European Journal of Preventive Cardiology

ESC European Society of Cardiology

Position paper

European Journal of Preventive Cardiology
2019, Vol. 26(7) 709–727

DOI: 10.1177/2047487318820420
journals.sagepub.com/home/ejpc

SAGE

Exercise training for patients with type 2 diabetes and cardiovascular disease: What to pursue and how to do it. A Position Paper of the European Association of Preventive Cardiology (EAPC)

Hareld Kemps[1], Nicolle Kränkel[2,3], Marcus Dörr[4,5], Trine Moholdt[6,7], Matthias Wilhelm[8], Francesco Paneni[9], Luis Serratosa[10,11], Erik Ekker Solberg[12], Dominique Hansen[13,14], Martin Halle[15,16] and Marco Guazzi[17,18]; on behalf of the European Association of Preventive Cardiology (EAPC)

Abstract

Patients with type 2 diabetes mellitus suffer from dysregulation of a plethora of cardiovascular and metabolic functions, including dysglycaemia, dyslipidaemia, arterial hypertension, obesity and a reduced cardiorespiratory fitness. Exercise training has the potential to improve many of these functions, such as insulin sensitivity, lipid profile, vascular reactivity and cardiorespiratory fitness, particularly in type 2 diabetes mellitus patients with cardiovascular comorbidities, such as patients that suffered from an acute myocardial infarction, or after a coronary intervention such as percutaneous coronary intervention or coronary artery bypass grafting. The present position paper aims to provide recommendations for prescription of exercise training in patients with both type 2 diabetes mellitus and cardiovascular disease. The first part discusses the relevance and practical applicability of treatment targets that may be pursued, and failure to respond to these targets. The second part provides recommendations on the contents and methods to prescribe exercise training tailored to these treatment targets as well as to an optimal preparation and dealing with barriers and risks specific to type 2 diabetes mellitus and cardiac comorbidity.

[1]Department of Cardiology, Máxima Medical Centre, Veldhoven, The Netherlands
[2]Charité – Universitätsmedizin Berlin, Klinik für Kardiologie, Campus Benjamin Steglitz, Germany
[3]DZHK (German Centre for Cardiovascular Research), partner site Berlin, Germany
[4]University Medicine Greifswald, Department of Internal Medicine B, Germany
[5]DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Germany
[6]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology Trondheim, Norway
[7]St Olav's Hospital, Trondheim, Norway
[8]Department of Cardiology, Bern University Hospital and University of Bern, Switzerland
[9]Centre for Molecular Cardiology and Cardiology, Zurich University Hospital, University of Zurich, Switzerland
[10]Hospital Universitario Quironsalud, Madrid, Spain
[11]Ripoll & De Prado Sport Clinic, FIFA Medical Centre of Excellence, Murcia, Spain
[12]Diakonhjemmet Hospital, Department of Medicine, Oslo, Norway
[13]Hasselt University, Faculty of Rehabilitation Sciences, Diepenbeek, Belgium
[14]Heart Centre Hasselt, Jessa Hospital, Belgium
[15]Technical University Munich, Department of Prevention, Rehabilitation and Sports Medicine, Germany
[16]DZHK (German Centre for Cardiovascular Research), partner site Munich, Germany
[17]University Cardiology Department and Heart Failure Unit and Cardiopulmonary Laboratory, Cardiology, I.R.C.C.S., Milan, Italy
[18]Policlinico San Donato University Hospital, Milan, Italy

Corresponding author:
Hareld Kemps, Máxima Medical Centre, De Run 4600, Veldhoven, Postbox 77, The Netherlands.
Email: h.kemps@mmc.nl

Keywords
Type 2 diabetes mellitus, exercise training, cardiovascular disease

Received 4 July 2018; accepted 29 November 2018

Introduction

The presence of type 2 diabetes mellitus (T2DM) doubles the risk of mortality, regardless of the presence or absence of cardiovascular disease (CVD).[1] Exercise training improves a broad panel of cardiovascular and metabolic outcomes, including insulin sensitivity, lipid profile, vascular reactivity and cardiorespiratory fitness (CRF), thereby especially benefitting patients with T2DM.[2,3] In patients with T2DM without cardiovascular comorbidities, exercise training can be performed non-supervised on an individual basis. Patients with T2DM who have suffered an acute myocardial infarction, or after a coronary intervention such as percutaneous coronary intervention or coronary artery bypass grafting, should be referred to a cardiac rehabilitation programme, where exercise training can be started under supervision.

In daily practice, however, the large majority of T2DM patients, including those with coronary artery disease (CAD), are not engaged in regular exercise training.[4] Although multiple internal and external physical activity barriers have been identified, a lack of motivational support is considered an important determinant of loss of motivation even after initial participation in an exercise training programme.[5] In patients that *are* engaged in regular exercise training, training adaptations are individually determined. In fact, exercise training can improve distinct target parameters (such as glucose control, blood pressure, lipid status or body composition) to a different extent in each patient.[6] Therefore type and intensity of exercise training needs to be adjusted to the patient's characteristics individually to achieve the optimal effect. In addition, in patients with cardiac comorbidities, treatment goals should be tailored to both diseases and associated cardiac barriers and risks typical for T2DM patients should be taken into account by prescribers of exercise interventions.

The aim of this paper is to provide recommendations for prescription of exercise training in patients with both T2DM and CVD. The first part discusses the relevance and practical applicability of treatment targets that may be pursued, and failure to respond to these targets. The second part provides recommendations on the contents and methods to prescribe exercise training tailored to these treatment targets as well as to an optimal preparation and dealing with barriers and risks specific to T2DM and cardiac comorbidity.

Exercise training for patients with T2DM and cardiovascular disease: What to pursue?

Patients with T2DM suffer from dysregulation of a number of cardiovascular and metabolic functions, including dysglycaemia, dyslipidaemia, arterial hypertension, obesity and often a reduced CRF. These functions are inter-related and strongly affected by the patient's lifestyle as well as by their genetic and epigenetic background. Adipose tissue lipid storage capacity is challenged by an inactive lifestyle, characterized by a chronic excess of calorie intake versus energy expenditure through physical activity. As a result, plasma free fatty acid levels increase and lead to a number of cellular stress responses including peripheral insulin insensitivity, increased inflammatory activation of various tissues and dysfunction of vasculature and skeletal muscle metabolism.[3,7] Regular exercise training can target many of these factors, yet not all of the mentioned parameters are improved by all exercise protocols in every patient.[8] In addition, not all perceived target parameters might have merit in patients with T2DM. In particular, the value of fat mass loss as a target parameter of exercise training in patients with T2DM has been challenged,[9] while metabolic and functional parameters might have a higher relevance. Some target variables, although not immediately involved in the improvement of cardiovascular risk, can have a high motivational value, thereby potentially improving long-term adherence, a major factor for therapy success of exercise training. Weight loss is a classical parameter patients are interested in, yet can lead to discontinuation of the exercise training programme if it is not achieved.

Exercise training targets

This section outlines the different targets that may be pursued by exercise training in T2DM patients according to recent evidence (Table 1 [10–54]) and discusses reasons for non-response.

Physical activity and CRF. CRF, commonly measured by peak oxygen uptake (VO_2peak) or calculated based on peak workload during cycle ergometry or treadmill speed and elevation, is a strong and independent morbidity and mortality predictor in diabetic patients as well as across the general population.[27,55–57]

Table 1. Target parameters of exercise training in patients with type 2 diabetes mellitus.

	Parameter	Relevance as a target for ET in T2DM patients with cardiac comorbidity	Effective exercise strategy to address this parameter	References
Metabolic	Glycaemic control	Major target parameter	Combined AET/RT > AET > RT	10–19
	Dyslipidaemia	Relevant target parameter, ET may serve as an adjunct to medication	AET (insufficient data for RT)	10, 12, 18, 20, 21
	Inflammation	Relevant target parameter, monitoring not feasible	Combined AET/RT > AET or RT alone	10, 22–26
Functional	Cardiorespiratory fitness	Major target parameter Motivational role	Combined AET/RT > AET > RT High-intensity > moderate-intensity AET	13, 27, 28
	Vascular function	Major target parameter, difficult to use for monitoring	AET	16, 29–38
	Muscle strength	Potentially relevant target parameter (insufficient data) Motivational role	Combined AET/RT	39, 40
	Blood pressure	Relevant target parameter, ET may serve as an adjunct to medication. Not an independent target parameter (associated with BMI changes)	AET No or only small effects of RT	11, 12, 41–44
	Autonomic regulation	Potentially relevant target parameter (insufficient data)	AET	45–47
Structural	Body weight	Relevant target parameter only in severely obese patients and when other reasons recommend weight loss Motivational role	Longer protocols > shorter protocols; combination with diet and good supervision/counselling	10, 41, 48, 49, 50
	Body composition	Potentially better target parameter than body weight, but insufficient data	High-intensity > moderate-intensity AET Longer protocols > shorter protocols Combination with diet and good supervision/counselling	12, 20, 41, 43, 49–54

ET; exercise training: T2DM: type 2 diabetes mellitus; AET: aerobic exercise training; RT: resistance training

Also, improvement in physical fitness was shown to be associated with reductions in all-cause and CVD mortality to a similar extent in diabetic patients as in men without CVD.[48,58] In addition, increasing physical activity, subsequently leading to improvements in CRF, is also associated with improvements of cardiovascular mortality in CAD patients, revealing that 10 metabolic equivalent tasks per hour per week (MET*h/week) equivalent to 2 h of brisk walking per week may significantly reduce cardiovascular morbidity and mortality.[59] Moreover, changes in CRF are associated with improvements in other modifiable cardiovascular risk factors independently of weight loss in subjects with T2DM, such as HbA1c, the coronary heart disease risk score and high-density lipoprotein cholesterol (HDL-C).[10] Similar to healthy subjects, aerobic exercise training (AET) programmes with intensities ranging from 50% to 75% of maximal exercise capacity improve VO_2peak by approximately 12% in patients with T2DM.[8,60–63] Resistance training also has documented effects on VO_2peak albeit to a significantly lower extent than AET.[11–14] Assessment of exercise capacity may not only serve as a basis for exercise prescription and monitoring the response to exercise training regimens,[64] but may also improve motivation and adherence.[65]

Intensity of exercise is an essential determinant in the treatment of patients with T2DM. Although improvements of glucose metabolism are observed during moderate intensity endurance exercise, more pronounced effects are seen during more vigorous exercise. Particularly interval exercise, alternating moderate and vigorous walking, may have the most beneficial effects and can be successfully performed even in obese diabetics.[51] However, this exercise may be limited during the early phases of the exercise programme, but may be added after moderate intensity exercise has been successfully initiated. However, submaximal exercise intensity as in high intensity interval training may even acutely increase glucose levels when performed at anaerobic intensities. Therefore, steadily increasing exercise intensity over a period of several weeks is essential in these patients. For this patients have to be stable from a cardio-circulatory viewpoint and ischaemia excluded.

