

Exercise Prescription in Patients with Different Combinations of Cardiovascular Disease Risk Factors: A Consensus Statement from the EXPERT Working Group

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Abstract Whereas exercise training is key in the management of patients with cardiovascular disease (CVD) risk (obesity, diabetes, dyslipidaemia, hypertension), clinicians experience difficulties in how to optimally prescribe exercise in patients with different CVD risk factors. Therefore,

a consensus statement for state-of-the-art exercise prescription in patients with combinations of CVD risk factors as integrated into a digital training and decision support system (the EXercise Prescription in Everyday practice & Rehabilitative Training (EXPERT) tool) needed to be established. EXPERT working group members systematically reviewed the literature for meta-analyses, systematic reviews and/or clinical studies addressing exercise prescriptions in specific CVD risk factors and formulated exercise recommendations (exercise training intensity, frequency, volume and type, session and programme duration) and exercise safety precautions, for obesity,

EXPERT stands for ‘EXercise Prescription in Everyday practice & Rehabilitative Training’, this working group is endorsed by the European Association of Preventive Cardiology (EAPC).

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arterial hypertension, type 1 and 2 diabetes, and dyslipidaemia. The impact of physical fitness, CVD risk altering medications and adverse events during exercise testing was further taken into account to fine-tune this exercise prescription. An algorithm, supported by the interactive EXPERT tool, was developed by Hasselt University based on these data. Specific exercise recommendations were formulated with the aim to decrease adipose tissue mass, improve glycaemic control and blood lipid profile, and lower blood pressure. The impact of medications to improve CVD risk, adverse events during exercise testing and physical fitness was also taken into account. Simulations were made of how the EXPERT tool provides exercise prescriptions according to the variables provided. In this paper, state-of-the-art exercise prescription to patients with combinations of CVD risk factors is formulated, and it is shown how the EXPERT tool may assist clinicians. This contributes to an appropriately tailored exercise regimen for every CVD risk patient.

Key Points

The EXPERT tool (a digital training and decision support system) has recently been launched to improve exercise prescription for patients with cardiovascular disease (CVD) risk.

This consensus statement sets out the EXPERT working group's state-of-the-art recommendations on exercise prescription for reducing CVD risk, focusing on different combinations of CVD risk factors, intake of medications, physical fitness variants and the potential for adverse events during exercise testing.

The EXPERT tool will assist clinicians in the selection of appropriate exercise training modalities in different CVD risk subpopulations.

1 Introduction

Exercise training is a cornerstone in the management of cardiovascular disease (CVD) risk (e.g. physical inactivity, arterial hypertension, dyslipidaemia, obesity and diabetes). Body composition, blood pressure, lipid profile and

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glycaemic control improve substantially in patients with CVD risk when participating in exercise training interventions [1–3]. In addition, via the positive impact of exercise training on the cardiovascular system [4], patients with coronary artery disease and heart failure also benefit from significant clinical benefits [5, 6].

Exercise training is therefore classified as a type 1A intervention in the treatment of CVD risk, and its importance is endorsed by numerous international position statements [7, 8]. In general, it is recommended that patients with CVD risk should perform at least 150 min of aerobic exercise training per week, ideally spread over 3–5 days per week. An energy expenditure of 1000–2000 kcal per week should be achieved in this way, and aerobic exercise training should be complemented by resistance exercise training two times per week at a moderate intensity [7]. Moreover, the application of high-intensity interval training has gained significant interest in the last decade, and the impact of this type of exercise training is now intensively studied in patients with CVD risk [9].

However, to optimally reduce adipose tissue mass or arterial blood pressure, or to improve blood lipid profile or glycaemic control, more tailored exercise prescriptions are required. Even though detailed exercise requirements for different CVD risk factors have been reported in a recommendation [10], tailoring the exercise training program to each single patient according to his/her overall CVD risk profile remains difficult as the CVD risk factors are often considered separately. Moreover, the intake of certain medications, physical fitness or the presence of abnormalities or adverse events during exercise testing warrant further individualized adjustment of these exercise prescriptions. Accordingly, it has been observed that there is great heterogeneity in exercise prescription (exercise type, frequency, volume and intensity, session and programme duration, objective and progressive training adaptations) among cardiovascular rehabilitation programs within different institutes/hospitals and between clinicians, and the implementation of clinical guidelines into current cardiovascular rehabilitation programs is problematic [11, 12]. We therefore speculated that current exercise training interventions for CVD risk patients can benefit from a more standardized way of prescribing exercise training, aiming for greater clinical benefits but with optimal medical safety and exercise adherence.

However, combining different exercise prescriptions (based on CVD risk profile, medication intake and

observations during exercise testing) within a single patient can be complex. Currently, clinicians involved in cardiovascular rehabilitation are in need of a decision support system that, based on the variables provided in this system, can calculate how exercise should be prescribed. Such an interactive decision support system can provide an exercise prescription, still leaving the clinician the opportunity to fine-tune the programme, based on specific patient characteristics or needs, and available infrastructure. For this purpose, we, in close collaboration with Hasselt university, recently developed the EXercise Prescription in Everyday practice & Rehabilitative Training (EXPERT) tool [13].

The aim of this manuscript is to provide a consensus statement for state-of-the-art exercise prescription and exercise training safety precautions for patients with different CVD risk factor combinations (obesity, dyslipidaemia, type 1 and 2 diabetes, and/or arterial hypertension), as integrated into a digital training and decision support system (EXPERT tool), taking into account the impact of the intake of CVD risk altering medications, adverse events during exercise testing and physical fitness. Finally, simulations of exercise prescriptions for patients with CVD risk as provided by the EXPERT tool will be presented.

2 Methods

2.1 Formulation of Exercise Prescriptions and Construction of EXPERT Tool

Previously, details on the composition and activities of the EXPERT working group, how exercise prescriptions were collected from the literature, and on the development and functioning of the EXPERT tool, definitions for CVD risk factors and goals of exercise intervention were published [13]. This project is endorsed by the European Association of Preventive Cardiology (EAPC).

