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Exercise-induced alterations of retinal vessel diameters and cardiovascular risk reduction in obesity

H. Hanssen[a,e,*], T. Nickel[b,1], V. Drexel[a], G. Hertel[a], I. Emslander[b], Z. Sisic[b], D. Lorang[a], T. Schuster[c], K.E. Kotliar[d], A. Pressler[a], A. Schmidt-Trucksäss[e], M. Weis[b], M. Halle[a]

[a] Department of Prevention and Sports Medicine, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
[b] Medizinische Klinik und Poliklinik 1, Campus Grosshadern, Ludwig-Maximilians-Universität, Munich, Germany
[c] Department for Medical Statistics and Epidemiolgy, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
[d] Department of Ophthalmology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
[e] Division of Sports Medicine, Institute of Exercise and Health Sciences, Medical Faculty, University of Basel, Switzerland

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ABSTRACT

Background: The retinal microcirculation is affected early in the process of atherosclerosis and retinal vessel caliber is an emerging cardiovascular risk factor. Obesity is associated with vascular dysfunction. Here, we investigate the effect of regular exercise on retinal vessel diameters in lean and obese runners. We analyze a possible link to alterations of the nitric oxide (NO)-asymmetric dimethylarginine (ADMA) pathway.

Methods: Retinal vessel diameters were assessed by means of a static vessel analyzer (SVA-T) in 15 obese athletes (OA), 14 lean amateur athletes (AA) and 17 lean elite athletes (EA) following a 10 week training program. ADMA serum levels were detected by ELISA and dimethylarginine dimethylaminohydrolase (DDAH) -1/-2 mRNA-expression in peripheral mononuclear cells (PBMC) was analyzed by real time PCR.

Results: At baseline, the mean (±SD) arteriolar to venular diameter ratio (AVR) was impaired in obese (OA: 0.81 ± 0.05) compared to lean subjects (AA: 0.87 ± 0.07; EA: 0.94 ± 0.05). The individual fitness levels correlated with AVR (rho = +0.66; $P < 0.001$) and the training program improved AVR in all groups ($P < 0.001$), normalising AVR in the obese (OA: 0.86 ± 0.1). A training-induced arteriolar dilatation was found in OA ($P = 0.01$), which was accompanied by a significant decrease of ADMA levels (0.56 ± 0.12–$0.46 \pm 0.12\ \mu mol\ l^{-1}$; $P < 0.028$). DDAH-1 mRNA levels in PBMC increased in all groups ($P < 0.01$).

Conclusions: Cardiovascular fitness and body composition affect retinal vessel diameters. Regular exercise reverses the subclinical impairment of the retinal microvasculature in obesity by inducing retinal arteriolar dilatation. The NO/ADMA pathway may play a key role in the training-induced improvement of microvascular function, which has the potential to counteract progression of small vessel disease.

1. Introduction

There is compelling evidence that overweight and obesity are associated with increased cardiovascular risk and all cause mortality [1,2]. It has been shown that obesity is accompanied by the development of arterial stiffness and microvascular dysfunction [3,4]. The retinal microcirculation is an easily accessible vasculature that is affected early in the process of structural and functional changes of atherosclerosis [5,6]. Large cohort studies have previously shown that narrower retinal arterioles, wider retinal venules and a resulting lower arteriolar to venular diameter ratio (AVR) are associated with the presence and severity of hypertension [7], risk of stroke and a higher cardiovascular mortality [8–10]. Furthermore, wider retinal venular diameters are associated with risk of obesity [11].

Lifestyle modifications, including increased physical activity, have been shown to improve endothelial function and microvascular reactivity in obese subjects [12,13]. However, no interventional study to date has investigated the effect of regular aerobic exercise training on retinal vessel diameters in subjects with different training status and body composition.

Nitric oxide (NO) plays a central role in the regulation of vasomotor tone. Retinal vessels are part of the cerebral vasculature and are mainly regulated by nitric oxide [14]. Asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor and a

* Corresponding author at: Department of Prevention and Sports Medicine, Technische Universität München, Connollystrasse 32, 80809 Munich, Germany.
Tel.: +0041 61 3778759; fax: +0041 61 3778758.
E-mail address: henner.hanssen@unibas.ch (H. Hanssen).
[1] Equally contributed author.

