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Review Article

Circulating microRNA profiles in different arterial territories of stable atherosclerotic disease: a systematic review

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Abstract: Aims: Atherosclerosis is associated with altered circulating microRNA profiles. It is yet unclear whether the expression of these potential biomarkers differs according to the location of atherosclerosis. We assessed whether atherosclerosis of different arterial territories, except the coronary, is associated with specific circulating microRNA profiles. Methods: A systematic search in PubMed, Web of Science, Embase, and Cochrane Library was carried out using a retrieval strategy including MESH and non-MSH terms. Eligible studies have compared circulating microRNA profiles between individuals with and without stable atherosclerotic disease of large or medium size arteries. The review protocol was registered in PROSPERO database (reference CRD42017073846). Results: Eighteen studies were selected for qualitative synthesis: ten focused on carotid, six on lower limbs, and two on renal arteries atherosclerosis, none reporting on other locations. A common microRNA profile to different atherosclerotic disease locations was identified, including deregulation of miR-21, miR-30, miR-126, and miR-221-3p. Specific microRNA profiles for each territory were also identified, with consistency across studies, such as deregulation of miR-21 and miR-29 in carotid atherosclerosis, and let 7e, miR-27b, miR-130a, and miR-210 in lower limbs atherosclerosis. The robustness of the results was very high for let 7e, miR-29, miR-30, considering both the adjustment of microRNA expression for baseline variables and the replication of results in different studies (miR-29 in carotid, let 7e in lower limbs, and miR-30 in carotid and lower limbs atherosclerosis). Globally, the deregulated microRNAs are associated with control of angiogenesis, endothelial cell function, inflammation, cholesterol metabolism, oxidative stress and extracellular matrix composition. Conclusions: A common microRNA profile to different atherosclerotic disease locations and specific microRNA profiles for each territory were identified. These findings may provide insights into pathophysiology and be useful for selecting potential biomarkers for clinical practice. To the best of our knowledge, no systematic data on this subject has been reported.

Keywords: Atherosclerosis, circulating, disease location, microRNA

Introduction

MicroRNAs are endogenous, non-coding small (18-22 nucleotides) RNA molecules that mediate complex biological processes [1, 2]. The presence of atherosclerotic disease is associated with altered circulating microRNA profiles, which have been studied for a better understanding of pathophysiology and as potential biomarkers for diagnosis [1-3]. Nevertheless, it is unclear whether the expression profile of these mediators differs according to the location of atherosclerosis. For coronary artery disease, several reviews report a specific microRNA signature [3-5], including a recent systematic review that has compiled the most relevant microRNAs described in the literature for diagnostic purposes [3]. The identified microRNAs were found to regulate endothelial function and angiogenesis (miR-1, miR-133), vascular smooth muscle cell differentiation (miR-133, miR-145), communication between vascular smooth muscle and endothelial cell to stabilize plaques (miR-145), apoptosis (miR-1, miR-133,

miR-499), cardiac myocyte differentiation (miR-1, miR-133, miR-145, miR-208, miR-499), and cardiac hypertrophy (miR-133) [3]. For other locations of atherosclerotic disease data are heterogeneous and it may be difficult to select the most appropriate microRNAs for research or clinical purposes. The knowledge of how circulating microRNA profiles vary according to the presence of atherosclerosis in different arterial territories could provide further insights into pathophysiology and be useful for selecting potential biomarkers for clinical practice [1, 2]. Of note, since circulating microRNAs are more likely to be used as biomarkers in the near future than microRNAs isolated from tissues or cells, the former should be given more relevance in research targeting new diagnostic methods [2].

We aimed to assess whether atherosclerosis of each of the main arterial territories, apart from the coronary, is associated with specific circulating microRNA profiles. We focused the search on atherosclerosis of the aorta and aortic branches with large or medium size diameter.

Methods

This study followed the PRISMA reporting guidelines for systematic reviews [6]. The review protocol was registered in PROSPERO (International database of prospectively registered systematic reviews in health and social care), reference CRD42017073846.

Literature search

Eligible studies published up to 1 December 2017 with no lower date limit were selected through conducting a systematic literature search of public databases including PubMed, Web of Science, Embase, and Cochrane Library, without language limitation.

A retrieval strategy including MESH and non-MSH terms was created with the input from an expert librarian, and was used in each database: ("human" OR "humans" OR "patient" OR "patients" OR "control" OR "controls" OR "group" OR "groups") AND ("plasma" OR "serum" OR "blood" OR "circulating" OR "circulation") AND ("atherosclerosis" OR "arteriosclerosis" OR "artery" OR "aorta" OR "aortic" OR "aorto" OR "carotid" OR "cerebrovascular" OR "brachiocephalic trunk" OR "superior limbs" OR "subclavian" OR "vertebral" OR "axillary" OR "brachial" OR "renal" OR "mesenteric" OR "celiac trunk" OR "lower limbs" OR "peripheral artery disease" OR "iliac" OR "femoral" OR "popliteal") AND ("microrna" OR "micro RNA" OR "micrornas" OR "mirs" OR mirna").

