European Journal of Preventive Cardiology

Management of patients with type 2 diabetes in cardiovascular rehabilitation

--Manuscript Draft--

Manuscript Number:	EJPC-D-19-00804R1
Full Title:	Management of patients with type 2 diabetes in cardiovascular rehabilitation
Article Type:	Supplement "Diabetes and CV Risk"
Section/Category:	Diabetes and Metabolic Syndrome
Keywords:	diabetes; cardiovascular rehabilitation; exercise
Corresponding Author:	Dominique Roger Marie Jose Hansen, PhD Hasselt University Diepenbeek, BELGIUM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Hasselt University
Corresponding Author's Secondary Institution:	
First Author:	Dominique Roger Marie Jose Hansen, PhD
First Author Secondary Information:	
Order of Authors:	Dominique Roger Marie Jose Hansen, PhD
	Nicolle Kraenkel
	Hareld Kemps
	Matthias Wilhelm
	Ana Abreu
	Andreas FH Pfeiffer
	Alda Jordão
	Veronique Cornelissen
	Heinz Völler
Order of Authors Secondary Information:	
Manuscript Region of Origin:	BELGIUM
Abstract:	The clinical benefits of rehabilitation in cardiovascular disease (CVD) are well-established. Among CVD patients, however, patients with type 2 diabetes mellitus (T2DM) require a distinct approach. Specific challenges to clinicians and healthcare professionals in T2DM patients include the prevalence of peripheral and autonomic neuropathy, retinopathy, nephropathy, but also the intake of glucose-lowering medication. In addition, the psychosocial well-being, driving ability and/or occupational status can be affected by T2DM . As a result, target parameters of cardiovascular rehabilitation and the characteristics of the cardiovascular rehabilitation program in T2DM patients often require significant reconsideration and a multidisciplinary approach. This review explains how to deal with diabetes-associated co-morbidities in the intake screening of patients with T2DM entering a cardiovascular rehabilitation program. Furthermore, we discuss diabetes-specific target parameters and characteristics of cardiovascular rehabilitation programs for T2DM patients in a multidisciplinary context, including implementation of guideline-directed medical therapy.

Hasselt, September 6, 2019

Dear Sir,
Dear Editor,

With this letter we would like to thank you for allowing us to revise our manuscript and hereby increasing the likelihood for publication. In this letter, all comments are addressed in a point-by point fashion and changes in the manuscript are underlined. We hope that these revisions are satisfactory.

With kind regards,

Dominique Hansen, PhD, FESC (on behalf of all authors)

Editors' comments

The manuscript is currently too lengthy and should be reduced by at almost 30%, and this objective is easily attainable by reducing some redundancies among several chapters, and this will provide more consistency throughout the paper. The manuscript as it is now gives the impression of being an aggregate of chapters written by different authors and needs a global revision to make a consistent document without redundancies:

- The investigation of other comorbidities (nephropathy, etc) could be enlisted briefly in a table as a checklist. This would much more convenient for the reader.

We agree with the Editor and have now included such a checklist.

- The chapter “Education, self-empowerment, adherence and behavioural change” is extensively addressed in another paper of the same issue entitled “Life style factors, self-management & Patient empowerment in diabetes care”. While you do not have access to this reference yet, you may refer to this paper y referencing it as it is (add “to be completed”) and shorten your paragraph to the essentials.

We now have shortened to the essentials and refer to this paper.

- The social and nutritional aspects should be shortened as you address these issues twice (see “nutritional assessment” where you have also included “psychosocial factors” within it, and later in the text the paragraphs “nutrition” and “psychosocial status”. All these need to be dramatically shortened.

Revised accordingly.

- The “return to work” and “driving” chapters should be shortened and merged as there are interconnections. For the latter point, please consider the issue of screening sleep apnoea syndrome, a frequent condition in these patients.

We executed these revisions.

- Many sentences are too wordy. Consider a revision by a native-English speaker.

We carefully revised the full paper and had it checked by a native English speaking person..

Authorship: below the list of authors, there is “*On behalf of the EAPC Cardiovascular Prevention and Rehabilitation Section” but the asterisk does not refer to any place and could be deleted. If you want to keep this, an official letter from the chair/responsible of that section, or the EAPC, would be necessary. I would rather strongly suggest to delete it, as this document has not gone through the official steps necessary prior to its writing.

This is now deleted.

References
The number of references is too high. Please consider a substantial shortening of this list, avoiding redundancies.

We reduced the number of references considerably.

Ref 146: please rather consider the last ESC guidelines on CVD prevention, published in the EJPC.
Also, please consider to refer to the upcoming ESC/EASD guidelines, to be released in September 2019. While you do not have still access to these guidelines, this documents will be the reference for the management of all CVDs in diabetic patients, so you could use it to shorten some paragraphs and decrease the number of references in this document. As you do not have the exact reference of this document, please create it in your reference list as “ESC/EASD 2019 Guidelines on CVD & Diabetes, to be completed” where appropriate. This will then be easily modified at the last step prior to the publication of your journal.

Revised accordingly.

Reviewers' comments:

Reviewer #1:

The authors reviewed the management of patients with type 2 diabetes in cardiovascular rehabilitation. This review seems to be well-written and educative. As a reviewer, I have some comments regarding the present review.

#1 This review seems to be too lengthy. Some paragraphs such as nutrition and psychosocial factors were overlapped. The authors should shorten the whole of manuscript. In addition, the authors had better reconsider whether "return to work" or "driving ability" are actually necessary in the "EJCP.

These suggestions are well in line with those from the Editor. We have therefore revised and shortened the entire manuscript.

#2 The authors had better delete the word "see" before a table or figure. In addition, there were some sentences with double parentheses. The authors should revise these sentences to make the readers to read them easily.

Revised accordingly.

Reviewer #2:

Authors did a great job. The topic of an article is interesting and the literature is relevant to the study.

There is no need for any additional tables or figures.

We thank the reviewer for his/her appreciation: no additional revisions were executed for this reviewer.

Reviewer #3:

1. Please change the word re-event

Revised accordingly.

2. Author needs to revise the writing in this paper. Many sentences are either confusing or redundant such as: "Living alone is predictive for self-management negligence, while being not alone, having a mutual, intimal, satisfactory relation with someone, is essential regarding how the diabetic patient faces the disease".

This is now revised accordingly in the entire manuscript.

3. Why the level of education also is related to the perceived family social support?

This section is reduced drastically, so this sentence is no longer present in the paper.

4. Author needs to re-organize the paper. It is very confusing, many of the content in this study did not necessarily for CVD patients who have diabetes. It also works for CVD alone or other diseases.

We agree with the reviewer: we have now re-organised the paper.

5. The conclusion of this study also did not match with all the description of the study.

We now rephrased our conclusion.

Management of patients with type 2 diabetes in cardiovascular rehabilitation

Dominique Hansen[1,2,3]; Nicolle Kraenkel[4,5]; Hareld Kemps[6], Matthias Wilhelm[7], Ana Abreu[8], Andreas FH Pfeiffer[4,9], Alda Jordão[10], Veronique Cornelissen[11], Heinz Völler[12,13]

1. REVAL – Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium

2. Jessa Hospital, Heart Center Hasselt, Hasselt, Belgium

3. BIOMED - Biomedical Research Center, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

4. Charité - Universitätsmedizin Berlin, Department of Endocrinology, Diabetes and Nutrition, Berlin, Germany

5. DZHK (German Centre for Cardiovascular Research), partner site Berlin

6. Department of Cardiology, Maxima Medical Centre, Veldhoven, The Netherlands

7. Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Switzerland

8. Serviço de Cardiologia, Hospital Universitário de Santa Maria/Centro Hospitalar Universitário Lisboa Norte (CHULN), Centro Académico de Medicina de Lisboa (CAML), Centro Cardiovascular da Universidade de Lisboa (CCUL), Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

9. DZD (German Centre for Diabetes Research), partner site Berlin/Nuthetal

10. Department of Internal Medicine, CHULN, Hospital Pulido Valente, Lisbon, Portugal

11. Cardiovascular Exercise Physiology Group, Department of Rehabilitation Sciences, KU Leuven, Belgium

12. Center of Rehabilitation Research, University of Potsdam, Germany

13. Klinik am See, Rehabilitation Center for Internal Medicine, Rüdersdorf, Germany

Funding: None.