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known independent cardiovascular risk factor, has been shown to directly affect retinal arteriole and venule diameter [15]. Next to other detrimental cardiovascular effects, ADMA is a biomarker for the development of hypertension [15], atherosclerosis [16], stroke [17] and insulin resistance [18]. A strong relationship between body mass index (BMI) and plasma levels of ADMA has also been found [19]. The metabolism of ADMA is facilitated by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). Changes in DDAH activity are likely to affect NO synthesis, since 90% of ADMA is hydrolyzed by the DDAH-1 and -2 isoforms [20,21].

A handful of studies have examined the effect of exercise training on ADMA serum concentrations in disease states. Exercise has been shown to decrease circulating ADMA levels in patients with metabolic syndrome and subjects at risk of coronary events [22,23]. This is the first study to date to examine DDAH mRNA gene-expression in vivo in human PBMCs as an accessible model for DDAH expression in vascular cells.

No study to date has examined the effects of an exercise intervention on retinal vessel diameters. Therefore, our primary objective was to investigate the effects of regular exercise training on AVR as a cardiovascular risk factor. Furthermore, we aimed to investigate changes in obesity-related impairments of the retinal microcirculation and to analyze a possible link between an exercise-induced improvement of the microvasculature, circulating ADMA levels and the expression of DDAH in vascular cells.

2. Materials and methods

2.1. Study design

60 recreational runners with different fitness levels were recruited by a study appeal in a local newspaper and by written invitations sent to local running clubs. Due to musculoskeletal injuries and respiratory tract infections, 14 participants dropped out of the study in the course of the 10 week training program. The study was approved by the Hospital's Ethics Committee. Recruitment was limited to male candidates who volunteered for an individually tailored, supervised training program.

The sample size was restricted in order to ensure optimal individual state of the art supervised exercise training over a time period of 10 weeks. Subjects were divided into two age-matched groups depending on the extensiveness of training. Training group one was scheduled for $\leq$40 km/week, characterized by seasonal exercise only. Group two was scheduled for $\geq$70 km/week with regular exercise training throughout the year (elite athletes; EA). Within the first group of recreational runners, subjects were divided into obese (obese athletes; OA) and non-obese participants (lean amateur athletes; AA). The study design was set to analyze the effect of different levels of physical fitness and body composition on the retinal microcirculation before and after the training program.

A medical history and general questionnaire, a physical examination including blood pressure measurements and fasting blood samples were obtained. Assessments included fundoscopy for analysis of retinal microcirculation and a symptom-limited treadmill ergometry for determination of the individual aerobic–anaerobic threshold (IAT). Screening was performed less than one week before and after the training program.

2.2. Inclusion and exclusion criteria

Inclusion criteria were male recreational runners aged 30–60 years with or without obesity as a cardiovascular risk factor, who were otherwise healthy. Criteria for obese subjects were a waist circumference (WC) of $\geq$102 cm (NCEP-ATP-III criteria) with a body mass index (BMI) of $\geq$27 kg/m^2. Exclusion criteria consisted of known coronary or structural heart disease, insulin-dependent diabetes mellitus, drug treatment for type 2 diabetes or hypertension, renal dysfunction, chronic inflammatory and musculoskeletal disease. All participants gave written informed consent.

2.3. Exercise training protocol

Participants took part in a 10 week endurance exercise program developed by sports scientists according to the current guidelines [24]. The exercise program consisted of continuous aerobic exercise and anaerobic interval training including concomitant warm-up and cool-down periods with a gradual increase in duration and intensity during the cause of the 10 week training program.

Before the start of the training program each participant performed a symptom-limited treadmill ergometry to determine the individual anaerobic threshold, allowing exact classification of training intensity and fitness levels. Accordingly, an individual training program for each participant was prescribed with regard to current fitness levels and health state. The intensity of training was calculated from individual target heart rates and was monitored during training. Supervised exercise training was offered four times a week. Training was documented with respect to intensity, duration and kilometres run per week by a written protocol. Improvement of cardiovascular fitness was evaluated comparing the individual IAT pre- and post-training of the treadmill ergometry.

2.4. Retinal microcirculation and the arteriolar to venular ratio

Analysis was performed using the Static Retinal Vessel Analyzer (SVA-T, Imedos Systems UG, Jena, Germany). The system allows non-invasive online measurement of the diameter of retinal vessels without mydriasis. It consists of a fundus camera and an advanced image processing unit [25].