Recommendation. *Increasing CRF should be an important goal of exercise training programmes in T2DM with cardiac comorbidities given its strong relation with prognosis and other cardiovascular risk factors. Optimal exercise intensity to improve CRF and improve glycaemic control is essential. Assessment of CRF is therefore recommended for risk stratification, exercise prescription and effect monitoring, preferably by cardiopulmonary exercise testing.*

Glycaemic control. The development of T2DM is mainly due to the resistance of several tissues, such as skeletal muscle, liver and adipose tissue, to the action of insulin, resulting in a limitation to import glucose. The restoration of proper glucose handling is therefore paramount in patients with T2DM. Regular physical activity has demonstrated consistent beneficial effects on glycaemic control, with the highest gain in patients with higher HbA1c values.[12,14–16] However, physical activity advice alone does not affect glycaemic control in T2DM patients.[66]

AET and, to a lower extent, also resistance training, effectively improve glucose control.[11,14] Yet combined AET/resistance training appears to be even more efficient, potentially due to the effects of resistance training on muscle mass and function in combination with the oxidative action of AET.[13,49,67,68]

Recommendation. *Given its central role for treatment of patients with T2DM, glycaemic control should be considered a key target parameters of exercise training in these patients.*

Cardiovascular risk. Despite improvements in the cardiovascular risk profile after AET, studies on its effect on cardiovascular morbidity and mortality in T2DM patients are scarce. The largest trial evaluating effects of an intensive lifestyle intervention in diabetes mellitus patients focused on weight loss achieved through healthy eating and increased physical activity, the Look AHEAD trial, revealed a clear benefit for microvascular events such as subsequent development of diabetic nephropathy,[69] but failed to show a significant reduction in macrovascular events after a median follow-up of 9.6 years.[52] However, several characteristics of the trial design, especially the reduction of counselling and motivation after four years within the trial and fewer medications in the lifestyle group (particularly statins) were associated with a decline of the initial benefits and therefore preclude any clear conclusion from this trial as to the role of exercise training alone on cardiovascular morbidity and mortality.

Recommendation. *To date, data neither support nor refute a reduction of cardiovascular morbidity or mortality as a central target parameter for exercise training in T2DM patients. However, there is evidence that microvascular complications may be reduced by lifestyle intervention.*

Vascular function. Endothelial dysfunction is a precursor of atherosclerosis and holds prognostic relevance for cardiovascular morbidity and mortality.[70,71] Consequently, therapy-related improvement of endothelial dysfunction is associated with a reduction in cardiovascular events.[29,30] Interestingly, exercise-related improvement of endothelial function in T2DM seems to be independent of glycaemic control and insulin resistance.[61] Instead, pro-survival pathways, activated by shear stress, and acting via nitric oxide synthesis as well as via the upregulation of antioxidant defence enzymes, are considered to mediate exercise-induced improvement of vascular function.[72,73] The lowering of humoral stressors, such as angiotensin II, and increase in myocyte-derived growth and anti-inflammatory factors – myokines – probably contribute.[73,74] Several exercise training protocols have been reported to improve flow-mediated dilatation (FMD), a measure of peripheral endothelial function, in T2DM patients.[16,31,62] Also, studies in cardiovascular patients showed that exercise training induces an improvement in symptoms of erectile dysfunction, which is caused among others by endothelial dysfunction and is an important symptom in T2DM patients.[75–77] Although these studies indicate that improving FMD should be an important target of exercise training programmes in T2DM patients, and in particular in those with established cardiovascular disease, methodological and technical limitations still hamper routine use of FMD assessment in clinical practice.[78] Alternatively, arterial

stiffness may be used as an indicator of vascular function as it is easier to measure, has prognostic value in T2DM and can be modified with exercise.[79,80]

Recommendation. *Improving vascular function is an important aim of exercise training programmes in patients with T2DM and cardiac comorbidity as it is associated with a decline in cardiovascular events and symptoms (e.g. erectile dysfunction) independent from improvements in glycaemic control. However, due to methodological limitations, routine monitoring of peripheral endothelial function cannot be recommended.*

Inflammation. Inflammation is intrinsically implicated in the development of metabolic disturbances and an adverse cardiovascular risk profile in T2DM.[81,82] Exercise training in T2DM patients was shown to lower adipocyte stress and circulating metabolite levels, as well as release of anti-inflammatory myokines from the active skeletal muscle.[74,83,84] Also from a clinical point of view, studies in T2DM patients repeatedly demonstrated that beneficial effects of exercise training are associated with a decline in diabetes-related low-grade chronic inflammation, indicating that lowering of the systemic inflammatory load is a relevant target of exercise training in these subjects.[10,22–26] While it is often not feasible to monitor markers of inflammation on a routine basis, they might be useful to monitor the overall cardiovascular risk in T2DM patients and should be included in exercise-related research.

Recommendation. *Although reduction of inflammation is a relevant target of exercise training in T2DM patients, monitoring of the inflammatory load is not feasible routinely and therefore not recommended in clinical practice.*

Dyslipidaemia. Regular physical activity has been shown to reduce levels of triglycerides and low-density lipoprotein cholesterol (LDL-C) and to elevate HDL-C in patients with T2DM to a small extent,[85] acting via increased mitochondrial oxidation efficiency, contraction-induced mechanisms or adrenal stimulation that differentially affect non-esterified fatty acid levels, and increased expression of lipase and fatty acid transporters, as well as mitochondrial biogenesis.[86,87] While AET improves lipid status, insufficient studies make it difficult to draw conclusions on the effect of resistance training on blood lipids.[11,12,41,42,88] Importantly, patients with T2DM and documented cardiovascular disease have a high risk for recurrent cardiovascular events. Recommended target values for LDL-C are very strict (<1.8 mmol/l or a reduction of at least 50%).[89] In most T2DM patients, exercise training alone does not have the potential to reach these target values.[55] On the other hand, the influence of statins on exercise training adaptations is not well established.[90] Whereas in obese subjects statins were shown to attenuate CRF and skeletal and muscle mitochondrial content,[90,91] a study in T2DM patients demonstrated no change in mitochondrial function after exercise training in subjects treated with statins.[92]

Recommendation. *Improvement of dyslipidaemia is a relevant treatment goal in T2DM patients with cardiac disease. However, exercise training can support but not replace lipid-lowering medication for achieving target values indicated by current guidelines.*[93] *Further research is needed to elucidate the influence of statins on exercise training adaptations.*

Muscle strength. Many chronic diseases, including T2DM, have been shown to accelerate the ageing-related decrease of muscle mass and strength.[39] Consistently, measures of muscle strength have been found to be inversely associated with all-cause and CVD mortality in coronary heart disease.[94–96] In T2DM, reduced muscle strength and mass are strongly related to an impaired glycaemic control and adverse prognosis.[39] The downregulation of catabolic mechanisms and upregulation of PGC-1α signalling by exercise training might explain the increased muscle strength and mass, but also glucose handling and – potentially – humoral changes via improved mitochondrial oxidation.[97,98] Combination of endurance and resistance training as well as higher exercise intensity impact upon the balance between AMPK/PCG-1α and mTOR activation, as well as the splicing of PCG-1α, thus increasing muscle anabolism.[98–100] However, more studies are needed in T2DM patients to establish long-term effects of resistance training on muscular fitness and its relation to the risk of recurring cardiovascular events.

Recommendation. *Muscle strength is a prognostic indicator and appears to be a relevant target parameter for exercise training in T2DM patients with cardiac comorbidity. However, long-term effects of resistance training on muscular fitness and its prognostic implications in T2DM patients remain to be determined.*

Body weight. There is strong scientific evidence for recommending weight reduction in overweight and obese people as part of primary and secondary cardiovascular as well as diabetes prevention strategies.[101–103] A higher body mass index (BMI) is associated with an increased risk of diabetes, CVD and all-cause mortality[104,105] and intentional weight loss, accomplished through lifestyle

change including exercise training, can improve CVD risk factors.[106–108] However,[106–108] this is not true for all kinds of diseases, as described by the 'obesity paradox'. Better outcomes have been observed in overweight and mildly obese subjects with CVD than in normal or underweight individuals.[109] In subjects with T2DM, U- or J-shaped associations,[110–112] inverse associations[113] or no associations[114] between BMI and mortality have been described. Moreover, both intentional and unintentional weight loss in overweight T2DM subjects and CVD were not associated with a reduction in all-cause and cardiovascular mortality.[9,115] Interpretation is further impeded by the observation that exercise training improves CVD risk factors independently of weight loss[10] and increased physical activity is linked to reduction of mortality independently of BMI in both subjects with T2DM[48] and subjects with CVD.[116–118] Furthermore, larger trials evaluated weight loss interventions consisting of a combination of exercise training and dietary interventions, making it difficult to draw conclusions on the effect of exercise training alone.[50,119]

Recommendation. *Although a higher BMI is associated with worse prognosis, weight loss is not necessarily a relevant target parameter of exercise training in all T2DM patients with CVD. Moreover, increasing exercise and physical fitness might serve as a better pathophysiological as well as motivational parameter than weight loss.*