Conflicts of interest: none to be declared.

Full text word count: 4617

Contact details:

REVAL – Rehabilitation Research Centre

Hasselt University, Faculty of Rehabilitation Sciences

Agoralaan, Building A, 3590 Diepenbeek, Belgium

e-mail: Dominique.hansen@uhasselt.be

Phone: 0032 497875866

Abstract

The clinical benefits of rehabilitation in cardiovascular disease (CVD) are well-established. Among CVD patients, however, patients with type 2 diabetes mellitus (T2DM) require a distinct approach. Specific challenges to clinicians and healthcare professionals in T2DM patients include the prevalence of peripheral and autonomic neuropathy, retinopathy, nephropathy, but also the intake of glucose-lowering medication. In addition, the psychosocial well-being, driving ability and/or occupational status can be affected by T2DM. As a result, target parameters of cardiovascular rehabilitation and the characteristics of the cardiovascular rehabilitation program in T2DM patients often require significant reconsideration and a multidisciplinary approach. This review explains how to deal with diabetes-associated co-morbidities in the intake screening of patients with T2DM entering a cardiovascular rehabilitation program. Furthermore, we discuss diabetes-specific target parameters and characteristics of cardiovascular rehabilitation programs for T2DM patients in a multidisciplinary context, including implementation of guideline-directed medical therapy .

Keywords: diabetes, cardiovascular rehabilitation, pre-participation screening, exercise

Introduction

Structured rehabilitation programs are an integral part of care for patients suffering from a cardiovascular event. They facilitate the restoration of the patients' functional capacity, improve the quality of life, enable optimal re-integration into daily life and reduce the risk to suffer from a subsequent cardiovascular event or experience hospitalisations.[1,2] Components of such cardiovascular rehabilitation program encompass implementation of guideline-directed medical therapies, psychological support or counselling, the facilitation of (early) return to work and reconsideration of driving ability, as well as lifestyle measures such as smoking cessation, dietary adjustments and physical activity. The latter includes specific exercise programs and the integration of sufficient physical activity into the daily life.

A large portion of patients who recover from a cardiovascular event, however, also suffer from diabetes mellitus (e.g. in ±30% of patients recovering from an acute myocardial infarction)[3], which affects the content of a cardiovascular rehabilitation program. For example, typical diabetes-related co-morbidities and/or the intake glucose-lowering medication may hamper direct translation of physical activity recommendations from non-diabetic to diabetic cardiovascular disease (CVD) patients. In addition, specific dietary measures and additional psychosocial support may be indicated in T2DM patients. As a result, adjusting and personalising a rehabilitation program to CVD patients with T2DM may be challenging to clinicians.

This paper summarises the current state-of-the-art rehabilitation for CVD patients with T2DM and addresses key differences compared to non-diabetic CVD patients. First, the intake screening will be described in greater detail, followed by what to target as well as a detailed description of the components of a rehabilitation program for CVD patients with T2DM.

Intake screening in CVD patients with type 2 diabetes

The optimisation of rehabilitation in CVD patients with co-existent T2DM starts with a proper intake screening, in which the glycaemic control, co-morbidities and functional status are key elements.

Assessment of glycaemic control

The diagnosis of T2DM is established when either the fasting plasma glucose concentration equals or exceeds 126 mg/dL (7.0 mmol/L), 2-h plasma glucose concentration during a 75-g oral glucose tolerance test is ≥200 mg/dL (11.1 mmol/L), or HbA1c is ≥6.5% (48 mmol/mol), respectively.[4,5] However, for feasibility reasons clinicians mostly rely on fasting blood glucose concentrations and/or capillary blood glucose measurements, as regular follow-up is warranted in these individuals. Optimal fasting blood glucose concentrations then typically range between 80-120 mg/dl (4.4-6.7 mmol/l) and postprandial concentrations should not exceed 180 mg/dl (10.0 mmol/l). However, older patients

could experience hypoglycaemia more frequently in response to blood glucose-lowering therapies.[5] Therefore, in these patients, and without established micro- and macrovascular complications, higher blood glucose concentrations are acceptable.

Investigation of co-morbidities

MICRO/MACROVASCULAR AND ORTHOPAEDIC COMPLICATIONS

At entry of rehabilitation, the presence of microvascular complications should be assessed in T2DM patients (Table 1). Such co-morbidity is clearly associated with an elevated risk for cardiovascular events, may require specific treatment, or represents a contraindication to some antidiabetic medications or types of exercise/physical activity. As a result of the potential presence of microvascular disease, retinal complications such as maculopathy or proliferative retinopathy should be ruled out. Systemic microvascular deterioration might also lead to peripheral and/or autonomic neuropathy, as well as nephropathy. As a result, these aspects should deserve significant attention during such assessment as well. Simple clinical tests are available to rule out peripheral neuropathy (e.g. vibration sense test, monofilament test) and/or autonomic neuropathy (e.g. heart rate (HR) variability, supine-to-stand manoeuvre with blood pressure (BP) assessment). Autonomic neuropathy can also be verified by cardiopulmonary exercise testing, in which altered HR changes are most apparent. The aetiology of chronotropic incompetence (the inability to reach a normal peak HR) in T2DM is multifactorial, including altered blood catecholamine and/or potassium concentrations during exercise, structural myocardial abnormalities, ventricular and/or arterial stiffness, impaired baroreflex sensitivity and cardiovascular autonomic neuropathy.[6] Chronotropic incompetency is associated with exercise intolerance and increased risk for major CV events and premature death.[7] Several standardized criteria (e.g. approach from Wilkoff et al.)[8] can be used to establish chronotropic incompetence. Moreover, an attenuated heart rate recovery (HRR) may also reflect the grade of autonomic dysfunction.[9] The HR recovery is calculated as the difference of peak HR and HR at one to five minutes post exercise. In patients with T2DM, HR recovery is an independent predictor of reduced exercise capacity, CVD and all-cause mortality.[7,10] To assess renal function or rule out nephropathy, clinicians are advised to execute routine blood and/or urine sample analyses.

To assess/examine the presence of macrovascular complications, the peripheral vascular status of the lower extremities and ECG during exercise testing should be evaluated closely. Visual inspection of the lower extremities, arterial pulse palpation and ankle/brachial index assessment is well capable to reveal significant peripheral arterial disease. Special attention should be paid to silent myocardial ischemia during cardiopulmonary exercise testing. Silent myocardial ischemia may be present in one of five T2DM patients.[11,12] Among men with diabetes mellitus, equivocal and abnormal exercise ECG responses are associated with higher risk of all-cause, CVD, and coronary heart disease mortality.[13] In

patients with chest pain (present in ±16% of T2DM patients), CPET shows a better diagnostic and predictive accuracy than traditional ECG stress testing to detect or exclude myocardial ischemia.[14] An echocardiogram should be performed to rule out myocardial dysfunction.

