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REVIEW ARTICLE

Exercise therapy in Type 2 diabetes

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Abstract Structured exercise is considered an important cornerstone to achieve good glycemic control and improve cardiovascular risk profile in Type 2 diabetes. Current clinical guidelines acknowledge the therapeutic strength of exercise intervention. This paper reviews the wide pathophysiological problems associated with Type 2 diabetes and discusses the benefits of exercise therapy on phenotype characteristics, glycemic control and cardiovascular risk profile in Type 2 diabetes patients. Based on the currently available literature, it is concluded that Type 2 diabetes patients should be stimulated to participate in specifically designed exercise intervention programs. More attention should be paid to cardiovascular and musculoskeletal deconditioning as well as motivational factors to improve long-term treatment adherence and clinical efficacy. More clinical research is warranted to establish the efficacy of exercise intervention in a more differentiated approach for Type 2 diabetes subpopulations within different stages of the disease and various levels of co-morbidity.

Keywords Exercise prescription · Pathophysiology · Type 2 diabetes · Treatment adherence · Complications · Safety

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Type 2 diabetes: a modern, but not modest, health threat

Already in the first century, the ancient Greek physician *Aretaeus of Cappadocia* described the term diabetes (*diabaínein*) as '…a wonderful affection, not very frequent among men…' [1]. However, it was not until 1675 that Thomas Willis, an English physician, added the word *mellitus*, as a reference to the sweet taste of a diabetes patient's urine. Whether this condition referred to Type 1 (autoimmune disease) or Type 2 (relative insulin deficiency) diabetes mellitus is unknown. However, it lasted another 200 years before the French physician Lanceraux made the distinction between diabetes in lean and obese men: *diabete gras* and *diabete maigre* [2]. In the 1930 s, the diabetologist Joslin c.s. noted that the incidence of diabetes in lean individuals was relatively constant in each decade of life, while diabetes in the obese was related to age [3]. Already in those days he attributed the increasing prevalence of diabetes in the 1930 s to increasing obesity [3].

The sharp rise in Type 2 diabetes prevalence during the second half of the twentieth century first occurred in developing countries, parallel to the rapid socio-economic development and dramatic changes in lifestyle in these countries [4]. In traditionally more affluent societies, the prevalence of Type 2 diabetes showed a clear rise in the early 1990 s [5, 6], almost parallel to the increase in the prevalence of obesity [7]. Although genome-wide association studies have revealed that certain single nucleotide polymorphisms (SNPs) related to beta-cell function predispose to the development of Type 2 diabetes [8–11], clinical characteristics such as obesity and lack of physical activity are regarded as the most important risk factors, both independently associated with diabetes and diabetes-related co-morbidities [12–14].

According to the International Diabetes Federation (IDF), the disease now affects 246 million people worldwide and is expected to affect some 380 million by 2025, representing as much as 7.1% of the global adult population [15]. As such, the associated health burden in terms of cardiovascular disease, kidney failure, blindness, amputations and premature death will increase progressively, unless more effective primary and secondary pharmaceutical and/or lifestyle interventional strategies become more widely available.

Metabolic disturbances associated with Type 2 diabetes

Hyperglycemia in the insulin-resistant state

The main feature of Type 2 diabetes is formed by the relative resistance to peripheral insulin action, resulting in impaired glycemic control. According to WHO criteria, someone is considered to have Type 2 diabetes if fasting plasma glucose levels are equal or above 7.0 mmol/l or if 2 h following an 75 g oral glucose tolerance test (OGTT) plasma glucose concentration rises $\geq$ 11.1 mmol/l [16]. Although still subject of intense debate, these diagnostic cut-off points have been based on epidemiological studies that have examined the risk of developing retinopathy over a range of plasma glucose levels [17]. However, even in 'high-risk' obese subjects without blood glucose abnormalities during an OGTT, real-life hyperglycemia was already detectable for almost 14% throughout the day [18]. This indicates that even in the absence of formal intermediate hyperglycemia, as defined by the IDF/World Health Organisation (WHO) [17], so-called post-prandial hyperglycemic spikes are probably an early feature of the insulin-resistant state. The difficulties to manage this post-prandial hyperglycemia were exemplified in two of our most recent continuous glucose monitoring studies in Type 2 diabetes patients [19, 20]. In these studies, we show that hyperglycemia is experienced for as much as 8–13 h/day under strict dietary standardization, but otherwise free-living conditions. A strong correlation was observed between the prevalence of hyperglycemia and HbA_{1c} content in the Type 2 diabetes patients, but even patients with apparent acceptable glycemic control ($HbA_{1c} \leq 7.0\%$) were still experiencing hyperglycemia for 11 $\pm$ 0.9 h throughout the day [20]. It has been suggested that these hyperglycemic blood glucose excursions may contribute to the development of macro- and/or microvascular complications in prediabetic states [21, 22]. However, many different pathophysiological pathways may be simultaneously activated (see below). Therefore, its separate contribution to macro- or microvascular complications is currently unknown.

