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Do diabetes and obesity affect the metabolic response to exercise?

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Abstract

Purpose of review

Exercise is recommended as therapeutic intervention for people at risk to develop type 2 diabetes to prevent or treat the disease. Recent studies on the influence of obesity and type 2 diabetes on the outcome of exercise programs are discussed.

Recent findings

Poor glycemic control before an intervention can be a risk factor of reduced therapeutic benefit from exercise. But the acute metabolic response to exercise and the transcriptional profile of the working muscle is similar in healthy controls and type 2 diabetic patients, including but not limited to intact activation of skeletal muscle AMPK signaling, glucose uptake and expression of PGC1α. The increase in plasma acylcarnitines during exercise is not influenced by type 2 diabetes or obesity. The hepatic response to exercise is dependent on the glucagon/insulin ratio and the exercise-induced increase in hepatokines such as FGF21 and follistatin is impaired in type 2 diabetes and obesity, but consequences for the benefit from exercise are unknown yet.

Summary

Severe metabolic dysregulation can reduce the benefit from exercise, but the intact response of key metabolic regulators in exercising skeletal muscle of diabetic patients demonstrates the effectiveness of exercise programs to treat the disease.

Keywords (3-5)

Acylcarnitines, AMPK, hepatokines, hyperglycemia, metabolic control

Introduction

Health benefits of exercise for type 2 diabetes patients are for a long time well-acknowledged and regular physical activity is recommended as therapeutic intervention to prevent and treat chronic disorders including obesity, insulin resistance and type 2 diabetes [1]. Exercise initiates transcriptional and (post)translational mechanisms that increase the capacity and efficiency of the organism to utilize and supply fuels thereby counteracting the insufficient and disturbed capacity to store and oxidize glucose and lipids in chronic metabolic disorders linked to obesity and insulin resistance [2].

Great effort is being undertaken to provide tailored motivating exercise programs for people at high risk to develop type 2 diabetes and to optimize the efficacy of exercise as therapeutic intervention for diabetic patients. In the last years, special attention is paid to high-intensity interval training (HIIT) as an alternative intervention to improve metabolic control in type 2 diabetic patients. The studies validated improvement of glycemic control after HIIT [3▪-6▪] and Jelleyman et al. reviewing existing literature came to the conclusion that HIIT can be superior to continuous exercise for type 2 diabetic patients or people at risk to develop diabetes [7]. Cassidy et al. also concluded that HIIT has a small but significant benefit on peripheral insulin sensitivity, but may be superior to moderate intensity continuous training in terms of cardiorespiratory fitness [8]. Thus, HIIT is clearly a valuable alternative training program in the treatment of type 2 diabetes and adherence in free-living conditions need to be evaluated.

Further recent studies investigated the exercise response of specific aspects potentially related to metabolic disturbances in type 2 diabetes and obesity. Kruse et al. investigated markers of autophagy, since abnormal protein metabolism is found in insulin resistant skeletal muscle and autophagy is activated by exercise [9]. They found that the abundance of autophagy-related proteins in the muscle of obese subjects and type 2 diabetic patients is not altered [10],

and that initiation of autophagy following acute exercise is preserved in type 2 diabetic patients [11]. These results suggest that physical activity is an effective tool to preserve muscle mass despite existing diabetes. The benefit of exercise on microvascular dysfunction in the insulin resistant and diabetic skeletal muscle is reviewed by Olver et al. [12].

An important consideration is whether the altered metabolism in the obese or diabetic state has consequences for the acute response and long-term metabolic adaptations to exercise. First studies in this field focused on substrate metabolism during exercise and showed that contraction-induced and insulin-independent glucose uptake is not impaired in type 2 diabetes [13]. Oxidation and uptake of plasma non-esterified fatty acids was found to be reduced in diabetes during exercise, while the oxidation of triacylglycerol-derived fatty acids is higher [14].