Inclusion and exclusion criteria

To be eligible, studies had to fulfill the following criteria: 1) to compare circulating microRNA profiles between individuals with and without *de novo* stable atherosclerotic disease of the aorta or aortic branches with large or medium size diameter; and 2) to be performed in humans. Exclusion criteria were: 1) studies reporting microRNA profiles obtained from specific cells, or tissues other than blood (studies reporting on microRNA profiles obtained from specific blood cells were excluded); 2) studies only addressing microRNA profiles for acute ischemic processes, such as stroke; 3) studies only addressing microRNA profiles for the coronary artery territory; 4) studies only addressing microRNA profiles for restenosis after revascularization; 5) studies with duplicate data reported in other studies; and 6) letters, editorials, case reports or reviews.

Data extraction

A title and abstract screening of all unique articles retrieved was performed by two independent reviewers (TPS and MCC). From this screening, a full text assessment was carried out for potentially eligible articles; in case of doubt, the article was accepted for full text assessment.

After final agreement on the eligible studies, the reviewers independently extracted data from these studies using a predefined form sheet, including: name of the first author, country of origin of the study, possible coincident samples with other eligible studies, arterial disease location, diagnostic method and definition of atherosclerosis, exclusion of atherosclerosis in other territories, sample size, inclusion of a derivation and a validation cohort, age, male: female ratio, particular/specific sample characteristics, baseline differences between groups, methods of microRNA quantification, type of specimens for microRNA quantification, pool of

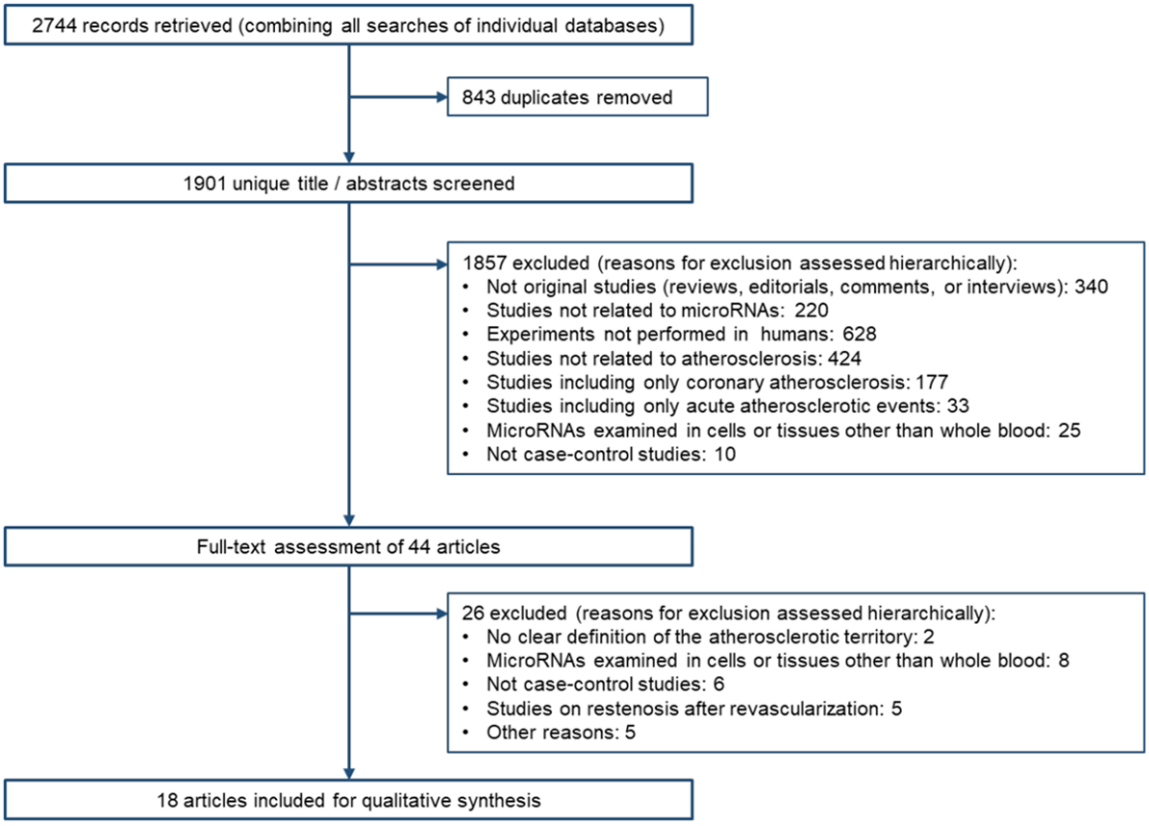

Figure 1. Selection of studies. Flowchart with records identification, screening, eligibility and inclusion.

microRNAs tested in the derivation, validation, and total cohorts, RNA quality assessment, use of internal control, microRNAs up- and down-regulated, statistical test used, and adjustment of altered microRNA expression for baseline clinical or demographical differences. Missing data were requested from corresponding authors.

Quality assessment

The quality of each included study was scored independently by two reviewers (TPS and MCC), using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria [7]. The four key domains (patient selection, index test, reference standard, and flow and timing) were assessed using seven questions applied to each study. The answer "no" (scores 1) means that the risk of bias or applicability concerns can be judged low, the answer "yes" (scores 0) means that the risk can be judged high, and the score for the answer "unclear" was judged by the two reviewers. The maximum score for each study was 7. The individual scores were recorded for each study.

At any step, a third reviewer was consulted in case of discordance, and disagreement was settled through multilateral discussion.

