Utility of Contrast-Enhanced Ultrasound for the Assessment of Skeletal Muscle Perfusion in Diabetes Mellitus: A Meta-Analysis

Lin-lin Chen
Jun-xiu Zhai
Jie Kang
You-shan Li

Corresponding Author: Jun-xiu Zhai, e-mail: jxzhai_med@126.com
Source of support: This study was supported by the Science Foundation for Young Scholars of Beijing University of Chinese Medicine (No.2017-JYB-JS-15)

Background: This study evaluated the effectiveness of contrast-enhanced ultrasonography for the assessment of skeletal muscle perfusion in diabetes mellitus.

Material/Methods: Electronic databases (Embase, Google Scholar, Ovid, and PubMed) were searched for required articles, and studies were selected by following pre-determined eligibility criteria. Meta-analyses of mean differences or standardized mean differences (SMD) were performed to evaluate the significance of difference in contrast-enhanced ultrasonography measured muscle perfusion indices between patients with diabetes and healthy individuals or between basal and final values of perfusion indices after insulin manipulation or physical exercise in patients with diabetes or healthy individuals.

Results: There were 15 studies included, with 279 patients with diabetes and 230 healthy individuals in total. The age of the study patients with diabetes mellitus was 55.8 years (95% CI: 49.6 years, 61.9 years) and these patients had disease for 11.4 years (95% CI: 7.7 years, 15.1 years). The percentage of males in group of patients with diabetes was 66% (95% CI: 49%, 84%), body mass index was 29.4 kg/m^2 (95% CI: 26.5 kg/m^2, 32.3 kg/m^2), hemoglobin A1c was 7.3% (95% CI: 6.7%, 7.9%), and fasting plasma glucose was 149 kg/m^2 (95% CI: 118 kg/m^2, 179 kg/m^2). Time to peak intensity after provocation was significantly higher in patients with diabetes than in healthy individuals (SMD 1.18 [95% CI: 0.60, 1.76]; P<0.00001). In patients with diabetes, insulin administration did not improve contrast-enhanced ultrasonography measured muscle perfusion indices but exercise improved muscle perfusion but at a level that was statistically non-significant (SMD between basal and post-exercise values (1.03 [95% CI: –0.14, 2.20]; P=0.08). In healthy individuals, lipids in addition to insulin administration was associated with significantly reduced blood volume and blood flow.

Conclusions: Our review showed that the use of contrast-enhanced ultrasonography showed that diabetes mellitus was associated with altered muscle perfusion in which insulin-mediated metabolic changes played an important role.

MeSH Keywords: Microscopy, Acoustic • Ultrasonography • Ultrasonography, Doppler

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915252
Background

Contrast-enhanced ultrasound (CEU) is a noninvasive technique for quantitative imaging used for several purposes, including vascular perfusion. In this technique, a contrast agent containing inert gas-filled microbubbles (equivalent to red blood cells in size) is injected/infused into the blood circulation. Upon exposure to high-energy ultrasound in the region of interest (ROI), these microbubbles are destroyed. Microbubble replenishment starts from neighboring part of blood vessel and gradually the microbubble intensity is restored in the ROI. Kinetics of microbubbles in ROI are used to estimate perfusion indices, e.g., the concentration of microbubbles when fully replenished is proportional to the microvascular blood volume (MBV), and the rate at which the microbubbles replenish determines the microvascular flow velocity (MFV). MBV represents the total amount of capillaries participating in the microcirculation at a given moment whereas the blood flow is the product of blood volume and flow velocity [1–6].

CEU is used for the measurement of perfusion in skeletal muscles [7–9], cerebral perfusion [10], cranial surgery [11], renal blood flow [12,13], and vascular integrity of free-flap grafts [14,15]. CEU is also a promising method for noninvasive diagnosis of carotid atherosclerotic plaque neovascularization and for the prediction of cerebrovascular and cardiovascular events [16]. CEU may be the preferred method for the assessment of defective skeletal muscle blood flow responses to exercise and to investigate and quantify responses to therapy [17].