In brief, working group members (see author list) were allocated to specific CVD risk factors (obesity, type 1 and 2 diabetes, dyslipidaemia and arterial hypertension) and were then requested to: (1) define the diagnostic criteria for CVD risk factors, (2) identify the primary goal of exercise training intervention for each CVD risk factor, (3) provide exercise training recommendations, and (4) highlight exercise safety precautions. These recommendations and definitions had to be based on current clinical guidelines and position statements, meta-analyses, systematic reviews, randomised controlled trials, cohort studies, observational studies or expert opinions addressing exercise prescriptions in specific CVD risk factors obtained from a systematic review of the literature. PubMed was used for this literature search up to February 2018. The

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allocation of these experts to specific steering groups was based on specific scientific/clinical expertise. All this information was handed over to the project coordinator, who, in collaboration with computer scientists from EDM (Expertise Centre for Digital Media) of Hasselt University, developed the EXPERT tool. During this development phase, human–computer interaction techniques such as observations and thinking aloud were used to optimally capture the user requirements. Throughout the prototyping process, attention was given to the recommendation algorithm, functional features of the EXPERT tool and user experience.

2.2 Classification of Level of Evidence and Grades of Recommendation

To classify the level of evidence and the grade of recommendation for exercise prescription, a validated system was used throughout this paper, as shown in Electronic Supplementary Material Table S1 [14].

2.3 Classification of Exercise Training Intensity

Electronic Supplementary Material Table S2 shows the classification of exercise training intensity, based on a previous recommendation paper [10].

2.4 Recommended Infrastructure and Knowledge/Skills of Healthcare Professionals

Patients with CVD risk can be more prone to develop cardiovascular, metabolic or ventilatory complications during exercise. Therefore, it is advised that rehabilitation or exercise training facilities are specifically designed and equipped, and healthcare professionals are properly educated [15]. According to guidelines, the following emergency equipment should be available directly in the rehabilitation/exercise training room: portable defibrillator, (portable) oxygen tank, nasal cannula, Vent Mask, non-rebreathing mask, oxygen mask, oral and nasal airways, bag-valve-mask hand respirator, syringes and needles, intravenous tubing, solutions and stand, and a suction apparatus and supplies (such as gloves). In addition, emergency drugs and solutions should be directly available. Although rehabilitation programmes within hospitals are often coordinated by a physician, the direct assistance and guidance during exercise training to patients (especially in peripheral centres or private practices) is nearly always offered by allied healthcare and exercise professionals (such as physiotherapists, nurses, clinical exercise physiologists). To ensure sufficient patient safety, it is recommended that these allied healthcare professionals have acquired specific clinical competencies, including:

core knowledge (e.g. clinical exercise physiology, pathology, pharmacology), professional behaviour, communication skills, preparation of the individual for supervised exercise training, assessment/testing skills (e.g. heart rate and blood pressure measurement, exercise, functional capacity and muscle strength testing), physical activity planning and exercise prescription, abilities to lead and deliver the supervised exercise session, forward planning, management of the unwell individual (e.g. symptom recognition, care in case of syncope, resuscitation), service planning and management, and service evaluation [16].

3 Exercise Prescriptions and Safety Precautions for Each CVD Risk Factor Separately

3.1 Obesity

3.1.1 Definition of Obesity

A person with a body mass index (BMI) $> 30 \text{ kg/m}^2$ or (preferentially) a waist circumference $> 94 \text{ cm}$ for males and $> 80 \text{ cm}$ for females (both for Europeans) is considered obese [17, 18].

3.1.2 Intervention Aim in Patients with Obesity

The intervention aim is to lower adipose tissue mass (BMI $< 25.0 \text{ kg/m}^2$ or (preferentially) a waist circumference $< 94 \text{ cm}$ for males and $< 80 \text{ cm}$ for females) [17, 18].

3.1.3 Exercise Training Recommendations in Patients with Obesity

A large body of evidence has been published on how to prescribe exercise in patients with obesity [19–25]. Body weight loss as a result of long-term (> 3 months) exercise intervention is modest to low in obese subjects (by 2 kg in 6 months) [20], although significant and still clinically relevant. The greatest reductions in body weight may be anticipated in subjects with a higher BMI and when exercise training is combined with caloric intake restriction (up to 8 kg in 6 months) [20]. However, most studies focus on changes in body weight only (and not on changes in adipose tissue mass) and apply rather low (to $< 250 \text{ min/week}$) exercise volumes. Reductions in body weight however underestimate the factual reductions in adipose tissue mass (especially when resistance training exercises are implemented, which will increase lean tissue mass). Moreover, despite modest body weight losses, other important health-related aspects improve in obese subjects (e.g. blood pressure, blood lipid profile, insulin sensitivity, systemic inflammatory markers, physical fitness and

quality of life). Exercise training is also very important in severely obese patients with huge and rapid body weight loss, as typically observed after bariatric surgery, to prevent a decrease in lean tissue mass.

It is recommended to increase the weekly aerobic exercise volume > 250 min (or > 1500 kcal) (level of evidence: 1++, grade of recommendation: A) and achieve a permanently (life-long) increased physical activity level. A minimal exercise program duration of 6 months is recommended to achieve a significant and clinically relevant adipose tissue mass loss and it is advised to permanently increase daily physical activity next to supervised exercise training to minimize body weight regain (level of evidence: 2++, grade of recommendation: B). To sustain these high exercise training volumes and to maximize total caloric expenditure during exercise training, moderate-intensity (moderate effort) aerobic exercises involving large muscle groups (e.g. walking, stepping, rowing, cross-training) are recommended (level of evidence: 2++, grade of recommendation: B). Cycling exercises should thus only be used as a warming-up mode, and for a limited duration (up to 5–10 min), except for patients experiencing joint pain or knee-hip arthrosis: such exercise types may be ideal to start-up an exercise programme. Recommended exercise training frequency is at least three and progressively build up to 5 days per week (level of evidence: 1++, grade of recommendation: A). The evidence for the implementation of low-intensity aerobic exercise in obese persons, with the aim to burn more fat and thus elicit a greater fat mass loss, is virtually absent [26]. The implementation of resistance exercise training (on top of caloric restriction and aerobic training) is not primarily recommended when the aim is to maximize adipose tissue mass loss in obese participants (level of evidence: 2++, grade of recommendation: B), although the addition of resistance exercise training to an aerobic exercise training intervention is warranted to increase resting caloric expenditure, improve blood high-density lipoprotein (HDL) cholesterol concentrations, and increase muscle strength and lean tissue mass. Deficits, or anticipated deficits (due to caloric intake restriction or after bariatric surgery), in one or more of the latter health parameters further warrant the addition of resistance exercises (60–70% 1 repetition maximum (RM), 12–15 repetitions for three series each exercise targeting large muscle groups, such as quadriceps femoris, hamstrings, calves, abdominal and back muscles, biceps brachii, triceps brachii, shoulder muscles).