Results

A flowchart describing records identification, screening, eligibility and inclusion is presented in **Figure 1**. A total of 1901 unique title/abstracts were retrieved, after combining all searches of individual databases and eliminating duplicates. A full-text assessment was carried out in 44 articles and 18 were included for qualitative synthesis.

Data extracted from the 18 included studies, which were all case-control studies, are presented in **Tables 1-4** [8-25]. Ten studies focused on carotid arteries, six on lower limbs arteries, of which two were on atherosclerosis obliterans, and two on renal arteries. There were no studies addressing the circulating microRNA profiles of atherosclerosis of other arteries with large or medium size diameter. Carotid artery disease was defined according to ultrasound criteria in all studies, lower limbs atherosclero-

Table 1. Basic data and sample groups definition of each included study

Study	Disease location	Country	Possible coincident patients*	Diagnostic method	Disease definition	Search in other arterial territories
Tsai PC et al. [8]	Carotid	Taiwan	-	US	Atherosclerosis: *score* (grade and extension) (plaque: ≥50% thickness)	No previous myocardial infarction
Zhang X et al. [9]	Carotid	China	-	US	IMT >1.3 mm	No ischemic heart disease
Zhang R et al. [10]	Carotid	China	-	US	Plaque: IMT >1.3 mm, >0.5 mm thicker, IMT ≥150% or lumen defect ≥10 mm^2	No
Zhang JY et al. [11]	Carotid	China	-	US	Not specified**	No
Huang YQ et al. [12]	Carotid	China	[13-16]	US	Atherosclerosis: IMT ≥1.2 mm Normal: IMT ≤0.9 mm	No history of CAD or CV disease
Huang Y et al. [13]	Carotid	China	[12, 14-16]	US	IMT >0.9 mm	No history of CAD, carotid artery occlusion, previous CV disease or PVD
Huang Y et al. [14]	Carotid	China	[12, 13, 15, 16]	US	IMT >0.9 mm	No history of CAD, PVD or carotid artery occlusion
Liu CZ et al. [15]	Carotid	China	[12-14, 16]	US	IMT >1.2 mm	No history of CAD
Huang YQ et al. [16]	Carotid	China	[12-15]	US	IMT >0.9 mm	No history of CAD
Liu K et al. [17]	Carotid	China	-	US	Not specified	No history of CAD
Stather PW et al. [18]	LL	UK	[18]	Not specified	IC + TAISC II type B or C lesion on imaging	No chest pain
Stather PW et al. [19]	LL	UK	[17]	US	IC + arterial stenosis/occlusion on US	No
Signorelli SS et al. [20]	LL	Italy	-	US	IC/vasodilators/revascularization + ABI ≤0.9 Controls: ABI >1.0 and no risk factors for LL atherosclerosis	No
Vegter EL et al. [21]	LL	Netherlands (17 centers)	-	Not specified ("medical history of LL")	Not specified (medical history of LL atherosclerosis)	Yes (21/24 patients with CAD and/or previous CV event)
Li T et al. [22]	LL/AO	China	-	Angiography (ABI and PWV complementary)	IC/ischemic rest pain + angiography Controls: no symptoms	No
He XM et al. [23]	LL/AO	China	-	Angiography (ABI and PWV complementary)	IC/ischemic rest pain + angiography Controls: no symptoms	No
Park MY et al. [24]	Renal	USA	[25]	US or MR/CT angio	Peak systolic velocity >200 cm/s/stenosis >60%/post-stenotic dilation	No CAD
Zhu XY et al. [25]	Renal	USA	[24]	Not specified	Not specified	No

*Reference number is presented; **Images acquired according to the American Society of Echocardiography Carotid Intima-Media Thickness Task Force [26]. ABI-ankle-brachial index; AO-atherosclerosis obliterans; CAD-coronary artery disease; CT-computed tomography; CV-cerebrovascular; IC-intermittent claudication; IMT-intima-media thickness; LL-lower limbs; MR-magnetic resonance; PVD-peripheral vascular disease; PWV-pulse wave velocity; TAISC-Trans-Atlantic Inter-Society Classification; UK-United Kingdom; US-ultrasound; USA-United States of America.

sis according to clinical and imaging criteria (with some heterogeneity across studies), and renal artery disease according to Doppler ultrasound or noninvasive angiography criteria. Concomitant atherosclerotic disease in other major arterial territories was excluded systematically in only two studies addressing carotid artery disease. Regarding clinical and demographic characteristics, age and gender distribution were similar across most studies; classical cardiovascular risk factors were more prevalent in patients compared to controls, as expected. Of note, four studies included both derivation and validation cohorts. Considering the methods for microRNA quantification, microRNAs were analyzed from serum or plasma samples, using robust reverse transcription polymerase chain reaction techniques. The selected microRNAs for analysis differed across studies, including studies on the same disease location. Complete data on quality assessment of each study, according to QUADAS-2, is presented in **Table 5**. Most studies scored 4 points according to QUADAS classification.