In final, the orthopaedic system should be examined for specific symptoms and/or movement limitations, and the clinician should be aware of increased hip fracture risk.[15] The feet deserve great attention for dermatologic and musculoskeletal risk factors. The diabetic foot may be defined as a group of syndromes in which neuropathy, ischaemia and infection lead to tissue breakdown, resulting in morbidity and possible amputation.[16]

Unhealthy diet and Nutritional co-morbidities

Unhealthy eating patterns can cause a significant excess mortality primarily due to a deficiency in legume, vegetable, fibre and unsaturated fatty acid intake and excessive intake of salt, sugar sweetened beverages and saturated fat as well as processed meat.[17,18] Food intake determines blood glucose concentrations, in which the intake of carbohydrates is of particular importance to T2DM patients. Therefore, the assessment of nutrition and diet is important in T2DM patients. In this regard, food diaries or food-frequency questionnaires should be used and reviewed by dieticians.

Moreover, malnutrition, sarcopenia, or obesity with sarcopenia, is frequently present in older and frail patients, while obesity is highly prevalent in T2DM patients. Sarcopenia, which is in essence the combination of muscle weakness and low muscle mass, may be verified by the assessment of arm and leg circumference or a simple timed stand-up and walking test. A reduced muscle function is also detected by a reduced gait speed, reduced handgrip strength, or failure to stand up from sitting in a chair without assistance by the arms. Nutritional deficiencies are frequent in older people for various reasons and vitamin D deficiency is present in over 50% of the elderly. Blood vitamin B12 may be lowered due to metformin therapy or low meat intake and may contribute to peripheral and autonomic neuropathy. Therefore, the assessment of blood vitamin D and/or B12 concentrations may be relevant in subgroups of T2DM patients.

Psychosocial co-morbidities

People with T2DM more often struggle with psychosocial difficulties, hereby inducing a higher risk for experiencing a diminished psychological well-being.[19,20] Strained coping with life routines change, concerns about hypoglycaemia and diabetes complications, and low social support can elicit psychosocial difficulties.[19,21,22] Compared with healthy persons, clinical depression and anxiety therefore occur twice more often in diabetic patients.[23] Moreover, social support, especially family support, can be a vital component in the successful control of diabetes, and is related to a better quality of life.[24]

For all these reasons, all individuals with T2DM need to have a psychosocial evaluation at entry of rehabilitation. Besides the clinical interview, there are many standardised, age- and literacy-appropriate assessment and diagnostic tools that can be used to better evaluate psychological and social issues that could compromise successful management of disease, when suspected.[25]

SLEEP APNOEA SYNDROME

Around 50-90% of all T2DM patients suffer from the obstructive sleep apnoea syndrome (OSA), which is diagnosed when apnoea-hypopnoea index equals or exceeds 15 events/h, or between 5-15 events/h with excessive daytime sleepiness (which can be quantified by sleep study and questionnaire), or laboured breathing during the apnoea event.[26] OSA can lead to insomnia and is highly unfavourable as it elicits hypertension, increased activity of the sympathetic nervous system, and systemic insulin resistance that can exacerbate the pathophysiology of T2DM.[26] Therefore, OSA should be ruled out or treated when detected.

After this intake screening, the clinician should be aware of conditions that can have a significant impact on the content of the rehabilitation program (e.g. feasibility and medical safety). By a further assessment of the functional status, however, the clinician also obtains objective and modifiable targets for rehabilitation.

Functional status

RISK FACTORS

Since most patients with T2DM are overweight/obese and such clinical state relates to prognosis, the determination of the waist circumference or fat mass is crucial. The waist circumference must be assessed mid-way between the lowest rib and the iliac crest.[27] In European men and women, a waist circumference of <94 cm and <80 cm, respectively, is considered normal. Bio-impedance analysis (BIA) is a simple and clinically useful tool to assess body composition (in particular fat mass) but needs appropriate software and interpretation.[28]

The prevalence of hypertension in patients who have T2DM (defined as a BP >140/90 mmHg) is up to three times higher than in patients without diabetes,[29] and is a strong independent risk factor for CVD and chronic kidney disease. A strict follow-up of the BP in the setting of T2DM is therefore recommended.[5] In this regard, the BP response during exercise should always be assessed as well, as apparently normotensive T2DM patients still can experience a hypertensive response during physical exertion.[30]

Blood lipid profile abnormalities are highly common in T2DM patients, and are particularly characterised by elevations in blood low-density lipoprotein (LDL) cholesterol concentrations. As a result, blood LDL cholesterol should be evaluated.[5]

PHYSICAL ACTIVITY

A sedentary lifestyle and reduced exercise capacity are common features in T2DM and is associated with a worse prognosis.[31,32] The assessment of physical activity (PA) is therefore clinically relevant. Physical activity can be estimated by questionnaires, motion sensors, accelerometers or pedometers.[33] Self-report instruments are the most widely used tools to assess PA, despite limitations like reliability in self-assessment, difficulties in ascertaining the frequency, duration and intensity of PA, social desirability bias and the cognitive demands of recall.[33] The International Physical Activity Questionnaire seems, however, adequate for clinical assessment in patients with T2DM.[34] Step counters may help to further objectively assess PA in patients with T2DM and can easily be employed using modern smartphones (5000-10.000 daily steps: insufficiently active, <5000 daily steps: inactive).[35]

EXERCISE CAPACITY

Cardiopulmonary exercise testing is the gold standard to accurately quantify cardiorespiratory fitness, identify exercise-limiting pathophysiological mechanisms, formulate function-based prognostic stratification, and determine exercise training zones based on ventilatory thresholds.[36] In T2DM patients, a reduced cardiorespiratory fitness is usually associated with subclinical left ventricular dysfunction, insulin resistance and a poor glycaemic control.[37] A peak oxygen uptake (VO_{2peak}) <75% of the normal value is considered as significantly reduced, in which the aetiology for such deconditioning should be explored.[37]

After completion of this part of the intake screening, clinicians can define the personalised goals of the rehabilitation program.

What to target and how to intervene in CVD patients with diabetes

Glycaemic control

According to guidelines, an HbA1c target for most adults with T2DM is <7.0% (<53 mmol/mol).[5] However, more-stringent HbA1c goals of <6.5% (48 mmol/mol) may be suggested on a personalised basis if this can be achieved without significant hypoglycaemia or other adverse effects of treatment. Less stringent HbA1c goals of <8% (64 mmol/mol) or <9% (75 mmol/mol) may be adequate for the elderly.

Physical activity and exercise training

Improving exercise capacity and daily physical activity levels are crucial components of the treatment of patients with CVD and T2DM (Table 2). Documented effects include improved physical fitness, muscle strength, glycaemic control (reductions in HbA1c by ~0.7%), vascular function and inflammation. Moreover, exercise training (ET) increases the effect of pharmacologic or dietary strategies for lowering BP, blood LDL cholesterol and fat mass.[39] However, the largest trial evaluating the effect of a combined exercise and weight loss intervention in T2DM patients failed to show a decline in cardiovascular events in the long-term.[40] However, this was mainly due to non-adherence to lifestyle and medication prescriptions. Therefore, future strategies to improve physical activity and physical fitness in patients with DM and CVD should not only consist of structured supervised ET programs aiming at short-term improvements in exercise capacity. They should rather be combined with strategies aiming at improving long-term adherence and incorporating an active lifestyle in daily life in which patients play a more active role.