Hyperglycemia and beta-cell failure

The pathophysiological basis for aforementioned post-prandial hyperglycemic spikes lies in a disturbed first-phase insulin response of the pancreatic beta-cell, which normally suppresses endogenous glucose production. Subsequently, beta-cell function further deteriorates and endogenous insulin production is insufficient to fully compensate for the peripheral insulin insensitivity in muscle, liver and/or fat cells [23]. Although the susceptibility for a glucose-stimulated insulin secretory defect has a genetic origin [24], it only becomes apparent in the context of peripheral insulin resistance [25, 26]. Once the beta-cell fails, post-prandial hyperglycemia may induce large amounts of reactive oxygen species (ROS) that can cause further damage to cellular components of insulin production and induce apoptosis in beta-cells [27]. In addition, lipotoxicity [28] and possibly also amyloid deposits [29] may contribute to further deterioration of beta-cell function. Certain drugs, such as sulfonylurea (SU) derivatives, are still widely applied to stimulate glucose-dependent insulin release. Although these drugs temporarily improve glucose homeostasis, they do not restore beta-cell function and may accelerate loss of long-term glycemic control [30]. In a quest to improve long-term diabetes outcome, a whole new line of drugs has become available that try to mimic the release of specific gut hormones [31]. These incretin mimicking drugs have been shown to improve islet-cell function, and both fasting and post-prandial glycemic control [32–36]. Nevertheless, more long-term efficacy of incretin mimicking drugs should be awaited before their clinical value as a mono- or add-on therapy can be established [37–39]. Besides medication, dietary measures such as slowly digestible carbohydrates [40] and the application of amino acid induced insulin secretion [41–43] and/or high protein diets [44] can modulate post-prandial hyperglycemia as well. As such, structured lifestyle interventions combined with metformin remain the first treatment of choice. If oral dose adjustment is not sufficient to meet therapeutic targets, early exogenous insulin therapy should be initiated [45].

Obesity and insulin resistance

Over the past three decades, the etiology of insulin resistance and beta-cell dysfunction has been subject to intense study [23, 46]. Obesity, as a result of inactivity in combination with overeating, plays a key role in the development of pancreatic beta-cell dysfunction as well as insulin resistance. Several mechanisms mediating this interaction have been identified. It is now well established that a number of circulating hormones, cytokines, and metabolic fuels, such as non-esterified fatty acids (NEFAs), are being

released by adipose tissue and can modulate insulin action. An increased mass of stored triglyceride, especially in visceral or deep subcutaneous adipose depots, leads to large adipocytes that are themselves resistant to the ability of insulin to suppress lipolysis. This results in increased release and circulating NEFA and glycerol levels. Both aggravate insulin resistance in skeletal muscle [47, 48] and the liver [49, 50].

Adipokines and chronic inflammation

Besides increased concentrations of NEFA, expanded visceral adipose tissue also releases pro-inflammatory cytokines [e.g., tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1)]. Pathways regulating suppression of cytokine signaling proteins [51] and inducible nitric oxide synthase [52] may be involved in mediating cytokine-induced insulin resistance. Secretion of these cytokines, particularly MCP-1 by adipocytes, endothelial cells and monocytes, increases macrophage recruitment and subsequently amplifies cytokine-induced insulin resistance in a feed forward manner [53]. TNF-α and IL-6 act through classical receptor-mediated processes, resulting in upregulation of potential mediators of systemic inflammation that can lead to insulin resistance.