3.1.4 Exercise Training Safety Precautions in Patients with Obesity

Obese individuals are prone to the development of (degenerative and inflammatory) overuse symptoms due to

elevated mechanical loads and altered biomechanics. Therefore, the musculoskeletal system should be evaluated thoroughly and exercise training modalities should be adapted accordingly. These symptoms can be reduced or even prevented by progressive exercise training adaptations, altering the type of aerobic exercise training and by incorporating low-weight bearing exercise training sessions (e.g. aquatic exercise, cycling, rowing, etc.).

3.2 Arterial Hypertension

3.2.1 Definition of Arterial Hypertension

A person with a systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg is considered hypertensive [27].

3.2.2 Intervention Aim in Patients with Arterial Hypertension

The intervention aim is to reduce both arterial systolic and diastolic blood pressure (< 140/90 mmHg) [27].

3.2.3 Exercise Training Recommendations in Patients with Arterial Hypertension

A large body of evidence has been published on how to prescribe exercise in patients with arterial hypertension [28–54]. As a result of long-term exercise training intervention, modest but significant reductions in systolic (by – 7 mmHg) and diastolic (by – 5 mmHg) BP are observed (level of evidence: 1++, grade of recommendation: A) [54].

Ideally, an exercise prescription aimed at lowering BP in individuals with normal BP or hypertension would include a mix of predominantly aerobic exercise training supplemented with dynamic resistance exercise training. It is recommended to perform aerobic exercise training at a moderate intensity (40–60% of heart rate reserve) for at least 30 min per day (continuously or intermittently in bouts of at least 10 min) at least 5 days per week (level of evidence: 1++, grade of recommendation: A). Vigorous exercise training intensities (60–80% of heart rate reserve) may be considered in patients with low CVD risk (level of evidence: 1++, grade of recommendation: A), and some evidence is available indicating that aerobic exercise training with higher intensities may be more effective (level of evidence: 1-, grade of recommendation: A). As a single bout of exercise may cause acute reductions in arterial BP that might last for several hours, daily aerobic exercise training should be emphasized in the hypertensive patient (level of evidence: 1++, grade of recommendation: A). Furthermore, reductions in BP following aerobic

exercise training, acute or chronic, are greater in hypertensive patients compared to normotensive individuals. Dynamic resistance exercise training at a moderate intensity (50–70% of one repetition maximum (1RM)), including 8–10 exercises for the large muscle groups (one set/exercise: 8–12 repetitions per set, with progressive build up to two or three sets per exercise), can be added twice weekly, as it has been shown to lower BP in pre-hypertensive individuals and does not increase BP in hypertensive patients. Although it has been shown that dynamic resistance exercise training may lower BP by itself (level of evidence: 1++, grade of recommendation: A), there is no convincing evidence that the combination of aerobic and resistance exercise training lowers BP more than aerobic exercise training alone. Finally, promising data suggest the use of static or isometric resistance training using handgrip exercise training at low intensity (< 40% of one maximal volitional contraction), performed as several intermittent bouts of handgrip contractions lasting 2 min each for a total of 12–15 min per session, as an adjunct tool to lower BP. However, given the paucity of data, this exercise training method requires further research (level of evidence: 2+, grade of recommendation: C).

3.2.4 Exercise Training Safety Precautions in Patients with Arterial Hypertension

Hypertensive patients should be informed about the nature of cardiac prodromal symptoms and exercise-related warning symptoms including chest pain or discomfort, abnormal dyspnoea, dizziness or malaise, and should seek prompt medical care if such symptoms develop. Regular follow-up depending on severity of arterial hypertension and the category of risk is recommended. Intensive heavy weight lifting, that might appear as dynamic (e.g. some limb and joint movement), often includes substantial isometric (static) muscle work which can have a marked pressor effect and should be avoided. Avoidance of the Valsalva manoeuvre in particular is warranted. This manoeuvre is characterised by significant increments in intrathoracic pressures leading to (greater) elevations in (especially) systolic and diastolic blood pressure, when holding the breath during muscular contraction [55]. If arterial hypertension is poorly controlled (resting systolic BP > 160 mmHg), high-intensity exercise training as well as maximal exercise testing should be discouraged or postponed until appropriate drug treatment has been instituted and arterial BP is lowered. In addition to the generally recommended assessment tests, the indication for exercise testing depends on the patient's risk profile and on the exercise characteristics (e.g. in patients with arterial hypertension who are about to engage in high-intensity exercise, a medically supervised peak or symptom limited

exercise test with electrocardiographic and BP monitoring is warranted). If systolic BP rises to > 250 mmHg or diastolic BP > 115 mmHg during exercise (testing), the training/test session should be terminated and the person should be advised to visit their doctor as there is an obvious need to adjust medical therapy.

