RT can improve insulin action and glycemic control in subjects with T2D. In a meta-analysis, Umpierre et al. [45] have reported a reduction of 0.67% in Hb1Ac levels in T2D subjects undergone to 12-week RT compared with sedentary controls. In another meta-analysis comprising ten supervised studies, HbA1c decreased by 0.48% with RT [46]. Most individuals are able to better control their blood glucose levels and body weight [47] via RT-induced increase in lean body mass and insulin sensibility. In particular, RT prevents lean body mass loss in those aiming at weight loss with caloric restriction [38]. Insulin sensitivity and glycemic control can be improved with RT owing to diversified adaptations. The first of these entails the increase of level, density, and translocation of glucose transporter 4 (GLUT4) receptors [48]. Likewise, the protein expression of insulin receptors is increased, with a consequent insulin-sensitizing effect of the training. The improved insulin action is evidenced by the growth in protein-kinase B-α/β content. As an acute training effect, the glucose disposal (glucose clearance) was found accelerated in the leg trained with 6 weeks of RT compared to the non-exercising leg, paralleled by an increase of whole activity and concentration of glycogen synthetase. In another study [49], 16 weeks of supervised, high intensity, PRT, three times per week, increased muscle glycogen storage by 31% in old subjects with T2D, while controls reported a significance decrease in glycogen content (−23%). The PRT-trained group, moreover, reported a decrease of HbA1c from 8.7 to 7.6%. Increasing muscle mass in conjunction with reducing HbA1c would support the hypothesis according which RTs improve glycemic control by increasing muscle glucose storage [49]. On a singular note, prescribed diabetic medications were reduced in 72% of the subjects in the PRT group compared with the control group [49].

RT can improve glucose transport in normal and insulin-resistant skeletal muscle by activation of the insulin signal pathway [50]. Peculiarly, these RT-induced modifications can improve metabolic profile of skeletal muscle, independently from the increase in lean mass [51].

In one of the first randomized controlled trial, weight lifting at moderate intensity in a circuit training (three times/week, 55% 1RM per 8 weeks) showed a decreased insulin response during an oral glucose tolerance test in diabetic patients with respect to controls at rest [52]. During an hyperinsulinemic euglycemic clamp, the glucose disposal was increased by 48% in T2D subjects trained with 4–6 weeks of moderate-intensity RT, compared to controls, at rest [53].

Recently, Bacchi et al. [54] showed how 4 months of RT and aerobic training were both effective to improve liver fat storage, insulin sensibility, total fat mass and HbA1c in adults with T2D and nonalcoholic fatty liver disease. Ideally, endurance/aerobic training and RT should be combined in order to increase the benefits for subjects with T2D and prediabetes [55]. Positive effects of combined training in subjects with T2D have been demonstrated in several well-sized trials. In the HART-D trial [38], 262 patients with T2D were randomized to four training groups (aerobic, RT, combinated, control) per 3 weekly sessions with the same energy expenditure (12 kcal/kg/week): the best glycemic control was obtained in the combined training group, with an absolute reduction of 0.34% in HbA1c compared to the other groups. The same design was used in the DARE trial [56] with 251 patients randomized in four groups: the best glycemic control was obtained in the combined training group (−0.97% Hb1Ac vs control). Yet in the DARE trial, the RT group showed further improvements in mental health, vitality and quality-of-life compared to the aerobic-only or control groups. In the IDES Italian study [13], 606 patients with T2D from 22 centers (40–75 years old, HbA1c average levels equal to 7.13%) were randomized to two intervention groups: the first group trained in the gym with combined program twice a week with personal trainers' supervision; the second group, as control, self-trained, following a non-supervised program. As a result, the first group observed improvements in all profiles: aerobic fitness, strength, blood pressure, waist circumference, lipids, inflammatory markers, and cardiovascular risk.

The study of Sparks et al. [57] represents the first clear demonstration that RT induces an increase in mitochondrial content in the skeletal muscle of T2D patients trained for 9 months. These adaptations were also associated to other clinical improvements referred to functional performance (VO_2 max) and glycemic control (HbA1c). The other subjects of the same study were randomized to the aerobic training group, combined, or to nonexercising controls. The combined training group improved, amongst others, all the markers of long- and medium-chain fatty acid oxidation, increased tricarboxylic acid (TCA) cycle flux, as well as mitochondrial content and enzymatic activity. Overall, a number of studies have confirmed a synergistic, addictive effect of combined training (RT + AE) on glycemic control (up to −1.5% in HbA1c) [58], insulin action, exercise tolerance and muscular capacity, in the long term.