More recently, a new adipokine, named retinol binding protein-4, has been discovered that is directly linked to the level of obesity-induced insulin resistance, both in cross-sectional [54, 55] and longitudinal studies [54, 56–58]. Another adipokine, subject to intense study, is adiponectin. Low adiponectin levels have been correlated with visceral obesity and whole-body insulin sensitivity [59]. This fat cell hormone acts as an insulin sensitizer, inhibiting triglyceride formation in liver and stimulating fatty acid oxidation in muscle in an AMP-activated protein kinase (AMPK) and peroxisome proliferators activated receptor alpha (PPAR-α)-dependent way [60]. Despite their apparent importance in the insulin resistance syndrome, aforementioned adipokines are just examples of a family of adipocyte-derived factors that modulate insulin resistance and systemic inflammation. Besides new adipokines, also certain myokines now appear to affect insulin sensitivity and inflammatory responses [61]. As such, the list of insulin (de)sensitizing proteins and cytokines is still far from complete.

Ectopic fat storage causes insulin resistance in muscle and liver

In the context of a low habitual physical activity level and low oxidative capacity, excess intramyocellular lipid (IMCL) storage has been associated with skeletal muscle insulin resistance [62]. In accordance, intervention studies indicate that insulin sensitivity can change independently of IMCL contents [63–68]. Indeed, not IMCL content itself, but rather the peroxidation of inactive pools of IMCL and intra-cellular fatty acids may explain the apparent correlation between IMCL content and insulin resistance [69]. In addition, intra-cellular lipid metabolites such as diacylglycerol (DAG), long chain fatty-acyl CoA and ceramides have been shown to interfere with the insulin signaling pathway [70]. These metabolites activate a protein kinase leading to the phosphorylation of serine/threonine sites on the insulin receptor substrate 1, subsequently hampering glucose transport activity and insulin-stimulated myocellular glucose uptake [71].

Ectopic fat storage in hepatocytes, so-called intrahepatic lipids (IHL), has also been related to the development of hepatic insulin resistance [72] and hepatic inflammation, initiating non-alcoholic fatty liver disease [73]. In rodents, 3 days of a high-fat diet induces hepatic insulin resistance, while no significant changes in fat content in muscle or visceral tissue could be detected [74]. Experimental research now suggests that hepatic insulin resistance arises from DAG-induced activation of protein kinase Cε, which directly binds to and inhibits insulin receptor tyrosine kinase activity [75]. As such, fat-induced hepatic insulin resistance and hepatic inflammation are considered important etiological factors in the development of systemic insulin resistance.

Glucolipotoxicity and long-term complications in Type 2 diabetes

Besides inhibiting intra-cellular insulin signaling, aforementioned metabolic disturbances in glucose and fat metabolism increase the formation of Amadori-glycated proteins and advanced glycation end-products (AGE) impairs receptor function for AGE (RAGE) and increases exposure to ROS in almost any organ system [76–78]. Chronic exposure to Amadori products, AGE and ROS, so-called glucolipotoxicity, can cause vasculopathy [76], glomerulopathy [79, 80] and potentially also induce nerve cell damage [81]. In accordance, hyperglycemia-induced AGE and ROS formation provide a unifying model for the high incidence of microvascular disease, retinopathy, nephropathy [80, 82], and possibly also neuropathy [83] prevalent in long-term Type 2 diabetes [84]. In accordance, certain pharmaceutical [85, 86], nutritional [81] and/or exercise interventions [87–89] that modulate AGE, RAGE and/or ROS formation have been reported to improve insulin sensitivity in experimental rodent models. In humans, both structured exercise and alpha lipoic acid have been suggested to reduce neuropathic symptoms [90, 91]. However, it is unknown whether such a combined and

long-term approach can modulate glucolipotoxicity and prevent diabetes-related complications [92].