The optimal composition of ET programs in CVD patients with T2DM is dependent on individual treatment targets. When targeting the glycaemic control and physical fitness, the most optimal training program should consist of at least 3-5 aerobic exercise training (AET) sessions of at least 30 minutes/week at a moderate-to-high intensity (i.e. at least 50-70% VO_{2peak}).[41-43] In particular a higher exercise frequency relates to greater improvements in glycaemic control in T2DM patients. High-intensity interval (HIIT) training at 90-95% VO_{2peak} might potentially be superior to moderate-intense programs for improving glycaemic control, although the study samples sizes are small.[44] Yet, HIIT is not yet a sufficiently established feasible and safe modality for all T2DM patients due to the high level of required motivation and disease-related barriers for performing training at high-intensity (e.g. cardiac autonomic neuropathy, peripheral arterial disease, cardiac arrhythmias, (silent) myocardial ischemia). So, data from large trials are still to be awaited. Resistance training (RT) is effective as an adjunct to AET for further improving glycaemic control.[45] Guidelines generally recommend 2-3 sessions/week involving large muscle groups at an intensity of 75-85% of 1 repetition maximum (8-10 repetitions).[39] In T2DM patients the volume of RT seems, however, to be the most important training modality. When 21 or more sets of RT are offered, significant greater decrements in blood HbA1c may be anticipated.[46] Besides participating in structured ET programmes, CVD patients with T2DM should be strongly encouraged to adopt a healthy lifestyle and to increase daily physical activity levels. As such, easily implementable lifestyle changes, such as reducing sedentary time by interrupting sitting with light exercise, seem to be effective in improving glycaemic control in T2DM patients.[47-49] In addition, although previous trials showed that long-term adherence to lifestyle advice in these patients remains challenging, the introduction of new digital health-based healthcare models and innovations in telecommunication technologies provide new opportunities to T2DM patients.[50] So, to conclude, when

T2DM is also present in a patient with CVD, exercise frequency should be increased, large-volume RT should be added and daily-life physical activity should be increased.

On the other hand, when such exercise is planned, the medical safety should be maximised as well. Hypoglycaemia may form an important barrier for adherence to ET programs to T2DM patients. Therefore, blood glucose monitoring (by capillary measurements) is recommended in T2DM patients during the first weeks of ET programs.[51] This particularly applies to patients with a higher age, lower body mass index, impaired renal function, a history of microvascular complications, dementia, previous hypoglycaemic events, longer duration of T2DM and lower education.[52] Also caution is warranted in patients using insulin, glinides and/or sulphonylureas as hypoglycaemic events are observed more frequently in these subjects. Flowcharts should be used how to adjust medication dose in relation to the observed blood glucose concentrations ahead of, and during, exercise training.[53] When retinopathy and/or nephropathy is diagnosed, high-intense exercise and/or hypertensive responses to exercise should be avoided. In patients with significant peripheral arterial disease and/or peripheral neuropathy, the feet should be checked regularly to rule out (small) wounds.

Risk factor control: blood pressure, lipids, body weight and composition

In addition to the favourable effects of exercise training and physical activity on glycaemic control in CVD patients with T2DM, such intervention also leads to reductions in blood lipids, BP and fat mass. However, it should be stressed that the proper selection of training modalities is instrumental to improve these cardiovascular risk factors.[54]

In the prevention and management of high BP, aerobic exercise training is recommended.[55] In particular, a sufficient intensity (at least moderate-intense) and frequency (up to five days/week) seems key to optimise BP. As an adjunct, dynamic resistance exercise can be advised on 2-3 days per week.[55] As dynamic resistance exercise training might temporarily increase BP, dynamic resistance exercises at greater intensities (>70% of 1-repetition maximum) with fewer repetitions (n=<10) actually elicits smaller increments in systolic BP and cardiac output, when compared to lower intensities (<50% of 1-repetition maximum) with more repetitions n=>20)).[56] Furthermore, there is some evidence that the addition of isometric strength training exerts a larger reduction in BP in hypertensive patients.[57]

The impact of exercise training and physical activity on the blood lipid profile differs between different patient populations. In patients with CVD,[58] reductions in blood total cholesterol and triglycerides may be expected while in patients with T2DM reductions in blood LDL cholesterol and improvements in HDL cholesterol may be anticipated.[59] However, the impact of the intake of blood lipid-lowering drugs (such as statins), but also caloric intake restriction, is of such magnitude on the blood lipid profile that it may overrule/mask the impact of exercise training. Aerobic moderate-intense exercise training is most often implemented with the aim to improve the blood lipid profile. In this regard, it is important

to achieve a minimal weekly energy expenditure of ≥900 kcal to maximise the improvements in blood HDL cholesterol concentration, preferentially by prolonging the exercise session.[60] Moreover, the influence of physical activity on blood lipid profile takes a while to be noticed, so prolonged exercise interventions seem needed to significantly affect the blood lipid profile (≥12 weeks).[54] Also, there is evidence that (the addition of) resistance training exercises positively affect blood HDL cholesterol concentrations as well as other lipoproteins and total cholesterol.[61] Therefore, resistance/strength training could be added to endurance training to further improve the blood lipid profile in patients with CVD and T2DM.

It is well known that exercise intervention or physical activity only leads to marginal changes in body weight.[62] Therefore, the addition of energy intake restriction is key to maximise weight loss in patients with obesity. However, the focus of these studies was body weight and not fat mass, and it remained uncertain whether the correct exercise modalities were selected. Nonetheless, T2DM patients who manage to lose at least 10% of their body weight have a 20% lower risk of incident cardiovascular disease, so weight loss in an important aim.[63] To reduce fat mass in obese individuals, a high energy expenditure should be strived at:[64] 225-420 min of exercise/week should be achieved to significantly affect fat mass.[65] Although resistance training should be added on top of endurance training to affect lean tissue mass, muscle strength, blood lipid profile and resting metabolic rate, such addition does not lead to greater reductions in fat mass.[66] Moreover, there is no evidence to prefer exercise training in the fasted state,[67] or exercise training at the maximal fat oxidation rate,[68] to maximise fat mass reductions.

Exercise should be viewed as complement to guideline-directed medical therapy. Antihypertensive and lipid-lowering therapy should be initiated and/or up-titrated during the program to achieve diabetes-specific BP and lipid goals.[5]

Psychosocial status

How to optimise the psychosocial status in CVD patients with T2DM, is addressed in greater detail in another manuscript in this issue.[69] In T2DM patients with clinical depression and/or psychosocial difficulties, access to illness-management resources and social support, psycho-education, distress-management, and strengthening self-efficacy may improve the treatment adherence, diabetes self-management, and/or the quality of life. Care models that consider cultural influences, as well as personal, family, and community resources are herein more likely to be successful.[70]

Sleep apnoea syndrome

In the treatment of OSA, continuous positive airway pressure during sleeping, aerobic exercise training and dietary intervention is advocated.[26] If insomnia is co-existent, the addition of certain drugs can be

considered, such as γ-aminobutyric-acid (GABA) A receptor modulators or orexin receptor antagonists, as well as cognitive behavioural therapy.[26]

Return to work and driving ability

Employment decisions can have an impact on mental health[71] and can have economic repercussions. As a result, decisions for professional reintegration should be individualised. For T2DM patients with a stable glycaemic control there are only few restrictions on occupational reintegration. In particular, the risk of hypoglycaemia and coincidental diabetes-related complications (e.g. neuropathy, retinopathy) are limiting for professional reintegration. Basically, the following aspects should be taken into account when considering occupational reintegration: endangering themselves or others, long-term quality/stability of metabolic control, type of antidiabetic medication, characteristics of hypoglycaemia (e.g. frequency, perception, need of external assistance), current disease management and psychosocial coping with the illness.[72] In physically demanding jobs, the monitoring of blood glucose concentrations can be recommended in the first few weeks to avoid severe hypoglycaemia. However, a single episode of severe hypoglycaemia should not per se disqualify an individual from employment, but may reinforce the awareness for the safety of the individual safety.[73] The risk of hypoglycaemia is particularly relevant for activities that may lead to self-hazard and/or possible harm to other people due to confusion or short loss of consciousness (e.g. danger of falling, working in overpressure system, driving work). If the medication is stable, there are no restrictions on shift, night or piece work. Unusual breaks are not generally required.