Diabetes mellitus is a chronic endocrine and metabolic disorder with increasing global prevalence. Complexity of its pathophysiological mechanisms and adverse effects on metabolic and vascular processes leading to neuropathies and cardiovascular complications forms the basis of high morbidity and mortality [18]. The global prevalence of diabetes in adults has increased from 4.7% in 1980 to 8.5% in 2014. In 2015, diabetes caused an estimated 1.6 million deaths [19]. Type 2 diabetes mellitus is associated with a high risk of macrovascular and microvascular complications for which insulin resistance and endothelial dysfunction play a major role. Insulin also plays important roles in the regulation of vascular tone and tissue perfusion by vasodilating the pre-capillary arterioles in muscle and hence increasing the microvascular perfusion and capillary exchange surface area in muscle [20]. Muscle perfusion changes according to the metabolic demand of skeletal muscle as changes in oxygen consumption and metabolite supply are large and quick. For this to be accurately detected, measuring the low skeletal muscle perfusion at rest and particularly capillary blood flow in a defined muscle volume is essential [4].

Several studies have used CEU for the assessment of muscle perfusion in patients with diabetes as well as in healthy individuals to evaluate the effect of insulin modulation in muscle perfusion at rest or during exercise. However, there has been no synthesis of such studies so far. The present study was designed to conduct a literature survey of relevant studies and to perform a meta-analysis of CEU measured muscle perfusion indices in patients with diabetes and healthy individuals in order to evaluate the effectiveness of this diagnostic tool in measuring diabetic muscle perfusion.

Material and Methods

The present study was carried out by following Cochrane Collaboration guidelines and is reported in accordance with PRISMA statement.

Inclusion and exclusion criteria

Inclusion criteria were as follows: a study a) used CEU for skeletal muscle perfusion evaluations in diabetes mellitus patients and matched the outcomes in non-diabetic controls; b) evaluated the effect of insulin administration on muscle perfusion in diabetic patients; c) evaluated the effect of muscle exercise on muscle perfusion in diabetic patients; and d) evaluated the effect of insulin administration with or without lipid administration in healthy individuals. Exclusion criteria were as follows: a study a) used CEU in diabetic patients but did not use a control group for comparison; b) reported associational outcomes rather than values or changes of indices; c) used ultrasonography without contrast agents; and d) used CEU for related conditions such as peripheral artery disease or systemic sclerosis in non-diabetic patients.

Literature search

A comprehensive literature search was carried out in electronic databases (Embase, Google Scholar, Ovid, and PubMed) for the identification and acquisition of relevant research articles. Important keywords and MeSH terms used in logical combinations were: contrast enhanced ultrasound/sonography, CEU/CEUS, diabetes mellitus, insulin, resistance, exercise, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), time to peak intensity (TTP), maximum time, occlusion, provocation, contrast agent, microbubbles, MBV, blood flow, flow velocity, diagnosis, diagnostic accuracy, calf muscles, forearm flexor, microvasculature and muscle reperfusion. The search encompassed research articles published before September 2018 in the English language. Additionally, research articles were manually searched from the references list of relevant original studies and review articles.
Data and analyses

Data regarding the demographic, anthropometric, clinical, pathological characteristics of the patients and methodological, analytical, and outcome data of the included studies along with other relevant information were obtained from research articles retrieved from databases and were organized in datasheets. Quality of the included studies was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the United States National Institutes of Health [21].

Meta-analysis endpoints were: a) difference in “time to peak intensity” after a provocation between patients with diabetes and healthy individuals; b) difference in blood flow indices between patients with diabetes and healthy individuals; c) change in blood flow indices in patients with diabetes after insulin administration or muscle exercise; and d) effect of lipid addition to insulin administration on muscle perfusion indices in healthy individuals.

Meta-analyses of mean differences (MD) or standardized mean differences (SMD) were performed with RevMan software (version 5.3; Cochrane Collaboration) under random effects model. Overall effect size of each meta-analysis was an inverse variance weighted average of the individual studies outcome. I² index was used to estimate statistical heterogeneity between the studies. Data are presented as weighted average with 95% confidence interval (CI).