Table 2. Sample size and baseline patient's characteristics of each included study

Study	Sample size (patients vs. controls)	Derivation (D) and validation (V) cohorts	Mean age (SD), or median age (range)	Male ratio	Specific sample characteristics	Differences in clinical and demographic data	Differences in treatment
Tsai PC et al. [8]	66 vs. 157	No D cohort	61 (7) vs. 56 (9)	48% vs. 60%	NA	Age, DM, HTN, hyperlipidemia	Not specified
Zhang X et al. [9]	22 vs. 22	No D cohort	50 (1) vs. 45 (2)	18% vs. 23%	NA	Age, total cholesterol, LDL-c, triglyceride levels	Not specified
Zhang R et al. [10]	177 vs. 155	D: 4 vs. 4	66 (11) vs. 56 (12)	Not specified	NA	Age, smoking history, LDL-cholesterol, history of HTN, DM, CVD and CAD	Not specified
Zhang JY et al. [11]	285 vs. 285	Screening set: 25 vs. 25 Training set: 40 vs. 40 Validation set: 200 vs. 200 Double-blind set: 20 vs. 20	70% vs. 68%>60 years	62% vs. 59%	All diabetic	Not specified (possibly smoking status and body mass index)	Not specified
Huang YQ et al. [12]	45 vs. 85	No D cohort	49 (5) vs. 51 (5)	42% vs. 54%	NA	C-reactive protein	No previous medication*
Huang Y et al. [13]	26 vs. 14	No D cohort	46 (5) vs. 49 (6)	58% vs. 36%	NA	None	No previous medication*
Huang Y et al. [14]	60 vs. 60	No D cohort	51 (6) vs. 50 (6)	47% vs. 53%	NA	Not specified**	No previous medication*
Liu CZ et al. [15]	85 vs. 85	No D cohort	52 (6) vs. 50 (5)	48% vs. 56%	NA	None	Not specified
Huang YQ et al. [16]	60 vs. 60	No D cohort	51 (6) vs. 50 (6)	47% vs. 53%	Non-hypertensive	Renal function, C-reactive protein, heat rate, blood pressure	No previous medication*
	60 vs. 60	No D cohort	51 (6) vs. 50 (5)	53% vs. 57%	Hypertensive		
Liu K et al. [17]	25 vs. 20	No D cohort	47 (5) vs. 48 (4)	60% vs. 50%	NA (subjects without hyperhomocysteinaemia)	Lipid profile	Not specified
	55 vs. 50	No D cohort	48 (5) vs. 47 (7)	64% vs. 53%	Subjects with and without hyperhomocysteinaemia in each group	Not specified	Not specified
Stather PW et al. [18]	25 vs. 26	D: 5 vs. 6 V1: 10 vs. 10 V2:10 vs. 10	69 [55-77] vs. 65 [65-65] in V2	100%	All white patients	None (except age in V2)	None (except acetylsalicylic acid in D1)
Stather PW et al. [19]	28 vs. 35	No D cohort for LL atherosclerosis	67 [55-89] vs. 64 [64-65]	100%	All white patients	Not specified	Not specified
Signorelli SS et al. [20]	27 vs. 27	No D cohort	66 (8)	100%	NA	DM, dyslipidemia, HTN	Acetylsalicylic acid, statins
Vegter EL et al. [21]	21 vs. 90	No D cohort	73 (7) vs. 71 (11)	79% vs. 62%	All hospitalized with heart failure	CAD, renal function, potassium levels	None
Li T et al. [22]	104 vs. 105	No D cohort	Not specified	Not specified	NA	Not specified	Not specified
He XM et al. [23]	58 vs. 57	D: 3 vs. 3 V: 55 vs. 54	76 (10) vs. 74 (7)	60% vs. 63%	NA	Smoking, white blood cells, homocysteine, cystatin C (age-matched controls)	Not specified
Park MY et al. [24]	13 vs. 13	No D cohort	71 (6) vs. 70 (7)	69% vs. 39%	NA	eGFR, SBP, triglycerides, (age, weight and BMI-matched)	ACEi/ARB, CCB, beta-blocker, statins
Zhu XY et al. [25]	12 vs. 12	No D cohort	70 (2) vs. 70 (2)	58% vs. 42%	NA	SBP, triglycerides, plasma renin activity, renal function markers	ACEi/ARB, statins

*Lipid-lowering, antiplatelet or antihypertensive drugs; **possibly renal function, heat rate, blood pressure, and carotid-femoral pulse wave velocity. ACEI-angiotensin-converting enzyme inhibitor; ARB-angiotensin receptor blocker; BMI-body mass index; CAD-coronary artery disease; CCB-calcium channel blocker; CVD-cerebrovascular disease; D-derivation; DM-diabetes mellitus; eGFR-estimated glomerular filtration rate; HTN-hypertension; LDL-c-low-density lipoprotein cholesterol; LL-inferior limbs; NA-not applicable; SBP-systolic blood pressure; SD-standard deviation; V-validation.