The individual ability to drive is an important aspect in certain T2DM patients, and is aligned to the group of driving classes, the glucometabolic stability and the individual risk of hypoglycaemia.[74] Sudden hypoglycaemia followed by unconsciousness is the most important concern when assessing the ability to drive, whereas the tendency is more pronounced in T2DM patients treated with insulin, sulfonylureas or glinides.[75] In general, a distinction is made between private (cars and motorcycles: group 1) and professional drivers (trucks/lorries, bus driver, pilot, taxi driver: group 2). Recent recommendations emphasize that well-trained and educated people with T2DM can take part in traffic. The Second European Working Group on Diabetes and Driving (advisory board to the Driving Licence Committee of the European Union) recommends that for group 1 drivers: “driving licences may be issued to, or renewed for, applicants or drivers who have diabetes mellitus. When treated with medication, they should be subject to authorised medical opinion and regular medical review, appropriate to each case, but at no greater than a 5-year interval.”.[76] However, stronger restrictions for group 2 have to be considered (e.g. no severe hypoglycaemia in the last 12 months, no hypoglycaemic perception disorder, verification of adequate surveillance of the disease through periodic blood glucose tests performed at least twice daily and at times relevant to driving a vehicle,

negation of complications of diabetes that exclude driving).[77] It is also required that the driving license should be issued only with the consent of a competent medical authority and provided that there is a regular medical check-up at least every three years.

Nutrition

While older nutritional recommendations targeted specific ranges of macronutrients, newer recommendations rather focus on dietary patterns.[5,78] T2DM patients need structured instructions by trained dietitians in order to achieve nutritional changes. There is agreement that hydrogenated and hardened fats should be avoided and saturated fats kept to a minimum. Therefore, animal fat from butter, cream, meat, cookies should be avoided. Sugar should be kept to a minimum, i.e. 25 g/day according to the World Health Organisation. Carbohydrate quality, i.e. the avoidance of rapidly digestible starches in white bread, rice or pasta/noodles, cakes and cookies causing rapid and dose dependent increases in blood glucose while preferring whole grain cereals, brown rice is widely accepted. The quantity of carbohydrate plays an important role in postprandial glycaemia and should be limited per meal. Fruits low in sugar such as berries should be preferred to fruits rich in sugar (e.g. grapes, banana) and fruit quantity should not exceed 300 g/day. Non-starchy vegetables should be a preferred food and eaten in amounts of over 400 g/day. This will supply many micronutrients and help in weight management. Legumes (e.g. beans, peas, lentils) cause only moderate rises in blood glucose and represent healthy and nutritious foods with a high content of protein, fibre, minerals and slow carbohydrates. Healthy mono- and polyunsaturated fatty acids (MUFA and PUFA) are generally under-consumed which may contribute to excess mortality.[15,16] The intake of seeds and nuts with a high content of PUFA and MUFA, and additionally of minerals and plant proteins is generally recommended, but in well-controlled quantities, because of the high energy density. Different dietary patterns can be successfully applied to control blood glucose, such as low carbohydrate, low fat, vegan, vegetarian, protein-rich low-carbohydrate diets. In addition, a Mediterranean diet, rich in polyunsaturated and monounsaturated fats (with inclusion of olive oil), should be considered to reduce CV events.[5] Several specific patterns such as the DASH diet, a low sodium, plant food and protein emphasizing diet to reduce hypertension and many variants thereof can be successfully applied.[78,79] Low carbohydrate diets containing 5-40% of the energy intake as carbohydrate are successful to rapidly control blood glucose. Long-term studies however usually do not observe advantages of low carb over low fat diets.[78,79] This leaves significant space to shape the diets to individual preferences and thereby support long-term adherence in T2DM patients.

Education, self-empowerment, adherence and behavioural change

Lifestyle changes are an essential part of diabetes treatment together with adherence to pharmacological treatment and glycaemic control/monitoring. The clinical outcomes in T2DM will however depend on the self-management: good self-care protects against diabetes-related complications and the patient must actively manage the disease's requirements in order to achieve optimal glycaemic control.[81]

For this self-management, T2DM patients should receive education in a group and also individually, together with personalised counselling. Until very recently, the health professional was the authority responsible for the diagnosis and treatment, while patient education was generally prescriptive. Evidence is mounting that these models are, however, not effective in diabetes care.[82] In the modern optimised approach, T2DM patients should be in control and responsible for the daily self-management of their condition, consisting of a self-management plan to fit the patients' goals, priorities, and lifestyle as well as their diabetes.[83] This approach is based on three aspects of chronic illness care:[84]

1. Choices - The choices that patients make each day, as well as their care for diabetes, have a greater impact on their outcomes than those made by health professionals;

2. Control - Patients are in charge of their self-management behaviours. Once patients leave the medical ' offices, they are in control of which recommendations they should implement or ignore;

3. Consequences - Because the consequences for these decisions accrue directly to patients, they have both the right and the responsibility to manage diabetes in the way that is best suited to the context and culture of their lives.

In this process, patient empowerment is important. Empowerment is a patient-centred, collaborative approach tailored to match the fundamental realities of diabetes care, in which education is a crucial component. Patient empowerment is defined as helping patients to discover and develop the inherent capacity to be responsible for one's own life. Approaches to education within the empowerment philosophy incorporate interactive teaching strategies designed to involve T2DM patients in problem solving and address their cultural and psychosocial needs. There is indeed a growing recognition that, although health professionals are experts on diabetes care, patients are the experts on their own lives. Personal setting within the empowerment approach[85] is a five-step process that provides patients with the information and clarity they need to develop and reach their diabetes- and lifestyle-related goals (Figure 1).

Conclusion

In patients with CVD, T2DM is highly prevalent. Such co-morbidity should trigger clinicians and healthcare providers to execute a thorough intake screening and intervene, both on lifestyle and medication, in a multidisciplinary context during cardiovascular rehabilitation.

Acknowledgements

Conflicts of interest: none to be declared.

Authorship

DH, NK, HK, MW, AFHP, AJ, AA, VC and HV contributed to the conception or design of the work, acquired data, 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.

References

1. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-177.
2. Rauch B, Davos CH, Doherty P, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). Eur J Prev Cardiol 2016; 23: 1914-1939.
3. Ahmed B, Davis HT, Laskey WK. In-hospital mortality among patients with type 2 diabetes mellitus and acute myocardial infarction: results from the national inpatient sample, 2000-2010. J Am Heart Assoc 2014; 3: e001090
4. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019; 42: S13-S28.
5. The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019; e-pub ahead of print. doi:10.1093/eurheartj/ehz486.
6. Keytsman C, Dendale P, Hansen D. Chronotropic Incompetence During Exercise in Type 2 Diabetes: Aetiology, Assessment Methodology, Prognostic Impact and Therapy. Sports Med 2015; 45: 985-995.
7. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. Circulation 2011; 123: 1010-1020.
8. Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992; 10: 705-717.
9. Qiu SH, Xue C, Sun ZL, et al. Attenuated heart rate recovery predicts risk of incident diabetes: insights from a meta-analysis. Diabet Med 2017; 34: 1676-1683.
10. Jolly MA, Brennan DM, Cho L. Impact of exercise on heart rate recovery. Circulation 2011; 124: 1520-1526.
11. Lievre MM, Moulin P, Thivolet C, et al. Detection of silent myocardial ischemia in asymptomatic patients with diabetes: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening. Trials 2011; 12: 23.
12. Zellweger MJ, Haaf P, Maraun M, et al. Predictors and prognostic impact of silent coronary artery disease in asymptomatic high-risk patients with diabetes mellitus. Int J Cardiol 2017; 244: 37-42.