Results

Fifteen studies [22–36] were included in the meta-analysis (Figure 1). These observational studies recruited a total of 279 patients with diabetes and 230 healthy individuals to assess skeletal muscle perfusion. ROI in these studies was either in the deep forearm flexor muscle or in the calf muscle. Contrast agents consisted of either lipid microbubbles containing sulphur hexafluoride gas (Sonovue brand) or microbubbles containing lipid-shelled octafluoropropane (Definity brand). In these studies, the contrast agents were either given as bolus injection or infused at a rate of 1 mL to 1.5 mL per minute.

Characteristics of the included studies are given in Table 1. Age of diabetes mellitus patients was 55.8 years (95% CI: 49.6 years, 61.9 years) and these patients had disease for 11.4 years (95% CI: 7.7 years, 15.1 years). Percentage of males in the healthy individuals was 48% (95% CI: 40%, 56%). In general, the quality of the included studies was moderate. Outcomes of the quality assessment of the included studies are presented in Table 2.

TTP after provocation was significantly higher in patients with diabetes than in healthy individuals (SMD 1.18 [0.60, 1.76]; P<0.00001). The blood flow was also significantly less in patients with diabetes in comparison to healthy individuals (–0.49 [–0.94, –0.05]; P=0.03) (Figure 2).

In patients with diabetes, insulin administration did not significantly improve muscle perfusion (SMD between post-insulin and basal values was –0.16 (95% CI: −0.86, 0.54; P=0.65) (Figure 3). In obese non-diabetic individuals too, the insulin administration significantly improved muscle perfusion (SMD between post-insulin and basal values –1.56 (95% CI: −2.49, –0.64; P=0.0009). On the other hand, exercise improved muscle perfusion in patients with diabetes, but statistically non-significantly (SMD between post-exercise and basal values 1.03 [95% CI: −0.14, 2.20]; P=0.08).

In healthy individuals, insulin administration significantly increased skeletal muscle blood volume (MD final minus baseline values 0.76 [95% CI: 0.37, 1.15]; P=0.0001), and blood flow (MD 0.82 [95% CI: 0.28, 1.35]; P=0.003) but not blood flow velocity (MD –1.32 [95% CI: −3.42, 0.79]; P=0.22) after 120 minutes of infusion. In these healthy individuals, lipids in addition to insulin administration was associated with significantly reduced blood volume and blood flow (Figure 4). The SMD of the mean change between insulin-lipid and insulin-only administration was −0.54 (95% CI: −0.92, −0.16, P=0.006) for blood volume and −0.62 (95% CI: −1.17, −0.06, P=0.03) for blood flow. However, SMD of the mean change in blood flow velocity between insulin-lipid and insulin-only administration was not significantly different (1.07 [95% CI: −0.54, 2.67]; P=0.19).
Discussion

CEU studies in patients with diabetes and healthy individuals have shown that muscle perfusion in diabetes is altered, in which insulin resistance plays an important role. Moreover, exercise may improve muscle perfusion in people with diabetes. CEU studies in healthy individuals have shown that insulin administration enhances muscle perfusion, but the addition of lipids to insulin administration attenuates this improvement, which supports the understanding that fats play a role in insulin resistance.
Table 2. Quality assessment of the included studies.

| Criteria                                                                 | Reference number of the study |
|--------------------------------------------------------------------------|-------------------------------|
| Was the research question or objective in this paper clearly stated and appropriate? | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
| Was the study population clearly specified and defined?                  | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | N | N | N |
| Did the authors include a sample size justification?                     | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? | NA | NA | NA | Y | Y | N | Y | N | Y | NA | NA | Y | NA | Y | NA | Y |
| Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Were the cases clearly defined and differentiated from controls?          | NA | NA | NA | Y | Y | N | Y | NA | NA | Y | NA | Y | NA | Y | NA | Y |
| If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Was there use of concurrent controls?                                    | NA | NA | NA | Y | Y | N | Y | NA | NA | Y | NA | Y | NA | Y | NA | Y |
| Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Were the assessors of exposure/risk blinded to the case or control status of participants? | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

N = no; NA = not applicable; Y = yes.

