Assessing the evidence: exploring the effects of exercise on diabetic microcirculation

LENASI, Helena and KLONIZAKIS, Markos <http://orcid.org/0000-0002-8864-4403>

Assessing the evidence: exploring the effects of exercise on diabetic microcirculation

Helena Lenasi[1]*, Markos Klonizakis[2]

[1]Institute of Physiology, Faculty of Medicine, University of Ljubljana, Slovenia
[2]Centre for Sport and Exercise Science, Sheffield Hallam University, U.K

* corresponding author: Helena Lenasi, Institute of Physiology, Faculty of Medicine, University of Ljubljana, Slovenia, Zaloška 4, 1000 Ljubljana, Slovenia; Tel: + 386 1 543 7513; Fax: 386 1 543 7501; E-mail: helena.lenasi.ml@mf.uni-lj.si

Abstract

Diabetes mellitus (DM) is associated with cardiovascular complications. Impairment of glycemic control induces noxious glycations, an increase in oxydative stress and dearangement of various metabolic pathways. DM leads to dysfunction of micro and macrovessels, connected to metabolic, endothelial and autonomic nervous system. Thus, assessing vascular reactivity might be one of the clinical tools to evaluate the impact of harmful effects of DM and potential benefit of treatment; skin and skeletal muscle microcirculation have usually been tested. Physical exercise improves vascular dysfunction through various mechanisms, and is regarded as an additional effective treatment strategy of DM as it positively impacts gylcemic control, improves insulin sensitivity and glusose uptake in the target tissues, thus affecting glucose and lipid metabolism, and increases the endothelium dependent vasodilation. Yet, not all patients respond in the same way so titrating the exercise type individualy would be desired. Resistance training has, apart from aerobic one, been shown to positively correlate to glycemic control, and improve vascular reactivity. It has been prescribed in various forms or in combination with aerobic training. This review would assess the impact of different modes of exercise, the mechanisms involved, and its potential positive and negative effects on treating patients with Type I and Type II DM, focusing on the recent literature.

Keywords: Diabetes, exercise, aerobic training, resistance training, high intensity interval training, microcirculation, laser Doppler fluxmetry

1. Introduction

Diabetes mellitus (DM) is a chronic endocrine and metabolic disorder, the prevalence and incidence of which is increasing all over the world: according to the World Health Organisation (WHO), in 2014, 422 million of people were suffering from DM [1]. DM induces, due to its pathophysiological mechanisms, a series of complex metabolic and vascular changes, associated with neuropathies, which subsequently compromise vascular function, and lead to cardiovascular complications and increased morbidity and mortality [2].

Type 2 Diabetes Mellitus (T2DM) is the most frequent type of DM, accounting for 90 % of cases and affecting older population, and related to age, to inhealthy diet habits and lifestyle. T2DM is mainly characterised by insulin resistance, associated with impaired insulin-mediated glucose uptake resulting in systemic hyperglycemia. In early phases, there may be compensatory hyperinsulinemia produced by compensatory increased pancreatic insulin secretion,which progressively turns into insulin deficiency due to pancreatic exhaustion and dysfunction [2-6]. Due to insiduous onset and progression, the disease may be diagnosed several years after the onset, when complications have already been establisheed. Another concerning fact is that even younger adults could be affected. In addition, T2DM patients often present with other comorbidities aggreviating the symptoms of DM such as high blood pressure (BP), dyslipidemia, obesity and physical inactivity [7-9].

It is a well-known fact that the progression of T2DM could successfully be delayed with suitable lifestyle modifications, i.e. diet and exercise training programmes [3, 9-18].

On the other hand, Type 1 DM (T1DM), is much less frequent, and is characterised by an absolute deficiency of insulin due to pancreatic insufficiency of yet unknown cause; the most probable cause being autoimmune disorder. As such, insulin substitution therapy is unavoidable and it is yet to be determined if and to what extendits progression could be altered by lifestyle modifications [15].

The hallmark of both types is impairement of glycemic control, with subsequent hyperglycemia leading to noxious glycation of the plasma and vessel wall proteins and increased generation of reactive oxygen species (ROS) as well as derangement of various metabolic pathways, aggreviating serum lipid profile, markers of inflammation and hemostasis, dysbalance of the autonomic nervous system, all of which favour accelerated development of atherosclerotic vascular changes [6, 10, 19]. In this respect, DM leads to the dysfunction of macro- and micro-vessels, with this being related to metabolic, endothelial and autonomic nervous system dysfunction, which are in turn linked to altered vascular reactivity [2, 20-22].

The beneficial effects of regular exercise to treat DM and postpone its complications have been well-documented and advocated in large, cross-sectional, studies, reviews and meta-analyses [13-16, 23]. However, the optimal and most favourable exercising modality in terms of type, volume and intensity, frequency and duration and its effect on improving vascular dysfunction on one side and the least negative outcomes on the other has yet to be established [3, 9, 11, 12, 17, 18, 24]. While studies mostly focused on elucidating potential

mechanisms in animal models, or assessing human macrocirculation and cardiovascular events, there is surprisingly little information on microcirculation. In the light of this, we undertook a review on the currently available and most-recent (e.g. 2000-onwards) literature on the impact of different exercise modalities and training protocols on various aspects of human microcirculation, assessing their strengths and weaknesses, and also suggest some future directions in establishing appropriate measures in terms of physical activity.

2. Diabetic-induced changes in the human microcirculation

DM is associated with structural and functional vessel alterations, including generalized endothelial dysfunction of both, macro- and micro-vasculature [6, 22], as well as altered responsiveness of vascular smooth muscle cells (VSMC) [25], predisposing an increased vasoconstrictor response. The mechanisms affecting endothelial function in DM include: altered metabolism due to hyperglycaemia and associated increased ROS and protein kinase C (PKC) activation [19, 26, 27], dyslipidaemia and elevated levels of fatty acids [4, 29], hyperinsulinaemia and insulin resistance [4, 6, 27, 29], activation of the sympathoadrenal system [8, 30], altered cytokine release and increased inflammatory activation [31-33], the induction of a prothrombotic diathesis predisposing to hypercoability [34] and finally an impaired angiogenesis [8, 27, 35].

Most frequently-used methods for the dynamic *in vivo* assessment of microcirculation include laser Doppler fluxmetry (LDF) and its successor laser Doppler imaging (LDI) [36, 37], (contrast-enhanced) ultrasonography (CEUS) [38], or dynamic capillaroscopy [39, 40]. *In vivo* human studies have confirmed a decrease in endothelium-dependent vasodilatation of skin microvessels in T2DM patients [20, 21, 34, 41, 42]. This decrease appears to correlate in most [41, 42] but not all cases [20] with macrovascular dysfunction.

A large body of evidence confirms a reciprocal relationship between insulin resistance and endothelial dysfunction [29]. In physiological concentrations, insulin favours the generation of nitric oxide (NO) by endothelial NO synthase (eNOS) via the activation of Akt-dependent pathway [4, 6, 35]. Using LDF to asssess microcirculation in skin and skeletal muscles, physiological hyperinsulinaemia has been shown to increase cutaneus microvascular perfusion, and augment human skeletal muscle microvascular recruitment and vasomotion in humans [40].On the other hand, insulin is also involved in the generation of endothelial vasoconstrictor endothelin via MAPK/ERK kinase whose action is attenuated by high levels of AMP kinase which could be stimulated by adiponectin [43]. The levels of adiponectin, in turn, have been shown to be decreased in DM [6, 27]. The dysbalance of vasoconstrictors and vasodilators in DM is thought to contribute to deranged vascular tone. Concommitant neuropathy and sympathoadrenal dysbalance might aggreviate the microvascular dysfunction [21]. Additionaly, in the settings of decreased insulin sensitivity, high glucose levels also decrease the availability of NO, either by directly inhibiting eNOS through the activation of PKC or, independently, favouring oxidation and uncoupling of eNOS [25]. Apart

from reduced bioavailability of NO, increased production of cytochrome P450 (CYP)- derived vasoconstrictor metabolites, 20-hydroxy-eicosatetraenoic acids (20-HETE) have also been implicated in the dysbalance of vascular tone [44]. Hyperglycemia concomitantly with deranged metabolic pathways of lipids and mitochondrial dysfunction may lead to intracellular changes in the redox state increasing the formation of ROS [5]. In addition, the increased production of advanced glycation end products and increased activity of the polyol pathway induced by hyperglycemia increase ROS production via NADPH oxidase [5, 6]. Therefore, the overproduction of ROS, through their NO-scavenging effect, is involved in T2DM-induced vascular dysfunction.