For static analysis, 3 valid images were taken from the retina of the left and right eye, with an angle of 30° and the optic disc in the center. Retinal arterioles and venules, coursing through an area of 0.5–1 disc diameter from the margin of the optic disc, were identified using special analyzing software identifying retinal vessels in ring-zones (Vesselmap 2, Visualis, Imedos Systems UG) (Fig. 1). A detailed and standardized evaluation of retinal vessel diameters was performed on higher-magnification images. All retinal arterioles and venules were differentiated by the examiner in the outer ring zone and measured by the automated software. Vessel diameters below $\leq$45 μm were generally discarded. Diameters were calculated to central retinal arteriolar and venular equivalents (CRAE, CRVE), using the Parr-Hubbard formula described elsewhere [25]. The CRAE and CRVE were used to calculate the arteriolar-to-venular-ratio (AVR), taking the mean of the right and left eye results. Vessel diameters are presented in measuring units (mu). In the model of Gullstrand's normal eye, 1 mu relates to 1 μm. The assessment of the retinal vessels was performed by a single experienced examiner.

2.5. Blood sampling and laboratory methods

2.5.1. Measurement of ADMA

Before and after the 10 week exercise training program blood samples of each participant were drawn. For the analysis of ADMA concentrations, serum samples were collected and immediately centrifuged. The serum was extracted and immediately frozen at −80 °C. Measurements of ADMA levels were performed using a commercially available ELISA as recommended by the manufacturer (DLD Diagnostika GmBH, Hamburg, Germany) and as described recently [26]. The ELISA is a competitive enzyme

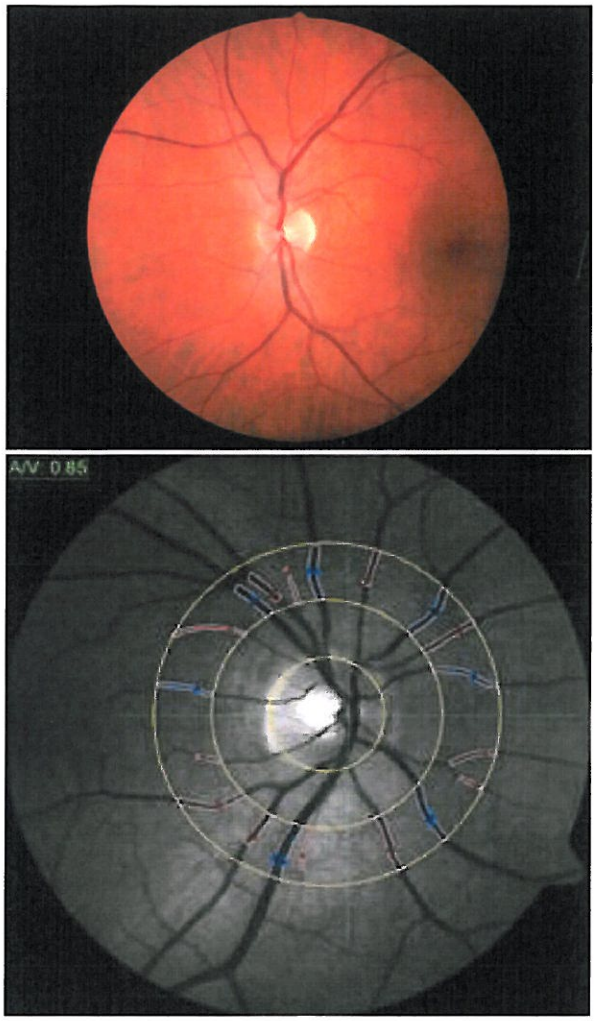

Fig. 1. Above: Fundoscopy of the human retina taken with the Retinal Vessel Analyzer (RVA). Below: Visualis analyzing software identifying retinal vessels in ring-zones and measuring arteriolar and venular diameters and calculating the central retinal arteriolar equivalent (CRAE), the central retinal venular equivalent (CRVE) and the arteriolar-to-venular ratio (AVR).

immunoassay that has been validated against high-performance liquid chromatography [27].

2.5.2. DDAH gene-expression

In an animal model, Dayal et al. recently showed that tissue mRNA- expression of DDAH-1 and -2 correlate both with the tissue protein expression as well as the tissue activity of DDAH-1 and -2 [28]. We therefore targeted the mRNA gene-expression of both isoforms in readily accessible circulating human peripheral blood mononuclear cells.