Body composition. In recent years, the value of body weight as a CVD predictor or therapeutic target parameter has been challenged since it is not a direct indicator of total body fat.[120,121] Indeed, body weight should be regarded as a composite 'end-score' of fat mass, muscle mass and bone mass, each with distinct impact on health and prognosis. In fact, in patients with T2DM, measures of visceral and subcutaneous abdominal fat have shown stronger associations with CVD risk than has BMI.[122–124] Additionally, recent data suggest that reduced muscle size mediates the elevated mortality risk in normal weight compared with overweight subjects with T2DM.[124] Exercise training might improve parameters relating to muscle mass and the muscle-to-fat ratio. In particular, preliminary studies suggest that high-intensity and long-duration exercise training programmes, or more comprehensive strategies including dietary advice, can positively affect body composition in subjects with T2DM, while studies focusing on short-term AET programmes (average 18 weeks) failed to demonstrate significant changes.[20,41,43,49,50,53,125] In addition, improvements in body composition increase when exercise training is combined with counselling strategies aimed at increasing self-efficacy and adherence.[50,52,54] Although resistance training is expected to induce an increase in muscle mass, insufficient data preclude conclusions on the effect of resistance training on body composition.[12,42]

Recommendation. *To date, not enough data are available to support or refute the choice of body composition as a central target parameter for exercise training in T2DM patients.*

Blood pressure. Elevated blood pressure (BP) is a well-established prognostic marker for long-term cardiovascular events and outcome in T2DM patients with and without established CVD.[126] In fact T2DM patients have a three- to six-fold higher risk to develop hypertension as compared with non-diabetes mellitus subjects.[127] Moreover, in T2DM patients, masked hypertension is not infrequent and monitoring 24 h ambulatory BP may be a useful approach.[128] Reductions of BP were achieved by some exercise training protocols, mostly AET programmes,[11,12,41,42,52,56] but were accompanied by significant changes of the mean BMI, making the interpretation of BMI-independent effects difficult. In contrast, a trial in 140 T2DM patients did not find any changes in BP after six months of supervised combined AET/resistance training, while fitness and body composition were improved significantly.[43] Meta-analyses demonstrated no or only small effects of resistance training on systolic BP.[12,42]

Recommendation. *Optimal BP control is a general treatment goal in T2DM. It is likely that an optimally adjusted long-term exercise programme will also have positive impact on BP control, mainly driven by a reduction of BMI. To achieve an optimal effect, though, exercise will mostly have to be combined with pharmacological treatment. Further research needs to determine which mode, intensity and duration of exercise training is most likely related to improved BP values in T2DM.*

Autonomic regulation. A major complication observed in T2DM patients is cardiovascular autonomic neuropathy (CAN), a severe clinical problem accounting for resting tachycardia, orthostatic hypotension, decreased heart rate variability, cardiorespiratory instability, silent myocardial infarction and, importantly, increased mortality risk.[129,130] The earliest manifestations of autonomic neuropathy in T2DM patients tend to be associated with parasympathetic denervation. By contrast, the sympathetic system is affected only at an advanced stage of the disease.[131] As a result, a common sign suggestive of CAN is the early augmentation of the sympathetic tone, which may clinically manifest with an elevation of resting heart rate

(HR; 90–100 beats/min), with increments up to 130 beats/min. When the disease starts to affect the sympathetic fibres – a combined parasympathetic and sympathetic damage – resting HR decreases to near-normal levels.[113] An important factor related to CAN affecting exercise tolerance is the reduction of maximal HR and BP response. In T2DM patients, lower heart rate variability (HRV) is an early consequence of CAN, which critically affects cardiac adaptation to exercise.[132,133] In addition, CAN affects heart rate recovery, which has been shown to be a risk factor for incident T2DM[134] and predictive for reduced long-term survival, both in patients with and patients without T2DM.[135] Whereas exercise training has been shown to contribute to the restoration of the cardioprotective autonomic modulation in T2DM patients,[45–47] to date, it is not clear whether exercise training-induced improvements of autonomic regulation lead to actual clinical improvements such as a reduction in cardiovascular events and reversibility of nephropathy and other cardiac denervation-associated phenomena, such as increased microalbuminuria and decreased glomerular filtration rate.

Recommendation. *Despite its prognostic value, there is insufficient evidence to recommend assessment of autonomic neuropathy as a target variable for exercise training in T2DM patients.*

Failure to respond

In T2DM patients, exercise training regimes are often incorporated into comprehensive lifestyle interventions which promote weight loss through decreased caloric intake and increased physical activity.[136] Lack of improvement by such interventions in some studies may have resulted from one or both of two main mechanisms: 1) absence of (short-term) response to intervention; 2) positive short-term response to intervention but failure of long-term maintenance of these effects; and 3) selection of improper exercise modalities. Consequently, intervention success depends on the duration of follow-up as well as the choice of measured outcome variables.

Approximately 15–20% of T2DM patients fail to improve their metabolic profile and CRF with a structured exercise programme.[137] Moreover, in a recent meta-analysis 8–13% of individuals even showed an adverse response to exercise training, defined as worsening of at least one cardiovascular risk factor.[138] In addition to compliance, genetic and epigenetic factors may contribute to a failure to respond or even a negative response to an exercise intervention. In fact, the extent of maximum oxygen uptake improvement in response to exercise training might be largely heritable.[139] Exercise places an increased energy demand on skeletal muscles, met through the generation of adenosine triphosphate as well as cellular components, and orchestrated by key metabolism genes. Regulation of the transcription of these genes via various elements may serve as potential points of regulation of the adaptations to exercise. DNA sequence variation and/or epigenetic modifications in any of these elements may, therefore, modulate the response to exercise training.[137]

Aside from the minority of patients who do not show a favourable training response, the majority of patients show at least some positive short-term effects on surrogate markers of cardiovascular health.[49,52,63,140,141] However, evidence for long-lasting effects on hard cardiovascular endpoints (e.g. acute myocardial infarction, stroke, hospitalization) is missing.[52] A large multicentre study, the LookAHEAD trial, randomized more than 5000 patients with T2DM to an intensive lifestyle or control intervention and reported the largest benefits with reduction of body weight, waist circumference and HbA1c, as well as an improvement in CRF in the intervention group during the first year, followed by a gradual loss of the beneficial effects during the next years. This loss of benefit coincided with a gradual decline of counselling frequency after the first six months, suggesting reduced adherence to the exercise regimen thereafter. A lower adherence to training regimes in diabetic compared with non-diabetic patients has also been demonstrated in participants of cardiac rehabilitation programmes. In a retrospective cohort study including more than 8500 patients, participants with T2DM, especially females, were less likely to complete the programme, and to attend the one-year follow-up. Improvement in CRF during the first three months was lower and less well sustained after one year in diabetic compared with non-diabetic participants.[142] In addition to a decline in motivation, diabetic comorbidities like overweight, polyneuropathy and vascular complications may also result in early discontinuation of training.[136]

Recommendation. *In order to improve adherence, the type of activity needs to be carefully adapted to the patient's preferences and comorbidities and adjusted to training progress over time (type, intensity, duration). Regular motivational feedback, for example by telemonitoring, is crucial to adherence and needs to be maintained.*

Exercise training for patients with T2DM and cardiovascular disease: How to do it?

An important determinant of the success of exercise training programmes in T2DM patients is the choice

of exercise modalities. Traditional exercise programmes for cardiovascular rehabilitation have mainly employed continuous AET, such as walking, running, cycling or swimming. Such exercise training protocols use large muscle groups and increase heart rate and the duration of these protocols can be increased gradually. Supported by data from numerous studies, AET is recommended for T2DM patients by most national and international guidelines.[143–146] In particular, cycling is recommended in selected patients with orthopaedic handicaps. In order to increase strength of selected muscle groups, resistance training – the repetitive exercising of individual muscle groups against an opposing force – has been included in rehabilitation exercise programmes. Resistance training has also been shown to be safe in T2DM patients.[13] This section discusses how these exercise modalities should be applied considering specific risks and barriers associated with T2DM.

Patient assessment and risk factor control

Prior to the uptake of a structured moderate to high intensity exercise training programme silent myocardial ischaemia should be ruled out with an appropriate test; a cardiopulmonary exercise test is more accurate than electrocardiogram (ECG) stress testing alone in diagnosing haemodynamic relevant coronary stenosis,[147] and the ventilatory thresholds can be used for the definition of training zones. Cardiovascular risk factors, in particular LDL-C, should be optimally controlled prior to increasing exercise intensity.

Parameters of exercise training programmes

Duration of exercise training programmes. The optimal duration of exercise training programmes in T2DM patients with cardiac comorbidity is highly dependent on training goals. Whereas improvements in vascular function or CRF have already been observed after high intensity exercise training programmes of 2–8 weeks,[60,148,149] programmes of longer duration (i.e. months to years) are more successful in improving body mass and body composition and lipid profile.[49,53] Moreover, detraining leads to a decline in the beneficial effect of exercise training. Physical activity should therefore be incorporated into daily routine as a lifelong behaviour, instead of exercise training programmes being seen as temporarily limited units. However, motivation and thus adherence might be improved by early achievement of certain exercise training goals. The communication of early and late exercise training goals should therefore be a part of motivational/counselling sessions.