Positive correlation between the levels of glycated haemoglobin (HbA1c), and the endothelial dysfunction has been confirmed in many *in vivo* human studies which assessed microvascular reactivity and thus indirectly support the involvement of hyperglycemia in endothelial dysfunction [45, 46]. Interestingly, the endothelium-dependent, acetylcholine (ACh)-induced vasodilation has been shown to be readily impaired in non-diabetic women with insulin resistance, suggesting an important role of insulin in vascular homeostasis [47]. Endothelial function has also been related to increased levels of oxidative stress in diabetic patients [35, 48, 49]. Moreover, the skeletal muscle microvascular responses to insulin were abnormal in late-stage diabetes and in obesity [50, 51].

The use of LDF in T1DM patients belonging to a wide age-range (children, adolescents, and young adults) has shown decrased endothelium-dependent and independent vasodilation possibly due to poor glycemic control and T1DM duration [42, 52-55]. Moreover, a recent study by Tibirica et al [56] in young T1DM patients without other chronic co-morbidities, assessed by intravital video capillaroscopy, has shown significantly impaired skin capillary function in both fingers and toes. Additionally, their capillary density did not increase in either extremity during venous occlusion suggesting that their capillaries at rest are already maximally recruited [56].

Although the data on the involvement of VSMC in the progression of microvascular dysfunction are not consistent, indices suggest adecreased sensitivity of VSMCs to NO donors [25]. Similarly, Walther et al have shown decreased endothelium-dependent and independet vasodilation in macro- and microcirculation in T2DM patients, which was more pronounced in patients suffering also from metabolic syndrome [41]. This suggests the involvement of central abdominal fat and systemic inflammation in the pathogenesis of vascular dysfunctions in patients with metabolic syndrome and T2DM. This notion is supported by the fact that the metabolic signalling between adipose tissue and muscle in DM is altered [4], with *in vivo* human studies having confirmed a link between lowered adiponectin levels and microvascular function [57].

Other studies have demonstrated a decreased capillary density of skeletal muscles in patients with DM microcirculation, which additionaly compromises the delivery of nutrients and insulin to skeletal muscle [58, 59] and aggraviates the symptoms of the condition. In insulin-resistant patients and animals, capillary blood volume and capillary blood flow do not

increase normally in response to insulin, which may contribute to abnormal glucose homeostasis and microvascular complications [50, 51].
Insulin sensitivity determines also the level of capillarization as it is indicated in animal [60, 61] and healthy human studies. In humans, physiological hyperinsulinaemia increased the intramuscular microvascular reactive hyperaemia and vasomotion [40]. Insulin-mediated capillary recruitment has been shown to be largely NO-dependent [62] and since in DM, the bioavailability of NO is reduced, this might additionaly contribute to microvascular dysfunction. Apart from functional alterations, structural changes of VSMCs in terms of remodeling of small resistance arteries have also been confirmed in DM [8, 63]. The angiogenetic potential seems to be altered in DM, which might partly be associated with decreased levels of circulating endothelial progenitor cells (EPCs) shown in DM [35, 64, 65]. This data suggest a link between EPCs and T2DM-associated vasculopathies and glucose intolerance.
Therefore, endothelial and VSMC dysfunction may be critical targets for prevention and treatment of DM progression.

3. Impact of acute exercise in diabetic microcirculation

It is well-accepted that even a single bout of exercise, in both healthy and patient populations, elicits changes in microvascular responsiveness, particularly regarding endothelial function. However, the exact impact on diabetic populations is yet to be determined, as studies gave inconclusive results. This might partly be accounted for on the different modes of exercise applied and on different microcirculatory bed and parameters tested.
A single session of low intensity exercise (50 - 65% of maximal oxygen uptake; VO2max) has been shown to increase insulin sensitivity (as assessed by hyperinsulinemic-euglycemic clamp) for up to 72 hours after exercise sessation in healthy and obese patients [66]. This in turn might positively affect endothelial function due to reducing hyperglycemia as a consequence of increased glucose uptake in muscles.
Additional mechanisms of acute changes of endothelial function might reflect an increased eNOS expression and NO production, induced by increased shear stress which in turn augments the endothelium-dependent vasodilation. Other vasodilators may also be involved [67, 68].
In larger conductance arteries, increased endothelium-.dependent vasodilation after an acute bout of exercise has been confirmed in healthy [69], but the data on microvascular reactivity are scarce.
Acute changes in endothelial function might also be related to acute effects of exercise on glucose uptake and lipid profile which switches the metabolism and induces changes in capillary perfusion [70, 71]. As for the mode of exercise and glucose uptake, strength and resistance exercise have been shown to increase glucose uptake even more than aerobic exercise [Holten, Santos]. Postulations based on animal studies indicate that muscle

contraction induces glucose transporter (GLUT4) intracellular trafficking into the cell membrane and thus increases glucose uptake in skeletal muscle, independently of insulin action [72-74]. This may be an additional beneficial mechanism of decreasing hypergycemia in diabetes on a longer-term basis [75]. Indeed, Jorge et al [76] have shown that insulin sensitivity depends on intensity and mode of exercise as they confirmed chronically-increased levels of insuline receptor substrate (IRS) in muscle biopsy samples after training. An interesting speculation on reducing hyperglycemia has been proposed by Metcalfe et al [77] who have suggested that high levels of glycogen depletion during strenous execrise contribute to improvement in insulin sensitivity following high-intensity interval training (HIIT). For example, muscle glycogen availability has been shown to be inversely related to muscle GLUT4 content during insulin stimulation [78]. Furthermore, exercise has been shown to induce capillary growth: during muscle contraction, the level of vascular endothelial growth factor (VEGF) in interstitium increases and acts on capillary endothelium, thereby stimulating angiogenesis [79].

On the other hand, resistance and strenght as well as aerobic exercise also increase ROS production, which in turn compromises endothelial function [80, 81]. To what extent the increased ROS affect endothelial function on acute basis depends on exercise intensity and the level of ROS removal [80]. The net effect on vascular reactivity thus depends on the balance between vasodilator and vasoconstrictor effects. It is obvious that there is a complex interplay of many factors that determines the final vascular response to exercise [67, 82, 83].

Responses to an acute exercise bout differ between healthy and diabetic populations: e.g. study by Simoes et al has shown that an acute bout of moderate-intensity aerobic exercise in T2DM patients lowered plasma NO and bradykinin concentrations and kallikrein activity as compared to healthy indivuiduals [84]. Moreover, Womack et al have shown that DM patients with microvascular complications had lower skeletal muscle capillary recruitment and capillary volumen in response to a single bout of exercise during low or high-intensity contractile exercise (25% and 80% maximal handgrip), assessed by CEUS as compared to DM patients without complications and healthy controls [58]. Unexpectedly, these abnormalities were independent of disease duration [58]: abnormalities in capillary recruitment may be related to abnormal hemorheology as patients exhibited elevated whole blood viscosity that correlated with plasma glucose and C-reactive protein (CRP).

Furthermore, Franklin et al have shown that flow-mediated dilation (FMD) of the large conductance (brachial) artery was lower in obese women compared to lean ones, reflecting diminished endothelial response to exercise [Franklin2014]. They also postulated that the sensitivity of VSMC to NO is diminished in obesity [85].