Reduced oxidative capacity and mitochondrial function in insulin-resistant states

It has been well established that most patients with Type 2 diabetes have a significantly lower oxidative capacity (VO_{2peak}) than age-matched controls [93–95]. Whether this lower oxygen uptake capacity is attributed to a low habitual physical activity level, reduced mitochondrial content or an intrinsic mitochondrial defect is a topic of intense debate [96–109]. Recent experimental evidence indicates that mitochondrial respiration is not abnormal when normalized for mitochondrial content [104, 110], which implies that low habitual physical activity level and/or cardiovascular dysfunction may explain the generally deconditioned state in the Type 2 diabetes patient [97, 106]. Although the debate will probably continue whether the lower oxidative capacity represents either cause or consequence [97, 111], future exercise studies should be aimed at answering the question whether a substantial long-term increase in physical activity level by implementing a well-structured exercise intervention program can reverse the deconditioned state of Type 2 diabetes patients and improve the metabolic profile.

Hyperinsulinemia, autonomic dysregulation and cardiovascular disease

Above-mentioned metabolic disturbances in oxidative capacity, glucose homeostasis and fat metabolism not only affect systemic insulin resistance, but also appear to influence long-term energy homeostasis [112]. Animal studies indicate that long-term energy balance is coordinated through the combined action of insulin and leptin in the brain [113]. Interestingly, these studies have suggested that insulin action in certain hypothalamic centers reduces food intake while increasing sympathetic nervous system (SNS) outflow to brown adipose tissue to produce heat from fatty acid oxidation as a mechanism to increase energy expenditure [113]. As such, these chronically elevated insulin [114, 115] and leptin concentrations [116] further contribute to obesity-associated hypertension through activation of the SNS and release of catecholamines in the basal state [117]. Indeed, early-stage insulin resistance appears to cause sympathovagal imbalance in normoglycemic, insulin-resistant offspring of Type 2 diabetes patients [118]. Also in more advanced insulin-resistant states, aforementioned increases in sympathetic tone have been associated with changes in cardiac and vascular function that lead to hypertension, left ventricular dysfunction and/or cardiac autonomic neuropathy [119]. Such changes set the stage for arrhythmia, silent infarction and sudden death [120, 121]. Because potentiation of atherogenesis and cardiac dysfunction occurs in the presence of early diabetic symptoms as well as in the established disease [122, 123], early implementation of strategies to reduce cardiovascular risk factors and to attenuate diabetes progression may help to improve long-term outcomes for at-risk individuals. Such interventions may include well-established pharmaceutical treatments for hypertension and dyslipidemia, dietary modulation and/or energy restriction, weight loss, and exercise intervention [121].

Exercise as opposed to pharmaceutical therapy in Type 2 Diabetes

Over the past 5 years, both lipid lowering therapy [124, 125] and blood pressure lowering therapies [126, 127] have been proven effective to improve cardiovascular outcome in Type 2 diabetes patients. The effectiveness of these drugs may explain why the additive benefits of intensive glycemic control are more difficult to demonstrate, even in large and long-term clinical trials such as ACCORD, ADVANCE and VADT [128]. Nevertheless, much effort is currently put into the discovery of novel pharmacological solutions that may further improve metabolic control and prevent diabetes-related co-morbidities. Although the combination of intense blood pressure and blood glucose lowering therapy has been shown to reduce (microvascular) complications [129–131], stringent application of multiple blood glucose lowering drugs does not necessarily result in a further reduction of macrovascular events [130, 132–135]. Especially, in more advanced Type 2 diabetes, more intensive blood glucose lowering strategies may have counter-balancing consequences for cardiovascular disease, such as hypoglycemia, weight gain, or other metabolic changes [128]. Although results of long-term intervention studies are underway, the current increase in Type 2 diabetes incidence and concomitant cardiovascular co-morbidities may benefit more from therapeutic strategies entailing structured exercise interventions with [136–138] or without [137, 139, 140] dietary modulation and/or oral blood glucose lowering medication [136, 141, 142].

Does exercise reverse chronic inflammation?