Table 3. MicroRNA analysis process

Study	Laboratory test	Product	miRNAs tested in D cohort	miRNAs identified in D cohort	miRNAs tested in V or total cohort	RNA quality assessment	Internal control
Tsai PC et al. [8]	RT-PCR TaqMan	Serum	-	-	miR-21, miR-145, miR-221	Not specified	miR-16
Zhang X et al. [9]	RT-PCR SYBR Green	Serum	-	-	miR-21-5p, miR-125a-5p, miR-126-3p, miR-210, miR-221-3p, miR-222-3p	NanoDrop 1000 (quantification of RNA concentration)	Cel-miR-39
Zhang R et al. [10]	RT-PCR	Serum	Agilent Human miRNA kit (8*60K, Design ID: 046064): 2006 human miRNAs	32 miRNA (24 miRNAs up-, 8 downregulated)	The 8 miRNAs downregulated (not the miRNAs upregulated)	Formaldehyde electrophoresis, Nanodrop ND-2000 (Thermo Scientific); RNA integrity: Agilent Bioanalyzer 2100 (Agilent Technologies)	No
Zhang JY et al. [11]	RT-PCR-based TaqMan	Plasma	TaqMan low density array v2.0	miR-17, miR-21, miR-25, miR-31, miR-103, miR-105, miR-141, miR-211, miR-218	miR-17, miR-21, miR-25, miR-31, miR-103, miR-105, miR-141, miR-211, miR-218	Not specified	U6 (internal reference), cel-miR-39 (external normalization)
Huang YQ et al. [12]	S-Poly (T) RT-qPCR	Plasma	-	-	miR-29a	Not specified	miR-54
Huang Y et al. [13]	S-Poly (T) RT-qPCR	Plasma	-	-	miR-30	Not specified	miR-54
Huang Y et al. [14]	S-Poly (T) RT-qPCR	Plasma	-	-	miR-92a	Not specified	miR-54
Liu CZ et al. [15]	S-Poly (T) RT-qPCR	Plasma	-	-	miR-29a	Not specified	miR-54
Huang YQ et al. [16]	S-Poly (T) RT-qPCR	Plasma	-	-	let-7	Not specified	miR-54
Liu K et al. [17]	RT-qPCR FastKing RT Kit	Plasma	-	-	miR-143, miR-145	Not specified	miR-54
Stather PW et al. [18]	RT-PCR TaqMan	Whole blood	aqMan Array Human MicroRNA A + B Cards Set v3.0 (Life Technologies Corporation, Foster City, CA): 754 miRNAs	53 miRNAs (34 down- and 19 upregulated)	V1: 53 miRNAs from D cohort + 14 miRNAs from literature V2: same except miR-720 and miR-1274	Nanodrop 8000: ratios 280/260 and 26/230. Agilent 2100 Bioanalyzer: Agilent small RNA chips and Agilent RNA 6000 Nano chips (Agilent Technologies, UK) (If RIN>7 and no DNA contamination)	No
Stather PW et al. [19]	RT-PCR TaqMan	Whole blood + plasma	-	-	29 miRNAs ("D1") + miRNAs from literature	Plasma: NanoDrop™ spectrophotometer (ThermoScientific, Waltham, Massachusetts, USA) (260/280 ratios, RNA integrity numbers, RNA concentration)	No
Signorelli SS et al. [20]	RT-PCR SYBR Green	Serum	-	-	miR-130a, miR-27b, miR-210	NanoDrop ND-1000 spectrophotometer (Thermo Scientific, Milan, Italy)	No
Vegter EL et al. [21]	RT-PCR LightCycler® 480	Plasma	-	-	let-7i-5p, miR-16-5p, miR-18a-5p, miR-26b-5p, miR-27a-3p, miR-30e-5p, miR-106a-5p, miR-199a-3p, miR-223-3p, miR-423-5p, miR-652-3p	Control for isolation yield (UniSp4), cDNA synthesis (UniSp6) and PCR efficiency (UniSp3). Only miRNAs with Ct values less than 37 were included in further analyses.	let-7a-5p
Li T et al. [22]	RT-PCR SYBR Green	Serum	-	-	miRNAs deregulated in intima samples (miR-21, miR-221, miR-222, miR-130a, miR-27b, let-7f, miR-210)	NanoDrop ND-1000 spectrophotometer (Thermo Scientific)	No

He XM et al. [23]	RT-PCR miScript II RT Kit	Plasma	miRCURY LNA™ microRNA Hi-Power Labeling Kit, Hy3/Hy5 (Exiqon): 3100 microRNAs	24 miRNAs (4 up- and 20 down-regulated)	miR-124, miR-5004, miR-4284, miR-432, miR-221-5p, miR-221-3p, miR-4463, miR-4306, miR-4301 (selected from D cohort)	Yield of RNA could not be assessed by NanoDrop spectrophotometer (Thermo Scientific): Used fixed volume for RNA isolation and RT	No
Park MY et al. [24]	RT-PCR TaqMan	Plasma (renal vein, IVC and PV)	-	-	miR-21, miR-124a, miR-126, miR-155, miR-210	Not specified	No
Zhu XY et al. [25]	RT-PCR	Plasma (systemic vein)	-	-	miR-26	Not specified	No

D-derivation; IVC-inferior vena cava; miRNA-microRNA; PV-peripheral vein; RT-PCR-reverse transcription polymerase chain reaction; V-validation.