13. Lyerly GW, Sui X, Church TS, et al. Maximal exercise electrocardiography responses and coronary heart disease mortality among men with diabetes mellitus. Circulation 2008; 117: 2734-2742.
14. 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.
15. Gehling DJ, Czernik BL, Ebraheim NA. Orthopedic complications in diabetes. Bone 2016; 82: 79-92.
16. National Institute for Health and Clinical Excellence. Type 2 diabetes: prevention and management of foot problems. 2004. http://guidance.nice.org.uk/CG10.
17. Collaborators GBDD. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019; 393: 1958-1972.
18. Micha R, Penalvo JL, Cudhea F, et al. Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. JAMA 2017; 317: 912-924.
19. Rane K, Wajngot A, Wandell PE, et al. Psychosocial problems in patients with newly diagnosed diabetes: number and characteristics. Diabetes Research and Clinical Practice 2011; 93: 371-378.
20. Robertson SM, Stanley MA, Cully JA, et al. Positive emotional health and diabetes care: concepts, measurement, and clinical implications. Psychosomatics 2012; 53: 1-12.
21. Polonsky WH, Fisher L, Hessler D, et al. Identifying the worries and concerns about hypoglycemia in adults with type 2 diabetes. J Diabetes Complications. 2015; 29: 1171-1176.
22. Hinder S, Greenhalgh T. "This does my head in". Ethnographic study of self-management by people with diabetes. BMC Health Services Res 2012; 12: 83.
23. Johansen C. Barriers to Addressing Psychological Problems in Diabetes: Perspectives of Diabetologists on Routine Diabetes Consultations in Denmark. J Psychol Psychother 2014; 4: 2-7.
24. Rad GS, Bakht LA, Feizi A, et al. Importance of social support in diabetes care. J Educ Health Promot 2013; 2: 62.
25. Young-Hyman D, de Groot M, Hill-Briggs Fet al. Psychosocial Care for People With Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care 2016; 39: 2126-2140.
26. Tan X, van Egmond L, Chapman CD, et al. Aiding sleep in type 2 diabetes: therapeutic considerations. Lancet Diabetes Endocrinol 2018; 6: 60-68.
27. Wang J, Thornton JC, Bari S, et al. Comparisons of waist circumferences measured at 4 sites. Am J Clin Nutr 2003; 77: 379-384.
28. Miyatani M, Yang P, Thomas S, et al. Bioelectrical impedance and dual-energy x-ray absorptiometry assessments of changes in body composition following exercise in patients with type 2 diabetes mellitus. J Obes 2012; 953060.
29. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. Hypertension 2001; 37: 1053-1059.

30. Kramer CK, Leitao CB, Canani LH, et al. Blood pressure responses to exercise in type II diabetes mellitus patients with masked hypertension. J Hum Hypertens 2009; 23: 620-622.
31. Wei M, Gibbons LW, Kampert JB, et al. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000; 132: 605-611.
32. Church TS, LaMonte MJ, Barlow CE, et al. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med 2005; 165: 2114-2120.
33. Warren JM, Ekelund U, Besson H, et al. Assessment of physical activity - a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 2010; 17: 127-139.
34. Mynarski W, Psurek A, Borek Z, et al. Declared and real physical activity in patients with type 2 diabetes mellitus as assessed by the International Physical Activity Questionnaire and Caltrac accelerometer monitor: a potential tool for physical activity assessment in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2012; 98: 46-50.
35. Qiu S, Cai X, Chen X, et al. Step counter use in type 2 diabetes: a meta-analysis of randomized controlled trials. BMC Med 2014; 12: 36.
36. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Eur Heart J 2012; 33: 2917-2927.
37. Fang ZY, Sharman J, Prins JB, et al. Determinants of exercise capacity in patients with type 2 diabetes. Diabetes Care 2005; 28: 1643-1648.
38. 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.
39. Kemps H, Krankel N, Dorr M, et al. 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). Eur J Prev Cardiol 2019: 26: 709-727.
40. Look ARG, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. New Engl J Med 2013; 369: 145-154.
41. 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.

42. 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.

43. 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.

44. Liu JX, Zhu L, Li PJ, et al. Effectiveness of high-intensity interval training on glycemic control and cardiorespiratory fitness in patients with type 2 diabetes: a systematic review and meta-analysis. Aging Clin Exp Res 2019; 31: 575-593.

45. 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.

46. Ishiguro H, Kodama S, Horikawa C, et al. In Search of the Ideal Resistance Training Program to Improve Glycemic Control and its Indication for Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Sports Med 2016; 46: 67-77.

47. 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.

48. 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.

49. 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.

50. Frederix I, Caiani EG, Dendale P, et al. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine. Eur J Prev Cardiol 2019: e-pub ahead of print, DOI 2047487319832394.

51. 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.

52. Ponikowski P, Jankowska EA. Hypoglycaemia in diabetic patients: highly undesirable by cardiologists. Eur Heart J 2013; 34: 3102-3105.

53. 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.

54. Hansen D, Niebauer J, Cornelissen V, et al. Exercise Prescription in Patients with Different Combinations of Cardiovascular Disease Risk Factors: A Consensus Statement from the EXPERT Working Group. Sports Med 2018; 48: 1781-1797.

55. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. J Hypertens 2018; 36: 1953-2041.

56. Hansen D, Abreu A, Doherty P, Völler H. Dynamic strength training intensity in cardiovascular rehabilitation: is it time to reconsider clinical practice? Eur J Prev Cardiol 2019; e-pub ahead of print. DOI 10.1177/2047487319847003.

57. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2013; 2: e004473.

58. Kelley GA, Kelley KS, Franklin B. Aerobic exercise and lipids and lipoproteins in patients with cardiovascular disease: a metaanalysis of randomized controlled trials. J Cardiopulm Rehabil 2006; 26: 131-139.

59. 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.

60. Kodama S, Tanaka S, Saito K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. Arch Intern Med 2007; 167: 999-1008.

61. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. Prev Med 2009; 48: 9-19.

62. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc 2007; 107: 1755-1767.

63. Gregg EW, Jakicic JM, Blackburn G, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016; 4: 913-921.

64. 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.

65. Swift DL, Johannsen NM, Lavie CJ, et al. The role of exercise and physical activity in weight loss and maintenance. Prog Cardiovasc Dis 2014; 56: 441-447.

66. Schwingshackl L, Dias S, Strasser B, et al. Impact of different training modalities on anthropometric and metabolic characteristics in overweight/obese subjects: a systematic review and network meta-analysis. PLoS One 2013; 8: e82853.

67. Hackett D, Hagstrom AD. Effect of Overnight Fasted Exercise on Weight Loss and Body Composition: A Systematic Review and Meta-Analysis. J Funct Morphol Kinesiol 2017; 2: 43.

68. Besnier F, Lenclume V, Gérardin P, et al. Individualized Exercise Training at Maximal Fat Oxidation Combined with Fruit and Vegetable-Rich Diet in Overweight or Obese Women: The LIPOXmax-Réunion Randomized Controlled Trial. PLoS One 2015; 10: e0139246.

69. Reference in this issue of EJPC. 2019

70. Kahn R, Anderson JE. Improving diabetes care: the model for health care reform. Diabetes Care 2009; 32: 1115-1118.

71. Ghosh S, Bajaj S, Mukhopadhyay P, et al. Diabetes and Employment. Int J Diabetes Dev Ctries 2018; 38: 133-137.

72. Merendino JJ Jr. What Factors Must One Consider When Evaluating an Individual With Diabetes for Return to Work? J Occup Environ Med 2016; 58: e154-6.