Peripheral mononuclear cells (PBMC) were isolated from fresh ETDA blood by ficol gradient. For the measurement of DDAH mRNA gene-expression in PBMC, the RNeasy Mini Kit (Cat. 74104) from Qiagen (Hilden, Germany) was used according to the manufactures recommendations. The chosen quantitative RT-PCR-System allows optimal implementation of the SYBR Primer (Qiagen, Germany). RT-PCR was established by the use of the ABIPRISMTM 7700 System (Applied Biosystems, Germany). Data analysis was performed using the delta-CT-method. The primer sequences (MWG-Biotech AG, Germany) are as follows:

GAPDH: 1 5′-CGG AGT CAA CGG ATT TGG TCG TAT-3′; 2 5′-AGC CTT CTC CAT GGT GGT GAA GAC-3′. DDAH-1: 1 5′-GGC AAT ACT GGA AAG GTG GA-3′; 2 5′AAC CTG CAG GAA TCA GCC TA 3′. DDAH-2: 1 5′-AGC-TGC-TGA-CTG-CCT-CTT-TC-3′; 2 5′-CCA-GTT-CTG-AGC-AGG-ACA-CA-3′.

2.6. Statistical analysis

2.6.1. Sample size considerations

This is the first study to assess the effect of exercise training on retinal vessel diameters. Therefore, sample size calculations were not possible to be performed on the basis of expected exercise-induced changes of retinal vessel diameter in an interventional study approach. However, power calculations based on our data (standard deviation of AVR changes) revealed that, with a sample size of 46, changes in AVR of $\geq$0.025 were detectable with 80% power at a two-sided level of significance of 5%. A previous study by Wang et al. on a population-based cohort study demonstrated that changes in AVR of $\geq$0.01 are relevant comparing obese with normal weight individuals [11]. Additional power calculations for the smallest group ($n = 14$) revealed detectable changes in AVR of $\geq$0.057 with 80% power at a two-sided level of significance of 5%

2.6.2. Data analysis

Statistics were performed using the SPSS statistical package version 16.0 (SPSS, Inc., Chicago, IL). The mean ± standard deviation was reported for descriptive purposes and box plots were chosen to illustrate the distribution of quantitative data. To compare anthropometric parameters, serum biomarkers and data from the retinal vessel analysis between the subgroups, analysis of variance (ANOVA) and/or Kruskal–Wallis test were used followed by pairwise Student's *t*-tests and/or Mann–Whitney-*U* tests in terms of a hierarchical test procedure. The paired sample *t*-test or Wilcoxon-signed rank test was used to assess differences in two related measurements. For quantification of bivariate monotonous correlation, the Spearman correlation coefficient (rho) was determined. A *P*-value <0.05 was considered to indicate statistical significance.

3. Results

3.1. Clinical characteristics

All groups were aged matched. At baseline, OA showed a WC of 106 ± 5 cm, a BMI of 30 ± 2 kg/m^2 and a body fat composition of 27 ± 3%. The IAT was lowest in the group of obese athletes with 10.6 ± 0.8 km/h compared to AA (11.9 ± 0.9 km/h) and EA (13.3 ± 1.4 km/h) (Table 1). During the 10 week training program all three groups improved their IAT with the most significant increase in OA (0.58 ± 0.51; $P = 0.001$) (Table 1). Exercise-induced changes in IAT, vital parameters and body composition are shown in Table 1.

3.2. Retinal microcirculation

The lowest baseline AVR was found in obese subjects (OA) (0.81 ± 0.05). AVR in lean amateur athletes (AA) was lower compared to lean elite athletes (EA) (0.87 ± 0.07, $P = 0.004$ and 0.94 ± 0.05, $P < 0.001$; respectively and compared to OA). Endurance training improved AVR significantly in all groups (post-training: OA 0.86 ± 0.07; AA 0.91 ± 0.07; EA 0.96 ± 0.06; $P < 0.001$ for all). Interestingly, AVR in obese amateur runners reached normal values post-training, comparable to those of lean amateur runners before training (Fig. 3a). There was a substantial positive correlation between AVR and the individual fitness level before training (rho = +0.66; $P < 0.001$) and after training (rho = +0.61; $P < 0.001$) Fig. 2.