Parameters of aerobic endurance training. Meta-analyses have shown that there is a dose–response relation with respect to the volume of AET that is required to decrease HbA1c enough to reduce the risk of diabetic complications, with an optimal training frequency of 3–5 exercise training sessions per week.[14,53,66] Both determinants of training volume, intensity and duration, determine the effect of exercise training. In patients with a high risk for cardiovascular events, larger training volumes (20 MET*h/week) are recommended to obtain greater health benefits.[150] In particular, the optimal training volume for improving body composition and long-term weight loss is substantially higher than for other purposes such as improving glycaemic control and CRF. While in the past high-volume, moderate-intensity training (typically at 50–70% of VO_2peak) was recommended for cardiovascular and T2DM prevention, more recent studies have indicated a greater benefit of higher intensity exercise training on CRF and HbA1c.[63,151] While continuous exercise at high intensity would lead to fatigue soon, alternation of high intensity blocks with low-to-moderate intensity blocks, called high intensity interval training (HIT), allows the patient to repeatedly achieve a high intensity level. In addition, a shorter duration might be necessary to reach an effective exercise volume, thus facilitating integration of exercise training into daily routine and thus potentially improving adherence.[63,152] Studies in T2DM patients demonstrated favourable-to-superior effects of HIT (i.e. high intensity work bouts varying from one to four minutes, typically at 90–95% of maximal work rate, maximal heart rate or heart rate reserve) on glycaemic control, CRF, body composition, systolic BP and cardiac function as compared with a continuous training.[16,51,63,153–158] Yet, HIT requires high levels of motivation and capability of the patient and it is more demanding with regard to supervision, equipment and the need of a structured training plan that is adapted to the patient's progress. It therefore remains to be established whether the implementation of high intensity exercise training strategies may translate into comparable outcomes in clinical practice. Another promising exercise intervention that may improve glycaemic control is interrupted sitting. In fact, several recent small trials showed that reducing sedentary time by interrupting prolonged sitting with brief bouts of walking or light exercise reduces hyperglycaemia and improves insulin sensitivity in sedentary T2DM patients.[159–161] However, long-term effects of interrupting sitting time remain to be determined for individuals with and without diabetes.

Recommendation. *The optimal duration, volume and intensity of AET in diabetes mellitus patients with cardiac comorbidity varies with respect to training goals and*

should therefore be personalized. High-volume moderate-intensity training is recommended for improving body composition and cardiovascular risk factors, preferably by combining training with dietary interventions and counselling/education. HIT might be considered an alternative to moderate intensity training, especially for improvements in CRF and glycaemic control. Also reducing sedentary time by interrupted sitting is a promising intervention for improving glycaemic control.

Parameters of resistance training. The optimal volume and intensity of resistance training programmes are not well established. Resistance training units are usually recommended to improve structure and strength of individual muscle groups. In a meta-analysis of 26 randomized controlled trials (RCTs), it was shown that the reduction in HbA1c in T2DM patients was correlated with the weekly volume of resistance training when combined with AET, and not with resistance training intensity.[14] A more recent meta-analysis of 37 RCTs showed that compared with either supervised aerobic or supervised resistance exercise alone, combined exercise showed more pronounced improvement in HbA1c levels; however, there was a less marked improvement in some cardiovascular risk factors.[162] Based on expert opinion mainly, guidelines recommend that resistance training should be performed involving large muscle groups, 2–3 times per week in combination with AET, gradually increasing the volume to 2–4 sets per muscle group with intensities suitable to achieve 8–10 repetitions per set (i.e. 75% to 85% of one repetition maximum). Individual studies showed a strength gain superior to AET, but comparable improvements in glycaemic control, body composition, muscle mass and CRF.[163]

Recommendation. *Although there is insufficient evidence to recommend resistance training as an alternative to AET, high-volume resistance training has beneficial effects in combination with AET with respect to glycaemic control, body composition and muscle strength.*

Training barriers

Patients with T2DM and cardiac comorbidity entering an exercise training programme carry a consistent risk of cardiovascular problems during exercise. In this setting, two main clinical questions need to be answered: 1) How do we understand who is suitable or not for an exercise programme? and 2) which is the safer exercise modality for the specific diabetes mellitus patient? A scrutiny assessment of clinical history and examination, in combination with instrumental tests, is key to estimate the probability of exercise-related cardiovascular complications in T2DM patients.[164] In addition to assessment of potential physical training barriers and risks, the patients' motivation should also be taken into account. In order to maintain motivation, practitioners and patients should select relevant and achievable targets, such as improvement of quality of life and daily exercise activity as well as CRF, improved glucose control and, in general, overall risk reduction. Nevertheless, it should be noted that these targets may be transient. Once patients achieve an optimal glycaemic control or CRF, the motivation to remain exercising may decrease again. Therefore, intrinsic motivation is still a crucial determinant of long-term adherence to structured exercise training.

CAN. CAN is a major risk factor in T2DM patients, contributing to exercise intolerance and subclinical myocardial dysfunction.[129] One of the clinical manifestations of CAN In T2DM patients is an impairment of HRV, which can be detected through the deep breathing test, a quick test (1 min) which provides real-time information about the HRV status or by calculation of indices based on statistical analyses of R-R intervals.[129,132,165] For individuals with autonomic neuropathy, increases in exercise intensity levels must be approached with caution because the autonomic nervous system is highly implicated in hormonal and cardiovascular regulation during exercise.[131] Furthermore, prescription and monitoring of exercise intensity cannot be based on HR in these patients but rather on other parameters such as the subjective ratings of perceived exertion (Borg scale) or percentage HR reserve. Another clinical manifestation of CAN, orthostatic hypotension, has been formally defined as a fall in systolic BP of at least 20 mmHg and/or diastolic BP of at least 10 mmHg within 3 min of standing.[166] Orthostatic symptoms in T2DM patients are the result of progressive damage to the efferent sympathetic vasomotor fibres, particularly in the splanchnic vasculature,[167] and consist of weakness, faintness, dizziness, visual impairment and syncope.[168] Notably, orthostatic hypotension is an independent predictor of mortality.[169] Orthostatic hypotension is claimed based on clinical history and symptoms, while its presence should be confirmed by the lying-to-standing orthostatic test or the head-up tilt test. Exercise programmes in T2DM patients at risk of orthostatic hypotension should entail easily tolerated, lower intensity activities ($VO_2max < 40\%$, Borg < 12) which do not require rapid movements, such as recumbent cycling or water aerobics.[170,171]

Myocardial ischaemia. Silent myocardial ischaemia in diabetes mellitus patients is likely due to dysfunction of afferent cardiac autonomic nerve fibres and affects approximately 20–35% of patients.[172] Since T2DM

patients with CAN and CAD have longer ischaemic thresholds which permit them to continue exercising despite ischaemia,[129] it is very important to screen asymptomatic T2DM entering exercise training programmes. The initial evaluation of diabetes mellitus patients undergoing exercise programmes should entail: 1) assessment of CAD risk; 2) risk of CAN (signs/symptoms, risk factors, physical examination, autonomic tests). In asymptomatic T2DM patients at risk for CAD or CAN it is advisable to proceed with cardiac tests such as ECG stress test, myocardial scintigraphy or stress echocardiography.[173] Patients at low risk of CAD but with evidence of CAN should also undergo a stress test before commencing exercise, given the likelihood of silent myocardial ischaemia (due to microvascular dysfunction), and for assessment of HR and BP alterations. Moreover, the Detection of Ischemia in Asymptomatic Diabetics study showed that CAN was an independent predictor of myocardial ischaemia in 1123 patients with T2DM.[174] In patients planning to participate in low-intensity forms of physical activity (<60% of maximal HR) such as walking, the physician should use clinical judgment in deciding whether to recommend an exercise stress test.[175] Patients with known CAD should undergo a supervised evaluation of the ischaemic response to exercise, ischaemic threshold and the propensity to arrhythmia during exercise, as well as left ventricular systolic function.[173,174]

Arrhythmias. T2DM patients have a higher risk of life-threatening arrhythmias as compared with non-diabetic individuals,[176,177] mainly due to ventricular tachyarrhythmia as a consequence of silent myocardial ischaemia or infarction.[176] Arrhythmias are also triggered by myocardial fibrosis, as observed in T2DM subjects with marked diastolic dysfunction or systolic heart failure. Prolonged QT intervals corrected for heart rate (QTc) have been observed in diabetic patients with CAN[129,178] and were shown to be associated with an increased risk for sudden cardiac death in T2DM patients.[129] Hence, ECG evaluation of QT/QTc interval should be conducted to evaluate CAN. Premature ventricular complexes are not uncommon in persons with T2DM and, when frequent and repetitive, identify a population at high risk for arrhythmia-induced syncope or sudden cardiac death.[179] Therefore, individual risk stratification (i.e. Holter monitoring, ECG stress test, coronary imaging (coronary angiography, coronary computed tomography scan)) is important before considering any exercise programme. The identification of asymptomatic patients at risk of bradyarrhythmias also represents a major task for the cardiologist. These types of arrhythmias are indeed a major cause of syncope and, more in general, haemodynamic instability during exercise. Diabetic cardiomyopathy is associated with myocardial fibrosis, a condition which may favour sino-atrial and atrioventricular node dysfunction.[180] A standard 12-lead ECG may already provide important information. Sinus bradycardia (<50 beats/min) in non-trained patients and bifascicular or left bundle branch block as well as first-degree atrioventricular (A-V) block are all signs deserving further diagnostic investigation by 24-h ECG monitoring.

Left ventricular dysfunction. In the Framingham study, diabetic men and women had a six- to eight-fold increase in the prevalence of heart failure as compared with subjects without diabetes.[181] Although T2DM is strongly associated with CAD, many cases of heart failure occur in subjects with non-obstructive CAD, a cardiac phenotype known as diabetic cardiomyopathy.[182,183] Diabetic cardiomyopathy is characterized by myocardial stiffness with reduced compliance precipitating diastolic heart failure and systolic heart failure at a later stage. The impairment of diastolic function in T2DM patients may represent an important determinant of exercise intolerance.[184] However, exercise training may have beneficial effects on diastolic function and left ventricular (LV) geometry.[173] In general, dynamic endurance training causes parallel increases in LV end-diastolic radius and wall thickness, without an increase in wall stress. Dynamic training also induces a relative sinus bradycardia, due to increased vagal tone or volume-induced baroreceptor activation, which prolongs the time for diastolic filling. Exercise stress echocardiography is perhaps the best method to evaluate cardiac function during exercise, as it provides information on many parameters, including pulmonary pressures, diastolic and systolic function, gradients across heart valves and ischaemia.[185]

Ongoing randomized studies will clarify the effect of exercise training on LV remodelling in diabetes mellitus patients with diastolic dysfunction.[186] Exercise programmes in diabetes mellitus patients with systolic heart failure are associated with higher risk since physical activity may induce post-exercise hypotension, atrial and ventricular arrhythmias and worsening heart failure symptoms.[173] These patients may eventually participate in a supervised training programme for a brief time to obtain instructions for self-monitoring before proceeding with a programme of unsupervised exercise. Careful patient selection and follow-up are fundamental in this setting.