Only few recent studies directly compared the exercise response of type 2 diabetic patients and obese subjects with a matched control group allowing to assess the impact of diabetes and obesity on exercise-induced metabolic adaptations. Findings will be discussed below. For the influence of type 1 diabetes on metabolic response to exercise readers are referred to a recent review in this journal [15].

Effect of hyperglycemia

Hyperglycemia is a hall mark of type 2 diabetes and has consequences for the acute response to exercise. A consistent finding in earlier [13] and recent reports [16▪▪] are higher plasma lactate levels in exercising type 2 diabetic patients compared with controls. Using a complementary metabolomics/transcriptomics approach we investigated the effect of type 2 diabetes on acute changes of plasma metabolites and skeletal muscle transcripts after one bout of cycling exercise [17▪]. Type 2 diabetic patients had higher plasma lactate and alanine levels as transamination product from pyruvate during exercise and showed upregulation of glycolytic enzymes in skeletal muscle following exercise indicating a compensatory response to the higher glycolytic flux compared to controls. Notably, higher glucose rate of appearance and disappearance, higher plasma lactate and plasma insulin were normalized following exercise in the diabetic group. The skeletal muscle of type 2 diabetic patients also showed increased abundance of regulators of glucose transporter-4 transcription and function underlining that type 2 diabetic patients had no impaired metabolic response to exercise but exhibit even greater benefit as control participants. Notably, patients in this study were lean and had comparable fitness levels (VO_2max) as the healthy control group, which is in contrast to large parts of the diabetic population.

While the presence of hyperglycemia has apparently no negative impact on the acute metabolic and transcriptional changes following exercise, it might have consequences for the long-term therapeutic outcome. The influence of hyperglycemia on exercise capacity of skeletal muscle and potential consequences for improvement of glycemic control were investigated in studies led by Thomas P. J. Solomon [18-20]. Hyperglycemia and markers of glycemic control are related to reduced capillary density in skeletal muscle, lower fasting plasma nitric oxide levels and reduced cardiorespiratory fitness suggesting a role for muscle nutrient availability in the progression of glucose intolerance and exercise impairment [19].

Poor glycemic control before exercise training determined as 2-hour OGTT glucose levels above 13.1 mmol/L was related to an impaired response in glycemic control and cardiorespiratory fitness after intervention [18] similar to higher HbA1c levels in the look AHEAD study [21]. These data suggest that good glycemic control in patients with type 2 diabetes before exercise intervention can support the metabolic benefit from exercise intervention.

Muscle glucose uptake and glycogen storage

The preserved contraction-induced glucose uptake in skeletal muscle of type 2 diabetic patients suggests an intact regulation of AMPK activity since AMPK is considered as central regulator of muscle glucose uptake during exercise and involved in regulation of muscle gene transcription and insulin sensitivity [22]. While agreement exists about a similar AMPK abundance and activity in resting muscle of diabetic patients and healthy controls a recent study by Jørgen Wojtaszewski's group provide novel insight into the regulation of AMPK signaling network in exercised diabetic muscle [16▪▪]. They studied skeletal muscle AMPK in overweight/obese patients with type 2 diabetes and weight-matched controls who performed one bout of cycling exercise. They found intact and comparable AMPK regulation and signaling following exercise in both groups shown as AMPK activity and phosphorylation of downstream targets ACC and TBC1D1. These data argue against a general functional defect of AMPK in type 2 diabetes. Notably, upregulation of PGC1α mRNA abundance in skeletal muscle was also similar in diabetic patients and controls following exercise [16▪▪] well in line with Hansen et al. [17▪]. These results showing intact activation of two key regulators AMPK and PGC1α of skeletal muscle metabolism and the adaptation to exercise support the relevance of muscle work as promising intervention to treat and prevent type 2 diabetes in lean and obese subjects.