In insulin-resistant populations, several adipokines, such as leptin and adiponectin, as well as muscle contraction-induced factors, so-called myokines (i.e., IL-6), have been shown to modulate insulin resistance and inflammatory status [143]. Although there is consensus that weight loss is associated with an increase in adiponectin and decreased levels of leptin, TNF-α and high sensitivity C-reactive

protein (hsCRP) [144, 145], studies on the medium-term effects of exercise without concomitant weight loss are limited and produce somewhat inconsistent results [146–148]. Nevertheless, the finding in longitudinal studies that regular exercise training induces a reduction in hsCRP indicates that physical activity may help to suppress systemic low-grade inflammation [149–151]. An experimental study using endotoxin-induced chronic inflammation showed that physical exercise directly inhibits endotoxin-induced TNF-α production in humans, most likely through IL-6 release from exercising muscle [152]. Clearly, more long-term intervention studies are warranted to see to what extent the proposed anti-inflammatory effect of exercise training modulates peripheral insulin sensitivity in Type 2 diabetes patients.

Exercise as an antihypertensive agent

Besides improving glycemic control, a recent meta-analysis showed that structured exercise intervention studies in non-insulin-dependent Type 2 diabetes patients reduce systolic blood pressure with −4.16 mmHg (95% CI −9.46 to 1.14) [153]. Such reductions in mean arterial blood pressure are clinically relevant and are similar to the effects of add-on blood pressure lowering therapy using a combination of an ACE inhibitor and thiazide diuretic [126]. Although both resistance- and endurance-type exercise seem to reduce mean arterial blood pressure to a similar extent in Type 2 diabetes populations [154], further research is needed to explore their separate contribution and way of action in different insulin-resistant (sub)populations.

Does exercise therapy improve lipid metabolism?

Although fasting blood lipid profiles in Type 2 diabetes populations have been shown to improve following long-term exercise interventions with [136, 137, 155] or without dietary restriction [142, 156], recent exercise intervention studies in Type 2 diabetes patients showed few to no additional benefits on top of lipid lowering agents [146, 157]. The latter may be related to the lack of a simultaneously diet-induced weight loss [158], a compensatory decline in daily physical activity level [159] or the fact that in most Type 2 diabetes populations baseline total-cholesterol, LDL-cholesterol and triglycerides levels were already 15–35% lower in comparison with aforementioned 'exercise-only' intervention studies [142, 156]. Nevertheless, in accordance with earlier reports (for references see [160]), detailed body composition analyses using dual energy X-ray absorptiometry (DEXA) and MRI revealed that, despite an unaltered body weight, 5–6 months of combined endurance and resistance type of exercise training is able to induce regional changes in fat and lean muscle mass in obese Type 2 diabetes patients [146, 157]. Indeed, several lines of research [68, 161–163] now indicate that exercise interventions of sufficient volume and intensity may also modulate post-prandial lipid handling. Interestingly, higher levels of habitual physical activity were reported to be strongly associated with reduced IHL content [164], while intervention studies using dietary or exercise intervention report somewhat contrasting results [165, 166], supporting the idea that nutritional modulation may be more effective in reducing IHL content. Future studies should aim to unravel the mechanisms of action and modulating effects of different modes of exercise training on post-absorptive and post-prandial lipid handling in Type 2 diabetes patients [167]. Ideally, dietary intake and hormonal responses should be monitored to differentiate between the impact of isocaloric exercise bouts of different volumes and intensities on both post-prandial glycemia and lipidemia.

Exercise prescription in Type 2 diabetes

Current guidelines from the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) or the American College of Physicians (ACP) all acknowledge the therapeutic strength of exercise intervention [45, 168–170]. The ADA states that '*to improve glycemic control, assist with weight maintenance, and reduce risk of CVD, at least 150 min/week of moderate-intensity aerobic physical activity is recommended and/or at least 90 min/week of vigorous aerobic exercise, … distributed over at least 3 days/week and with no more than 2 consecutive days without physical activity.' Since 2006, the ADA guidelines explicitly mention and recognize that 'in the absence of contraindications, people with Type 2 diabetes should be encouraged to perform resistance exercise 3 times a week, targeting all major muscle groups, progressing to 3 sets of 8–10 repetitions at a weight that can not be lifted more than 8–10 times*' [169]. However, these clinical guidelines generally do not include detailed information on the preferred type and intensity of exercise that should be applied to maximize the benefits of exercise for different subgroups of Type 2 diabetes patients and further research is needed.