Peripheral arterial disease and other vascular complications. Peripheral artery disease is the most common presentation of CVD in T2DM patients, and may account for exercise intolerance or exercise-related

complications, namely acute ischaemia of lower limbs.[187,188] For the clinical diagnosis, the palpation of pulses and visual inspections of feet are an essential step. A reliable indicator of peripheral artery disease is the ankle brachial index (ABI).[189] This test is done by measuring blood pressure at the ankle (posterior tibial or dorsalis pedal level) and in the arm (brachial systolic BP) while a person is at rest. If uncertainties remain, post-exercise ABI or other non-invasive tests, which may include imaging, should be used.[189]

Another vascular complication of T2DM requiring consideration before starting an exercise training programme is retinopathy. Based on expert opinion, patients with retinopathy are recommended not to perform high-intensity exercise (i.e. exceeding the anaerobic threshold).[145] Currently no clear recommendations exist with respect to patients with a nephropathy.

Hypertension. A large proportion of T2DM patients present with uncontrolled BP values, which requires implementation of medical therapy before commencing an exercise training programme. Current guidelines recommend a BP goal of $<130/80$ mmHg.[190,191] Besides a careful analysis of blood pressure profile, a cardiac stress test to evaluate hypertensive response to exercise is warranted.[192]

Glycaemic status. In patients with poor glycaemic status (HbA1c $> 7.5\%$) an intensive glycaemic control has shown to increase the incidence of severe hypoglycaemia three- to four-fold in T2DM.[193] Post-hoc analyses from recent randomized trials have shown that hypoglycaemia has a detrimental impact on cardiovascular morbidity and mortality.[194] Furthermore, recent work suggests that hypoglycaemia, frequently asymptomatic and prolonged, may increase the risk of arrhythmias in patients with T2DM and high cardiovascular risk.[195,196] In addition, hypoglycaemia may trigger systemic inflammation and hypercoagulability, thus favouring platelet activation and acute myocardial ischaemia.[197] Diabetic patients who are more likely to develop severe hypoglycaemic events are older, have lower BMI, impaired renal function, a history of microvascular complications, dementia, previous hypoglycaemic events, longer duration of T2DM and lower education.[198] Another precipitating factor is the impaired hypoglycaemic awareness, which increases with duration of diabetes and is a significant risk factor for hypoglycaemia.[199] In this regard, autonomic neuropathy plays a central role by dampening counter-regulatory sympathetic responses.[200] The choice of anti-diabetic treatment is another key factor which may contribute to increase the risk of hypoglycaemia.[201] Hypoglycaemic episodes have been reported with sulphonylureas and metiglinides, and insulin, and patients taking these drugs should be strictly monitored by analysis of glycaemic profile and blood glucose monitoring, particularly during the first weeks of treatment.[201] A careful evaluation of glycaemic status is mandatory in diabetes mellitus patients for whom an exercise programme is planned.[170] This should include risk factors for hypoglycaemia, history of hypoglycaemic episodes, presence of autonomic neuropathy, anti-diabetic treatment and physiological status.

Recommendation. *Patients with T2DM – especially with long-standing disease – need to be carefully checked and regularly monitored, especially for cardiac autonomic neuropathy and hypoglycaemia. Patients at risk or severely detrained patients should start exercising at low intensity, with each increment to be supervised closely, aiming at integration of regular physical activity into daily routine.*

Concluding remarks – what can we do?

Recent research and debate in the field have led to a change of perceived relevance of target parameters, questioning, for example, the relevance of weight loss as a main goal in non-severely obese T2DM patients in favour of metabolic and functional parameters, such as glycaemic control, vascular function and CRF. Optimal exercise parameters vary depending on the individual importance of target parameters for each patient and should therefore be personalized. High-volume moderate-intensity training is safe and proven to improve glycaemic control and CRF in T2DM patients with cardiac comorbidity. High-intensity interval training is a promising strategy to improve CRF, glycaemic control and body composition, as well as cardiac function. Combined high-volume resistance training/AET may add to improvements in glycaemic control and body composition. Despite these potentially favourable effects, not all T2DM patients improve their metabolic profile and CRF after exercise training and may even show adverse effects. This may be explained by genetic factors influencing the response to exercise training but also by a decline in adherence to exercise training programmes in the longer term due to a lack of motivation and/or specific cardiac and diabetes-related training barriers such as CAN, silent ischaemia, arrhythmias, diastolic heart failure, peripheral artery disease, hypertension and hypoglycaemia. Therefore, in T2DM patients with cardiac comorbidities, exercise training programmes should be adjusted to individual exercise training targets and potential training barriers, established after a careful initial evaluation. However, the main common problem of all exercise interventions aiming at long-term improvements remains adherence, which is severely affecting the outcome of many trials.

We should therefore consider the importance of motivation, improving self-management skills and integration of exercise into daily routine when designing exercise training programmes. This can very well be supported by multi-professional teams, including physicians, psychologists and counsellors in addition to dieticians and exercise scientists.

Author contributions

HK, NK, MD, TM, MW, FP, LS, ES, DH, MH and MG contributed to the conception or design of the work, contributed to the acquisition, analysis, or interpretation of data for the work, drafted the manuscript and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Beckman JA, Paneni F, Cosentino F, et al. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: part II. *Eur Heart J* 2013; 34: 2444–2452.
2. Zinman B, Ruderman N, Campaigne BN, et al. Physical activity/exercise and diabetes mellitus. *Diabetes Care* 2003; 26(Suppl. 1): S73–S77.
3. Krankel N, Bahls M, Van Craenenbroeck EM, et al. Exercise training to reduce cardiovascular risk in patients with metabolic syndrome and type 2 diabetes mellitus: How does it work? *Eur J Prev Cardiol* 2019; 26: 701–708.
4. Morrato EH, Hill JO, Wyatt HR, et al. Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care* 2007; 30: 203–209.
5. Adeniyi AF, Anjana RM and Weber MB. Global account of barriers and facilitators of physical activity among patients with diabetes mellitus: A narrative review of the literature. *Curr Diabetes Rev* 2016; 12: 440–448.
6. Pandey A, Swift DL, McGuire DK, et al. Metabolic effects of exercise training among fitness-nonresponsive patients with type 2 diabetes: The HART-D study. *Diabetes Care* 2015; 38: 1494–1501.
7. Malandrino MI, Fucho R, Weber M, et al. Enhanced fatty acid oxidation in adipocytes and macrophages reduces lipid-induced triglyceride accumulation and inflammation. *Am J Physiol Endocrinol Metab* 2015; 308: E756–E769.
8. Thomas DE, Elliott EJ and Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006; 19(3): CD002968.
9. Koster-Rasmussen R, Simonsen MK, Siersma V, et al. Intentional weight loss and longevity in overweight patients with type 2 diabetes: a population-based cohort study. *PLoS One* 2016; 11: e0146889.
10. Balducci S, Zanuso S, Cardelli P, et al. Changes in physical fitness predict improvements in modifiable cardiovascular risk factors independently of body weight loss in subjects with type 2 diabetes participating in the Italian Diabetes and Exercise Study (IDES). *Diabetes Care* 2012; 35: 1347–1354.
11. Schwingshackl L, Missbach B, Dias S, et al. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetologia* 2014; 57: 1789–1797.
12. Chudyk A and Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: A meta-analysis. *Diabetes Care* 2011; 34: 1228–1237.
13. Yang Z, Scott CA, Mao C, et al. Resistance exercise versus aerobic exercise for type 2 diabetes: A systematic review and meta-analysis. *Sports Med* 2014; 44: 487–499.
14. Umpierre D, Ribeiro PA, Schaan BD, et al. Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: A systematic review with meta-regression analysis. *Diabetologia* 2013; 56: 242–251.
15. Oliveira C, Simoes M, Carvalho J, et al. Combined exercise for people with type 2 diabetes mellitus: A systematic review. *Diabetes Res Clin Pract* 2012; 98: 187–198.
16. Mitranun W, Deerochanawong C, Tanaka H, et al. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scand J Med Sci Sports* 2014; 24: e69–e76.
17. Dalleck LC, van Guilder GP, Richardson TB, et al. A community-based exercise intervention transitions metabolically abnormal obese adults to a metabolically healthy obese phenotype. *Diabetes Metab Syndr Obes* 2014; 7: 369–380.
18. Vinetti G, Mozzini C, Desenzani P, et al. Supervised exercise training reduces oxidative stress and cardiometabolic risk in adults with type 2 diabetes: a randomized controlled trial. *Scientific reports* 2015; 5: 9238.
19. Lucotti P, Monti LD, Setola E, et al. Aerobic and resistance training effects compared to aerobic training alone in obese type 2 diabetic patients on diet treatment. *Diabetes Res Clin Pract* 2011; 94: 395–403.
20. Hamasaki H, Kawashima Y, Tamada Y, et al. Associations of low-intensity resistance training with body composition and lipid profile in obese patients with type 2 diabetes. *PLoS One* 2015; 10: e0132959.
21. Herbst A, Kapellen T, Schober E, et al. Impact of regular physical activity on blood glucose control and cardiovascular risk factors in adolescents with type 2 diabetes mellitus – a multicenter study of 578 patients from 225 centres. *Pediatr Diabetes* 2015; 16: 204–210.
22. Mendham AE, Duffield R, Marino F, et al. A 12-week sports-based exercise programme for inactive Indigenous Australian men improved clinical risk factors associated with type 2 diabetes mellitus. *J Sci Med Sport* 2015; 18: 438–443.