An interesting approach for evaluation of vascular function might be the determination of the EPCs level. Although the potential of acute (sub-maximal) exercise to stimulate and mobilize the EPCs has been shown to be blunted in T2DM patients as compared to healthy controls [65], Aoki et al [86] have proven an increment of EPCs during acute exercise load in diabetic patients, which seems an additional promising beneficial effect of exercise [65]. A

recent study, however, by Waclawovsky et al failed to show an increase of EPCs after an acute combined, aerobic and resistance training (ART) session in young T1DM patients in spite of increased response to postocclusive reactive hyperaemia (PORH), assessed by venous occlusion plethysmography [87]. In contrast, healthy controls did exhibit increased number of EPCs after exercise session [87]. The authors concluded that the unchanged number of EPCs in T1DM after exercise sessions might indicate a blunted endothelium regenerating capacity, revealing an early deterioration of the functional arterial characteristics that were not obvious after testing the response to PORH. Yet, due to small number of T1DM study participants, additional larger trials studies are needed.

4. The effect of chronic exercise on diabetic microcirculation: effect of type and duration

Current literature suggests that many potential mechanisms might play a role in chronic exercise adaptations. In healthy populations, exercise training unequivocally exerts complex beneficial effects, affecting vascular function and structure and decreasing the risk for cardiovascular events: exercise increases the endothelium-dependent vasodilation, induces the upregulation of ROS metabolising enzymes, increases the mobilization of EPCs, affects the autonomic nervous system balance in decreasing arterial BP, and improves proinflammatory cytokines and adiponectine profile to list just some of the effects [88]. As most of those mechanisms are compromised in DM, they all appear to be potential targets for an exercise intervention.

Most studies are focused on studying macrovessels whereas relatively little is known about the potential effects and mechanisms on exercise-induced adaptation in human microcirculation. Apparently, the effects not only depend on the type, intensity, frequency and duration of exercise but also on the vascular bed studied. It seem reasonable to speculate that vascular beds more intensively engaged in exercise such as skeletal muscle microcirculation would be mostly affected.

Since insulin exerts metabolic and vascular effects, applying measures to increase insulin sensitivity might indirectly affect vascular tone. Indirect evidence of positive effects of exercise might be deduced from the study of Sonne et al who have shown that 10-days bed rest diminished the insulin-induced increase in blood flow in the brachial artery as assessed by venous occlusion plethysmography in T2DM patients as well as in healthy volunteers, pointing to beneficial effects of physical activity on insulin sensitivity [89]. A recent review by dos Santos et all discussed the effect of physical exercise on some known epigenetic modifications on GLUT4 and mitochondrial proteins that lead to impairment of skeletal muscle glucose uptake and DM2 development, and might also be linked to vascular effects [90]. The effects seem to be most pronounced in the vessels of tissues mostly engaged in exercise, such as skeletal muscles; on the other side, increasing glucose uptake and affecting metabolical pathways in skeletal muscle might reduce systemic hyperglycemia and thus indirectly impact also other vessels, such as skin microcirculation. Indeed, Meijer et al have recently shown that insulin induces capillary recruitment in skin and muscles which is related

to increased glucose uptake [91]. Potential impact of insulin on glucose uptake in skin microcirculation is only speculative as there are no available data on the expression of GLUT4 in human skin microcirculation.

Skin microcirulation is a good model to study microvascular changes as it is easily accessible and has been speculated to reflect generalized vascular function [92]. Moreover, it has, in particular its nutritive capillaries, often been compromised in DM patients, which predisposes to ischemia, and finally the development of detrimental ulcerations and limb amputation. Consequently, exercise might be a valuable intervention to postpone diabetic complications.

In terms of adaptation to exercise, skin microcirculation is essentialy involved in exercise as it is the main organ for thermoregulation. Taken these information into consideration, it is tempting to speculate that exercise might induce changes also in diabetic skin microcirculation. There are only few available studies that assessed the effects of different training regimes on cutaneous microvascular function, and the results are inconclusive. As previously noted, different responses might partly be explained by differences in the protocols used (e.g. differences in mode, volume and duration of exercise), or by the selection of patients (e.g. differences in age-groups, DM duration, medication etc) included. It is also common for interventions to include lifestyle modifications in the form of caloric restriction and diet apart from physical activity. Therefore, the observation (or not) of an effect might be attributed to the combination of more than one parameters.

4.1. Aerobic training

The study of Middlebrooke et al [93] which included 22 patients (aged 62) with mean diabetes duration of 4 years, showed no improvement in the response to local heating, ACh or sodium nitroprusside (SNP) iontophoresis after six months (30 min-exercise set, three times a week, 70–80% of maximal heart rate) of aerobic training. No changes were observed either in glycemic control, insulin sensitivity or VO2max, implying insufficient quantity of exercise in inducing any, not only vascular changes. Similarly, in a group of 10 DM patients (aged 54.5 years), Colberg et al [94] failed to show any effect of a 10-week aerobic training (3-times weekly for 45-min up to 65% VO2max) on microvascular reactivity in dorsal foot skin after local heating nor any increase of NO levels. In contrast to the microcirculation, patients' VO2max and lactate treshold improved after training protocol. The authors concluded that the programme duration might not have been long enough to induce changes of microvascular reactivity. On the other hand, Hamdy et al [95] in a study involving DM patients in a 6-month intervention programme of aerobic exercise (three times per week, 30 min each, at 60–80% max heart rate) and diet failed to show any effect on cutaneous microvascular function (assessed by LDI) whereas they showed an improvement in macrovascular endothelial function as assessed by FMD, improved glycemic control, and decreased levels of markers of endothelial activation and coagulation (ICAM and plasminogen activator inhibitor-1 (PAI-1)). Taking into consideration the existing knowledge

[36], it is therefore possible that the lack of sensitivity of the method to assess microvascular reactivity could have affected the "no microcirculatory impact" finding, rather than an actual difference between macro- and micro-vascular function.
In contrast to the above noted studies, Krcma et al have shown that even moderate 4-week exercise in terms of solely walking induced changes in microvascular response to local heating and PORH [96]. However, they included eight DM patients who were completely sedentary before the training protocol started, and the exercise protocol consisted of everyday walking for at least one hour. Nevertheless, no other parameter tested (i.e. fasting plasma glucose, Hb-gly, or lipid profile, or BP) did not change after finishing the programme [97].
The effect of aerobic exercise on VO2max, NO levels, and oxidative stress, which all affect endothelial function, depends on training intensity; nevertheless, the responses significantly differ between DM patients and healthy [48, 83]. These differences might also account for variations in microvascular responses between healthy and diabetics.

4.2. Resistance training

As DM patients might have difficulties in performing aerobic exercises, specially those with diabetic food and skin ulcerations associated with comorbidities, resistance training might be an alternative.
Colberg [97] did not report any changes in NO levels nor in the responsiveness of cutaneous perfusion in response to local heating after 8 weeks of moderate resistance training either in DM individuals or in their matched controls. This is in contrast to the findings of Cohen et al [45], who have confirmed that resistance training of high intensity and involving large muscle groups semi-weekly improved both the ACh- and SNP-mediated vasodilation of forearm skin microvessels in 29 DM patients (mean age 60 years) that were negatively correlated with Hb1Ac levels; in addition, they showed a decrease in BMI and systolic arterial BP. Interestingly, the observed changes were only significant after a 14-month training period, which was not the case 2 months after, suggesting the importance of regular training on a longer term basis. It is also worth noting that in the study by Cohen, rather than just being localised, as previously suggested [98], vascular effects seem to be systemic [45]. In favour of a longer training period is also the study by Sixt et al, who showed improved endothelial function of coronary arteries after a 5-month- and not after a 4-week period [99].
Duration however, is also one factor affecting the extend of adaptations; intensity can also be a crucial factor. However, with no high intensity, resistance exercise training studies in diabetic populations, current evidence is limited, with only speculations existing on causing impaired cerebral autoregulation due to greater systemic oxidative stress [83, 100]. Nevertheless, this mode of resistance exercise training might be inappropriate for this population [18] due to it being related to extremely high (e.g. up to 400 mm Hg) increases in systolic BP [101].