Muscle microvasculature forms an interface between the circulatory system and muscle interstitium for the exchange of nutrients and byproducts. Several factors including exercise, mixed meal, and pharmacological agents act to recruit muscle microvasculature, which may increase insulin delivery to cause. Thus, insulin resistance leads to altered muscle microvasculature recruitment. Inflammatory cytokines, free fatty acids, and angiotensin II type 1 receptor activation affect microvascular recruitment by affecting insulin resistance [20].

Amarteifio et al. [37] found a moderate inverse correlation between glycated hemoglobin, HbA1c, and the maximum CEU signal following the transient arterial occlusion (r=−0.53) in individuals with type 2 diabetes which indicated that elevated HbA1c might be directly associated with a decrease in local muscle micro-perfusion. Using ultrasound B-mode, color Doppler, and pulse wave Doppler imaging for foot arteries in 73 individuals with diabetes and non-diabetic individuals, Leoniuk et al. [38] found a positive correlation between HbA1c and flow resistance index in patients with type 2 diabetes. In the present study, a trend was seen between the%HbA1c and SMD of CEU measures of muscle perfusion between patients with diabetes and non-diabetic individuals (meta-regression coefficient 2.92 (CI 95%: −0.40, 6.23; P=0.073), although there was limited available data to study such a relationship collectively.

Other CEU studies have also reported important correlational data in this regard. In their regression analyses, Russel et al. [34] found that changes in muscle MBV response after resistance training significantly correlated with reductions in FPG and HbA1c after adjusting for age, sex, % body fat, and % lean mass. In the study of Lindner et al. [31], the combined angiographic severity score correlated with exercise blood flow (r=0.70, P=0.003) and flow reserve (r=0.56, P=0.047) in non-diabetic individuals with peripheral artery disease but not in diabetic peripheral artery disease patients. Chan et al. [24] found that diabetic microvascular complications were significantly correlating with the effect of supraphysiological insulin levels on capillary recruitment or de-recruitment in patients with type 1 diabetes. Thus, supraphysiological insulin levels increased...
### Table 3.1: Time to peak intensity after provocation

| Study or subgroup | Mean (SD) | Total | Weight | Std. mean difference (IV, random, 95% CI) |
|------------------|-----------|-------|--------|------------------------------------------|
| **Diabetes**     |           |       |        |                                          |
| Dourscheid 2008  | 25.5 (6)  | 10    | 16     | 14.2%                                    |
| Irace 2017 LV     | 89.1 (28.7) | 25 | 81.2 | 19.7%                                    |
| Irace 2017 SV     | 5.6 (2.2)  | 25    | 4      | 19.4%                                    |
| Song 2014         | 81 (37)   | 58    | 38     | 23.1%                                    |
| **Healthy**      |           |       |        |                                          |
| Total (95% CI)    |           |       | 170    | 100.0%                                   |

Heterogeneity: Tau² = 0.32, Chi² = 17.03, df=4 (P=0.002); I² = 77%
Test for overall effect: Z=2.18 (P=0.03)

### Table 3.2: Blood flow

| Study or subgroup | Mean (SD) | Total | Weight | Std. mean difference (IV, random, 95% CI) |
|------------------|-----------|-------|--------|------------------------------------------|
| Irace 2017 BF     | 133 (62)  | 25    | 121    | 15.9%                                    |
| Irace 2017 TAPV   | 35 (14)   | 25    | 34     | 15.9%                                    |
| Lindner 2008 BF   | 7.9 (5.9) | 19    | 20     | 16.3%                                    |
| Lindner 2008 FR   | 7.4 (5)   | 19    | 13.1   | 17.4%                                    |
| Wommack 2009 BF Exer | 312 (113) | 22 | 390 | 17.2%                                    |
| Wommack 2009 BF Rest | 150 (84.4) | 22 | 190   | 17.2%                                    |
| **Total (95% CI)** |           |       | 132    | 100.0%                                   |

Heterogeneity: Tau² = 0.20, Chi² = 14.04, df=5 (P=0.002); I² = 64%
Test for overall effect: Z=2.18 (P=0.03)

### Figure 2. A forest graph showing the outcomes of a meta-analysis of standardized mean difference between patients with diabetes and healthy individuals in CEU measured muscle perfusion indices. In study identities abbreviations are as follows.