23. Thompson D, Walhin JP, Batterham AM, et al. Effect of diet or diet plus physical activity versus usual care on inflammatory markers in patients with newly diagnosed type 2 diabetes: The Early ACTivity in Diabetes (ACTID) randomized, controlled trial. *J Am Heart Assoc* 2014; 3: e000828.
24. Liu Y, Liu SX, Cai Y, et al. Effects of combined aerobic and resistance training on the glycolipid metabolism and inflammation levels in type 2 diabetes mellitus. *J Phys Ther Sci* 2015; 27: 2365–2371.
25. Molanouri Shamsi M, Hassan ZH, Gharakhanlou R, et al. Expression of interleukin-15 and inflammatory cytokines in skeletal muscles of STZ-induced diabetic rats: Effect of resistance exercise training. *Endocrine* 2014; 46: 60–69.
26. Hopps E, Canino B and Caimi G. Effects of exercise on inflammation markers in type 2 diabetic subjects. *Acta Diabetol* 2011; 48: 183–189.
27. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346: 793–801.
28. Keteyian SJ, Brawner CA, Savage PD, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J* 2008; 156: 292–300.
29. Modena MG, Bonetti L, Coppi F, et al. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *J Am Coll Cardiol* 2002; 40: 505–510.
30. Kitta Y, Obata JE, Nakamura T, et al. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. *J Am Coll Cardiol* 2009; 53: 323–330.
31. Montero D, Walther G, Benamo E, et al. Effects of exercise training on arterial function in type 2 diabetes mellitus: A systematic review and meta-analysis. *Sports Med* 2013; 43: 1191–1199.
32. Matsuzawa Y, Guddeti RR, Kwon TG, et al. Treating coronary disease and the impact of endothelial dysfunction. *Progr Cardiovasc Dis* 2015; 57: 431–442.
33. Gielen S, Laughlin MH, O'Conner C, et al. Exercise training in patients with heart disease: Review of beneficial effects and clinical recommendations. *Progr Cardiovasc Dis* 2015; 57: 347–355.
34. Gielen S, Schuler G and Hambrecht R. Exercise training in coronary artery disease and coronary vasomotion. *Circulation* 2001; 103: E1–E6.
35. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000; 342: 454–460.
36. Huebschmann AG, Kohrt WM and Regensteiner JG. Exercise attenuates the premature cardiovascular aging effects of type 2 diabetes mellitus. *Vasc Med* 2011; 16: 378–390.
37. Schreuder TH, Maessen MF, Tack CJ, et al. Life-long physical activity restores metabolic and cardiovascular function in type 2 diabetes. *Eur J Appl Physiol* 2014; 114: 619–627.
38. Schreuder TH, van den Munckhof I, Poelkens F, et al. Combined aerobic and resistance exercise training decreases peripheral but not central artery wall thickness in subjects with type 2 diabetes. *Eur J Appl Physiol* 2015; 115: 317–326.
39. Kalyani RR, Corriere M and Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. *Lancet Diabetes Endocrinol* 2014; 2: 819–829.
40. Senechal M, Johannsen NM, Swift DL, et al. Association between changes in muscle quality with exercise training and changes in cardiorespiratory fitness measures in individuals with type 2 diabetes mellitus: Results from the HART-D Study. *PLoS One* 2015; 10: e0135057.
41. Chen L, Pei JH, Kuang J, et al. Effect of lifestyle intervention in patients with type 2 diabetes: A meta-analysis. *Metabolism* 2015; 64: 338–347.
42. Figueira FR, Umpierre D, Cureau FV, et al. Association between physical activity advice only or structured exercise training with blood pressure levels in patients with type 2 diabetes: A systematic review and meta-analysis. *Sports Med* 2014; 44: 1557–1572.
43. Dobrosielski DA, Gibbs BB, Ouyang P, et al. Effect of exercise on blood pressure in type 2 diabetes: A randomized controlled trial. *J Gen Intern Med* 2012; 27: 1453–1459.
44. Mobasseri M, Yavari A, Najafipoor F, et al. Effect of a long-term regular physical activity on hypertension and body mass index in type 2 diabetes patients. *J Sports Med Phys Fitness* 2015; 55: 84–90.
45. Howorka K, Pumprla J, Haber P, et al. Effects of physical training on heart rate variability in diabetic patients with various degrees of cardiovascular autonomic neuropathy. *Cardiovasc Res* 1997; 34: 206–214.
46. Sacre JW, Jellis CL, Jenkins C, et al. A six-month exercise intervention in subclinical diabetic heart disease: Effects on exercise capacity, autonomic and myocardial function. *Metabolism* 2014; 63: 1104–1114.
47. Voulgari C, Pagoni S, Vinik A, et al. Exercise improves cardiac autonomic function in obesity and diabetes. *Metabolism* 2013; 62: 609–621.
48. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 2004; 27: 83–88.
49. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: A randomized controlled trial. *JAMA* 2010; 304: 2253–2262.
50. Look ARG and Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four-year results of the Look AHEAD trial. *Arch Intern Med* 2010; 170: 1566–1575.
51. Karstoft K, Winding K, Knudsen SH, et al. The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients: A randomized, controlled trial. *Diabetes Care* 2013; 36: 228–236.
52. Look ARG, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369: 145–154.
53. Boule NG, Haddad E, Kenny GP, et al. Effects of exercise on glycemic control and body mass in type 2 diabetes

mellitus: A meta-analysis of controlled clinical trials. *JAMA* 2001; 286: 1218–1227.
54. Luley C, Blaik A, Reschke K, et al. Weight loss in obese patients with type 2 diabetes: Effects of telemonitoring plus a diet combination – the Active Body Control (ABC) Program. *Diabetes Res Clin Pract* 2011; 91: 286–292.
55. McAuley PA, Myers JN, Abella JP, et al. Exercise capacity and body mass as predictors of mortality among male veterans with type 2 diabetes. *Diabetes Care* 2007; 30: 1539–1543.
56. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* 2002; 106: 666–671.
57. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol* 2003; 42: 2139–2143.
58. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: The Aerobics Center Longitudinal Study. *Circulation* 2011; 124: 2483–2490.
59. Stewart RAH, Held C, Hadziosmanovic N, et al. Physical activity and mortality in patients with stable coronary heart disease. *J Am Coll Cardiol* 2017; 70: 1689–1700.
60. Schreuder TH, Green DJ, Nyakayiru J, et al. Time-course of vascular adaptations during 8 weeks of exercise training in subjects with type 2 diabetes and middle-aged controls. *Eur J Appl Physiol* 2015; 115: 187–196.
61. Okada S, Hiuge A, Makino H, et al. Effect of exercise intervention on endothelial function and incidence of cardiovascular disease in patients with type 2 diabetes. *J Atheroscler Thromb* 2010; 17: 828–833.
62. Sixt S, Beer S, Bluher M, et al. Long- but not short-term multifactorial intervention with focus on exercise training improves coronary endothelial dysfunction in diabetes mellitus type 2 and coronary artery disease. *Eur Heart J* 2010; 31: 112–119.
63. Boule NG, Kenny GP, Haddad E, et al. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. *Diabetologia* 2003; 46: 1071–1081.
64. Hansen D, Dendale P, Coninx K, et al. The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool: A digital training and decision support system for optimized exercise prescription in cardiovascular disease. Concept, definitions and construction methodology. *Eur J Prev Cardiol* 2017; 24: 1017–1031.
65. Van Sluijs EM, van Poppel MN, Twisk JW, et al. Physical activity measurements affected participants' behavior in a randomized controlled trial. *J Clin Epidemiol* 2006; 59: 404–411.
66. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: A systematic review and meta-analysis. *JAMA* 2011; 305: 1790–1799.
67. Strasser B and Pesta D. Resistance training for diabetes prevention and therapy: Experimental findings and molecular mechanisms. *Biomed Res Int* 2013; 2013: 805217.
68. Tresierras MA and Balady GJ. Resistance training in the treatment of diabetes and obesity: Mechanisms and outcomes. *J Cardiopulm Rehabil Prev* 2009; 29: 67–75.
69. Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: A secondary analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2014; 2: 801–809.
70. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115–126.
71. Xu Y, Arora RC, Hiebert BM, et al. Non-invasive endothelial function testing and the risk of adverse outcomes: A systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2014; 15: 736–746.
72. Kingwell BA. Nitric oxide-mediated metabolic regulation during exercise: Effects of training in health and cardiovascular disease. *FASEB J* 2000; 14: 1685–1696.
73. Newsholme P, Homem De Bittencourt PI, C OH, et al. Exercise and possible molecular mechanisms of protection from vascular disease and diabetes: The central role of ROS and nitric oxide. *Clin Sci* 2010; 118: 341–349.
74. Szostak J and Laurant P. The forgotten face of regular physical exercise: A 'natural' anti-atherogenic activity. *Clin Sci* 2011; 121: 91–106.
75. Begot I, Peixoto TC, Gonzaga LR, et al. A home-based walking program improves erectile dysfunction in men with an acute myocardial infarction. *Am J Cardiol* 2015; 115: 571–575.
76. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2012; 87: 766–778.
77. Musicki B, Bella AJ, Bivalacqua TJ, et al. Basic science evidence for the link between erectile dysfunction and cardiometabolic dysfunction. *J Sex Med* 2015; 12: 2233–2255.
78. Thijssen DH, Black MA, Pyke KE, et al. Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *Am J Physiol Heart Circ Physiol* 2011; 300: H2–H12.
79. Bellia A, Iellamo F, De Carli E, et al. Exercise individualized by TRIMPi method reduces arterial stiffness in early onset type 2 diabetic patients: A randomized controlled trial with aerobic interval training. *Int J Cardiol* 2017; 248: 314–319.
80. Ashor AW, Lara J, Siervo M, et al. Effects of exercise modalities on arterial stiffness and wave reflection: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2014; 9: e110034.
81. Buresh R. Exercise and glucose control. *J Sports Med Phys Fitness* 2014; 54: 373–382.
82. Mechanick JI, Zhao S and Garvey WT. The adipokine-cardiovascular-lifestyle network: Translation to clinical practice. *J Am Coll Cardiol* 2016; 68: 1785–1803.