RT augments excess oxygen delivery post-training (EPOC, Excess Postexercise Oxygen Consumption) [59]. This increase in oxygen uptake (VO_2), following a RT session is consistent with the energy expenditure rise in the recovery period. EPOC suggests an accelerated fat metabolism, which is determinant for weight loss. EPOC seems to be higher in RT compared to aerobic training [60]. Anyway, the increase of energy expenditure, either depending on EPOC or RT, is of pivotal importance to initiate an overall healthful metabolism.

Hereby the macro-molecular steps describing major phenomena induced by RT.

Hypertrophy

One of the main metabolic pathways responsible for muscle hypertrophy through the increased protein synthesis would be the IGF-1/PI3K/AKT pathway. AKT stimulates protein synthesis by the mammalian target of rapamycin (mTOR) [61]. In addition to the increase of the skeletal muscle transverse section and muscular mass, RT induces also a shift in the muscle fibers composition. From a histochemical standpoint, RTs would switch 2× fibers with low oxidative capacity to type 2a fibers, with a moderate oxidative capacity, these latter surely resulting more insulin-sensitive compared to the former ones [62] (Fig. 2). Altogether, these adaptations result in enhanced skeletal muscle quantity, quality (the amount of muscular strength/torque per unit of regional muscle mass), and function, i.e., muscle strength and power, and motor unit recruitment.

Metabolic control: glycemic control and insulin sensitivity

There are several adaptations through which regular RT may improve overall glycemic control (possibly even more than what AE can do) and insulin sensitivity: other than increasing GLUT4 levels, RT can augment protein kinase B, insulin receptors, muscle glycogen stores, glycogen synthase, and glycogen synthase total activity following acute training [48]. Recently, it was demonstrated that RT increased glycemic control in part by enhancing microvascular blood flow and substrate delivery to myocytes [63].

Although an enhancement in insulin action is usually related to greater skeletal muscle mass, insulin sensitivity may increase due to RT-procured qualitative changes, regardless of muscle mass gains. For instance, calmodulin-dependent protein kinase II (CaMKII) is stimulated in an exercise-intensity fashion, and it phosphorylates transcription factors like histone deacetylases (HDACs), which in turn leads to activation of transcription factors such as myocyte enhancing factor 2 (MEF2) and its target genes (PGC-1α, GLUT4) thus ameliorating glycemic control.

In a meta-analysis [64], intensity resulted to be more important than duration in enhancing insulin sensitivity. However, conclusive results are still lacking about the RT effects of different durations/intensities on muscle mass.

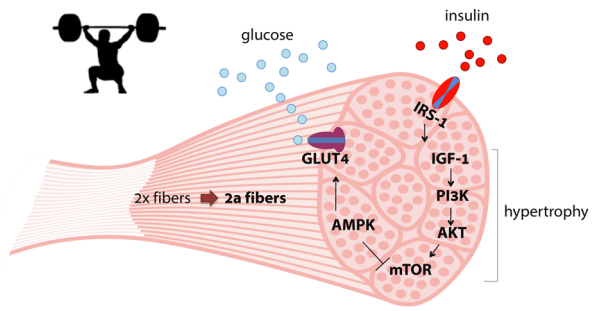

Fig. 2 Molecular mechanisms by which strength stimulation may improve metabolic health in skeletal muscle of patients with T2D. ⟶ Activation/phosphorylation. ⟞ Inhibition. ➡ Shift

Glucose clearance

Non-oxidative glucose disposal occurs as RT stimulates glycogen synthesis through AKT-mediated glycogen synthase activity. Specifically, RT activates AKT, which, in turn, can inhibit glycogen synthase kinase 3β (GSK3β). Inhibition of GSK3 promotes stimulation of glycogen synthase, therefore leading to the production of glycogen.

It has also been observed an increased activity of AMPK (phosphorylated adenosine monophosphate-activated protein kinase) as an acute phenotypic response to RT [65]. This activation inhibits mTOR signal that impedes protein synthesis during RT (Fig. 2). Transient AMPK activation can induce phosphorylation of target proteins involved in several metabolic pathways. Ultimately this can increase adenosine triphosphate (ATP) production with a higher glucose uptake due to an intensified GLUT4 translocation or lipid oxidation [66]. RT may lead to other adaptations with insulin-mimetics effects: increased fatty acid metabolism (metabolic flexibility) [67] or augmented protein expression of insulin receptors in response to exercise [48].