- BF – blood flow; FR – flow reserve; Exer – exercise; LV – large vessel; SV – small vessel; TAPV – time average peak velocity.

### Figure 3. A forest graph showing the outcomes of a meta-analysis of standardized mean difference between basal and post intervention values of muscle perfusion indices in patients with diabetes. In study identities abbreviations are as follows.

- BABF – brachial artery blood flow; MBF – microvascular blood flow; MBV – microvascular blood volume; MFV – microvascular flow velocity.

MBV in individuals with low insulin sensitivity and increased microvascular complications but decreased MBV in individuals with high insulin sensitivity and increased microvascular complications [24]. However, Emanuel et al. [29] found no correlation of peripheral insulin sensitivity with skeletal muscle MBV at baseline, or with MBV during hyperinsulinemia or with the percent change in MBV. Peripheral insulin sensitivity also did not significantly correlate with MBV during hyperinsulinemia and combined vasodilator (iloprost) infusion, or with the MBV percentage change.
induced by combined insulin and iloprost infusion in patients with type 2 diabetes.

Ultrasound studies have found that the intima-media thickness (IMT) correlates with age (r=0.6; P<0.05) as well as with the duration of diabetes (r=0.35; P<0.05) [39]. IMT values were significantly higher in children with insulin-dependent diabetes than in healthy children [40]. In children with diabetes, IMT values increased with age and were higher in boys in both diabetic and non-diabetic children. However, in children with diabetes, IMT did not correlate with disease duration [40].

In one study, a negative correlation was observed between the change in MBV and BMI (r=10.482, P=0.027) in response to insulin administration in obese individuals [26]. Age and ankle-brachial index are not found to correlate significantly with the TTP [28]. In the present study we also found that there was no significant relationship between age and SMD in CEU measured muscle perfusion indices between diabetic and non-diabetic individuals (meta-regression coefficient 0.053 (95% CI: -0.109, 0.215); P=0.487). In muscle, glucose metabolism is associated strongly with interstitial insulin levels in comparison with plasma insulin levels, and transendothelial transport acts as rate limiting factor for the action of insulin on muscle glucose metabolism. It has been shown that in patients with diabetes, exercise can improve impaired vasodilation in response to insulin infusion [41] and exercise increases arterial blood flow after glucose ingestion in patients with well-controlled type 2 diabetes [42]. In healthy individuals too, exercise has been found to be associated with significantly increased MBV acutely after exercise [43], whereas hemodynamic effects of insulin were blunted in patients with type 2 diabetes [44,45].

Using CEU in healthy individuals, studies have shown that insulin increases glucose uptake to increase capillary recruitment and consequently blood flow [7,46–48].

CEU is one of the useful methods to assess defective skeletal muscle blood flow responses to exercise and to quantify responses of a prescribed therapy. Weber et al. [3] found CEU feasible for skeletal muscle perfusion quantification when they used CEU for measuring skeletal muscle perfusion and compared it with microvascular density in muscle biopsies. They found that CEU measured local blood volume significantly related to fiber-adjacent capillarization reflective of physiologic capillary recruitment. Based on comparability of the coefficient of variation of MBV with previous findings [49,50], Mertz et al. 2011 [42], found CEU was as effective as contemporary methods for MBV assessment. However, technical issues need careful consideration to achieve reliable outcomes, e.g., selection of the ROI is a tedious and time-consuming process which needs the presence of a trained analyst. Availability of more systematic ROI selection methods can further improve the reliability of CEU-based outcomes [25].
The present study had several limitations. First, there was limited data available regarding CEU muscle perfusion for patients with diabetes, especially with regards to different indices such as TTP, MBV, MBF, and MFV, and conditions such as non-insulin dependent diabetes mellitus and type 1 diabetes mellitus. This necessitated us to use SMD-based meta-analyses, and therefore we could not estimate the quantum of difference. This may have also contributed to higher statistical heterogeneity. Because all of the included studies were observational in design, the qualitatively generated data may only be ranked at a moderate level. Some relevant studies could not be included because these studies lacked a control and still other studies reported associational outcomes rather than indices or their changes.