4.3. Combined aerobic and resistance training

Current physical activity guideliness favour combined activity (ART) over either aerobic or resistance training as it is considered to provide a combination of benefits. As for the effect of ART on skin microcirculation, Maiorana et al and Naylor et al confirmed improved endothelium-dependent and -independent vasodilation in older [102] and younger populations [103], pointing to beneficial effects irrespective of age already after 8- or 12-week exercising programme, respectively. Naylor did not find any changes in VO2max, body weight or BMI, which suggests that vascular effects are related to metabolic changes - this supports the notion of including ART in the lives of young T2DM patients, as early as possible. Hordern et al have shown that only 4 weeks of moderate-intensity ART improved glycemic control, VO2max, and caused a reduction in the resting heart rate and systolic BP [3].

This data suggests that the increased vasodilatory capacity could be attributed to endothelial and VSMC adaptations. Apart from NO, prostaglandins seem to play greater role in exercise-induced endothelial vasodilating capacity in DM [96]. As oxidative stress uncouples eNOS and reduces NO bioavailability, improved endothelium dependent vasodilation might also result from decrese in ROS induced by exercise that has been confirmed in DM patients [48]. Nojima et al [49] showed that 12-month 30 minutes at least thrice per week (either aerobic or ART) over a 12- month period improved glycemic control and attenuated oxidative stress as assessed by determination of urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG).

Additional confirmation on the efficiency of combined ART on microvasculature comes from the study of Vinet et al [104] who assessed microvascular reactivity concomitantly with other DM markers after a lifestyle intervention program, including diet and 6-month ART. They showed an increased response of skin microvessels to iotophoresis of insulin along with improved vasomotion profile, improved glycemia, Hb1Ac, as well as thrombotic and inflammatory markers, active PAI-1, CRP, and a decrease of systolic BP after intervention. As patients underwent diet and exercising programme, each parameter cannot be evaluated separately and positive effects might have resulted from both, metabolic and vascular effects. This is partly in contradiction with Lucotti et al, who have shown that the effect of aerobic training was more efficient than ART in improving BP, insulin sensitivity and endothelial factors, adipokines and pro-inflammatory marker release [105]. Furthermore, combined ART did not prove to be more efficient than aerobic one on arterial stiffnes of larger conductance arteries [106]. On the other hand, the improvement of insulin sensitivity as assessed by the expression of IRS seems to be more sensitive to ART and resistance training than to aerobic training alone [76].

Therefore, the contrasting findings confirm the need of additional, larger,longer-term studies in humans.

4.4. High intensity interval training

It is important to make a note about high intensity interval training (HIIT) which recently has been widely discussed as a less time-consuming, benefit-inducing mode for exercise. The only available study in T2DM patients confirmed that HIIT was more effective in improving microvascular function, as assessed by inducing PORH, as compared to continuous training of lower intensity and adjusted to the same energy expenditure per exercise session [107]. In addition, HIIT was also more efficient in improving glycemic control, physical fitness, and macrovascular function, whereas the reductions in erythrocyte malondialdehyde and serum von Willebrand factor and increases in plasma glutathione peroxidase and NO were only shown after HIIT, and not after continuous training [107]. Similarly, Tjonna et al have shown that aerobic interval training vs. continuous moderate was more effective in increasing VO2max, enhancing endothelial function (assessed by FMD of the brachial artery), insulin signaling in fat and skeletal muscle, skeletal muscle biogenesis and excitation-contraction coupling, and reducing blood glucose and lipogenesis in adipose tissue in patients with metabolic syndrome [108]. Considering potential proinflammatory effect of DM on micro-vasculature, Balducci et al have also shown that HIIT or ART are most effective in exerting their anti-inflammatory effect [32]. On the other hand, regarding eNOS expression, both types of training seem to be comparable, at least in skeletal muscle microvessels of healthy [109]. However, when high intensity exercise is applied, previous clinical evaluation as well as follow-up is strongly recommended in patients. It should however be noted that this kind of modality may not be appropriate for DM patients with multiple comorbidities [110]. Further work however, is needed to establish benefits and explore its impact in different age-groups.

4.5. Other aspects of regular training on diabetic microcirculation

As microvascular dynamics depends on viscosity, which is altered in DM [58, 111], it is necessary to note the study of Simmons et al [112] who have shown improved viscosity, inflammation and pro-aggregation profile after 12 weeks of superwised treadmill walking at an intensity equivalent to the gas-exchange threshold (120min·semi- or thrice-weekly). As for blood viscosity, a 2-month lasting low intensity exercise pilot study of Brun et al has shown that aerobic capacity improved blood viscosity via an increase in red blood cell deformability and decrease in hematocrite, associated with weight loss [113]. Apart from improved vascular reactivity after training programme, training might also induce structural changes in terms of beneficial angiogenesis: exercise is known to incerase the circulating levels of EPCs favouring the formation of new vessels [64, 114]. Yet, compared to healthy, the exercise-induced increase in EPCs was reduced in both T1DM [115] and T2DM patients [65].

4.6. The effect of exercise training in type 1 diabetes

As the etiopathogenesis and the age-group mostly affected differ in T1DM, it should be treated as a seperate entity, although existing data on microvascular function is even more limited. However, the available data suggests that exercise affects positively microvascular function in T1DM patients. A study by Roche et al with 29 adolescents and children with DM duration of at least two years, has shown a positive correlation between maximal skin microvascular vasodilation induced by local heating and VO2max [26]. On the other hand, no correlations were found between the level of Hb1Ac, glycemic control and microvascular reactivity, which seems to be worth of further investigation, considering the previously mentioned putative mechanisms. Nevertheless, they did not assess other markers such as oxidative stress or inflammation markers which also affect vascular function. Contrary to the observations of Roche et al, a four-week low intensity aerobic training programme in DM1 patients did not affect skin microvascular reativity, as assessed by local heating, PORH and iontophoresis of ACh and SNP [39]. On the other hand, capillary density in response to PORH, assessed by dynamic capillaroscopy, was increased in the same group of patients [39]. We might assume that the most effective and apparent changes are triggered in nutritive capillaries, which could be evaluated by capilaroscopy. It seems plausible to consider that changes did not affect more deeper, larger resistance vessels or pre-capilary sphincters that are also captured with LDF, which, on the other hand, might not be sensitive enough to detect subtle changes. Speculatively, an increase of free fatty acids level, which are the preferential skeletal muscle fuel during low intensity exercise (below 40% of VO2max), can activate peroxisome proliferator-activated receptor beta or delta (PPAR-β or PPAR-δ), and PPAR-δ coactivator-alpha (PGC-1α), contributing to the expression of VEGF and in this respect, favour angiogenesis.
To the best of our knowledge, there are no studies on different modalities of exercise training in T1DM.

5. Limitations and perspectives

We limited our review on microcirculation. The main limitation of the studies included in this review, is the small number of participants, which considering the noteable variability of the methods used to study microcirculation (e.g. LDF), might be accountable for the contrasting findings. Additionally, in many studies, no control group of healthy participants was included. A further problem might be the existence of comorbidities and medications which affect microvascular function and exercise adherence Moreover, the assessment of human microcirculation is limited to superficial vascular beds or associated with invasive techniques, such as muscle biopsy.
Another limitation of studies in humans is that elucidating potential mechanisms is rather speculative and could only be deduced from animal model or in vitro studies. In this respect, final outcome *in vivo* is a complex interplay of many mechanisms and individual genetic susceptibility. Last but not least, all persons do not respond equally or fail to respond which might partly be explained by their genetic susceptibility [116, 117].