Obese subjects had a significantly narrower retinal arteriolar diameter (CRAE) at baseline (170 ± 18 mu) compared to EA (190 ± 13 mu; $P < 0.001$), whereas the mean difference of about

Table 1
Clinical characteristics.

	OA age 40 ± 6 years (n = 15)			AA age 40 ± 6 years (n = 14)			EA age 40 ± 7 years (n = 17)		
	Pre	Post	P	Pre	Post	P	Pre	Post	P
BMI (kg/m^2)	30 ± 2	29 ± 2	0.014	25 ± 2	24 ± 2	0.058	23 ± 2	22 ± 1	0.007
WC (cm)	106 ± 5	103 ± 7	0.024	87 ± 8	86 ± 7	0.468	83 ± 8	81 ± 7	0.022
Body fat (%)	27 ± 3	24 ± 3	0.058	17 ± 5	15 ± 4	0.006	13 ± 4	11 ± 2	0.024
RRsystol (mmHg)	136 ± 12	138 ± 11	0.513	127 ± 15	131 ± 10	0.054	127 ± 9	128 ± 11	0.073
RRdiastol (mmHg)	89 ± 8	86 ± 9	0.039	84 ± 6	80 ± 8	0.002	84 ± 8	77 ± 4	0.006
Heart rate (min)	59 ± 9	54 ± 8	0.094	58 ± 10	58 ± 9	0.897	55 ± 10	53 ± 7	0.116
IAT (km/h)	10.6 ± 0.8	11.1 ± 1	0.001	11.6 ± 0.9	12.1 ± 0.7	0.003	13.6 ± 1.4	14.1 ± 1	0.006

10 mu compared to AA (180 ± 14 mu) was statistically not significant. At baseline, CRAE differed significantly between the two groups of lean athletes (P = 0.025). A significant training-induced arteriolar dilatation was only detectable in obese subjects (OA: from 170 ± 18 mu to 181 ± 13 mu; P = 0.01) and not in lean individuals (mean changes ± sd: AA 2.4 ± 4.7 (P = 0.083) and EA 0.5 ± 11.7 (P = 0.87); Fig. 3b).

There was no significant difference between the venular diameters (CRVE) of the groups at baseline, although OA showed a tendency for wider retinal venules. A significant exercise-induced venular constriction was seen in AA (from 206 ± 9 mu to 201 ± 10 mu; P = 0.013). A similar but statistically not significant tendency was seen in EA runners (203 ± 14 mu to 199 ± 11 mu; P = 0.063) and changes in obese runners where less pronounced in consideration of a higher data variability (211 ± 22 mu to 205 ± 33 mu; P = 0.11; Fig. 3c).

3.3. *ADMA levels and DDAH mRNA-levels*

There was a tendency for elevated baseline ADMA levels in obese subjects (OA: 0.56 ± 0.12 μmol l^{-1}, AA: 0.52 ± 0.13 μmol l^{-1}, EA: 0.47 ± 0.10 μmol l^{-1}). However, no significant heterogeneity in ADMA levels between the groups was detectable (P = 0.125). Most importantly, ADMA concentrations decreased significantly during

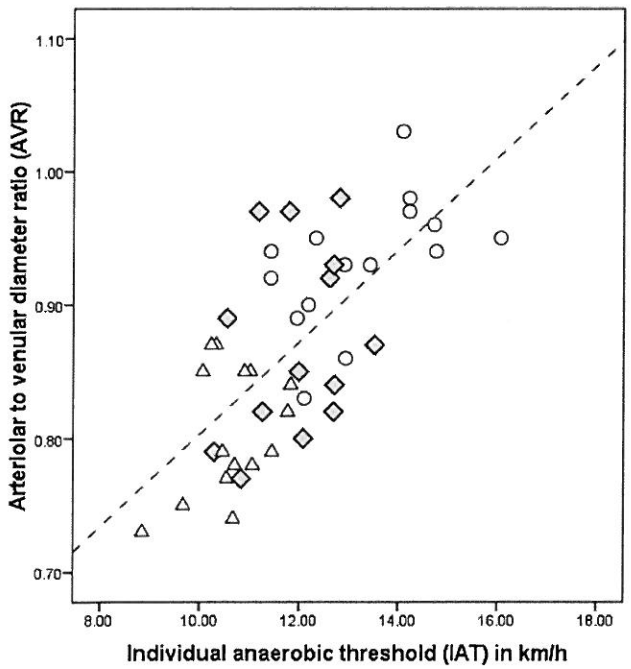

Fig. 2. Correlation between AVR and the individual fitness level (IAT); r^2 linear = 0.47. White triangles: obese athletes (OA), grey diamonds: amateur athletes (AA); white circles: elite athletes (EA).