References:

1. Wei K, Jayaweera AR, Fioozan S et al: Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation, 1998; 97: 473–83
2. Xirix M, Kiessling F, Farhan N et al: A multivessel model describing replenishment kinetics of ultrasound contrast agent for quantification of tissue perfusion. Ultrasound Med Biol, 2003; 29: 1421–30
3. Weber MA, Krakowski-Roosen H, Delorme S et al: Relationship of skeletal muscle perfusion measured by contrast-enhanced ultrasonography to histologic microvascular density. J Ultrasound Med, 2006; 25: 583–91
4. Weber MA, Xirix M, Delorme S: Quantitative evaluation of muscle perfusion with CEUS and with MR. Eur Radiol, 2007; 17: 2663–74
5. Mulder AH, van Dijk AP, Smits P, Tack CJ: Real-time contrast imaging: A new method to monitor capillary recruitment in human forearm skeletal muscle. Microcirculation (New York, NY), 1994, 2008; 15: 203–13
6. Sjöberg KA, Rattigan S, Hiscock N et al: A new method to study changes in microvascular blood volume in muscle and adipose tissue: Real-time imaging in humans and rat. Am J Physiol Heart Circ Physiol, 2011; 301: H450–58
7. Coggins M, Krakowski-Roosen H, Delorme S et al: Physiologic hyperinsulinemia enhances human skeletal muscle perfusion by capillary recruitment. Diabetes, 2001; 50: 2682–90
8. Dawson D, Vincent MA, Barrett EL et al: Vascular recruitment in skeletal muscle during exercise and hyperinsulinemia assessed by contrast ultrasound. Am J Physiol Endocrinol Metab, 2002; 282: E714–20
9. Ross RM, Downey K, Newman JM et al: Contrast-enhanced ultrasound measurement of microvascular perfusion relevant to nutrient and hormone delivery in skeletal muscle: A model study in vitro. Microvasc Res, 2008; 75: 323–29
10. Rim SJ, Leong-Poi H, Lindner JR et al: Quantification of cerebral perfusion with "Real-Time" contrast-enhanced ultrasound. Circulation, 2001; 104: 2582–87
11. Lekht I, Brauner N, Bakhshehsian J et al: Versatile utilization of real-time intraoperative contrast-enhanced ultrasound in cranial neurosurgery: Technical note and retrospective case series. Neurosurg Focus, 2016; 40: E6
12. Schneider AG, Goodwin MD, Scheltema A et al: Contrast-enhanced ultrasound to evaluate changes in renal cortical perfusion around cardiac surgery: A pilot study. Critical Care (London, England), 2013; 17: R138
13. Wang L, Wu J, Cheng JF et al: Diagnostic value of quantitative contrast-enhanced ultrasound (CEUS) for early detection of renal hyperperfusion in diabetic kidney disease. J Nephrol, 2015; 28: 669–78
14. Christiansen JP, Leong-Poi H, Amiss LR et al: Skin perfusion assessed by contrast ultrasound predicts tissue survival in a flap model. Ultrasound Med Biol, 2002; 28: 315–20
15. Prantz L, Pfister K, Kubale R et al: Value of high-resolution ultrasound and contrast enhanced US pulse inversion imaging for the evaluation of the vascular integrity of free-flap grafts. Clin Hemorheol Microcirc, 2007; 36: 203–16