83. Ringseis R, Eder K, Mooren FC, et al. Metabolic signals and innate immune activation in obesity and exercise. *Exerc Immunol Rev* 2015; 21: 58–68.
84. Youm YH, Nguyen KY, Grant RW, et al. The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med* 2015; 21: 263–269.
85. Hayashino Y, Jackson JL, Fukumori N, et al. Effects of supervised exercise on lipid profiles and blood pressure control in people with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* 2012; 98: 349–360.
86. Van Hall G. The physiological regulation of skeletal muscle fatty acid supply and oxidation during moderate-intensity exercise. *Sports Med* 2015; 45(Suppl. 1): S23–S32.
87. Sakamoto K and Goodyear LJ. Invited review: Intracellular signaling in contracting skeletal muscle. *J Appl Physiol* 2002; 93: 369–383.
88. Kelley GA and Kelley KS. Effects of aerobic exercise on lipids and lipoproteins in adults with type 2 diabetes: A meta-analysis of randomized-controlled trials. *Public Health* 2007; 121: 643–655.
89. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 253: 281–344.
90. Murlasits Z and Radak Z. The effects of statin medications on aerobic exercise capacity and training adaptations. *Sports Med* 2014; 44: 1519–1530.
91. Mikus CR, Boyle LJ, Borengasser SJ, et al. Simvastatin impairs exercise training adaptations. *J Am Coll Cardiol* 2013; 62: 709–714.
92. Meex RC, Phielix E, Schrauwen-Hinderling VB, et al. The use of statins potentiates the insulin-sensitizing effect of exercise training in obese males with and without type 2 diabetes. *Clin Sci* 2010; 119: 293–301.
93. Plaisance EP, Grandjean PW and Mahurin AJ. Independent and combined effects of aerobic exercise and pharmacological strategies on serum triglyceride concentrations: a qualitative review. *Phys Sportsmed* 2009; 37: 11–19.
94. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: Prospective cohort study. *BMJ* 2008; 337: a439.
95. Kamiya K, Masuda T, Tanaka S, et al. Quadriceps strength as a predictor of mortality in coronary artery disease. *Am J Med* 2015; 128(11): 1212–1219.
96. 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: 266–273.
97. Gielen S, Sandri M, Kozarez I, et al. Exercise training attenuates MuRF-1 expression in the skeletal muscle of patients with chronic heart failure independent of age: The randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging catabolism study. *Circulation* 2012; 125: 2716–2727.
98. Ruas JL, White JP, Rao RR, et al. A PGC-1alpha isoform induced by resistance training regulates skeletal muscle hypertrophy. *Cell* 2012; 151: 1319–1331.
99. Wang L, Mascher H, Psilander N, et al. Resistance exercise enhances the molecular signaling of mitochondrial biogenesis induced by endurance exercise in human skeletal muscle. *J Appl Physiol* 2011; 111: 1335–1344.
100. Atherton PJ, Babraj J, Smith K, et al. Selective activation of AMPK-PGC-1alpha or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. *FASEB J* 2005; 19: 786–788.
101. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; 33: 1635–1701.
102. Ryden L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013; 34: 3035–3087.
103. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: A scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007; 115: 114–126.
104. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies. *Lancet* 2009; 373: 1083–1096.
105. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010; 363: 2211–2219.
106. Ades PA, Savage PD, Toth MJ, et al. High-calorie-expenditure exercise: A new approach to cardiac rehabilitation for overweight coronary patients. *Circulation* 2009; 119: 2671–2678.
107. Lavie CJ and Milani RV. Effects of cardiac rehabilitation, exercise training, and weight reduction on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in obese coronary patients. *Am J Cardiol* 1997; 79: 397–401.
108. Aggarwal S, Arena R, Cuda L, et al. The independent effect of traditional cardiac rehabilitation and the LEARN program on weight loss: A comparative analysis. *J Cardiopulm Rehabil Prev* 2012; 32: 48–52.
109. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery

disease: A systematic review of cohort studies. *Lancet* 2006; 368: 666–678.
110. Khalangot M, Tronko M, Kravchenko V, et al. Body mass index and the risk of total and cardiovascular mortality among patients with type 2 diabetes: A large prospective study in Ukraine. *Heart* 2009; 95: 454–460.
111. Logue J, Walker JJ, Leese G, et al. Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. *Diabetes Care* 2013; 36: 887–893.
112. Tobias DK, Pan A, Jackson CL, et al. Body-mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med* 2014; 370: 233–244.
113. Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. *JAMA* 2012; 308: 581–590.
114. McEwen LN, Karter AJ, Waitzfelder BE, et al. Predictors of mortality over 8 years in type 2 diabetic patients: Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care* 2012; 35: 1301–1309.
115. Doehner W, Erdmann E, Cairns R, et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: An analysis of the PROactive study population. *Int J Cardiol* 2012; 162: 20–26.
116. Mons U, Hahmann H and Brenner H. A reverse J-shaped association of leisure time physical activity with prognosis in patients with stable coronary heart disease: Evidence from a large cohort with repeated measurements. *Heart* 2014; 100: 1043–1049.
117. McAuley PA, Artero EG, Sui X, et al. The obesity paradox, cardiorespiratory fitness, and coronary heart disease. *Mayo Clin Proc* 2012; 87: 443–451.
118. Goel K, Thomas RJ, Squires RW, et al. Combined effect of cardiorespiratory fitness and adiposity on mortality in patients with coronary artery disease. *Am Heart J* 2011; 161: 590–597.
119. Espeland MA, Rejeski WJ, West DS, et al. Intensive weight loss intervention in older individuals: results from the Action for Health in Diabetes Type 2 diabetes mellitus trial. *J Am Geriatr Soc* 2013; 61: 912–922.
120. Cepeda-Valery B, Pressman GS, Figueredo VM, et al. Impact of obesity on total and cardiovascular mortality – fat or fiction? *Nat Reviews Cardiol* 2011; 8: 233–237.
121. Gielen S and Sandri M. The obesity paradox – A scientific artifact? *Int J Cardiol* 2013; 162: 140–142.
122. Kokkinos P, Myers J, Faselis C, et al. BMI-mortality paradox and fitness in African American and Caucasian men with type 2 diabetes. *Diabetes Care* 2012; 35: 1021–1027.
123. Won KB, Hur SH, Cho YK, et al. Comparison of 2-year mortality according to obesity in stabilized patients with type 2 diabetes mellitus after acute myocardial infarction: Results from the DIAMOND prospective cohort registry. *Cardiovasc Diabetol* 2015; 14: 141.
124. Murphy RA, Reinders I, Garcia ME, et al. Adipose tissue, muscle, and function: Potential mediators of associations between body weight and mortality in older adults with type 2 diabetes. *Diabetes Care* 2014; 37: 3213–3219.
125. Maillard F, Rousset S, Pereira B, et al. High-intensity interval training reduces abdominal fat mass in postmenopausal women with type 2 diabetes. *Diabetes Metabol* 2016; 42: 433–441.
126. Sowers JR, Epstein M and Frohlich ED. Diabetes, hypertension, and cardiovascular disease: An update. *Hypertension* 2001; 37: 1053–1059.
127. Lastra G, Syed S, Kurukulasuriya LR, et al. Type 2 diabetes mellitus and hypertension: An update. *Endocrinol Metab Clin North Am* 2014; 43: 103–122.
128. Bayliss G, Weinrauch LA and D'Elia JA. Resistant hypertension in diabetes mellitus. *Curr Diabetes Rep* 2014; 14: 516.
129. Vinik AI and Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; 115: 387–397.
130. Serhiyenko VA and Serhiyenko AA. Diabetic cardiac autonomic neuropathy: Do we have any treatment perspectives? *World J Diabetes* 2015; 6: 245–258.
131. Hage FG and Iskandrian AE. Cardiac autonomic denervation in diabetes mellitus. *Circ Cardiovasc Imaging* 2011; 4: 79–81.
132. Kudat H, Akkaya V, Sozen AB, et al. Heart rate variability in diabetes patients. *J Int Med Res* 2006; 34: 291–296.
133. Schroeder EB, Chambless LE, Liao D, et al. Diabetes, glucose, insulin, and heart rate variability: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2005; 28: 668–674.
134. Yu TY, Jee JH, Bae JC, et al. Delayed heart rate recovery after exercise as a risk factor of incident type 2 diabetes mellitus after adjusting for glycometabolic parameters in men. *Int J Cardiol* 2016; 221: 17–22.
135. Sydo N, Sydo T, Merkely B, et al. Impaired heart rate response to exercise in diabetes and its long-term significance. *Mayo Clin Proc* 2016; 91: 157–165.
136. De Feo P and Schwarz P. Is physical exercise a core therapeutical element for most patients with type 2 diabetes? *Diabetes Care* 2013; 36(Suppl. 2): S149–S154.
137. Stephens NA and Sparks LM. Resistance to the beneficial effects of exercise in type 2 diabetes: Are some individuals programmed to fail? *J Clin Endocrinol Metab* 2015; 100: 43–52.
138. Bouchard C, Blair SN, Church TS, et al. Adverse metabolic response to regular exercise: Is it a rare or common occurrence? *PLoS One* 2012; 7: e37887.
139. Bouchard C, Rankinen T and Timmons JA. Genomics and genetics in the biology of adaptation to exercise. *Compr Physiol* 2011; 1: 1603–1648.
140. Bajpeyi S, Tanner CJ, Slentz CA, et al. Effect of exercise intensity and volume on persistence of insulin sensitivity during training cessation. *J Appl Physiol* 2009; 106: 1079–1085.
141. Sparks LM, Johannsen NM, Church TS, et al. Nine months of combined training improves ex vivo skeletal muscle metabolism in individuals with type 2 diabetes. *J Clin Endocrinol Metab* 2013; 98: 1694–1702.
142. Armstrong MJ, Martin BJ, Arena R, et al. Patients with diabetes in cardiac rehabilitation: Attendance and exercise capacity. *Med Sci Sports Exerc* 2014; 46: 845–850.