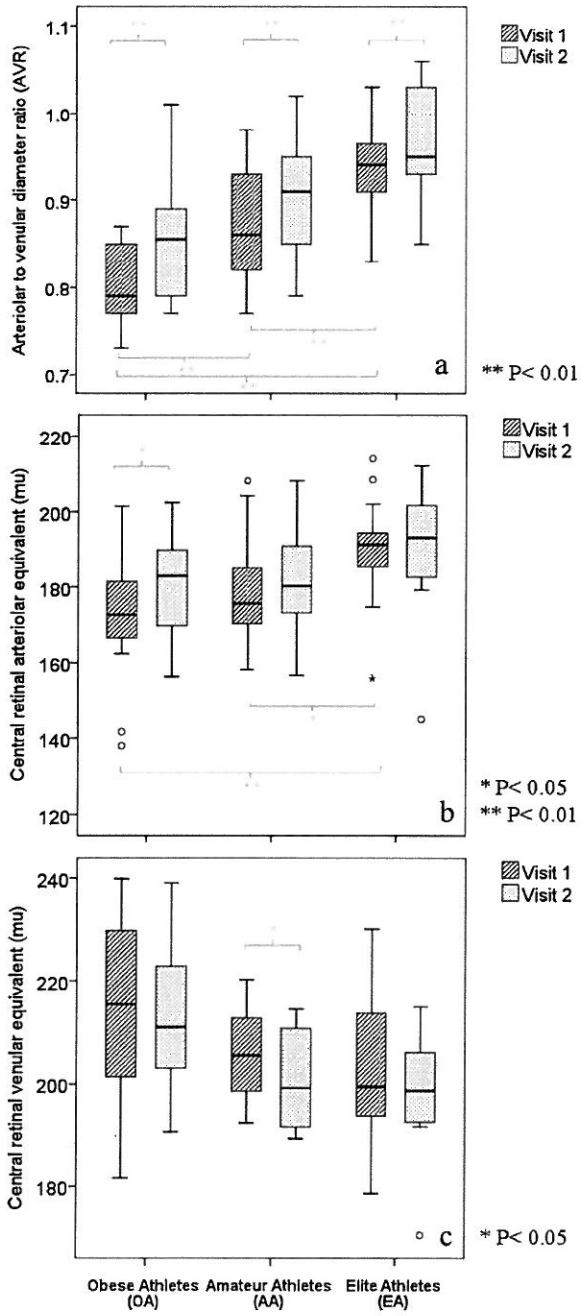

Fig. 3. (a) Group dependent retinal arteriolar-to-venular diameter ratio (AVR) before and after the training program; (b) group dependent retinal arteriolar diameters (CRAE); (c) group dependent retinal venular diameters (CRVE). Striped box-plots: baseline (Visit 1); dotted box-plots: post-training (Visit 2); * = significant increase.