Acute versus more longer term exercise responses

Both a single bout of endurance- [171] and resistance-type exercise [172, 173] have been shown to improve whole-body insulin sensitivity and/or oral glucose tolerance. Therefore, both types of exercise are of therapeutic use in an insulin-resistant state [154]. The acute effects of exercise on skeletal muscle insulin sensitivity are attributed to the prolonged activation of the skeletal muscle glucose

transporter system [174, 175], depletion of liver and muscle glycogen stores [174, 176–178], and/or increased skeletal muscle blood flow following the cessation of exercise [179]. The glucoregulatory benefits of either type of exercise training are represented by the sum of the effects of each successive bout of exercise [178]. In addition, more prolonged exercise training is accompanied by a more structural adaptive response. For instance, endurance training may upregulate mitochondrial enzyme activity in skeletal muscle and subsequently improve whole-body oxygen uptake capacity [180, 181]. However, the latter response may be attenuated in more advanced and older Type 2 diabetes patients [146, 182–185]. On the other hand, resistance-type exercise is able to induce muscle protein synthesis [186, 187] and, as such, represents an effective interventional strategy to increase lean body mass in both early [188] and advanced stage Type 2 diabetes patients [146, 189].

Exercise modality

In terms of physiological adaptations, apparent differences exist in the long-term adaptive response to endurance- or resistance-type exercise training. Prolonged endurance-type exercise training has been shown to improve insulin sensitivity in both young [190], elderly [191] and/or insulin-resistant subjects [178, 192–194]. The latter is attributed to the upregulation of skeletal muscle GLUT-4 expression, improved nitric oxide-mediated skeletal muscle blood flow and concomitant induction of weight loss [195], reduced hormonal stimulation of hepatic glucose output [196] and the normalization of blood lipids [197]. Long-term resistance-type exercise interventions have also been reported to improve glucose tolerance [157] and/or whole-body insulin sensitivity [172, 188, 198]. Besides the consecutive effects of each successive bout of exercise in acutely reducing glycogen stores [173, 199], resistance-type exercise training has been associated with a substantial gain in skeletal muscle mass, thereby improving whole-body glucose disposal capacity [172]. Besides the attenuation of the loss of muscle mass with aging, resistance-type exercise training also improves muscle strength and functional capacity, thereby allowing a healthier, more active lifestyle. Some studies report even greater benefits of resistance as opposed to endurance-type exercise training on glycemic control and insulin sensitivity in long-standing Type 2 diabetes patients [182]. However, recent evidence indicates that both types of exercise interventions have similar therapeutic strength in uncomplicated Type 2 diabetes patients [157]. Its combined application is probably more effective, especially in patients with HbA_{1c} levels $\geq$ 7.5% [157]. As such, it has been firmly established that both endurance- and resistance-type exercise training can be applied to improve metabolic control and quality of life in Type 2 diabetes patients [154].

Energy expenditure determines therapeutic strength of exercise

When prescribing exercise as treatment for an individual diabetes patient, it is important to estimate total energy expenditure that can be achieved through the recommended type of exercise. Several studies have shown that the energy equivalent of an endurance exercise bout represents the major determinant of the exercise-induced changes in glucose homeostasis [200–202]. To obtain durable metabolic improvements through exercise, the absolute minimum dose of weekly energy expenditure should entail 4.2 MJ ($\approx$1,000 kcal) [202], but for optimal results weekly energy expenditure should probably be twice as high [202, 203]. Therefore, a lesser exercise intensity should be compensated for by an increase in exercise duration.

Exercise in advanced stage Type 2 diabetes patients

Another expanding Type 2 diabetes subpopulation is formed by the long-standing, insulin treated, Type 2 diabetes patients [204]. These patients generally suffer from severe exercise intolerance due to the combination of low oxidative capacity [205], micro- and macrovascular disease [206, 207], neuropathy-related muscle weakness [207–210] and/or sarcopenia [211]. As generic exercise intervention programs are too demanding for most of these patients, it is of utmost importance to implement intermediate exercise intervention programs. Such intermediate programs are needed to bring the patient to a level at which they are able to participate in more generic diabetes intervention programs. Such intermediate programs should implement short, relatively high-intensity, exercise bouts applied in an intermittent fashion with the intention to increase muscle strength and functional performance. These so-called short 'ins-and-outs' exercises do not produce feelings of dyspnoea or discomfort and have been proven safe and effective in cardiac patients [212, 213]. The efficacy and safety of such intermediate programs in long-standing Type 2 diabetes patients with high cardiovascular risk profile was recently confirmed in a small scale study by our research group [146]. Nevertheless, more larger scale trials are warranted since exercise intervention studies generally exclude this specific Type 2 diabetes subpopulation.