3.3 Dyslipidaemia

3.3.1 Definition of Dyslipidaemia

A blood low-density lipoprotein (LDL) cholesterol concentration ≥ 100 mg/dl (2.5 mmol/L) for high-risk patients or > 70 mg/dl (< 1.8 mmol/L) for very high-risk patients is considered as dyslipidaemia [56]. High-risk patients are defined as subjects with (1) markedly elevated single risk factors, in particular LDL cholesterol > 8 mmol/L (> 310 mg/dl) (e.g. familial hypercholesterolaemia), or (2) most other people with diabetes mellitus (some young people with type 1 diabetes may be at low or moderate risk), or (3) moderate chronic kidney disease (glomerular filtration rate (GFR) 30–59 ml/min/1.73 m²), or (4) a $\geq 5\%$ and < 10% risk for 10-year risk of fatal CVD [48]. Very high-risk patients are defined as subjects with (1) documented CVD, clinical or unequivocal on imaging, or (2) diabetes mellitus with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia, or (3) severe chronic kidney disease (GFR < 30 ml/min/1.73 m²) or (4) $\geq 10\%$ risk for 10-year risk of fatal CVD [56].

3.3.2 Intervention Aim in Patients with Dyslipidaemia

The intervention aim is to lower blood LDL cholesterol concentration to < 100 mg/dl (2.5 mmol/L) for high-risk patients or to < 70 mg/dl (< 1.8 mmol/L) for very high-risk patients [56].

3.3.3 Exercise Training Recommendations in Patients with Dyslipidaemia

A large body of evidence on how to prescribe exercise in patients with dyslipidaemia has been published [57–65]. Greater physical activity levels are generally associated with higher blood high-density lipoprotein (HDL) cholesterol concentrations and lower LDL and triglyceride concentrations in healthy individuals. As a result, exercise training intervention should be recommended to improve blood lipid profile or lower blood LDL cholesterol concentration (level of evidence: 1++, grade of recommendation: A). However, the impact of exercise training on blood lipid profile is complex to analyse as different changes in blood lipid profiles occur in different patients.

In patients with CVD and obesity, reductions in blood total cholesterol and triglyceride concentrations may be expected. In patients with type 2 diabetes, on the other hand, reductions in blood LDL cholesterol and increments in blood HDL cholesterol may be expected. Moreover, the impact of the intake of blood lipid-lowering drugs (such as statins), but also caloric intake restriction, on blood lipid profile is of such magnitude that it may overrule the impact of exercise training. In addition, the greatest improvements in blood lipid profile may be anticipated in patients with the worst blood lipid profile.

Aerobic exercise training is most often implemented to improve blood lipid profile. In this regard, since the impact of high-intensity interval training on blood lipid profile is not well studied, continuous moderate-intensity exercise training may be preferred (level of evidence: 3, grade of recommendation: D). It is important to maintain a caloric expenditure > 900 kcal/week to maximize changes in blood lipid profile (especially blood HDL cholesterol concentration) (level of evidence: 1++, grade of recommendation: A). In this regard, it is advised to prolong the exercise sessions (> 40 min/session) as well as the total training programme duration (> 40 weeks) (level of evidence: 1++, grade of recommendation: A). As different types of exercise generate different caloric expenditures, it may be hypothesized to select exercise modes with the greatest caloric expenditure per time unit (see in Sect. 3.1.3 on exercise training in obesity), although supporting evidence has yet to be provided (level of evidence: 4, grade of recommendation: D). These exercise training recommendations may lead to favourable changes in blood triglyceride, total HDL and/or LDL cholesterol concentrations. Moreover, there is also evidence that (the addition of) resistance training exercises may positively affect blood HDL cholesterol concentrations (level of evidence: 1++, grade of recommendation: A). In this regard, it is proposed to prescribe lean tissue mass increasing (heavy) resistance exercise training (at least five large muscle groups), implemented as 8–10 repetitions of each series, at 70–85% of 1RM, for three series per exercise, which should be gradually attained.

3.3.4 Exercise Training Safety Precautions in Patients with Dyslipidaemia

No safety measures have to be undertaken.

3.4 Type 2 Diabetes Mellitus

3.4.1 Definition of Type 2 Diabetes Mellitus

A fasting blood glucose concentration ≥ 126 mg/dl (7.0 mmol/L), or a 2-h glycaemia ≥ 200 mg/dl (≥ 11.1 mmol/L) during oral glucose tolerance test, or glycated haemoglobin (HbA1c) $\geq 6.5\%$ (48 mmol/mol) is

considered as type 2 diabetes mellitus (T2DM) [66–68]. Type 2 diabetes mellitus is characterized by a combination of insulin resistance and beta-cell failure, in association with obesity (typically with an abdominal distribution) and sedentary lifestyle. Insulin resistance and an impaired first-phase insulin secretion causing postprandial hyperglycaemia characterise the early stage of T2DM. This is followed by a deterioration of the second-phase insulin response and persistent hyperglycaemia in the fasted state [66].

3.4.2 Intervention Aim in Patients with Type 2 Diabetes Mellitus

The intervention aim is to improve glycaemic control (blood glycated haemoglobin (HbA1c) < 7.0% or < 52 mmol/mol) [66–68].

3.4.3 Exercise Training Recommendations in Patients with Type 2 Diabetes Mellitus

A significant body of evidence has been published on how to prescribe exercise in T2DM [69–82]. In patients with glucose intolerance, exercise training lowers the risk of developing T2DM, whereas in T2DM patients, exercise interventions lead to significant and clinically meaningful reductions in blood HbA1c concentrations (by $\sim 0.7\%$) [74, 75] and improvements in insulin sensitivity, which are associated with improved peripheral and coronary endothelial function as well as coronary blood flow. More pronounced reductions in blood HbA1c concentrations are anticipated in T2DM patients with higher baseline blood HbA1c concentrations. Moreover, favourable effects of exercise training on other important health parameters, such as body composition, muscle strength and physical fitness, have been established in T2DM patients. Based on a strong body of clinical and scientific evidence there is almost unanimous agreement among the leading professional organizations (such as the European Society of Cardiology (ESC), the European College of Sports Science (ECSS), the American Heart Association (AHA) and the American College of Sports Medicine (ACSM)) with regard to their recommendations of physical activity and exercise training.