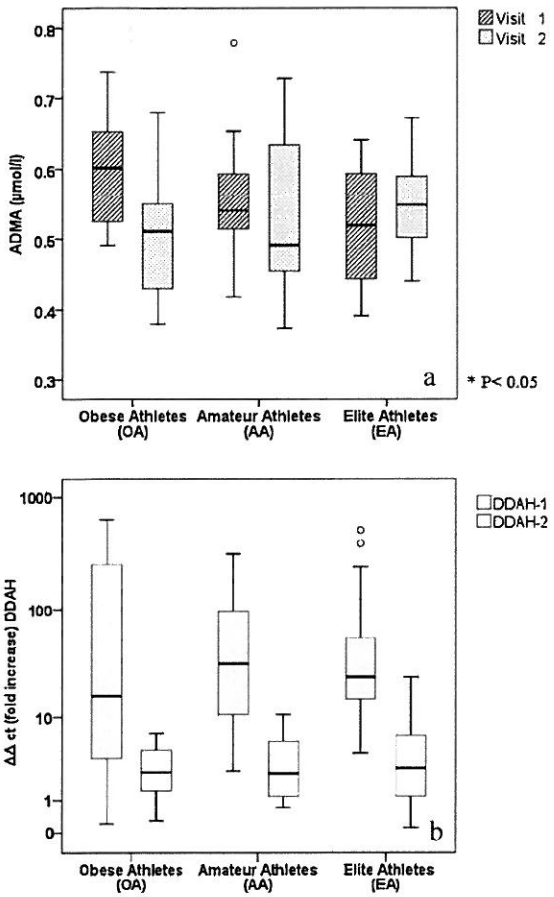

Fig. 4. (a) Group dependent ADMA levels before and after the exercise training program. Striped box-plot: baseline (Visit 1); dotted box-plots: post-training (Visit 2); * = significant increase. (b) Group dependent fold increase (Δct) of DDAH-1 (grey box-plot) and DDAH-2 (white box-plots) mRNA gene-expression after the training program.

training in OA only (0.56 ± 0.03–$0.46 \pm 0.03\ \mu mol\ l^{-1}$; $P = 0.028$). There were no significant exercise-induced ADMA changes in lean athletes (Fig. 4a).

DDAH-1 mRNA gene-expression increased in all groups after the training program (Fig. 4b, grey box-plots). Although the median fold increase was less pronounced in OA (16 fold, IQR: 3.4–283; $P < 0.01$) compared to AA (31 fold, IQR: 7.4–101; $P < 0.01$) and EA (23 fold, IQR: 6.5–56; $P < 0.01$), the highest absolute changes were observed in the OA group (Fig. 4b). There was a negative correlation between DDAH-1 mRNA and ADMA serum levels in obese subjects (rho = −0.51), which failed to reach statistical significance ($P = 0.10$) in this relatively small group.

The median increase of DDAH-2 mRNA in PBMC was less pronounced compared to DDAH-1 mRNA (OA: 2.5 fold, $P < 0.01$; AA: 3.0 fold, $P < 0.01$; EA: 3.7 fold, $P < 0.01$) (Fig. 4b, white box-plots). The differences of DDAH-1/2 expression between the groups were not significant.

4. Discussion

This study examined the effects of regular exercise training on the retinal microcirculation in obesity. Few studies to date have shown that obesity is associated with an impairment of the human microcirculation [11,29]. Our results demonstrate an association between obesity and an impaired retinal microcirculation in otherwise healthy humans. We are able to show, for the first time, that the retinal arteriolar to venular diameter ratio is strongly influenced by the level of cardiovascular fitness. There is a strong relation between retinal vessel diameters and the individual fitness level: the higher the individual physical fitness, the higher the AVR of retinal vessels. The work presented has several clinical implications. In addition to metabolic influences, physical fitness seems to play a central role in the regulation of the retinal microcirculation. This is strongly supported by our finding, that regular aerobic exercise improves the impairment of AVR in obesity. This is of clinical relevance, since alterations of retinal vessel diameters and AVR have been shown to predict cardiovascular morbidity and mortality [8–10].

Most previous studies focused on the assessment of AVR in the retinal microcirculation. This parameter has indeed been shown to be a valid indicator for cardiovascular risk. However, AVR does not sufficiently describe the differences of vascular adaptations in arterioles and venules, which has been demonstrated in the Rotterdam study [30]. Vessels of the microcirculation may contrarily react to different determinants. The Rotterdam study, for example, illustrated an association of arteriolar diameter with blood pressure and venular diameter with inflammation. A low AVR may be caused by narrow arterioles or wide venules. To discriminate the effects of exercise training on retinal vessels, the results are analyzed separately for CRAE and CRVE.

Exercise-induced arteriolar dilatation was significant in obese runners only. However, a tendency for increased arteriolar dilatation was also found in the lean groups. While regular exercise mediated dilatation in retinal arterioles, it caused enhanced constriction in retinal venules, reaching significance in lean amateur athletes. In consideration of the relatively high venular data variability, it is comprehendible that venular constriction failed to reach significance in all groups. The combination of increased arteriolar dilatation and venular constriction explains the significant increase of AVR observed in all groups. Interestingly, venular dilatation is associated with increased cardiovascular risk and inflammation in obesity [31,32] whereas arteriolar narrowing is related to incident hypertension and stroke [10,30]. On this basis it is feasible to suggest, that the detected exercise-induced arteriolar dilatation and venular constriction, together with the consequent reduction of AVR, have the potential to reduce cardiovascular risk and counteract progression of small vessel disease.