Table 4. MicroRNAs profiles

Study	MicroRNAs upregulated	MicroRNAs downregulated	Statistical test	Adjustment for baseline differences	QUA-DAS-2
Tsai PC et al. [8]	miR-21	-	ANOVA	No	4
Zhang X et al. [9]	miR-21-5p	miR-125a-5p, miR-126-3p, miR-221-3p, miR-222-3p	ANOVA	No	4
Zhang R et al. [10]	-	miR-320b	Student's t-test	No	4
Zhang JY et al. [11]	miR-21, miR-211, miR-218	miR-31	Mann-Whitney U-test	No	4
Huang YQ et al. [12]	miR-29a (adjusted)	-	Not specified	Yes (multiple linear regression analysis)	4
Huang Y et al. [13]	-	miR-30 (adjusted)	Not specified	Yes (multiple logistic regression analysis)	4
Huang Y et al. [14]	miR-92a	-	Not specified	No	4
Liu CZ et al. [15]	miR-29a (adjusted)	-	Student's t-test	Yes (multivariable regression)	4
Huang YQ et al. [16]	let-7 (adjusted)$^{\alpha}$	-	Not specified	Yes (multiple linear regression)	4
	let-7 (adjusted)$^{\beta}$	-	Not specified		
Liu K et al. [17]	-	miR-143$^{\gamma}$, miR-145$^{\gamma}$	Student's t-test	No	4
	-	miR-143$^{\delta}$, miR-145$^{\delta}$	Student's t-test	No	
Stather PW et al. [18]	-	let 7e, miR-15b, miR-16, miR-20b, miR-25, miR-26b, miR-27b, miR-28-5p, miR-126, miR-195, miR-335, miR-363	Mann-Whitney U test Consistent in the 3 cohorts	No	4
Stather PW et al. [19]	Whole blood: miR-411 (adjusted)	Whole blood: let-7e, miR-15a, miR-196b (adjusted) Plasma: miR-196b (nonadjusted)	Mann-Whitney U test	Yes (binary logistic regression)	3
Signorelli SS et al. [20]	miR-27b, miR-130a, miR-210	-	Student unpaired t test	No	4
Vegter EL et al. [21]	-	miR-18a-5p, miR-27a-3p, miR-30e-5p, miR-106a-5p, miR-199a-3p, miR-223-3p, miR-652-3p (adjusted)	Not specified (probably Mann-Whitney U test)	Yes (Cox proportional hazard regression)	1
Li T et al. [22]	miR-21, miR-27b, miR-130a, miR-210	-	Student's t-test	No	3
He XM et al. [23]	miR-124, miR-221-5p, miR-4284	miR-221-3p, miR-432, miR-4463, miR-4306	Student's t-test	No	3
Park MY et al. [24]	miR-126 (GFR-adjusted; systemic)	miR-21$^{\varepsilon}$, miR-155$^{\varepsilon}$, miR-210$^{\varepsilon}$ (GFR-adjusted)	Student's t-test or Wilcoxon rank-sum test	Yes (ANCOVA) (adjustment to GFR)	3
Zhu XY et al. [25]	-	-	Student's t-test	No	3

For studies adjusting circulating microRNA levels for baseline characteristics, only the microRNAs significantly up- or downregulated after such adjustment are presented, unless specified. $^{\alpha}$Subjects without hypertension; $^{\beta}$subjects with hypertension; $^{\gamma}$subjects without hyperhomocysteinaemia; $^{\delta}$subjects with and without hyperhomocysteinaemia; $^{\varepsilon}$renal vein in atherosclerotic vs. systemic in non-atherosclerotic. GFR-glomerular filtration rate.

Table 6 summarizes the deregulated microRNAs in different arterial locations of atherosclerotic disease. There was a common microRNA expression profile across different arterial disease locations, including upregulation of miR-21 and downregulation of miR-30, miR-126, and miR-221-3p in carotid and lower limbs atherosclerosis. Specific microRNA profiles for each disease location were also identified, and changes in the expression of some microRNAs were consistent in different studies on the same disease location, such as miR-21 and miR-29 in carotid atherosclerosis and let 7e, miR-27b, miR-130a, and miR-210 in lower limbs atherosclerosis. Of note, the altered expression profile of many microRNAs remained significant after adjusting for baseline characteristics, including miR-29 and miR-30 in studies on carotid atherosclerosis, and let 7e in studies on lower limbs atherosclerosis.

Discussion

To the best of our knowledge, this study is the first systematic review on different circulating microRNA profiles associated to atherosclerosis of the main arterial territories. Coronary artery disease was not the scope of the present review considering the extensive available systematic data published on this subject [3-5]. Eighteen eligible studies were included: ten focused on the carotid arteries, six on lower limbs arteries, and two on renal arteries. A common microRNA expression profile across

Table 5. QUADAS-2 classification of the included studies

Study	Risk of bias				Applicability concerns			Classification
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	QUADAS 2
Tsai PC et al. [8]	Yes	No	No	No	Yes	Yes	No	4
Zhang X et al. [9]	Yes	No	No	No	Yes	Yes	No	4
Zhang R et al. [10]	Yes	No	No	No	Yes	Yes	No	4
Zhang JY et al. [11]	Yes	No	No	No	Yes	Yes	No	4
Huang YQ et al. [12]	Yes	No	No	No	Yes	Yes	No	4
Huang Y et al. [13]	Yes	No	No	No	Yes	Yes	No	4
Huang Y et al. [14]	Yes	No	No	No	Yes	Yes	No	4
Liu CZ et al. [15]	Yes	No	No	No	Yes	Yes	No	4
Huang YQ et al. [16]	Yes	No	No	No	Yes	Yes	No	4
Liu K et al. [17]	Yes	No	No	No	Yes	Yes	No	4
Stather PW et al. [18]	Yes	No	No	No	Yes	Yes	No	4
Stather PW et al. [19]	Yes	No	No	Yes	Yes	Yes	No	3
Signorelli SS et al. [20]	Yes	No	No	No	Yes	Yes	No	4
Vegter EL et al. [21]	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Li T et al. [22]	Yes	No	No	Yes	Yes	Yes	No	3
He XM et al. [23]	Yes	No	No	Yes	Yes	Yes	No	3
Park MY et al. [24]	Yes	No	No	Yes	Yes	Yes	No	3
Zhu XY et al. [25]	Yes	No	Yes	Yes	Yes	Yes	No	3