A distinction is made in recommended daily physical activity level and recommended exercise prescription. In general, T2DM patients are advised to become or remain physically active by walking > 30 min on at least 5 days/week, preferably every day of the week (level of evidence: 1++, grade of recommendation: A). In addition to an increase in home-based physical activity, T2DM patients are strongly encouraged to follow a supervised exercise training intervention. An exercise volume of ≥ 150 min per week of moderate-intensity aerobic exercise and/or

90 min per week of vigorous-intensity aerobic exercise, ideally a total of 3–4 h per week, should be performed. Exercise training should amount to at least 30 min on at least 5 days per week and energy expenditure should be between 1000–2000 kcal per week (level of evidence: 1++, grade of recommendation: A). High-intensity interval training can be selected in such exercise interventions, as the first studies indicate a non-inferiority of this exercise training methodology. A programme duration of 12 weeks is the absolute minimum to detect changes in blood HbA1c concentrations, although patients should be stimulated to exercise in such a structured manner for at least 6 months, preferentially followed by a sustained increase in physical activity thereafter (level of evidence: 1++, grade of recommendation: A). In addition, resistance exercise training should be performed at least two, preferably three times per week either as hypertrophy or aerobic resistance training, since some studies found significantly greater improvements in insulin sensitivity or glycaemic control when resistance training exercises were added on top of aerobic exercise training. All major muscle groups should be targeted and two sets per muscle group should either be performed with 8–12 repetitions at 70–80% of the repetition maximum, or 25–30 repetitions at 40–55% of the repetition maximum, respectively (level of evidence: 1++, grade of recommendation: A). It remains uncertain whether different relative exercise intensities during resistance exercise training will exert a different impact on blood HbA1c concentrations in T2DM patients. However, a progressive increase in number of sets and resistance exercise intensity is recommended for training adaptations. Electro-muscle stimulation (EMS) for 10 weeks, twice weekly for 20 min can improve glucose homeostasis, blood HbA1c concentration, physical fitness and body composition in T2DM patients. This physiotherapy modality is thus of particular interest to patients with limited mobilisation/rehabilitation capacity (for example in T2DM patients with extreme muscle weakness or sedated patients) (level of evidence: 2-, grade of recommendation: C).

3.4.4 Exercise Training Safety Precautions in Patients with Type 2 Diabetes Mellitus

T2DM patients most often are sedentary older individuals with overweight/obesity and a lowered exercise capacity and/or increased risk of falling [82]. Therefore, safety precautions must be taken. At the commencement of an exercise intervention, measurements of blood glucose concentrations should be made before, during and at the end of each session to minimize the risk of hypo-/hyperglycaemia (the ideal blood glucose concentration is 90–250 mg/dl or 5.0–13.9 mmol/L). The risk for hypoglycaemia increases when taking insulin secretagogues or

administering subcutaneous insulin injections. Adjustments in dose and/or timing of these medications, and/or intake of carbohydrates during exercise, may be warranted when hypoglycaemia is regularly experienced and/or when hypoglycaemia is anticipated (for example during exercise with a significant energy expenditure (such as prolonged exercise)) (see Colberg et al. [81] for detailed decision schemes). In addition, exercise should be postponed when a hypoglycaemic episode has occurred during the last 24 h, as there is an increased risk for recurrent hypoglycaemia. Hyperglycaemia occurs less often in T2DM, but is not a contradiction for low-to-moderate-intensity exercise. On the other hand, high-intensity exercise must be avoided when blood glucose concentration is > 300 mg/dl or 16.7 mmol/L. When such blood glucose concentrations are observed, with the presence of ketones in the blood or urine, exercise must be postponed until appropriate medical care has been obtained. These capillary blood measurements become optional once patients have been in a programme for a longer duration and have repeatedly shown normoglycaemic values during exercise training. Patients with poorly controlled diabetes may experience polyuria and thus should avoid dehydration during exercise by drinking 0.4–0.8 L water during the exercise bout. In patients with nephropathy, elevated blood pressures during exercise should be avoided (systolic blood pressure should remain < 200 mmHg) as well as the Valsalva manoeuvre. In patients with retinopathy, high-intensity exercise (> 75% $\text{VO}_{2\text{peak}}$), high-impact activities with jumps, and the Valsalva manoeuvre should be avoided. The feet of T2DM patients (especially those with peripheral neuropathy or peripheral vascular disease) should always be inspected closely ahead of exercise intervention and once yearly afterwards. Patients with active foot lesions and/or ulcers should avoid weight-bearing exercise exercises, and instead execute non-weight-bearing exercises. In general, T2DM patients are advised to purchase proper sports footwear. Diabetic autonomic neuropathy may lead to significant abnormalities in cardiovascular function, as often evidenced by tachycardia (resting heart rate (HR) > 100 beats/min), orthostatic hypotension, inappropriate HR response to exercise and/or exercise intolerance. In addition, disturbed thermoregulation during exercise may occur. It is advised that when such symptoms (suggestive of autonomic dysfunction) are noted, the patient should be examined in greater detail (including cardiopulmonary exercise testing) and treated accordingly. Finally, T2DM patients are at increased risk of coronary artery and cardiovascular disease. Consequently, it is advised that the cardiovascular system is appropriately examined ahead of exercise intervention, patients are educated about typical cardiovascular symptoms and blood pressure is well-controlled during exercise training (to <

200 mmHg). Following the above-mentioned guidelines, cardiopulmonary exercise testing is only suggested in individuals with an elevated risk of, or symptoms of, coronary artery disease, or with microvascular disease (proliferative retinopathy or nephropathy, including microalbuminuria), peripheral vascular disease or autonomic neuropathy. Asymptomatic T2DM patients who want to follow a low-to-moderate intensity aerobic and resistance training programme should not be systematically examined by cardiopulmonary exercise testing except when detailed information about exercise responses and/or exercise programming is considered necessary.