Mitochondrial capacity

Mitochondrial dysfunction has been associated to aging and insulin resistance. Subjects with T2D have lowered mitochondrial oxidative capacity, with disrupted mitochondrial morphology a reduction in mitochondrial size. However, skeletal muscle oxidative capacity may be preserved in elderly as in young people, by performing regular, intense physical activity. Limited studies demonstrated the capability of RT in increasing mitochondrial oxidative capacity in healthy individuals. In the study of Sparks et al. [57], a 9-month RT program led to an increase in mitochondrial content in the skeletal muscle of T2D patients. Pesta et al. [68] showed that lean subjects had the same increase in mitochondrial respiration in skeletal muscle, following either 10-week RT or AE.

Aging per se leads to sarcopenic alterations of the skeletal muscle, nevertheless physical activity, and especially RT, can help maintain mito-functional and metabolic properties (oxidative) of the muscular tissue.

Which types of RT?

RT, as a synonymous of strength training, refers to using muscular contraction to move a load (including a natural one, like one's own body weight), to win a physical resistance: the most common use of opposing muscle contraction—to resist—is against gravity, elastic, or hydraulic forces. RT consists therefore in brief repetitive exercises with free weights (dumbbells and barbells), weight machines, resistance bands, isometric exercises, calisthenics mobilizing one's own body weight (e.g., pushups) to increase muscle strength and/or muscle endurance.

Performing whatever form of RT is important in T2D not only because of the aforementioned health benefits, but also because diabetic subjects are likely to be overweight or obese and therefore they are harshly able to fulfill the recommended doses of "effective" AE. Short and intense RT exercises, repeated manifold throughout the day, should be more feasible and similarly beneficial for these individuals. In the study of Hamasaki et al. [69], 12 weeks of low-intensity RT with slow movement and tonic force generation decreased body fat mass and body fat percentage in 50-years old obese subjects with T2D. In addition, muscle mass resulted increased, as well as lipidemic profiles ameliorated. Decreases in fat mass of 1–4.5 kg were achieved with RT, while AE can lower fat mass of a couple of kilograms, in a typical training program. Diminishing visceral adipose tissue is critical considering the associated chronic low-grade inflammation and cardiometabolic risks. RT appears most beneficial if performed in the long run, at high intensity. However, together with frequency and duration, this is still a matter of debate. In fact, a clear-cut dose dependency is undefined in the increasingly growing body of literature. In the discussed RT programs in T2D, a duration greater than or equal of 12 weeks, along with an estimated intensity ranging from 60 to 80% of 1RM, were shown sufficient to gain a 10–20% improvement in muscle mass, insulin sensitivity, body composition, and cardiovascular health. Typically these studies concern RT carried out with weight machines, free weights, and they cannot be generalized to other types of RT, such as resistance bands or exercises utilizing only one's own body weight. For these reasons, tailored RT programs, considering individual crucial factors (level of strength—or 1RM; BMI, physical fitness, severity of diabetes, medications, comorbidities, etc.), are urgently needed.

Supervision of expert personnel (diabetologists, healthcare providers, fitness professionals), within an omnicomprehensive educational approach, may represent a successful intervention strategy. Supervised exercise was shown to be more effective than self-reported physical activity in the compliance of the programs. Qualified trainers, by means of skilled competences and high-quality counseling, can exert a tremendous impact on these health measures, boosting the potential of RT, while minimizing the risks of adverse effects.

In conclusion, investigating the minimum effective dose of beneficial, customized RTs, is the key for the long-term adherence of individuals with T2D (and/or obesity), and for most of the people too.

Therapies combining RT and antidiabetic medications

A complex variety of factors must be medically addressed when prescribing RT in patients with T2D or prediabetes: severity of diabetes, duration of the disease, presence of comorbidities, regimens of multiple oral hypoglycemic agents and differently-acting insulins, intensity of strength training. High-intensity efforts may cause a robust depletion of muscle glycogen, therefore exposing patients to the risk of late-onset hypoglycemia, especially under poorly controlled circumstances. Nevertheless, intermittent high-intensity exercise was preferred over continuous moderate intensity AE in order to reduce glycemic excursions post-effort [70]. Blood glucose levels should be carefully managed prior to the initiation of any type of exercise training. Likewise, time of medications and meals ought be properly adjusted for a safe and effective RT participation.