Table 6. Circulating microRNA profiles according to different atherosclerotic disease locations

		Upregulated	Downregulated
Carotid		let-7$^{\zeta}$, miR-21$^{\alpha,\beta}$, miR-29a$^{\beta}$, miR-92a, miR-211, miR-218	miR-30$^{\gamma}$, miR-31, miR-125a-5p, miR-126-3p$^{\gamma,\zeta}$, miR-143, miR-145, miR-221-3p$^{\gamma}$, miR-222-3p, miR-320b
Inferior limbs	Whole blood	miR-411	let 7e$^{\delta,\zeta}$, miR-15a, miR-15b, miR-16, miR-20b, miR-25, miR-26b, miR-27b$^{\varepsilon}$, miR-28-5p, miR-126$^{\gamma,\zeta}$, miR-195, miR-196b miR-335, miR-363
	Plasma	miR-27b$^{\beta,\varepsilon}$, miR-130a$^{\beta}$, miR-210$^{\beta}$	miR-18a-5p, miR-27a-3p, miR-30e-5p$^{\gamma}$, miR-106a-5p, miR-196b, miR-199a-3p, miR-223-3p, miR-652-3p
Inferior limbs/arteriosclerosis obliterans		miR-21$^{\alpha,\beta}$, miR-27b$^{\beta,\varepsilon}$, miR-124, miR-130a$^{\beta}$, miR-210$^{\beta}$, miR-221-5p, miR-4284,	miR-221-3p$^{\gamma}$, miR-432, miR-4463, miR-4306
Renal artery		miR-126$^{\zeta}$	-

$^{\alpha}$Upregulated in atherosclerotic disease of different arterial territories; $^{\beta}$upregulated in different studies on atherosclerotic disease of the same arterial territory; $^{\gamma}$downregulated in atherosclerotic disease of different arterial territories; $^{\delta}$downregulated in different studies on atherosclerotic disease of the same arterial territory; $^{\varepsilon}$opposite trends in different studies on atherosclerotic disease of the same arterial territory; $^{\zeta}$opposite trends in different studies on atherosclerotic disease of the different arterial territories.

different territories of disease as well as specific microRNA expression profiles for each territory were identified.

Quantitative synthesis was not carried out due to the risk of bias, considering some degree of heterogeneity across studies regarding disease definition and diagnostic methods, including no systematic exclusion of concomitant atherosclerotic disease of other locations in most studies, and the heterogeneity of pre-selected microRNAs for analysis in different studies. Nevertheless, we were able to qualitatively detect consistent microRNA profiles according to the presence and location of atherosclerotic disease. The results suggest that, while some microRNAs may be involved in atherosclerotic expression in specific territories, others are involved in basic and general mechanisms of atherosclerosis, irrespective of location.

A common microRNA profile was identified for patients with carotid atherosclerosis and for those with lower limbs atherosclerosis, includ-

ing upregulation of miR-21 and downregulation of miR-30, miR-126, and miR-221-3p. Interestingly, each of these microRNAs plays different roles in atherosclerosis: miR-21 is proangiogenic, being involved in the control of vascular smooth muscle cell apoptosis and proliferation, and regulation of angiogenesis mediated by endothelial cells [27, 28]; miR-30 has a potent effect on the production of apoB-containing lipoproteins, contributes to the development of vascular smooth muscle cells and downregulates profibrotic proteins [13, 29, 30]; miR-126 is an endothelial-specific microRNA that governs vascular integrity and regulates the response of endothelial cells to vascular endothelial growth factor [31]; and miR-221 regulates inflammation and is antiangiogenic, by controlling endothelial cell migration, proliferation, and vascular smooth muscle cell growth [9, 32]. Of note, miR-21 has also been reported to be overexpressed in different studies on coronary artery disease [4]. These findings suggest that, although atherosclerosis is a complex process that involves distinct pathophysiologic mechanisms, several are shared irrespectively of the territory of disease, as reflected by the common microRNA profile. On the other hand, most of the remaining deregulated microRNAs, although not having a similar expression profile in atherosclerotic disease of different territories, are still involved in common pathophysiologic mechanisms related to atherosclerosis: regulation of angiogenesis by controlling vascular smooth muscle cell proliferation and function (miR-21, miR-29, miR-30, miR-143, miR-145, and miR-221 in carotid atherosclerosis; let-7, miR-21, miR-27b, miR-30, miR-130a, miR-195, miR-210, and miR-221 in lower limbs atherosclerosis) [9, 18-20, 28, 29, 32-36]; regulation of angiogenesis by controlling endothelial cell proliferation and function (miR-21, miR-92, miR-126, miR-218, miR-221, and miR-320b in carotid atherosclerosis; let-7, miR-15b, miR-16, miR-21, miR-27b, miR-126, and miR-221 in lower limbs atherosclerosis; miR-126 in renal artery stenosis) [9, 18, 19, 27, 28, 31, 32, 35, 37-39]; regulation of endothelial function and integrity (miR-31, miR-126, and miR-218 in carotid atherosclerosis; let-7, miR-27a-3p, miR-126, and miR-199a-3p in lower limbs atherosclerosis; miR-126 in renal artery stenosis) [18, 19, 21, 31, 35, 40, 41]; regulation of inflammation (miR-31, miR-92, and miR-125 in carotid atherosclerosis; miR-18a-5p, miR-106a-5p, miR-221-3p, miR-223-3p, miR-652-3p, miR-4284, miR-4306, and miR-4463 in lower limbs atherosclerosis) [9, 11, 21, 23, 27, 37, 42]; regulation of cholesterol metabolism (miR-30, miR-92, and miR-125 in carotid atherosclerosis; miR-27b and miR-30 in lower limbs atherosclerosis) [18, 28, 42, 43]; regulation of oxidative stress (miR-27b, miR-130a, and miR-210 in lower limbs atherosclerosis) [20, 44]; and regulation of extracellular matrix composition and mesenchymal cell differentiation (miR-29 and miR-30 in carotid atherosclerosis; miR-30 in lower limbs atherosclerosis) [30, 33].