Therefore, it is fair to state that the outcome on an exercise intervention programme depends on many facts: age of the participants,the primary status of microvessels prior to starting the exercise programme, the disease duration, potential comorbidities and medication and patients adherence which should all be taken into consideration when designing the study. Consequently, comparing studies should happen with caution as well as drawing general conclusions.

5. Conclusions

In conclusion, the available data confirm the importance of regular exercise to prevent further deterioration of microvascular function in DM. Data also suggests that exercise of longer duration is needed to elicit significant alterations of endothelium-dependent and -independent vasodilation, contributing to a decrease of cardiovascular events. As for microvascular adaptations, the combination of ART is supposed to be most efficient. Nevertheless, an optimal protocol is yet to be agreed, and consequently, larger observational studies on a large cohort of patients are warranted to further elucidate the impact of exercise and different modalities on diabetic microcirculation.

REFERENCES

1. World Health Organisation. Diabetes: Factsheet. http://www.who.int/mediacentre/factsheets/fs312/en Accessed: July 2016

2. Budoff MJ, Raggi P, Beller GA, Berman DS, Druz RS, Malik S, et al.; Imaging Council of the American College of Cardiology. Noninvasive Cardiovascular Risk Assessment of the Asymptomatic Diabetic Patient: The Imaging Council of the American College of Cardiology. JACC Cardiovasc Imaging. 2016;9(2):176-92. doi: 10.1016/j.jcmg.2015.11.011.

3. Hordern MD, Dunstan DW, Prins JB, Baker MK, Singh MA, Coombes JS. Exercise prescription for patients with type 2 diabetes and pre-diabetes: a position statement from Exercise and Sport Science Australia. J Sci Med Sport. 2012;15(1):25-31. doi: 10.1016/j.jsams.2011.04.005.

4. Kolka C. Treating Diabetes with Exercise - Focus on the Microvasculature. J Diabetes Metab. 2013 Nov 16;4:308

5. Hwang MH, Kim S. Type 2 Diabetes: Endothelial dysfunction and Exercise. J Exerc Nutrition Biochem. 2014;18(3):239-47. doi: 10.5717/jenb.2014.18.3.239.

6. Eringa EC, Serne EH, Meijer RI, Schalkwijk CG, Houben AJ, Stehouwer CD, et al. Endothelial dysfunction in (pre)diabetes: characteristics, causative mechanisms and pathogenic role in type 2 diabetes. Rev Endocr Metab Disord. 2013;14(1):39-48. doi: 10.1007/s11154-013-9239-7.

7. Roque FR, Hernanz R, Salaices M, Briones AM. Exercise training and cardiometabolic diseases: focus on the vascular system. Curr Hypertens Rep. 2013;15(3):204-14. doi: 10.1007/s11906-013-0336-5.

8. Nyberg M, Gliemann L, Hellsten Y. Vascular function in health, hypertension, and diabetes: effect of physical activity on skeletal muscle microcirculation. Scand J Med Sci Sports. 2015;25 Suppl 4:60-73. doi: 10.1111/sms.12591.

9. Hansen D, Dendale P, van Loon LJ, Meeusen R. The Impact of Training Modalities on the Clinical Benefits of Exercise Intervention in Patients with Cardiovascular Disease Risk or Type 2 Diabetes Mellitus. Sports Med. 2010;40(11):921-40. doi: 10.2165/11535930-000000000-00000.

10. Huang XL, Pan JH, Chen D, Chen J, Chen F, Hu TT. Efficacy of lifestyle interventions in patients with type 2 diabetes: A systematic review and meta-analysis. Eur J Intern Med. 2016; 27:37-47. doi: 10.1016/j.ejim.2015.11.016.

11. Zanuso S, Jimenez A, Pugliese G, Corigliano G, Balducci S. Exercise for the management of type 2 diabetes: a review of the evidence. Acta Diabetol. 2010; 47(1):15-22. doi: 10.1007/s00592-009-0126-3.

12. Blomster JI, Chow CK, Zoungas S, Woodward M, Patel A, Poulter NR, et al. The influence of physical activity on vascular complications and mortality in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2013;15(11):1008-12. doi: 10.1111/dom.12122.

13. Vita P, Cardona-Morrell M, Bauman A, Singh MF, Moore M, Pennock R, et al. Type 2 diabetes prevention in the community: 12-Month outcomes from the Sydney Diabetes Prevention Program. Diabetes Res Clin Pract. 2016;112:13-9. doi: 10.1016/j.diabres.2015.11.010.

14. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports. 2015;25 Suppl 3:1-72. doi: 10.1111/sms.12581.

15. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, et al. DPV Initiative. Impact of Physical Activity on Glycemic Control and Prevalence of Cardiovascular Risk Factors in Adults With Type 1 Diabetes: A Cross-sectional Multicenter Study of 18,028 Patients. Diabetes Care. 2015;38(8):1536-43. doi: 10.2337/dc15-0030.

16. Thent ZC, Das S, Henry LJ. Role of exercise in the management of diabetes mellitus: the global scenario. PLoS One. 2013;8(11):e80436. doi: 10.1371/journal.pone.0080436.

17. Mendes R, Sousa N, Almeida A, Subtil P, Guedes-Marques F, Reis VM, et al. Exercise prescription for patients with type 2 diabetes-a synthesis of international recommendations: narrativereview. Br J Sports Med. 2015. pii: bjsports-2015-094895. doi: 10.1136/bjsports-2015-094895.

18. Duclos M, Oppert JM, Verges B, Coliche V, Gautier JF, Guezennec Y, et al.; SFD diabetes and physical activity working group. Physical activity and type 2 diabetes. Recommandations of the SFD

(Francophone Diabetes Society) diabetes and physical activity working group. Diabetes Metab. 2013;39(3):205-16. doi: 10.1016/j.diabet.2013.03.005.

19. Hink U, Li H, Mollnau H, Oelze M, Matheis E, Hartmann M, et al. Mechanisms underlying endothelial dysfunction in diabetes mellitus. Circ Res. 2001;88(2):E14-22.

20. Meyer MF, Lieps D, Schatz H, Pfohl M. Impaired flow-mediated vasodilation in type 2 diabetes: lack of relation to microvascular dysfunction. Microvasc Res. 2008;76(1):61-5. doi: 10.1016/j.mvr.2008.03.001.

21. Brooks B, Delaney-Robinson C, Molyneaux L, Yue DK. Endothelial and neural regulation of skin microvascular blood flow in patients with diabetic peripheral neuropathy: effect of treatment with the isoform-specific protein kinase C beta inhibitor, ruboxistaurin. J Diabetes Complications. 2008;22(2):88-95. doi: 10.1016/j.jdiacomp.2007.07.002.

22. Krentz AJ, Clough G, Byrne CD. Interactions between microvascular and macrovascular disease in diabetes: pathophysiology and therapeutic implications. Diabetes Obes Metab. 2007;9(6):781-91.

23. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145-54. doi: 10.1056/NEJMoa1212914.

24. La Gerche A The Potential Cardiotoxic Effects of Exercise. Can J Cardiol. 2016;32(4):421-8. doi: 10.1016/j.cjca.2015.11.010.

25. Montero D, Walther G, Pérez-Martin A, Vicente-Salar N, Roche E, Vinet A. Vascular smooth muscle function in type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetologia. 2013;56(10):2122-33. doi: 10.1007/s00125-013-2974-1.

26. Roche DM, Edmunds S, Cable T, Didi M, Stratton G.Skin microvascular reactivity in children and adolescents with type 1 diabetes in relation to levels of physical activity and aerobic fitness. Pediatr Exerc Sci. 2008;20(4):426-38.

27. Zheng C, Liu Z. Vascular function, insulin action, and exercise: an intricate interplay. Trends Endocrinol Metab. 2015;26(6):297-304. doi: 10.1016/j.tem.2015.02.002

28. de Jongh RT, Serné EH, Ijzerman RG, de Vries G, Stehouwer CD. Free fatty acid levels modulate microvascular function: relevance for obesity-associated insulin resistance, hypertension, and microangiopathy. Diabetes. 2004;53(11):2873-82.

29. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation. 2006;113(15):1888-904.

30. Anaruma CP, Ferreira M Jr, Sponton CH, Delbin MA, Zanesco A. Heart rate variability and plasma biomarkers in patients with type 1diabetes mellitus: Effect of a bout of aerobic exercise. Diabetes Res Clin Pract. 2016;111:19-27. doi: 10.1016/j.diabres.2015.10.025.

31. Hansen D, Dendale P, Beelen M, Jonkers RA, Mullens A, Corluy L, et al. Plasma adipokine and inflammatory marker concentrations are altered in obese, as opposed to non-obese, type 2 diabetes patients. Eur J Appl Physiol. 2010;109(3):397-404. doi: 10.1007/s00421-010-1362-5.

32. Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis. 2010;20(8):608-17. doi: 10.1016/j.numecd.2009.04.015.

33. Rodríguez AJ, Nunes Vdos S, Mastronardi CA, Neeman T, Paz-Filho GJ. Association between circulating adipocytokine concentrations and microvascular complications in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of controlled cross-sectional studies. J Diabetes Complications. 2016;30(2):357-67. doi: 10.1016/j.jdiacomp.2015.11.004.

34. Beer S, Feihl F, Ruiz J, Juhan-Vague I, Aillaud MF, Wetzel SG, et al. Comparison of skin microvascular reactivity with hemostatic markers of endothelial dysfunction and damage in type 2 diabetes. Vasc Health Risk Manag. 2008;4(6):1449-58.

35. Avogaro A, Albiero M, Menegazzo L, de Kreutzenberg S, Fadini GP. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. Diabetes Care. 2011;34 Suppl 2:S285-90. doi: 10.2337/dc11-s239.

36. Park HS, Yun HM, Jung IM, Lee T. Role of Laser Doppler for the Evaluation of Pedal Microcirculatory Function in Diabetic Neuropathy Patients. Microcirculation. 2016;23(1):44-52. doi: 10.1111/micc.12254.

37. Klonizakis M, Manning G, Lingam K, Donnelly R, Yeung JM. Effect of diabetes on the cutaneous microcirculation of the feet in patients with intermittent claudication. Clin Hemorheol Microcirc. 2015;61(3):439-44. doi: 10.3233/CH-141907.

38. Sekiya N, Ichioka S. Efficacy of Ultrasonography at the Ankle Level for Estimation of Pedal Microcirculation. Ann Vasc Dis. 2015;8(3):198-202. doi: 10.3400/avd.oa.15-00078.

39. de Moraes R, Van Bavel D, Gomes Mde B, Tibiriçá E. Effects of non-supervised low intensity aerobic excise training on the microvascular endothelial function of patients with type 1 diabetes: a non-pharmacological interventional study. BMC Cardiovasc Disord. 2016;16:23. doi: 10.1186/s12872-016-0191-9.

40. de Jongh RT, Clark AD, IJzerman RG, Serné EH, de Vries G, Stehouwer CD. Physiological hyperinsulinaemia increases intramuscular microvascular reactive hyperaemia and vasomotion in healthy volunteers. Diabetologia. 2004;47(6):978-86.

41. Walther G, Obert P, Dutheil F, Chapier R, Lesourd B, Naughton G, et al. Metabolic syndrome individuals with and without type 2 diabetes mellituspresent generalized vascular dysfunction: cross-sectional study. Arterioscler Thromb Vasc Biol. 2015;35(4):1022-9. doi: 10.1161/ATVBAHA.114.304591.

42. Yeh SY, Doupis J, Rahangdale S, Horr S, Malhotra A, Veves A. Total serum bilirubin does not affect vascular reactivity in patients with diabetes. Vasc Med. 2009;14(2):129-36. doi: 10.1177/1358863X08098273.

43. Zhao L, Fu Z, Wu J, Aylor KW, Barrett EJ, Cao W, et al. Globular adiponectin ameliorates metabolic insulin resistance via AMPK-mediated restoration of microvascular insulin responses. J Physiol. 2015;593(17):4067-79. doi: 10.1113/JP270371.

44. Schäfer A, Galuppo P, Fraccarollo D, Vogt C, Widder JD, Pfrang J, et al. Increased cytochrome P4502E1 expression and altered hydroxyeicosatetraenoic acid formation mediatediabetic vascular dysfunction: rescue by guanylyl-cyclase activation. Diabetes. 2010;59(8):2001-9. doi: 10.2337/db09-1668.

45. Cohen ND, Dunstan DW, Robinson C, Vulikh E, Zimmet PZ, Shaw JE. Improved endothelial function following a 14-month resistance exercise training program in adults with type 2 diabetes. Diabetes Res Clin Pract. 2008;79(3):405-11.

46. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol. 2001;37(5):1344-50.

47. Pienaar PR, Micklesfield LK, Levitt NS, Gooding K, Shore AC, Goedecke JH, et al. Insulin resistance is associated with lower acetylcholine-induced microvascular reactivity in nondiabetic women. Metab Syndr Relat Disord. 2014;12(3):178-84. doi: 10.1089/met.2013.0126.

48. Krause M, Rodrigues-Krause J, O'Hagan C, Medlow P, Davison G, Susta D, et al. The effects of aerobic exercise training at two different intensities in obesity and type 2 diabetes: implications for oxidative stress, low-grade inflammation and nitric oxide production. Eur J Appl Physiol. 2014;114(2):251-60.

49. Nojima H, Watanabe H, Yamane K, Kitahara Y, Sekikawa K, Yamamoto H, et al. Effect of aerobic exercise training on oxidative stress inpatients with type 2 diabetes mellitus. Metabolism. 2008;57(2):170-6. doi: 10.1016/j.metabol.2007.08.021.

50. Clerk LH, Vincent MA, Barrett EJ, Lankford MF, Lindner JR. Skeletal muscle microvascular responses to insulin are abnormal in late-stage diabetes and are restored by angiotensin converting enzyme inhibition. Am J Physiol Endocrinol Metab. 2007;293:E1804–E1809.

51. Clerk LH, Vincent MA, Jahn L, Liu Z, Lindner JR, Barrett EJ. Obesity blunts insulin-mediated microvascular recruitment in human forearm skeletal muscle. Diabetes 2006;55:1436–1442.

52. Koïtka A, Abraham P, Bouhanick B, Sigaudo-Roussel D, Demiot C, Saumet JL. Impaired pressure-induced vasodilation at the foot in young adults with type 1 diabetes. Diabetes. 2004;53(3):721-5.

53. Khan F, Elhadd TA, Greene SA, Belch JJ. Impaired skin microvascular function in children, adolescents, and young adults with type 1diabetes. Diabetes Care. 2000;23(2):215-20.

54. Neubauer-Geryk J, Kozera GM, Wolnik B, Szczyrba S, Nyka WM, Bieniaszewski L. Decreased reactivity of skin microcirculation in response to L-arginine in later-onset type 1 diabetes. Diabetes Care. 2013;36(4):950-6. doi: 10.2337/dc12-0320.

55. Heimhalt-El Hamriti M, Schreiver C, Noerenberg A, Scheffler J, Jacoby U, Haffner D, et al. Impaired skin microcirculation in paediatric patients with type 1 diabetes mellitus. Cardiovasc Diabetol. 2013;12:115. doi: 10.1186/1475-2840-12-115.

56. Tibirica E, Rodrigues E, Cobas R, Gomes MB. Impairment of skin capillary recruitment precedes chronic complications in patients with type 1 diabetes. Rev Diabet Stud. 2007;4(2):85-8.

57. Rodríguez AJ, Nunes Vdos S, Mastronardi CA, Neeman T, Paz-Filho GJ. Association between circulating adipocytokine concentrations and microvascular complications in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of controlled cross-sectional studies. J Diabetes Complications. 2016;30(2):357-67. doi: 10.1016/j.jdiacomp.2015.11.004.