Interaction between exercise and blood glucose lowering medication

Type 2 diabetes is characterized by resistance to the actions of insulin in the presence of defects in insulin

secretion. Absolute insulin levels vary with the severity of the disease; early stages tend to be characterized by a compensatory hyperinsulinemic state, but progressive beta-cell failure eventually occurs in most patients, leading to low basal fasting insulin levels [214]. Circulating insulin plays a critical role in regulating hepatic glucose output during exercise and has been shown to modulate peripheral glucose uptake during exercise and recovery [215–217]. Depending on the remaining insulin secretory capacity, the use of insulin secretagogues [183, 218, 219], the type of exogenous insulin used [220], as well as the level of peripheral insulin resistance, the glucose lowering effect of single bout of resistance or endurance bout of exercise may vary considerably. Moreover, as discussed in aforementioned paragraphs, the type, intensity and duration of exercise may result in different glycemic responses [182]. In accordance, failure to adequately adjust medication and/or carbohydrate supplementation can result in inappropriate swings in blood glucose levels, either too low or too high. In accordance with Type 1 diabetes patients [221, 222], antecedent hypoglycemia may also result in hypoglycemia unawareness in Type 2 diabetes [223] However, circumstances that result in inappropriate elevations in blood glucose levels (such as excessive carbohydrate supplementation or too large reductions in insulin dosage) also have long-term adverse implications [224–226]. Knowledge of the factors that affect glucose metabolism is critical for designing strategies to minimize inappropriate swings in blood glucose control related to exercise. As such, more research is required to better understand the complex interaction between the different exercise modalities and blood glucose lowering drugs. Nevertheless, in long-standing insulin-treated Type 2 diabetes patients, we have shown that frequent self-monitoring of blood glucose levels before and after each exercise bout is safe and feasible and results in improved glycemic control [146, 227].

Prevention of overload injuries in exercise training

Many patients with Type 2 diabetes experience not only cardio-respiratory [205], but also musculoskeletal deconditioning [207–210]. Obesity- and diabetes-related subclinical osteoarthritis [228, 229] on top of neuropathy-related peripheral muscle weakness [210] have shown potential reasons for overload injuries and subsequent drop out [157, 230]. In future, endurance type of exercise interventions, certain overuse injuries, might be prevented through adaptations in biomechanical loading on feet and lower extremities [231–234] as well as through the application of resistance-type exercise aimed at strengthening myotendinous structures. The latter concept is supported by resistance-type exercise studies that report long-term program adherence between 68% [235] and 72% [236], without concomitant musculoskeletal overuse injuries. Nevertheless, more long-term tailored exercise intervention studies are needed to assess the usefulness of a differentiated approach.

Long-term program adherence in therapeutic exercise intervention programs

Long-term program adherence may vary between as much as 10 and 80% [142, 230, 235, 237, 238]. Therefore, motivational factors and time constraints should be considered to prevent long-term drop out rate. In accordance, future exercise interventions might benefit from psychological strategies such as motivational interviewing [239] or booster sessions [240–242]. Furthermore, restricting the travel time toward a training facility [243] and providing the patient with feedback on physical activity levels [244] may improve long-term adherence as well. Although aforementioned approaches are likely to reduce program drop out throughout the course of a supervised exercise program, scientific studies are warranted that combine aforementioned approaches.