Despite the presence of a common microRNA profile and shared pathologic mechanisms across different disease locations, the specific profiles of microRNAs did differ according to the diseased territory. The expression of some microRNAs even showed opposite trends in atherosclerosis of different territories, such as miR-126. Therefore, although most of the pathways are shared between different territories of atherosclerosis, their mediators are not. The mechanisms for this phenomenon are not clear. One possible explanation is the differential shear forces across different arterial beds. Indeed, it is well known that some microRNAs are mechanosensitive, such as miR-126 [45]; interestingly, miR-126 was upregulated in renal artery stenosis and downregulated in carotid and lower limbs atherosclerosis. Other possible explanation is that, in patients with a genetically predetermined deregulation of specific microRNAs, a particular vascular aggressor may preferentially induce atherosclerosis in a specific territory. An example is the deregulation of miR-30, miR-92, and miR-125 in patients with carotid atherosclerosis, and miR-27b and miR-30 in patients with lower limbs atherosclerosis [19, 28, 42, 43]; any of these microRNAs regulate cholesterol metabolism or cholesterol-induced lesions; under the presence of the same aggressor, such as dyslipidemia, the location of disease could be related to a predetermined differential microRNA expression. One consideration to be made is that some microRNAs may not have a causative role, but rather they may be a consequence of atherosclerosis. In fact, miR-27b, miR-130a, and miR-210 are upregulated by hypoxic conditions, and they serve as possible inhibitors of oxidative stress, which may represent an adaptive response [20, 44]. Since the consequences of luminal steno-

sis due to stable atherosclerosis differ according to disease location, the adaptive microRNA profile may also vary depending on disease location. For example, the presence of contralateral perfusion in the cerebral (carotid) territory in the contrary to iliofemoral arteries, and the highly demanding territory of the lower limbs muscles during effort (walking) could result in a higher degree of oxidative stress in the presence of severe stenosis of the lower limbs, comparing to the carotid arteries; this could explain why the expression of adaptive microRNAs to oxidative stress, such as miR-130a, miR-27b, and miR-210, is more altered in the presence of lower limbs atherosclerosis [20, 44].

Data was particularly robust for carotid and lower limbs atherosclerosis, while only few patients with renal atherosclerosis were analyzed. Two aspects reinforce the consistency and robustness of our data. First, the expression profiles of some microRNAs were replicated within the same territory of disease in different studies. There was an upregulation of miR-21 and miR-29 in different studies on carotid atherosclerosis; downregulation of let 7e and upregulation of miR-27b, miR-130a, and miR-210 in different studies on lower limbs atherosclerosis. Of note, miR-27b showed an opposite trend in one study on lower limbs atherosclerosis [18] compared to other studies on the same diseased territory [20, 22], although whole blood (including microRNA from whole blood cells) and not plasma was used for microRNA quantification in that study, which may explain the divergent results. Second, for many microRNAs the deregulated pattern was adjusted for baseline characteristics. Those include deregulation of miR-29 and miR-30 in studies on carotid atherosclerosis and let 7e in studies on lower limbs atherosclerosis. The consistency of the results was higher for these three microRNAs, considering both the adjustment for baseline variables and the replication of the results in different studies either on the same territory of disease (miR-29 in carotid and let 7e in lower limbs atherosclerosis) or on different territories (miR-30 in carotid and lower limbs atherosclerosis).

In conclusion, a common microRNA expression profile to different territories of atherosclerotic disease and specific microRNA expression profiles for each territory were identified. This suggests that some microRNAs may be involved in atherosclerotic expression in specific territories, while others may be involved in the common mechanisms of atherosclerosis. Our results may be useful for supporting further investigation with the aim of selecting potentially useful biomarkers for clinical practice, and possibly identifying therapeutic targets of antagomirs [46].

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Disclosure of conflict of interest

None.

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