73. American Diabetes Association. Diabetes and Employment. Diabetes Care 2009; 32: S80-84.

74. Hostiuc S, Negoi I, Hostiuc M. Diabetes and collision risk. A meta-analysis and meta-regression. Int J Clin Pract 2016; 70: 554–568.

75. Graveling AJ, Frier BM. Driving and diabetes: are the changes in the European Union licensing regulations fit for purpose? Br J Diabetes 2018; 18: 25-31

76.https://ec.europa.eu/transport/road_safety/sites/roadsafety/files/pdf/behavior/diabetes_and_driving_in_europe_final_1_en.pdf.

77. http://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX:32006L0126.

78. Evert AB, Dennison M, Gardner CD, et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care 2019; 42: 731-754.

79. Chiavaroli L, Viguiliouk E, Nishi SK, et al. DASH Dietary Pattern and Cardiometabolic Outcomes: An Umbrella Review of Systematic Reviews and Meta-Analyses. Nutrients 2019; 11(2).

80. Korsmo-Haugen HK, Brurberg KG, Mann J, et al. Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2019; 21: 15-27.

81. Albisser AM, Harris RI, Albisser JB, et al. The impact of initiatives in education, self-management training, and computer-assisted self-care on outcomes in diabetes disease management. Diabetes Technol Ther 2001; 3: 571-579.

82. Funnell MM, Anderson RM. The problem with compliance in diabetes. JAMA 2000; 284: 1709.

83. Funnell MM, Anderson RM. Empowerment and Self-Management of Diabetes. Clin Diabetes 2004; 22: 123-127.

84. Rubin RR, Anderson RM, Funnell MM: Collaborative diabetes care. Pract Diabetol 2002; 21: 29-32.

85.Heisler M, Bouknight RR, Hayward RA, et al. The relative importance of physician communication, participatory decision making, and patient understanding in diabetes self-management. J Gen Intern Med 2003; 17: 243-253.

86. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018; 41: 2669-2270.

87. Landgraf R, Kellerer M, Aberleet J, et al. Therapie des Typ 2 Diabetes. Diabetologie 2018; 13: S144-165.

Table 1 Checklist for assessment of co-morbidities in CVD patients with T2DM at entry of rehabilitation. A positive results warrants treatment and follow-up.

What to assess		How to assess	positive	negative
Microvascular status				
	Eyes	Use fundus camera with ocular coherence tomography.	☐	☐
	Peripheral nervous system	Execute clinical examination of extremities (foot deformities, dry and patchy skin, hyperkeratosis), vibration sense by tuning fork (with 128-Hz tuning fork with a damper on the branches resulting in 64 Hz at dorsum of great toe), and sensibility by mono filament test.	☐	☐
	Central nervous system	Assess heart rate variability by 24h ECG, the blood pressure response during supine-to-stand manoeuvre (decrease in systolic blood pressure (BP) of greater than 30 mmHg or a decrease in diastolic BP of greater than 10 mmHg when changing from a supine to standing position), and chronotropic response during cardiopulmonary exercise test.	☐	☐
	Kidneys	Urinary albumin excretion and estimated creatinine or cystatin C clearance rate.	☐	☐
Macrovascular status				
	Peripheral arteries	Execute clinical inspection of lower extremities (changes in extremity colour, temperature and appearance of toe nails) with assessment of peripheral pulsations (e.g. a. dorsalis pedis, a. tibialis posterior) and/or ankle/brachial index test. Assess arterial blood pressure at rest and during cardiopulmonary exercise test.	☐	☐
	Coronary arteries	Check ECG during cardiopulmonary exercise test for ST segment depression.	☐	☐
Orthopaedic system		Check for diabetic hand syndrome, Dupuytren contracture, trigger finger, frozen shoulder, Charcot foot, diffuse idiopathic skeletal hyperostosis, osteoarthritis and feet complications (e.g. abnormal colour, dryness, cracking, sweating, infection, ulceration, blistering, deformity). Be aware of increased hip fracture risk.	☐	☐
Nutritional status		Check diet by diaries or food frequency questionnaire. Check for reduced handgrip strength (<20 kg for women, <30 kg for men), deviating sit-to-stand test (failure to stand up from sitting in a chair without assistance by the arms), reduced walking speed (<1.0 m/s) and/or reduced muscle mass (appendicular skeletal muscle mass index <7.26 kg/m^2 for men) and <5.5 kg/m^2 for women).	☐	☐

		Assess blood vitamin D and B12 concentration in subpopulations.	☐	☐
Psychosocial status				
	Questionnaires are available to assess:			
	Diabetes-related distress	Problem areas in Diabetes (PAID)	☐	☐
		Diabetes distress scale (DDS)		
	Depression	Patients Health Questionnaire (PHQ-9)	☐	☐
		Beck Depression Inventory-II (BDI-II)		
	Anxiety	Beck Anxiety Inventory (BAI)	☐	☐
		Hypoglycaemia Fear Survey-II (HFS-II)		
	Cognition	Mini-Mental State Examination (MMSE)	☐	☐
		Telephone Interview for Cognitive Status (TICS) Cognitive Assessment toolkit		
	Adherence to self-care	Summary of Diabetes Self-Care Activities (SDSCA)	☐	☐
		Adherence to refills and medication scale (ARMS-D)		
	Social Support	Multidimensional scale perceived social support (MSPSS)	☐	☐
	Quality of Life	Diabetes Quality of Life (DQOL)	☐	☐
		Modified Diabetes Quality of Life (MDQoL)		
Sleep apnoea syndrome				
		Sleep study Epworth Sleepiness Scale	☐	☐

Table 2 What to target in T2DM patients during cardiovascular rehabilitation

Physical activity and optimisation of exercise capacity	
endurance and	Exercise for up to 5 days/week, at a moderate intensity (50-70% of peak oxygen uptake)
dynamic strength training	2-3 strength training sessions/week involving large muscle groups (>21 sets) at an intensity of 75-85% of 1 repetition maximum (8-10 repetitions)
minimise sedentary time and increase habitual physical activity	Provide step counter (target >10.000 steps/day)
Return to normal body weight	In case of obesity: aim for 5-7 % body weight reduction within one year by: Maximising energy expenditure by exercise training (225-420 min endurance exercise/week) Adjusting diet Ensure no further weight gain while on insulin
Reduction in LDL-cholesterol	In patients with T2DM at moderate CV risk, an LDL-C target of <2.5 mmol/L (<100 mg/dL) is recommended In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) is recommended In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) is recommended All by: Lipid-lowering drugs, sufficient energy expenditure (>900 kcal/week) by exercise training and adjusting diet (decreased consumption of fast-absorbed carbohydrates and alcohol)
Blood pressure reduction	Goal <130/80 mmHg of systolic blood pressure by: Blood pressure-lowering drugs, adjustment in exercise prescription (addition of isometric strength training, at least moderate intense, >30 min/session), alcohol restriction, sodium restriction, and increased consumption of fruits (e.g. 23 servings), vegetables (e.g. 23 servings), and low-fat dairy products
Optimisation of psychosocial status	Provide cognitive behavioural therapy if indicated Offer/facilitate self-management and empowerment Provide education
Facilitation of return to work	Discuss and plan personalised occupational re-integration
(Re)Consideration of driving ability	Discuss and plan how to safely drive vehicles
Optimise sleep quality	Start-up continuous positive airway pressure during sleeping, aerobic exercise training and dietary intervention. If insomnia is co-existent, the addition of certain drugs can be considered, such as γ-aminobutyric-acid (GABA) A receptor modulators or orexin receptor antagonists, as well as cognitive behavioural therapy.
Optimisation of glycaemic control	Metformin in the highest (max 3000 mg) tolerated dose (not if GFR <30 ml/min) Adjust diet Exercise/physical activity