143. O'Hagan C, de Vito G and Boreham CA. Exercise prescription in the treatment of type 2 diabetes mellitus: Current practices, existing guidelines and future directions. *Sports Med* 2013; 43: 39–49.
144. Hansen D, Peeters S, Zwaenepoel B, et al. Exercise assessment and prescription in patients with type 2 diabetes in the private and home care setting: Clinical recommendations from AXXON (Belgian Physical Therapy Association). *Phys Ther* 2013; 93: 597–610.
145. Marwick TH, Hordern MD, Miller T, et al. Exercise training for type 2 diabetes mellitus: Impact on cardiovascular risk: A scientific statement from the American Heart Association. *Circulation* 2009; 119: 3244–3262.
146. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. *Diabetes Care* 2010; 33: e147–e167.
147. Belardinelli R, Lacalaprice F, Tiano L, et al. Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. *Int J Cardiol* 2014; 174: 337–342.
148. Smith-Ryan AE, Trexler ET, Wingfield HL, et al. Effects of high-intensity interval training on cardiometabolic risk factors in overweight/obese women. *J Sports Sci* 2016; 34(21): 2038–2046.
149. Lanzi S, Codecasa F, Cornacchia M, et al. Short-term HIIT and fat max training increase aerobic and metabolic fitness in men with class II and III obesity. *Obesity* 2015; 23: 1987–1994.
150. Balducci S, Zanuso S, Nicolucci A, et al. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: A randomized controlled trial: The Italian Diabetes and Exercise Study (IDES). *Arch Intern Med* 2010; 170: 1794–1803.
151. Weston KS, Wisloff U and Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: A systematic review and meta-analysis. *Br J Sports Med* 2014; 48: 1227–1234.
152. Bartlett JD, Close GL, MacLaren DP, et al. High-intensity interval running is perceived to be more enjoyable than moderate-intensity continuous exercise: Implications for exercise adherence. *J Sports Sci* 2011; 29: 547–553.
153. Gillen JB, Little JP, Punthakee Z, et al. Acute high-intensity interval exercise reduces the postprandial glucose response and prevalence of hyperglycaemia in patients with type 2 diabetes. *Diabetes Obes Metab* 2012; 14: 575–577.
154. Little JP, Gillen JB, Percival ME, et al. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J Appl Physiol* 2011; 111: 1554–1560.
155. Karstoft K, Winding K, Knudsen SH, et al. Mechanisms behind the superior effects of interval vs continuous training on glycaemic control in individuals with type 2 diabetes: A randomised controlled trial. *Diabetologia* 2014; 57: 2081–2093.
156. Hollekim-Strand SM, Bjorgaas MR, Albrektsen G, et al. High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: A randomized controlled trial. *J Am Coll Cardiol* 2014; 64: 1758–1760.
157. Cassidy S, Thoma C, Hallsworth K, et al. High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: A randomised controlled trial. *Diabetologia* 2016; 59: 56–66.
158. Robinson E, Durrer C, Simtchouk S, et al. Short-term high-intensity interval and moderate-intensity continuous training reduce leukocyte TLR4 in inactive adults at elevated risk of type 2 diabetes. *J Appl Physiol* 2015; 119: 508–516.
159. Duvivier BM, Schaper NC, Hesselink MK, et al. Breaking sitting with light activities vs structured exercise: A randomised crossover study demonstrating benefits for glycaemic control and insulin sensitivity in type 2 diabetes. *Diabetologia* 2017; 60: 490–498.
160. Dempsey PC, Blankenship JM, Larsen RN, et al. Interrupting prolonged sitting in type 2 diabetes: Nocturnal persistence of improved glycaemic control. *Diabetologia* 2017; 60: 499–507.
161. Henson J, Davies MJ, Bodicoat DH, et al. Breaking up prolonged sitting with standing or walking attenuates the postprandial metabolic response in postmenopausal women: a randomized acute study. *Diabetes Care* 2016; 39: 130–138.
162. Pan B, Ge L, Xun YQ, et al. Exercise training modalities in patients with type 2 diabetes mellitus: A systematic review and network meta-analysis. *Int J Behav Nutr Phys Act* 2018; 15: 72.
163. Egger A, Niederseer D, Diem G, et al. Different types of resistance training in type 2 diabetes mellitus: Effects on glycaemic control, muscle mass and strength. *Eur J Prev Cardiol* 2013; 20: 1051–1060.
164. Riebe D, Franklin BA, Thompson PD, et al. Updating ACSM's recommendations for exercise preparticipation health screening. *Med Sci Sports Exerc* 2015; 47: 2473–2479.
165. Huikuri HV and Stein PK. Heart rate variability in risk stratification of cardiac patients. *Progr Cardiovasc Dis* 2013; 56: 153–159.
166. Perlmuter LC, Sarda G, Casavant V, et al. A review of the etiology, associated comorbidities, and treatment of orthostatic hypotension. *Am J Ther* 2013; 20: 279–291.
167. Vinik AI, Erbas T and Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Invest* 2013; 4: 4–18.
168. Naschitz JE and Rosner I. Orthostatic hypotension: Framework of the syndrome. *Postgrad Med J* 2007; 83: 568–574.
169. Shibao C and Biaggioni I. Orthostatic hypotension and cardiovascular risk. *Hypertension* 2010; 56: 1042–1044.
170. Sigal RJ, Kenny GP, Wasserman DH, et al. Physical activity/exercise and type 2 diabetes: A consensus

statement from the American Diabetes Association. *Diabetes Care* 2006; 29: 1433–1438.
171. Colberg SR and Vinik AI. Exercising with peripheral or autonomic neuropathy: What health care providers and diabetic patients need to know. *Phys Sportsmed* 2014; 42: 15–23.
172. Valensi P, Lorgis L and Cottin Y. Prevalence, incidence, predictive factors and prognosis of silent myocardial infarction: A review of the literature. *Arch Cardiovasc Dis* 2011; 104: 178–188.
173. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation* 2003; 107: 1210–1225.
174. Wackers FJ, Young LH, Inzucchi SE, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: The DIAD study. *Diabetes Care* 2004; 27: 1954–1961.
175. American Diabetes Association. Physical activity/exercise and diabetes. *Diabetes Care* 2004; 27(Suppl. 1): S58–S62.
176. Balkau B, Jouven X, Ducimetiere P, et al. Diabetes as a risk factor for sudden death. *Lancet* 1999; 354: 1968–1969.
177. Kannel WB, Wilson PW, D'Agostino RB, et al. Sudden coronary death in women. *Am Heart J* 1998; 136: 205–212.
178. Colberg SR and Sigal RJ. Prescribing exercise for individuals with type 2 diabetes: Recommendations and precautions. *Phys Sportsmed* 2011; 39: 13–26.
179. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006; 114: e385–e484.
180. Csepe TA, Kalyanasundaram A, Hansen BJ, et al. Fibrosis: A structural modulator of sinoatrial node physiology and dysfunction. *Front Physiol* 2015; 6: 37.
181. Kannel WB. Framingham study insights on diabetes and cardiovascular disease. *Clin Chem* 2011; 57: 338–339.
182. Boudina S and Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007; 115: 3213–3223.
183. Pappachan JM, Varughese GI, Sriraman R, et al. Diabetic cardiomyopathy: Pathophysiology, diagnostic evaluation and management. *World J Diabetes* 2013; 4: 177–189.
184. Grewal J, McCully RB, Kane GC, et al. Left ventricular function and exercise capacity. *JAMA* 2009; 301: 286–294.
185. Cotrim C, Joao I, Fazendas P, et al. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. *Cardiovasc Ultrasound* 2013; 11: 26.
186. Asrar Ul Haq M, Wong C, Levinger I, et al. Effect of exercise training on left ventricular remodeling in diabetic patients with diastolic dysfunction: Rationale and design. *Clin Med Insights Cardiol* 2014; 8: 23–28.
187. Jude EB, Eleftheriadou I and Tentolouris N. Peripheral arterial disease in diabetes – a review. *Diabet Med* 2010; 27: 4–14.
188. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1.9 million people. *Lancet Diabetes Endocrinol* 2015; 3: 105–113.
189. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: A scientific statement from the American Heart Association. *Circulation* 2012; 126: 2890–2909.
190. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
191. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018; 138: e484–e594.
192. Chrysohoou C, Skoumas J, Georgiopoulos G, et al. Exercise capacity and haemodynamic response among 12,327 individuals with cardio-metabolic risk factors undergoing treadmill exercise. *Eur J Prev Cardiol* 2017; 24: 1627–1636.
193. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: Systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* 2011; 343: d6898.
194. Goto A, Arah OA, Goto M, et al. Severe hypoglycaemia and cardiovascular disease: Systematic review and meta-analysis with bias analysis. *BMJ* 2013; 347: f4533.
195. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes* 2014; 63: 1738–1747.
196. Investigators OT, Mellbin LG, Ryden L, et al. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *Eur Heart J* 2013; 34: 3137–3144.
197. Frier BM, Schernthaner G and Heller SR. Hypoglycemia and cardiovascular risks. *Diabetes Care* 2011; 34(Suppl. 2): S132–S137.

198. Ponikowski P and Jankowska EA. Hypoglycaemia in diabetic patients: Highly undesirable by cardiologists. *Eur Heart J* 2013; 34: 3102–3105.
199. Ahren B. Avoiding hypoglycemia: A key to success for glucose-lowering therapy in type 2 diabetes. *Vasc Health Risk Manag* 2013; 9: 155–163.
200. Meyer C, Grossmann R, Mitrakou A, et al. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. *Diabetes Care* 1998; 21: 1960–1966.
201. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; 38: 140–149.