58. Womack L, Peters D, Barrett EJ, Kaul S, Price W, Lindner JR. Abnormal skeletal muscle capillary recruitment during exercise in patients with type 2 diabetes mellitus and microvascular complications. J Am Coll Cardiol. 2009;53(23):2175-83. doi: 10.1016/j.jacc.2009.02.042.

59. Clark MG. Impaired microvascular perfusion: a consequence of vascular dysfunction and a potential cause of insulin resistance in muscle. Am J Physiol Endocrinol Metab. 2008;295(4):E732-50. doi: 10.1152/ajpendo.90477.2008.

60. Akerstrom T, Laub L, Vedel K, Brand CL, Pedersen BK, Lindqvist AK, et al. Increased skeletal muscle capillarization enhances insulin sensitivity. Am J Physiol Endocrinol Metab. 2014; 307(12): E1105–16.

61. Bonner JS, Lantier L, Hasenour CM, James FD, Bracy DP, Wasserman DH. Muscle-specific vascular endothelial growth factor deletion induces muscle capillary rarefaction creating muscle insulin resistance. Diabetes. 2013; 62(2): 572–80.

62. Vincent MA, Barrett EJ, Lindner JR, Clark MG, Rattigan S. Inhibiting NOS blocks microvascular recruitment and blunts muscle glucose uptake in response to insulin. Am J Physiol Endocrinol Metab. 2003;285:E123–9.

63. Rizzoni D, Porteri E, Guelfi D, Muiesan ML, Valentini U, Cimino A, et al. Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin-dependent diabetes mellitus. Circulation. 2001; 103(9): 1238–44.

64. Reinhard H, Jacobsen PK, Lajer M, Pedersen N, Billestrup N, Mandrup-Poulsen T, et al.Multifactorial treatment increases endothelial progenitor cells in patients with type 2 diabetes. Diabetologia. 2010;53(10):2129-33. doi: 10.1007/s00125-010-1843-4.

65. Lutz AH, Blumenthal JB, Landers-Ramos RQ, Prior SJ. Exercise-induced endothelial progenitor cell mobilization is attenuated in impaired glucose tolerance and type 2 diabetes. J Appl Physiol (1985). 2016;121(1):36-41. doi: 10.1152/japplphysiol.00349.2016.

66. Newsom SA, Everett AC, Hinko A, Horowitz JF.A single session of low-intensity exercise is sufficient to enhance insulin sensitivity into the next day in obese adults. Diabetes Care. 2013;36(9):2516-22. doi: 10.2337/dc12-2606.

67. Durand MJ, Dharmashankar K, Bian JT, Das E, Vidovich M, Gutterman DD, et al. Acute exertion elicits a H2O2-dependent vasodilator mechanism in the microvasculature of exercise-trained but not sedentary adults. Hypertension. 2015;65(1):140-5. doi: 10.1161/HYPERTENSIONAHA.114.04540.

68. Colberg SR, Azoury KR, Parson HK, Vinik AI. Exercise status affects skin perfusion via prostaglandin, nitric oxide, and EDHF pathways in diabetes. Microvasc Res. 2009;77(2):120-4. doi: 10.1016/j.mvr.2008.11.004.

69. Tyldum GA, Schjerve IE, Tjønna AE, Kirkeby-Garstad I, Stølen TO, Richardson RS, Wisløff U. Endothelial dysfunction induced by post-prandial lipemia: complete protection afforded by high-intensity aerobic interval exercise. J Am Coll Cardiol. 2009;53(2):200-6. doi: 10.1016/j.jacc.2008.09.033.

70. Gill JM, Al-Mamari A, Ferrell WR, Cleland SJ, Packard CJ, Sattar N, Petrie JR, Caslake MJ. Effects of prior moderate exercise on postprandial metabolism andvascular function in lean and centrally obese men. J Am Coll Cardiol. 2004;44(12):2375-82.

71. Padilla DJ, McDonough P, Behnke BJ, Kano Y, Hageman KS, Musch TI, et al. Effects of Type II diabetes on capillary hemodynamics in skeletal muscle. Am J Physiol Heart Circ Physiol. 2006;291(5):H2439-44. Epub 2006 Jul 14.

72. Santos JM, Ribeiro SB, Gaya AR, Appell HJ, Duarte JA. Skeletal muscle pathways of contraction-enhanced glucose uptake. Int J Sports Med. 2008;29(10):785-94. doi: 10.1055/s-2008-1038404.

73. Lund S, Holman GD, Schmitz O, Pedersen O. Contraction stimulates translocation of glucose transporter GLUT4 in skeletal muscle through a mechanism distinct from that of insulin. Proc Natl Acad Sci U S A. 1995;92(13):5817-21.

74. Stanford KI, Goodyear LJ. Exercise and type 2 diabetes: molecular mechanisms regulating glucose uptake in skeletal muscle. Adv Physiol Educ. 2014;38(4):308-14. doi: 10.1152/advan.00080.2014.

75. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JFP, Dela F. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes. 2004;53(2):294-305.

76. Jorge ML, de Oliveira VN, Resende NM, Paraiso LF, Calixto A, Diniz AL, et al. The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and

muscle insulin signaling in patients with type 2 diabetes mellitus. Metabolism. 2011;60(9):1244-52. doi: 10.1016/j.metabol.2011.01.006.

77. Metcalfe RS, Babraj JA, Fawkner SG, Vollaard NB. Towards the minimal amount of exercise for improving metabolic health:beneficial effects of reduced-exertion high-intensity interval training. Eur J Appl Physiol. 2012;112(7):2767-75. doi: 10.1007/s00421-011-2254-z.

78. Derave W, Hansen BF, Lund S, Kristiansen S, Richter EA. Muscle glycogen content affects insulin-stimulated glucose transport and protein kinase B activity. Am J Physiol Endocrinol Metab. 2000;279(5):E947-55.

79. Hoier B, Hellsten Y. Exercise-induced capillary growth in human skeletal muscle and the dynamics of VEGF. Microcirculation. 2014;21(4):301-14. doi: 10.1111/micc.12117.

80. Dimauro I, Mercatelli N, Caporossi D. Exercise-induced ROS in heat shock proteins response. Free Radic Biol Med. 2016. pii: S0891-5849(16)30007-7. doi: 10.1016/j.freeradbiomed.2016.03.028.

81. Mason SA, Morrison D, McConell GK, Wadley GD. Muscle redox signalling pathways in exercise. Role of antioxidants. Free Radic Biol Med. 2016. pii: S0891-5849(16)00073-3. doi: 10.1016/j.freeradbiomed.2016.02.022.

82. Tanaka LY, Bechara LR, dos Santos AM, Jordão CP, de Sousa LG, Bartholomeu T, et al. Exercise improves endothelial function: a local analysis of production of nitric oxide and reactive oxygenspecies. Nitric Oxide. 2015;45:7-14. doi: 10.1016/j.niox.2015.01.003.

83. Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, et al. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. Circulation. 2003;108:530-5.

84. Simões HG, Asano RY, Sales MM, Browne RA, Arsa G, Motta-Santos D, et al.Type 2 diabetes elicits lower nitric oxide, bradykinin concentration and kallikrein activity together with higher DesArg(9)-BK and reduced post-exercise hypotension compared to non-diabetic condition. PLoS One. 2013;8(11):e80348. doi: 10.1371/journal.pone.0080348.

85. Franklin NC, Ali M, Goslawski M, Wang E, Phillips SA. Reduced vasodilator function following acute resistance exercise inobese women. Front Physiol. 2014;5:253. doi: 10.3389/fphys.2014.00253. eCollection 2014.

86. Aoki A, Murata M, Asano T, Ikoma A, Sasaki M, Saito T, et al. Prompt increases in retinol-binding protein 4 and endothelial progenitor cells during acute exercise load in diabetic subjects. Endocr J. 2012;59(12):1085-91.