What mechanisms may be responsible for the beneficial microvascular effects of exercise training? Regular endurance exercise is known for its anti-inflammatory effects in health and disease [33]. Since venular dilatation in obesity has been associated with systemic inflammation [31], the anti-inflammatory effect of regular endurance exercise is most likely to be responsible for the venular constriction after the training program.

The molecular mechanisms involved in the regulation of the retinal arteriolar tone in obesity are not known. Our results represent indirect evidence that the amelioration of AVR in obese subjects is mediated by an exercise-induced improvement of endothelial function in retinal arterioles. The vascular tone of retinal arteries in humans is mainly regulated by nitric oxide [14,34]. It is therefore plausible to assume that changes in nitric oxide availability in metabolic disease influence retinal arteriolar vessel diameters. The underlying mechanisms are likely to be multifactorial, but our results indicate a possible link to systemic ADMA levels and DDAH expression in vascular cells.

The plasma levels of ADMA in most human studies are within the range of 0.3–0.5 $\mu mol\ l^{-1}$ which is consistent with our findings [35]. In the obese group, ADMA serum concentrations decreased significantly during the 10 week training period. Since ADMA has been shown to be an independent cardiovascular risk factor [15–18], the exercise-induced reduction of ADMA levels in obesity, in addition

to the amelioration of AVR, reflects a relevant cardiovascular risk reduction in this cohort.

The reduction of ADMA levels was associated with an increased arteriolar dilatation in obese runners. The decrease in systemic ADMA levels was accompanied by an enhanced DDAH-1 mRNA gene-expression in PBMCs. Notably, DDAH mRNA expression has previously been correlated with tissue protein expression as well as tissue activity of DDAH [28].

Compared to the effect of training on the expression of DDAH-1, exercise-induced increase of DDAH-2 gene-expression was much lower. DDAH-1 gene expression in vascular cells seems more susceptible to exercise training than DDAH-2. We hypothesize that regular exercise affects the NO/ADMA pathway predominantly by an upregulation of DDAH-1. DDAH-1 may prove to be an important mediator of the adaptive effects of regular exercise on the vasculature. In our study, the negative correlation between DDAH-1 expression and ADMA levels (rho = −0.51) failed to reach significance due to the relatively small sample size. Therefore, the effect of DDAH-1 expression on systemic ADMA levels needs to be verified in larger cohort studies in order to prove the suggested mechanistic link of increased DDAH-1 mRNA expression, reduced ADMA serum levels and the presented microvascular changes in obesity.

There are some limitations to the present study. Due to the intensified supervised exercise training, the number of participants had to be restricted to small groups. In addition, the dropout rate was relatively high, as is often the case in exercise intervention studies. Larger studies, including physically inactive obese individuals undergoing less sophisticated training protocols, are warranted to determine achievable results.

From a methodological point of view, magnification of the lens needs to be considered when estimating individual absolute diameters of retinal vessels. This does not apply for the calculations of AV-Ratio and the analysis of changes comparing pre- to post-intervention data. Our study was performed under the assumption that the individual reproduction scales were equally and randomly distributed in all groups. When comparing baseline results, the individual variation of refraction is reflected in the statistical spread (SD/IQR) and is accounted for in the test of significance. In addition, our data is expressed as measuring units (mu), defining 1 mu as 1 μm in Gullstrand's normal eye. Vasomotion may also affect variation of vessel diameters. However, this will also have caused random misclassification. The strength of our study, in contrast to previous studies, is the fact that three valid photographs of each eye were taken to assess mean vessel diameters to optimize accuracy. By doing so, the effect of vasomotion on vessel diameter is substantially reduced.

In conclusion, retinal vessel caliber and AVR are strongly related to the individual physical fitness. An impairment of the retinal microcirculation has been shown to be associated with higher cardiovascular risk and mortality [8–10]. Our results show that regular exercise has the potential to improve retinal vessel caliber and decrease circulating ADMA levels in obesity. Regular exercise may prove to be an effective means to reverse the subclinical impairment of the retinal microvasculature and to prevent vascular manifestations in metabolic disease.

Disclosure

No author states any conflicts of interest.

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