Insulin-dependent regulation of glycogen synthase activity is consistently found to be defective in skeletal muscle of type 2 diabetic patients. Further investigations based on the study by Kjøbsted et al described impaired response of glycogen synthase phosphorylation and activity in the recovery period but not during exercise [23]. This could be of relevance for partitioning glucose towards glycogen storage in skeletal muscle in recovery following exercise, but muscle glycogen content was not different between the diabetic and control group indicating minor importance of glycogen synthase activity for glycogen storage following one bout of exercise.

Acylcarnitines and fatty acid oxidation

Acylcarnitines are lipid derivatives reflecting incomplete fatty acid β-oxidation and enhanced plasma acylcarnitine concentrations are found in obesity, insulin resistance and type 2 diabetes, metabolic states characterized by reduced fatty acid oxidation and impaired metabolic flexibility [24]. Thus it was hypothesized that the increase in acylcarnitines during exercise is influenced by type 2 diabetes or obesity. Surprisingly, in the study of Hansen et al. the regulation of plasma acetylcarnitine, medium and long chain acylcarnitine levels is strikingly similar in type 2 diabetic patients and controls during cycling exercise, and no difference was found in the ratio of acetyl- and propionylcarnitine to free carnitine as an indicator of β-oxidation activity [17▪]. Similarly, in the study of Zhang et al. reduced fat mass and improved fitness after a 14 week training and weight loss program did not alter the response of short chain and medium chain acylcarnitines to an acute exercise bout performed pre- and post-intervention [25▪▪]. These data indicate that limitations of complete fatty acid oxidation during exercise are not significantly influenced by alterations in mitochondrial substrate oxidation capacity and insulin sensitivity. In contrast, plasma long-chain acylcarnitines showed a clear increase during the acute exercise bout in the study of Zhang et

al but only after the 14 week intervention. This can reflect training-induced higher abundance and activity of carnitine palmitoyltransferase CPT1, but whether the increased generation of long chain acylcarnitines takes place in skeletal muscle needs to be clarified. Although long chain fatty acid carnitine esters increased in plasma and skeletal muscle tissue of exercising healthy lean subjects, a release from the exercising leg was not detected [26].

Effect on exercise-regulated hepatokines

Our recent studies add follistatin and FGF21 to exercise-regulated hormone-like factors [27, 28]. The exercise-induced secretion of both hepatokines is under the control of the glucagon-to-insulin ratio and thus subject to disturbed regulation in the insulin resistant state and type diabetes. Comparing the hepatokine response of type 2 diabetic and healthy individuals to acute exercise we found reduced (follistatin) or even blunted (FGF21) secretion in type 2 diabetes [29▪]. This may be due to hepatic insulin resistance or hyperinsulinemia in the type 2 diabetes group and indicates that the liver cannot respond adequately to exercise-induced stimuli in chronic metabolic disorders. Similarly, when studying an acute bout of exercise Slusher et al. found that obese subjects have an impaired exercise-induced increase in FGF21 [30]. Whether the altered FGF21 response observed with obesity is due to excess of hepatic lipids or the associated hepatic insulin resistance is difficult to tell. The consequences of this impaired hepatic exercise response are unknown, but may interfere with metabolic health promoting effects of FGF21 such as reducing fat mass and improving glucose tolerance and fatty liver disease [31].

Family history of type 2 diabetes

First-degree relatives of type 2 diabetic patients have an increased risk to develop the disease. Ekman et al. followed the hypothesis that the exercise response of healthy individuals with and without first-degree family history of type 2 diabetes differ due to already existing impairments in mitochondrial oxidation and metabolic flexibility [32▪]. They studied two groups matched for metabolic parameters and fitness albeit a direct comparison of the two groups in this study is difficult since the total exercise volume spent by the first-degree relatives was 61% higher. When related to exercise volume, first-degree relatives responded less in terms of weight, waist circumference, VO_2peak, and skeletal muscle genes involved in mitochondrial substrate oxidation. Although data need to be interpreted with caution, genetic determinants in individuals with family history of diabetes may exist that interfere with the dose-response to exercise.