3.5 Type 1 Diabetes Mellitus

3.5.1 Definition of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is diagnosed when the fasting blood glucose concentration exceeds 125 mg/dl (7.0 mmol/L), or the 2-h glycaemia exceeds 199 mg/dl (≥ 11.1 mmol/L) during an oral glucose tolerance test, or the HbA1c exceeds 6.4% (48 mmol/mol) [66]. This hyperglycaemia should be due to (sudden) pancreatic beta-cell destruction leading to absolute insulin deficiency [66].

3.5.2 Intervention Aim in Patients With Type 1 Diabetes Mellitus

The intervention aim is to enable good long-term glycaemic control (blood HbA1c $< 7.0\%$ or < 52 mmol/mol) [66].

3.5.3 Exercise Training Recommendations in Patients with Type 1 Diabetes Mellitus

The body of evidence on how to prescribe exercise in T1DM is rather limited [83–108]. In T1DM patients, concomitant overweight or obesity, arterial hypertension, dyslipidaemia and/or sedentarism are frequently documented, all of which are associated with a significantly elevated risk of cardiovascular disease and worsening glycaemic control. On the other hand, in T1DM patients, exercise training has been shown to improve glycaemic control (as evidenced by significant 0.7% reductions in blood HbA1c concentration) [107], to improve the CVD risk profile as well as to increase general well-being and physical fitness. Conversely, due to the brittle nature of the disease, the performance of physical exercise imposes high demands on individuals with T1DM. A variety of factors contribute to this problem: inadequate knowledge of exercise management (insulin and dietary changes), fear of hypoglycaemia and loss of glycaemic control.

Although recommended by treatment guidelines, exercise training may increase the risk of (late onset)

hypoglycaemia and carries the risk of deteriorating diabetes control due to complex interaction with the regulation of glucose transport in the working muscles. As a consequence, exercise training does not unequivocally improve metabolic control in type 1 diabetic individuals and may, if not embedded in an appropriate therapeutic setting, even result in a deterioration of diabetes control, thereby increasing the risk of diabetic complications.

There is conflicting evidence regarding the effectiveness of different training modalities (e.g. resistance training, combined aerobic and resistance training, or high-intensity interval training) on long-term glycaemic control. Unambiguous results exist concerning the effects of aerobic exercise, showing a decrease in glycaemia after exercise and an improvement in chronic glycaemic control. In essence, aerobic exercise training increases insulin sensitivity by increasing glucose transport across skeletal muscle membrane via glucose transporter 4 (GLUT-4) translocation. Activation of skeletal muscle GLUT-4 has been shown after only a single bout of exercise in numerous studies. With higher exercise training intensities ($> 75\%$ peak oxygen uptake (VO_{2peak})), the impact of associated factors (e.g. counter-regulatory hormones) becomes more important in exercise associated fuel metabolism. In particular, adding a single bout of high intensity exercise (high-intensity exercise (HIE), ‘near maximal’ efforts and sprint interval training (supramaximal intensity training (SIT); ‘supramaximal’ efforts) up to 10 s/bout) to moderate-intensity continuous exercises training may stabilize the fall in glucose concentrations during and after exercise training and may even reduce the risk of immediate post-exercise hypoglycaemia (level of evidence: 2++, grade of recommendation: B). This can be attributed to a greater increase in circulatory counter-regulatory hormones (e.g. catecholamines, cortisol and growth hormone) and hence in hepatic glucose production, which is observed during and after performing a HIE bout. Recent studies investigated whether the performance of repetitive bouts of HIE may further stabilize glucose concentrations throughout prolonged aerobic exercise sessions. As a result, ‘mixed’ exercise sessions characterised by short bursts of high-intensity exercise (such as during soccer, tennis, etc.) very often lead to a more stable glycaemia. However, there appears to be an increased risk of delayed post-exercise hypoglycaemia due to the increased consumption of glycogen during HIE. Resistance exercise can cause similar hormonal and metabolic responses to that of anaerobic exercise such as HIE, especially when only one or two sets are performed. However, three sets of resistance exercise (eight exercises, 60–70% 1RM, ten repetitions) attenuate the increase in blood glucose levels during exercise and give rise to a more stable blood glucose profile immediately after exercise, or even elevations in blood

glucose concentrations. Resistance exercise does not increase the risk of nocturnal hypoglycaemia [106].

There is conflicting evidence regarding the impact of aerobic exercise training on glycaemic stability in athletic/competitive T1DM patients. While some studies show a beneficial effect with regard to glycaemic control, others indicate an increased risk of repetitive hypoglycaemia and hypoglycaemia-unawareness, as well as a tendency towards higher average blood glucose values in competitive athletes. The latter is most likely due to increased carbohydrate intake and higher levels of psychological stress during competition.

Patients with T1DM are encouraged to perform at least 150 min of moderate-intensity aerobic exercise training per week, and, in the absence of contraindications such as moderate or severe proliferative retinopathy, resistance exercise training at least twice per week is recommended (three sets, ten repetitions/set, 60–70%1RM) (level of evidence: 1++, grade of recommendation: A). Resistance exercise training has been shown to enhance skeletal muscle insulin sensitivity and to improve glucose tolerance. Data on the long-term effect of resistance exercise training in T1DM are scarce. Studies with small sample sizes indicate a reduction in blood HbA1c concentrations over the long term. Based on this limited evidence, as well as on physiological reasons, resistance exercise training could therefore be recommended in addition to aerobic exercise training (level of evidence: 2-, grade of recommendation: D). Two sets of resistance exercise (eight exercises, 60–70% 1 RM, ten repetitions) will lead to increased blood glucose concentrations. The inclusion of a third set, however, seems to attenuate this exercise-induced hyperglycaemia. However, more specific exercise training thresholds have recently been shown to deliver significant improvements in glycaemic control. Chronic glycaemic control may improve in patients with T1DM when exercise training is performed for more than three months, 1–3 times a week, and when the patient is also receiving dietary or insulin administration advice from a healthcare professional (level of evidence: 2++, grade of recommendation: B).