Metformin, one of the most prescribed biguanide—the first-line oral anti-hyperglycemic medication recommended by ADA—has been shown to have pleiotropic effects similar to exercise. In fact, they both independently activate AMPK, therefore increasing insulin-stimulated glucose uptake. It is worth noting that, the magnitude of the RT-effect on HbA1c reduction ($-0.34\% \leq \times \leq -0.57\%$) [45, 71] is averagely inferior than the one procured by metformin (-0.97%) [71] or acarbose (-0.77%) [72]. These observations led to hypothesis that combining metformin with exercise would have synergistic effects on insulin sensitivity. On the contrary, according to certain studies, metformin plus exercise did not show addictive effects with respect to exercise alone in improving insulin sensitivity or HbA1c, in both nondiabetic and T2D individuals [73]. Yet, an extent exists, although unknown, by which metformin alters the beneficial effects of exercise in lowering CVD risk in diabetic people. It is possible that metformin triggers distinct adaptations within pancreatic beta cells and, primarily, in the liver. Conversely, metformin plus exercise seem to have addictive effects when weight loss is the outcome considered. Literature findings remain inconsistent and they need to be pursued sistematically. Besides, the majority of these studies have covered endurance training, which may rely much more on the AMPK signaling pathway than RT.

Another possible explanation is that ROS generation during exercise is a signal for the enhancement of insulin action [73]. Metformin opposes ROS signaling, thus blunting, to some extent, the beneficial adaptations procured by exercise (mitochondrial biogenesis, endothelial function, glucose uptake).

Hence, a doubly positive action coming from the proposition of exercise in conjunction with other compounds (either a drug or an antioxidant/ergogenic/dietary supplement) should be cautiously inferred.

Structured research should test diversified RT intensities and duration in the context of controlled diet and medications. The ultimate goal of combined strategies would be to maximize the metabolic health responses, on a personalized level.

Comprehensive educational programs in the management and care of patients with T2D

RT prescriptions alone are insufficient to modify, on the long term, the lifestyles of people living with T2D, especially if worsened by overweight and obesity. Barriers do exist for these subjects to comply with structured exercise: these individuals are generally unaccustomed to exercise, with a relevant history of sedentary behavior [74]. Therefore, exercise recommendations need to be personalized on the actual subjects' capabilities. Besides, in order to maximize the exercise benefits, recommendations should be incorporated into comprehensive educational programs, including multifactorial behavioral interventions. The glycemic benefits of RT can be, in fact, quite modest (an approximate decline in HbA1c of 0.5%), thus exercise cannot represent the sole "advocated" intervention, but it should be an adjunctive to both nutritional and medical therapies. Furthermore, when the disease is exacerbated by complications, a therapeutic patient education (TPE) is urgently needed in order to crucially prevent and reduce fatal events (mostly because of cardiovascular events) [75, 76] and the overall disability-free life expectancy. These education programs can have a greater effect on disability-free years than total life expectancy, among adults with diabetes [77]. A TPE entails all necessary skills a patient may need to cope with a chronic disease [75]. Several structured TPE programs have been outlined in the management of diabetes. Diabetes self-management education (DSME) embraces peculiar themes concerning basic knowledge on diabetes, physical activity, diet, diabetic medications, self-care, and decision making, while living with the disease [78–80]. These programs have been shown to be fundamental not only in the management of diabetes, but also in the prevention to develop it, or to develop its complications. In fact, complications are approximately four times more frequent in diabetic people with no education respect to patients exposed to educational programs [81]. When TPEs are delivered at individual level, the effects are greater in improving diabetes knowledge, metabolic parameters, and quality of life with respect to group-TPE [82]. Again, all these aspects, as essential part of DSME—from medical nutrition therapy to exercise prescriptions—are more effective when they are "personalized," according to the economic and cultural status of the individuals [2].

Even in the management of T1D, omnicomprehensive programs are capable to optimize and maintain positive metabolic outcomes, also assisted by telemedicine and diversified tele-health care systems [74, 83–85].

In summary, a multifaceted educational plan is highly warranted in diabetic people, firstly to acquire an adequate knowledge on various diabetes themes, and ultimately to gain a greater potential from active lifestyles, improving metabolic and psychosocial outcomes, and therefore reducing disability, morbidity, and mortality.

Conclusive comments

RT can improve glucose tolerance and insulin sensitivity by qualitative modifications independently of the muscle mass increase. It is well known, however, that insulin sensitivity is directly proportional to lean body mass. The increase of lean mass remains, therefore, a reasonable goal for T2D subjects performing RT: this increase is de facto accompanied by an enhancement of basal metabolism triggering a virtuous cycle (of metabolic health).

It is a vivid interest to consider strength stimulation among the diverse modalities of training doable by T2D subjects. In today's society, so committed in multiplying chances of being physically active, short-repeated exercise is a viable alternative to the traditional high-volume endurance training. High-intensity/low-volume RTs can be efficient strategies to obtain metabolic benefits. The beneficial effects of RT are achievable not only by T2D subjects, but also by a large part of society, maintaining a musculoskeletal health, independence in daily living activities, therefore reducing injury risks and the deleterious effects of aging (sarcopenia).

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Compliance with ethical standards

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