16. Huang R, Abdelmoneim SS, Ball CA et al: Detection of carotid atherosclerotic plaque neovascularization using contrast enhanced ultrasound: A systematic review and meta-analysis of diagnostic accuracy studies. J Am Soc Echocardiogr, 2016; 29: 491–502
17. Porter TR: Capillary blood flow abnormalities in the skeletal muscle and microvascular complications in diabetes lessons that cannot be learned from larger vessels. J Am Coll Cardiol, 2009; 53: 2184–85
18. Guthrie RA, Guthrie DW: Pathophysiology of diabetes mellitus. Crit Care Nurs Q, 2004; 27: 113–25
19. World Health Organization. Diabetes. Factsheet. http://www.who.int/en/news-room/fact-sheets/detail/diabetes
20. Liu Z, Ko SH, Chai W, Cao W: Regulation of muscle microcirculation in health and diabetes. Diabetes Metabol J, 2012; 36: 83–89
21. U.S. Department of Health & Human Services – National Institutes of Health. Study Quality Assessment Tools: Quality assessment tool for observational cohort and cross-sectional studies. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
22. Chai W, Liu J, Jahn LA et al: Salsalate attenuates free fatty acid-induced microvascular and metabolic insulin resistance in humans. Diabetes Care, 2011; 34: 1634–38
23. Chan A, Breton MD, Kovatchev BP: Contrast-enhanced ultrasound imaging of insulin-induced microvascular recruitment in type 1 diabetes. Proc 7th IFAC Symposium on Modelling and Control in Biomed Systems. Aalborg, Denmark, August 12–14, 2009
24. Chan A, Kovatchev BP, Anderson SM, Breton MD: Systematic method to assess microvascular recruitment using contrast-enhanced ultrasound. Application to insulin-induced capillary recruitment in subjects with T1DM. Comput Methods Programs Biomed, 2011; 102: 219–26
25. Clerk LH, Vincent MA, Jahn LA et al: Obesity blunts insulin-mediated microvascular recruitment in human forearm muscle. Diabetes, 2006; 55: 1436–42
26. Dueschmidt D, Maletzki P, Freudig C et al: Analysis of muscle microcirculation in advanced diabetes mellitus by contrast enhanced ultrasound. Diabetes Res Clin Pract, 2008; 81: 88–92
27. Dueschmidt D, Zhou Q, Rink E et al: Simplified contrast ultrasound accurately reveals muscle perfusion deficits and reflects collateralization in PAD. Atherosclerosis, 2009; 202: 505–12
28. Emanuel AL, de Clercq NC, Koopen AM et al: Iloprost infusion prevents the insulin-induced reduction in skeletal muscle microvascular blood volume but does not enhance peripheral glucose uptake in type 2 diabetic patients. Diabetes Obes Metab, 2018; 20(11): 2523–31
29. Iacce C, Messintti V, Tassone B et al: Evidence for congruent impairment in micro and macrovascular function in type 1 diabetes. PLoS One, 2017; 12: e0187525
30. Keske MA, Clerk LH, Price WJ et al: Obesity blunts microvascular recruitment in human forearm muscle after a mixed meal. Diabetes Care, 2009; 32(9): 1672–77