87. Waclawovsky G1, Umpierre D, Figueira FR, De Lima ES, Alegretti AP, Schneider L, et al. Exercise on Progenitor Cells in Healthy Subjects and Patients with Type 1 Diabetes. Med Sci Sports Exerc. 2016;48(2):190-9. doi: 10.1249/MSS.0000000000000764.

88. Schuler G, Adams V, Goto Y. Role of exercise in the prevention of cardiovascular disease: results, mechanisms and new perspectives. Eur Heart J. 2013;34(24):1790-9. doi: 10.1093/eurheartj/eht111.

89. Sonne MP1, Alibegovic AC, Højbjerre L, Vaag A, Stallknecht B, Dela F. Effect of 10 days of bedrest on metabolic and vascular insulin action: a study in individuals at risk for type 2 diabetes. J Appl Physiol (1985). 2010;108(4):830-7. doi: 10.1152/japplphysiol.00545.2009.

90. Dos Santos JM, Moreli ML, Tewari S, Benite-Ribeiro SA. The effect of exercise on skeletal muscle glucose uptake in type 2 diabetes: An epigenetic perspective. Metabolism. 2015;64(12):1619-28. doi: 10.1016/j.metabol.2015.09.013.

91. Meijer RI, De Boer MP, Groen MR, Eringa EC, Rattigan S, Barrett EJ, Smulders YM, Serne EH. Insulin-induced microvascular recruitment in skin and muscle are related and both are associated with whole-body glucose uptake. Microcirculation. 2012;19(6):494-500. doi: 10.1111/j.1549-8719.2012.00174.

92. Holowatz LA, Thompson-Torgerson CS, Kenney WL. The human cutaneous circulation as a model of generalized microvascular function. J Appl Physiol (1985). 2008;105(1):370-2.

93. Middlebrooke AR, Elston LM, Macleod KM, Mawson DM, Ball CI, Shore AC, et al. Six months of aerobic exercise does not improve microvascular function in type 2 diabetes mellitus. Diabetologia. 2006;49(10):2263-71.

94. Colberg SR, Parson HK, Nunnold T, Holton DR, Swain DP, Vinik AI. Change in cutaneous perfusion following 10 weeks of aerobic training in Type 2 diabetes. J Diabetes Complications.;19(5):276-83.

95. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle modification improves endothelial function in obese subjectswith the insulin resistance syndrome. Diabetes Care. 2003;26(7):2119-25.

96. Krcma M, Cechurova D, Jankovec Z, Lacigova S, Zourek M, Rusavy Z. Effect of mild increase of physical activity on microvasculary reactivity in obese subjects with diabetes mellitus type 2. Exp Clin Endocrinol Diabetes. 2009;117(3):150-2. doi: 10.1055/s-0028-1100417.

97. Colberg SR, Parson HK, Nunnold T, Herriott MT, Vinik AI. Effect of an 8-week resistance training program on cutaneous perfusion in type 2 diabetes. Microvasc Res. 2006;71(2):121-7.

98. Gokce N, Vita JA, Bader DS, Sherman DL, Hunter LM, Holbrook M, et al. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. Am J Cardiol. 2002;90(2):124-7.

99. Sixt S, Beer S, Blüher M, Korff N, Peschel T, Sonnabend M, et al. Long- but not short-term multifactorial intervention with focus on exercise training improves coronary endothelial dysfunction in diabetes mellitus type 2 and coronary artery disease. Eur Heart J. 2010;31(1):112-9. doi: 10.1093/eurheartj/ehp398.

100. Vianna LC, Deo SH, Jensen AK, Holwerda SW, Zimmerman MC, Fadel PJ. Impaired dynamic cerebral autoregulation at rest and during isometric exercise in type 2 diabetes patients. Am J Physiol Heart Circ Physiol. 2015;308(7):H681-7. doi: 10.1152/ajpheart.00343.2014.

101. MacDougall JD, Tuxen D, Sale DG, Moroz JR, Sutton JR. Arterial blood pressure response to heavy resistance exercise. J Appl Physiol. 1985;58:785–90.

102. Maiorana A, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001;38(3):860-6.

103. Naylor LH, Davis EA, Kalic RJ, Paramalingam N, Abraham MB, Jones TW, et al. Exercise training improves vascular function in adolescents with type 2 diabetes. Physiol Rep. 2016;4(4). pii: e12713. doi: 10.14814/phy2.12713.

104. Vinet A, Obert P, Dutheil F, Diagne L, Chapier R, Lesourd B, et al. Impact of a lifestyle program on vascular insulin resistance in metabolic syndrome subjects: the RESOLVE study. J Clin Endocrinol Metab. 2015;100(2):442-50. doi: 10.1210/jc.2014-2704.

105. Lucotti P, Monti LD, Setola E, Galluccio E, Gatti R, Bosi E, et al. Aerobic and resistance training effects compared to aerobic training alone in obese type 2 diabetic patients on diet treatment. Diabetes Res Clin Pract. 2011;94(3):395-403. doi: 10.1016/j.diabres.2011.08.002.

106. Montero D, Vinet A, Roberts CK. Effect of combined aerobic and resistance training versus aerobic training on arterial stiffness. Int J Cardiol. 2015;178:69-76. doi: 10.1016/j.ijcard.2014.10.147.

107. Mitranun W1, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. Scand J Med Sci Sports. 2014;24(2):e69-76. doi: 10.1111/sms.12112.

108. Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation. 2008;118:346–54.

109. Cocks M, Shaw CS, Shepherd SO, Fisher JP, Ranasinghe AM, Barker TA, et al. Sprint interval and endurance training are equally effective in increasing muscle microvascular density and eNOS content in sedentary males. J Physiol. 2013;591(3):641-56. doi: 10.1113/jphysiol.2012.239566

110. Cadore EL, Izquierdo M. Exercise interventions in polypathological aging patients that coexist with diabetes mellitus: improving functional status and quality of life. Age (Dordr);37(3):64. doi: 10.1007/s11357-015-9800-2.

111. Velcheva I, Damianov P, Antonova N, Stoyneva Z, Mantarova S, Dimitrova V. Hemorheology and vascular reactivity in patients with diabetes mellitus type 2. Clin Hemorheol Microcirc. 2011;49(1-4):505-11. doi: 10.3233/CH-2011-1501.

112. Simmonds MJ, Sabapathy S, Serre KR, Haseler LJ, Gass GC, Marshall-Gradisnik SM, Minahan CL. Regular walking improves plasma protein concentrations that promote blood hyperviscosity in women 65-74 yr with type 2 diabetes. Clin Hemorheol Microcirc. 2016 May 30.

113. Brun JF, Varlet-Marie E, Raynaud de Mauverger E, Fedou C, Pollatz M. Hemorheologic effects of low intensity endurance training in type 2 diabetic patients: A pilot study. Clin Hemorheol Microcirc. 2016;61(4):579-89. doi: 10.3233/CH-141916.

114. Koutroumpi M, Dimopoulos S, Psarra K, Kyprianou T, Nanas S. Circulating endothelial and progenitor cells: Evidence from acute andlong-term exercise effects. World J Cardiol. 2012;4(12):312-26. doi: 10.4330/wjc.v4.i12.312.

115. West DJ, Campbell MD, Gonzalez JT, Walker M, Stevenson EJ, Ahmed FW, et al. The inflammation, vascular repair and injury responses to exercise in fit males with and without Type 1 diabetes: an observational study. Cardiovasc Diabetol. 2015;14:71. doi: 10.1186/s12933-015-0235-y.

116. Böhm A, Weigert C, Staiger H, Häring H. Exercise and diabetes: relevance and causes for response variability. Endocrine. 2016;51(3):390-401. doi: 10.1007/s12020-015-0792-6.

117. Stephens NA, Sparks LM. Resistance to the Beneficial Effects of Exercise in Type 2 Diabetes: Are Some Individuals Programmed to Fail? J Clin Endocrinol Metab. 2015;100(1):43-52. doi: 10.1210/jc.2014-2545.