3.5.4 Exercise Training Safety Precautions in Patients with Type 1 Diabetes Mellitus

Depending on the type of exercise training, blood glucose levels can respond differently and consequently, subjects with T1DM can experience episodes of rapidly occurring hypoglycaemia as well as hyperglycaemia during and especially after exercising. Glycaemia during exercise training can vary inter- as well as intra-individually, given that it depends on various factors such as exercise modality and intensity, nutritional status, time of insulin injection,

pre-exercise glycaemia and glucose dynamics, and pre-exercise fuel stores (e.g. muscle and liver glycogen content) (see Riddell et al. [105] for detailed decision schemes). Frequent self-monitoring of blood glucose concentrations and/or the use of continuous glucose monitoring devices is thus mandatory before, during and after exercise to closely observe blood glucose concentrations and to reduce blood glucose excursions, especially during the onset of an exercise training intervention. In addition, adaptation of exogenous insulin doses (see below) and adequate intake of carbohydrates before and during exercise training are important to stabilise blood glucose concentrations. Such adaptations need to be managed by experienced specialists and on a highly individualised basis, adapted to duration and intensity of exercise training, exercise capacity, and dynamics of glucose values. Ideally, the starting blood glucose concentration ahead of aerobic exercise should be 126–180 mg/dL or 7–10 mmol/L. Guidelines suggest that if pre-exercise blood glucose concentration is below 5.6 mmol/L, carbohydrates should be consumed before performing exercise. If pre-exercise blood glucose concentration is above 14 mmol/L, urine should be tested for ketone bodies. If positive, exercise training should not be performed. If pre-exercise blood glucose concentration is above 17 mmol/L, exercise training should not be performed, regardless of urine ketone concentrations. In addition, a recent hypoglycaemia (during the last 24 h) is a contra-indication for exercise training as the risk for a new hypoglycaemic episode is significantly elevated.

An insulin pump may be the most flexible treatment option in patients with T1DM performing exercise, and a combination with continuous glucose monitoring (CGM) may improve glycaemic control during and after exercise training. However, the reliability of CGM is not always sufficient during exercise training in these patients. Exercise training is contraindicated in the presence of severe retinopathy (particularly dangerous are high-intensity aerobic exercises and resistance exercises). Peripheral neuropathy may limit the capability of performing certain types of exercise, although studies have shown that moderate-intensity walking does not increase the risk of foot ulcers/re-ulceration. All individuals with peripheral neuropathy must wear proper footwear. No weight-bearing exercises should be executed in patients with open foot lesions. Autonomic neuropathy may increase the risk of injury and/or adverse events and is associated with increased CVD risk. Therefore, pre-exercise cardiac stress testing is required in these situations. Cardiopulmonary exercise testing is only suggested in individuals with an elevated risk of, or symptoms of, coronary artery disease, or with microvascular disease (proliferative retinopathy or nephropathy, including microalbuminuria), peripheral

vascular disease or autonomic neuropathy. Asymptomatic T1DM patients who want to follow a low-to-moderate intensity aerobic and resistance training programme should not be systematically examined by cardiopulmonary exercise testing except when detailed information about exercise responses and/or exercise programming is considered necessary.

3.6 Adjustments in Exercise Prescription According to Intake of Various Cardiovascular Drugs, Adverse Events During Exercise Testing, and Physical Fitness

Patients with an elevated CVD risk are more frequently treated with cardioprotective medications, have an elevated risk for adverse events during exercise training and testing, and/or are deconditioned. These additional features/events can affect exercise prescription and thus should be taken into account.

3.6.1 Medications

Beta-blockers (for arterial hypertension or other indications) will lead to an altered heart rate– workload relationship, and may thus affect exercise training intensity determination [109]. In these patients, exercise testing is advised for objective exercise intensity determination. Some antihypertensive agents such as alpha blockers and vasodilators may exacerbate a reduction in blood pressure after exercise at higher intensities. Therefore, extending the cool-down phase is generally recommended. Beta-blockers and diuretics may also adversely affect thermoregulatory function, especially during exercise training in warmer temperatures, or cause hypoglycaemia in some individuals. For dyslipidaemia, the intake of simvastatins may lead to a development of myopathy (in 1–5% of cases), which is characterized by muscle cramps and lowered tolerance to exercise training. In such cases, it is recommended to prescribe a lower dose of simvastatin or use an alternative statin (e.g. pravastatin or rosuvastatin) [110]. If statins are not tolerated at all then ezetimibe can be used as a second-line drug. Sulfonylurea, meglitinide and exogenous insulin administration (for diabetes) may pose a greater risk for hypoglycaemia. In such cases, the exercise session should be carefully planned, taking the following aspects into account to adjust exogenous insulin dose and carbohydrate intake during exercise training: volume (caloric expenditure) of the exercise session, glycaemia before insulin administration and glycaemia at the start of exercise training. Schemes of how to adjust these factors ahead of and during exercise training to optimise glycaemic control can be consulted in guidelines [71, 81, 105]. In T1DM, suggestions for the reduction in bolus insulin dose before

exercise can be made based on intensity of exercise. Mild-to-moderate intensity aerobic exercise needs a 50–75% reduction (for exercise at 50% VO_{2peak}) in bolus insulin before exercise when performed for at least 30–60 min. High-intensity aerobic exercises (70–75% VO_{2peak}) performed for 30 min may require a 75% reduction in bolus insulin before exercising. However, there is no need to reduce bolus insulin dose before exercise when performing a high-intensity aerobic exercise (> 80% VO_{2peak}). Minimising the risk of exercise-induced late-onset hypoglycaemia can be achieved through a 50% bolus insulin reduction during the post-exercise meal and the consumption of a low glycaemic index-snack at bedtime (especially in T1DM).

3.6.2 Adverse Events During Exercise Testing

CVD risk patients are more prone to the development of (silent) myocardial ischemia (especially diabetes patients with neuropathy), which may be induced during exercise testing [111]. If the patient is not revascularised, it is advised to limit the workload during exercise training up to this myocardial ischemia threshold. Furthermore, cardiopulmonary exercise testing may be indicated in patients with different CVD risk factors due to increased test-sensitivity for myocardial ischemia and other co-morbidities.