Reduce dose/discontinue hypoglycaemia inducing medication
In patients on insulin: reinforce blood glucose self-monitoring
Replace with medication without increased risk of hypoglycaemia
Check use of insulin (formulation and dose)

Impaired glucose tolerance	**Newly diagnosed T2DM**	**T2DM, oral medication**	**T2DM, insulin**
Aim for weight reduction Consider GLP-1-agonists in patients with marked obesity	SGLT-2-inhibitors (SGLT2i) GLP-1-agonists (GLP1a) DPP-4-inhibitors (DPP4i) *In patients with CKD consider GLP1a > DPP4i > repaglinide* *In patients with systolic HF consider SGLT2i > GLP1a*	If HbA1c ≥7,5%: treatment intensification using medication without increased risk of hypoglycaemia	Assess risk of hypoglycaemia Reduce insulin dose (wherever possible) Eventually replace with/add on an insulin sparing medication (SGLT2i, GLP1a, DPP4i)

Set/check individualizedHbA1c-target

- HbA1c ≥7,5 % – treatment intensification with a second oral medication
- HbA1c ≥7,5 % – if already on dual therapy, consider a third oral medication
- HbA1c >9,0 % – consider insulin (eventually add on to oral medication)

Recommended combination therapy (stepwise approach)

- Dual therapy: metformin + SGLT2i/GLP1a or DPP4i
- Triple therapy: metformin + SGLT2i + GLP1a or DPP4i
- Triple therapy: metformin + GLP1a or DPP4i + SGLT2i

Partly based on refs 86 and 87.

Figure 1 Personal setting within the empowerment approach

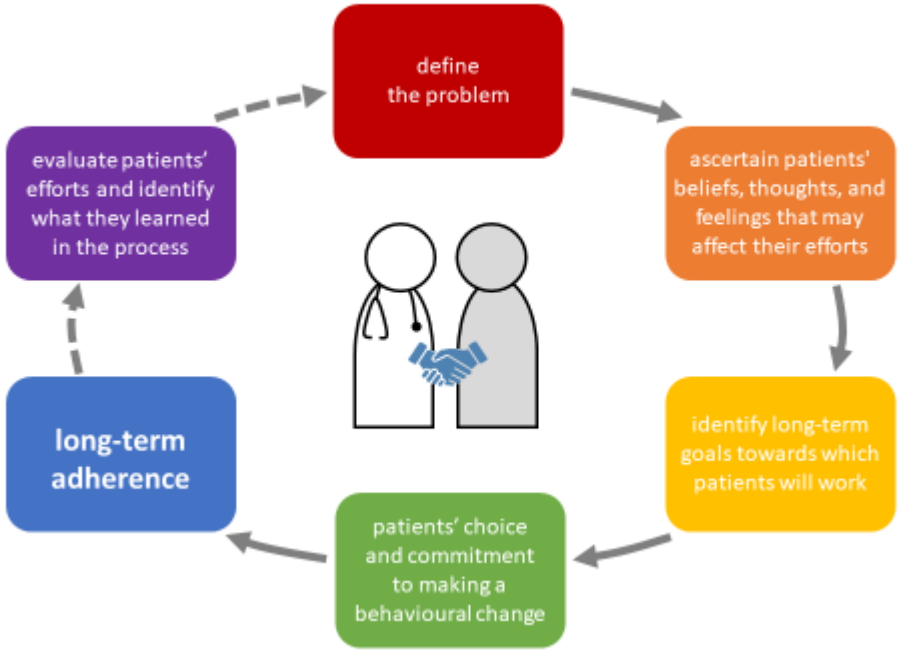
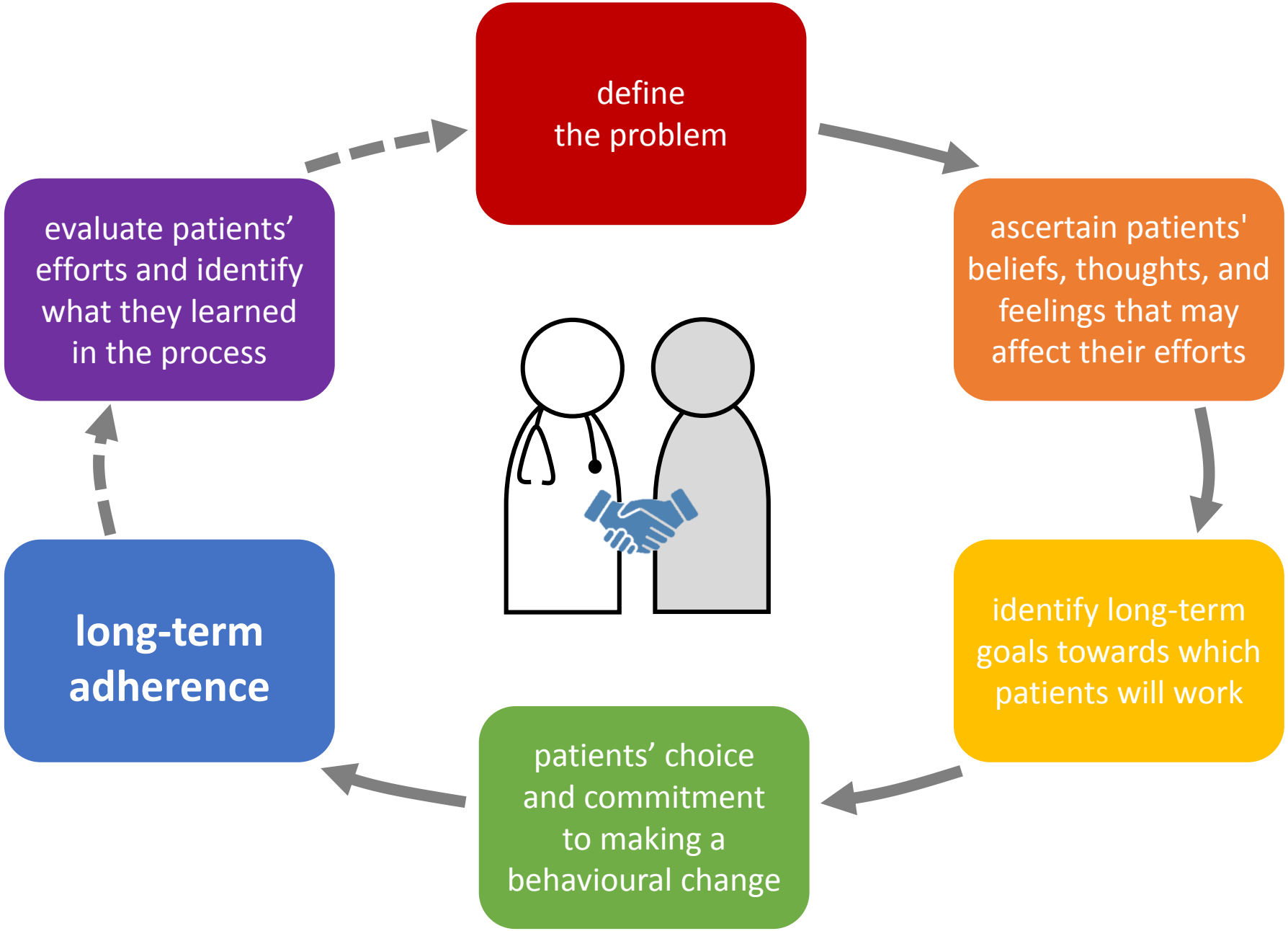


Figure 1


define
the problem
ascertain patients' beliefs, thoughts, and feelings that may affect their efforts
identify long-term goals towards which patients will work
patients' choice and commitment to making a behavioural change
long-term adherence
evaluate patients' efforts and identify what they learned in the process