Safety considerations before initiating exercise therapy

Before exposing patients with Type 2 diabetes to more vigorous exercise programs, the ADA and U.S. Preventive Services Task Force recommend exercise testing for silent myocardial ischemia (SMI) if 10-year cardiovascular risk exceeds 10% [169, 245]. Cardiac dysfunction [246] and SMI are estimated to be present between 6 and 22% [247] of the Type 2 diabetes patients, with cardiac autonomic dysfunction, disease duration and male gender being the best predictors for SMI [247]. Moreover, poor physical fitness [248], scintigraphy abnormalities [249], diabetic retinopathy [249] and an advancing age >60 years [250] in combination with the traditional cardiac risk factors also represent good predictors for the likelihood of a cardiac event. The UKPDS Risk Engine v2.0 (available free of charge at www.dtu.ox.ac.uk) may be of help to calculate an individual patient's risk for coronary heart disease [251]. Although arbitrary, the UKPDS Risk Engine indicates that ECG stress testing in Type 2 diabetes is useful in most patients with >2 cardiovascular risk factors, in middle-aged patients with a diabetes duration >5 years, as well in elderly patients >70 years. Although a stress ECG is not the most sensitive diagnostic tool to detect SMI [252] and predict coronary events [253], other research indicates that it is still the most cost-effective tool when trying to minimize the risk of a coronary event [254]. In case SMI is expected, more sensitive diagnostic tests such as myocardial perfusion scintigraphy [255], electron beam

computerized tomography [256] and/or coronary angiography [257] should be considered before more vigorous exercise is prescribed. Even in the absence of SMI, a stress test will detect chronotropic incompetence [258] as well as exercise-related hypertension and provide more objective information on the individual fitness level [205]. Ideally, this information should be used to further tailor an exercise program for the individual patient with Type 2 diabetes [259].

Are structured exercise interventions cost-effective?

Previous lifestyle intervention studies indicate that long-term health benefits mainly depend on long-term program adherence as well as the level of motivation, coaching and supervision [235, 236, 260–263]. Depending on the level and duration of exercise supervision and dietary guidance, direct health care costs vary between ~400 and ~2,000 euro per individual participant [230, 264]. Although the cost-effectiveness of such (theoretical) interventions is more favorable in groups with high-risk populations compared with mixed populations [264], lifestyle intervention is considered highly cost-effective for the prevention of Type 2 diabetes [264–270]. As far as we know, no study has been published on the cost-effectiveness of similar lifestyle interventions in patients that have already developed Type 2 diabetes. However, direct costs of either a brisk walking or medical fitness program in Type 2 diabetes seem to be within the aforementioned range [230]. Although we could not determine the cost-effectiveness in the latter study, several larger scale multidisciplinary lifestyle interventions (e.g., the 'BeweegKuur' in the Netherlands [265] and the LookAHEAD study in the USA) [271] are underway. These studies should provide more insight into the cost-effectiveness of well-structured exercise interventions as a part of a multidisciplinary Type 2 diabetes care program consisting of medication, diet and exercise.

Future research

Based on a thorough review of the literature, we recently have proposed a more differentiated approach for exercise therapy in Type 2 diabetes [259]. However, before more differentiated exercise prescription guidelines can be used as clinical treatment guidelines, its medium to long-term efficacy should first be evaluated in more large-scale randomized controlled clinical trials. By definition, most randomized clinical trials completely disregard a patient's free choice or preference for a specific type of exercise. In fact, potentially interested patients may feel excluded, while others may find it difficult to adhere to a non-preferred type of exercise intervention. Therefore, to simulate a more realistic type of health care environment, randomized clinical trials should be performed in which subjects can choose from different exercise programs. Moreover, for each type of exercise intervention, control groups should perceive a similar amount of supervision and guidance. Such an approach is likely to result in higher adherence rates and will provide us with more definitive answers on how to implement exercise therapy more effectively in the chain of diabetes health care.

On top of these clinical and methodological issues, recent studies suggest that genetic factors [272, 273] should be considered to determine which subgroup Type 2 diabetes patients is likely to benefit the most from tailored exercise interventions. However, to unravel the proposed genetic influences, well-defined exercise intervention studies with a high compliance rate will be essential. Although such mechanistic studies often do not represent a realistic clinical approach, these studies should provide more insight into the pathomechanics of exercise intervention in Type 2 diabetes patients with a different genetic and/or co-morbidity profile. The combined approach of mechanistic and clinical implementation studies is expected to lead toward more specific and evidence-based exercise prescription guidelines that can optimize long-term therapeutic outcome at an affordable socio-economic cost price. Given the size and expanding nature of the Type 2 diabetes pandemic, the field of clinical diabetes research has the scientific, socio-economic and medical ethical obligation to contribute to such studies and move the field of diabetes care into action.

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