3.6.3 Physical Fitness

It is generally recommended to start exercise training at a rather low exercise intensity, and to build it up to the originally recommended exercise intensity, in patients with a VO_{2peak} below 75% of the predicted normal value. On the other hand, it is equally important to adjust exercise intensity during the training programme due to physical adaptations to training loads. Moreover, patients' physical fitness will increase and training effects will further improve if exercise training intensity is adjusted properly. Monitoring of exercise training intensity (heart rate, ratings of perceived exertion) is thus of crucial importance.

4 Exercise Prescriptions for CVD Risk Patients by EXPERT Tool

To demonstrate how the EXPERT tool [13, 112] proposes exercise prescriptions in patients with different combinations of CVD risk factors, three patient cases with solutions are shown in Table 1 (exercise safety precautions are not shown). Despite the fact that these three subjects are all referred to exercise intervention for obesity, very different exercise prescriptions emerge based on CVD risk profile,

Table 1 Exercise prescriptions for simulated CVD risk patients by EXPERT tool

Patient characteristics		EXPERT exercise prescription	
1	Age: 27 years Body height: 185 cm Body weight: 133.8 kg BMI: 39.1 kg/m ² Sex: Male VO _{2max} : 2787 ml/min (82% of normal value) Resting HR: 70 bpm Peak exercise HR: 164 bpm Total cholesterol: 189 mg/dl LDL: 111 mg/dl Fasting glycaemia: 115 mg/dl Blood pressure: 115/75 mmHg Medication intake: None Co-morbidities: Metabolic syndrome	Intensity (HR) Frequency Session duration Programme duration Strength training Additional training advice	108–125 bpm 3–5 times > 60 min > 24 weeks No None
2	Age: 61 years Body height: 170 cm Body weight: 97 kg BMI: 33.56 kg/m ² Sex: Male VO _{2max} : 2283 ml/min (100% of normal value) Resting HR: 69 bpm Peak exercise HR: 141 bpm Total cholesterol: ? LDL: ? Fasting glycaemia: ? Blood pressure: 125/80 mmHg Medication intake: Beta blocker, ACE inhibitor, statin, antiplatelet Co-morbidities: None	Intensity Frequency Session duration Programme duration Strength training Additional training advice	98–111 bpm > 5 times 30–60 min > 40 weeks Yes > 900 kcal/week of energy expenditure should be achieved. Consider hand grip strength exercises
3	Age: 38 years Body height: 160 cm Body weight: 94.5 kg BMI: 36.9 kg/m ² Sex: Female VO _{2max} : 1140 ml/min (60% of normal value) Resting HR: 82 bpm Peak exercise HR: 150 bpm Total cholesterol: 183 mg/dL LDL: 90 mg/dL Fasting glycaemia: 81 mg/dL Blood pressure: 116/73 mmHg Medication intake: Selective serotonin re-uptake inhibitor, metformin Co-morbidities: None	Intensity (HR) Frequency Session duration Programme duration Strength training Additional training advice	109–122 bpm 3–5 times > 60 min > 24 weeks No Start at lower exercise intensity and build towards original proposal

BMI body mass index, VO_{2max} maximal oxygen uptake, HR heart rate, bpm beats per minute, LDL low-density lipoprotein

medication intake and physical fitness. The EXPERT tool always starts with the general recommendation for aerobic exercise prescription in (secondary) prevention of CVD (150 min low-to-moderate intensity aerobic exercise training per week, spread over 3–5 days, achieving 1000–2000 kcal, for a duration of at least 12 weeks) [7]. However, the tool further adjusts exercise prescription based on the input of other variables.

Case 1: A 27-year-old obese male with a slightly reduced physical fitness is referred for exercise training. In this patient, the primary aim is to reduce adipose tissue mass. It is therefore important to maximise exercise volume by prolonging exercise session duration (> 250 min/week), selecting a sufficient exercise intensity (moderate) and whole-body exercises (walking, stepping, rowing, cross-training), thus generating a caloric expenditure > 1500 kcal/week. In addition, to generate clinically relevant fat mass reductions, it is advised to prolong the exercise intervention up to at least 24 weeks. Such fat mass loss is automatically associated with improvements in other CVD risk factors and the implementation of exercise training will also automatically lead to improvements in physical fitness.

Case 2: A 61-year-old obese male with a preserved physical fitness is referred for exercise training. In this patient, the primary aim is to reduce adipose tissue mass as well, and thus similar exercise modalities should be selected as in case 1. However, this patient is also on statin therapy, indicating that he is by definition dyslipidaemic. For this CVD risk factor, it is important to add strength training and to prolong the exercise intervention up to 40 weeks. Moreover, the patient takes beta-blockers and ACE-inhibitors, indicating that he is by definition hypertensive. For this CVD risk factor, it is important to elevate the exercise frequency at least up to five days and add handgrip strength exercises.

Case 3: A 38-year-old obese female with a significantly lowered physical fitness is referred for exercise training. In this patient, the primary aim is to reduce adipose tissue mass as well (as in Case 1), and thus similar exercise modalities should be selected as in Case 1. However, this patient is also on metformin therapy, indicating that she is by definition a diabetic (type 2). For this CVD risk factor, it is important to elevate exercise frequency up to at least 5 days/week and add strength training. Moreover, the patient displays a significantly lowered physical fitness. Therefore, it is advised to start at a lower exercise intensity and build up towards moderate-intensity aerobic training within a few weeks.

5 Conclusion

In this manuscript, state-of-the-art exercise prescription, based on a robust review of evidence, has been proposed for the improvement in CVD risk, also explaining how to prescribe exercise in cases of different combinations of CVD risk factors, intake of certain medications, physical fitness variants and occurrence of adverse events during exercise testing. With the EXPERT tool, clinicians are assisted in the selection of proper exercise training modalities in these populations.

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Compliance with Ethical Standards

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