Primary myotube cultures to assess different responses to exercise

Another approach to study the influence of type 2 diabetes and obesity on exercise-induced metabolic adaptations is to apply electrical pulse stimulation (EPS) as in vitro exercise model to human myotubes [33]. Primary myotube cultures have clear limitations with regard to less pronounced oxidative metabolism compared with in vivo, but they have been proven as a valuable model to study different responses of molecular pathways to in vitro exercise and perturbations in skeletal muscle glucose and fatty acid oxidation can be preserved in myotube cultures from diabetic or obese donors. Feng et al. compared the EPS-response of myotubes obtained from lean and severely obese non-diabetic donors with severely obese diabetic donors [34▪]. EPS-treatment increased glucose oxidation in all groups, while fatty acid oxidation is only enhanced in myotubes from lean subjects. The cellular insulin response is enhanced in both severely obese groups, but not in the lean group. In contrast, EPS-induced upregulation of cytokines IL6 and IL8 is not found in myotubes from diabetic donors.

However, Feng et al. only showed relative responses to EPS; thus it remains unclear whether myotubes from diabetic donors had higher abundance of IL6 and IL8 mRNA at baseline reflecting low-grade inflammation which may hinder further increase of cytokine expression following EPS.

Mechanisms for reduced response to exercise

To conclude, present data do not indicate an impaired response to exercise in insulin resistant, obese or type 2 diabetic individuals in general. However, in most exercise intervention programs a subgroup of participants failed to improve in glycemic control or insulin sensitivity despite improvement in fitness parameters [35, 36]. In healthy individuals, improvement in cardiorespiratory fitness can be achieved in all participants by higher doses of exercise [37]. Whether this holds true for the metabolic ”non-response” in people at risk to develop diabetes needs to be shown. Currently, the mechanisms involved in reduced metabolic benefit are investigated. Stephens et al. described that several genes involved in oxidative substrate metabolism are differently expressed at baseline in type 2 diabetic patients with different response to a 9-month supervised exercise intervention [38]. Individuals who failed to improve glycemic control also showed no or less upregulation in genes regulating glucose and fatty acid oxidation and mitochondrial oxidative capacity [39, 40]. Böhm et al. reported for the first time a molecular mechanism that can explain why metabolic improvement can be suppressed in some participants of an exercise intervention program [40]. Individuals with impaired response in insulin sensitivity showed markers of activated TGFβ signaling in skeletal muscle after exercise intervention, and TGFβ is validated as inhibitor of genes important for substrate oxidation and mitochondrial biogenesis in myotubes and it reduces insulin signaling. Enhanced TGFβ signaling in skeletal muscle can indicate prolonged activation of inflammatory processes and muscle repair mechanisms. Thus, the data

demonstrate the need for carefully designed exercise intervention protocols to avoid unaccustomed skeletal muscle work load to achieve benefit in glycemic control for all people.

Conclusion

The general effectiveness of exercise programs including HIIT to improve metabolic control in obese and type 2 diabetic subjects is well-documented. Severe metabolic dysregulation and heritable factors can reduce the benefit from exercise. However, the intact response of key metabolic regulators in exercising skeletal muscle of diabetic patients demonstrates the effectiveness of exercise to treat the disease. The acute response of the liver to exercise, which is more dependent on hormonal regulation by glucagon and insulin, can be affected by type 2 diabetes as shown by the impaired regulation of hepatokines.

Key points

- Exercise is an effective therapeutic intervention to improve glycemic control in obese and type 2 diabetic patients, and HIIT is a valuable alternative training program
- Type 2 diabetic patients have intact regulation of key metabolic regulators (AMPK, PGC1α) in skeletal muscle during exercise
- Response of hepatokines regulated by glucagon/insulin is impaired in obesity and type 2 diabetes
- Plasma acylcarnitine profile during exercise do not reflect differences in insulin sensitivity and mitochondrial substrate oxidation
- Transcriptional profile of subjects with reduced metabolic benefit from exercise indicate the need for well-accustomed muscle work load

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Conflicts of interest

None.

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