Conclusions

Contrast-enhanced perfusing imaging of muscle perfusion indices such as TTP, MBV, MBF, and MFV have indicated that diabetes mellitus is associated with altered muscle perfusion in which insulin mediated metabolic changes play an important role as insulin administration to healthy but not diabetic individuals was associated with increased muscle perfusion. Moreover, the administration of lipids with insulin attenuated muscle perfusion in healthy individuals. Nevertheless, limited data were available for individual muscle perfusion indices in individuals with diabetes, which necessitates further studies for refinement of these outcomes.
31. Lindner JR, Womack L, Barrett EJ et al: Limb stress-rest perfusion imaging with contrast ultrasound for the assessment of peripheral arterial disease severity. JACC Cardiovasc Imaging, 2008; 1: 343–50
32. Liu J, Jahn LA, Fowler DE et al: Free fatty acids induce insulin resistance in both cardiac and skeletal muscle microvasculature in humans. J Clin Endocrinol Metab, 2011; 96: 438–46
33. Liu Z, Liu J, Jahn LA et al: Infusing lipid raises plasma free fatty acids and induces insulin resistance in muscle microvasculature. J Clin Endocrinol Metab, 2009; 94: 3543–49
34. Russell RD, Hu D, Greenaway T et al: Skeletal muscle microvascular-linked improvements in glycemic control from resistance training in individuals with type 2 diabetes. Diabetes Care, 2017; 40: 1256–63
35. Song Y, Li Y, Wang PJ, Gao Y: Contrast-enhanced ultrasonography of skeletal muscles for type 2 diabetes mellitus patients with microvascular complications. Int J Clin Exp Med, 2014; 7: 573–79
36. Womack L, Peters D, Barrett EJ et al: Abnormal skeletal muscle capillary recruitment during exercise in patients with type 2 diabetes mellitus and microvascular complications. J Am Coll Cardiol, 2009; 53: 2175–83
37. Amarteifio E, Wormsbecher S, Demirel S et al: Assessment of skeletal muscle microcirculation in type 2 diabetes mellitus using dynamic contrast-enhanced ultrasound: A pilot study. Diab Vasc Dis Res, 2013; 10: 468–70
38. Leonluk J, Lukasiewicz A, Szorc M et al: Doppler ultrasound detection of preclinical changes in foot arteries in early stage of type 2 diabetes. Pol J Radiol, 2014; 79: 283–89
39. Wolski C, Rotkiewicz A, Grzelak P et al: Comparison of tomographic coronary artery calcium score and ultrasound assessment of intima-media complexity thickness in diabetic subjects. Pol J Radiol, 2011; 76(4): 15–20
40. Tołwińska J, Urban M, Florys B et al: Ultrasonographic evaluation of common carotid artery wall in children with type 1 diabetes. Med Sci Monit, 1998; 4(3): CR72–80
41. Holten MK, Zacho M, Gaster M et al: Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes, 2004; 53: 294–305
42. Mikus CR, Fairfax ST, Libla JL et al: Seven days of aerobic exercise training improves conduit artery blood flow following glucose ingestion in patients with type 2 diabetes. J Appl Physiol (Bethesda, MD: 1985), 2011; 111: 657–64
43. Mertz KH, Bulow J, Holm L: Contrast-enhanced ultrasound using bolus injections of contrast agent for assessment of postprandial microvascular blood volume in human skeletal muscle. Clin Physiol Funct Imaging, 2018; 38: 864–71
44. Baron AD, Laakso M, Brechtle G et al: Reduced postprandial skeletal muscle blood flow contributes to glucose intolerance in human obesity. J Clin Endocrinol Metab, 1990; 70: 1525–33
45. Laakso M, Edelman SV, Brechtle G, Baron AD: Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. Diabetes, 1992; 41: 1076–83
46. Vincent MA, Clerk LH, Lindner JR et al: Microvascular recruitment is an early insulin effect that regulates skeletal muscle glucose uptake in vivo. Diabetes, 2004; 53: 1418–23
47. Zhang L, Vincent MA, Richards SM et al: Insulin sensitivity of muscle capillary recruitment in vivo. Diabetes, 2004; 53: 447–53
48. Clerk LH, Vincent MA, Lindner JR et al: The vasodilatory actions of insulin on resistance and terminal arteries and their impact on muscle glucose uptake. Diabetes Metab Res Rev, 2004; 20: 3–12
49. Mulder AH, Dijk APV, Smits P, Tack CJ: Real-time contrast imaging: A new method to monitor capillary recruitment in human forearm skeletal muscle. Microcirculation (New York, NY: 1994), 2010; 15: 203–13
50. Tobin L, Simonsen L, Bulow J: Real-time contrast-enhanced ultrasound determination of microvascular blood volume in abdominal subcutaneous adipose tissue in man. Evidence for adipose tissue capillary recruitment. Clin Physiol Funct Imaging, 2010; 30: 447–52

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]