Leukocyte count influences the relationship of circulating resistin concentrations with advanced atherosclerosis in rheumatoid arthritis

Sirs,

Resistin is an adipokine that, in humans, mostly originates in mononuclear leukocytes (1). Resistin is additionally implicated in the pathophysiology of rheumatoid arthritis (RA). Indeed, resistin colocalises with inflammatory cells in synovial tissue, upregulates cytokine production and associates with disease severity and, hence, is also a potential novel therapeutic target in RA (1, 2).

Whether resistin enhances cardiovascular risk in RA is currently uncertain. Resistin concentrations were found to be unrelated to carotid intima-media thickness (cIMT) (3) as well as coronary artery calcification scores (4) in RA. However, we recently documented an independent relationship between resistin concentrations and surrogate markers of early atherogenesis in RA (5). Importantly in the present context, carotid artery plaque is a more reliable indicator of increased cardiovascular risk than cIMT and coronary artery calcification (6). Plaque represents advanced atherosclerosis that is strongly related to coronary heart disease risk factors and incident coronary heart disease in both non-RA and RA subjects (7). Consideration of both cIMT and plaque can substantially improve cardiovascular risk stratification (7).

In the present study, we examined the independent relationships of resistin concentrations with cIMT and plaque in 217 (112 black and 105 white) patients that were us-

Table I. Resistin concentrations (ng/ml) and their relationships with cIMT and plaque (per 1 SD increment) in all RA patients and subgroups.

					Relationships with atherosclerosis				
		Concentrations			cIMT		Plaque		
Groups	Number	Median	IQR	*p*-value*	Partial R	*p*-value†	OR	95% CI	*p*-value†
All	217	33.9	22.7-53.1		-0.042	0.6	1.01	1.00-1.01	0.3
Population									
Black	121	37.8	24.0-56.3		-0.118	0.2	1.01	0.99-1.02	0.4
White	105	32.0	21.6-50.3	0.4	0.011	0.9	1.29	0.86-1.93	0.2
Age >55 years‡									
Yes	127	32.2	20.8-52.1		-0.009	0.9	1.00	0.99-1.01	1.0
No	90	38.1	25.1-54.5	0.6	-0.039	0.7	1.01	0.99-1.02	0.5
≥1 major risk factor¶									
Yes	151	38.2	25.1-55.6		0.054	0.7	1.05	0.92-1.19	0.5
No	58	33.1	22.4-52.1	0.9	-0.053	0.5	1.00	0.99-1.01	0.7
Missing	8								
BMI >29.9 kg/m^2									
Yes	64	38.6	22.7-58.4		-0.051	0.7	1.00	0.98-1.02	0.9
No	147	33.7	22.4-50.4	0.9	-0.014	0.9	1.01	1.00-1.02	0.1
Missing	6								
MetS waist									
Yes	100	33.8	22.7-55.6		-0.085	0.4	1.00	0.98-1.01	0.8
No	114	34.5	23.4-50.4	0.1	0.017	0.9	1.01	1.00-1.02	0.1
Missing	3								
RA duration >10 years									
Yes	116	33.8	22.4-53.3		-0.078	0.4	1.01	0.99-1.02	0.3
No	100	34.5	22.9-53.3	0.8	-0.096	0.4	1.00	0.99-1.02	0.6
Missing	1								
CDAI >10									
Yes	92	33.5	20.7-50.5		-0.059	0.6	1.00	0.98-1.02	1.0
No	124	34.0	24.0-56.3	0.7	-0.038	0.7	1.00	0.99-1.02	0.5
Missing	1								
ESR >12 mm/hr‡									
Yes	106	37.8	23.5-56.7		-0.049	0.6	1.06	0.92-1.21	0.4
No	105	31.9	21.6-50.5	0.2	-0.010	0.9	1.00	0.99-1.01	0.8
Missing	6								
CRP >6 mg/l‡									
Yes	104	37.6	24.0-58.8		0.090	0.4	0.95	0.62-1.46	0.8
No	107	31.9	20.4-50.4	0.4	-0.165	0.1	1.20	0.75-1.92	0.4
Missing	6								
Deformed joints									
Yes	165	37.9	22.1-58.2		-0.029	0.7	1.00	0.99-1.02	0.6
No	51	31.2	23.4-41.9	0.1	-0.111	0.5	1.01	0.99-1.03	0.4
Missing	1								
RF positive									
Yes	168	33.7	22.6-53.3		0.004	1.0	1.01	1.00-1.02	0.2
No	48	38.0	23.5-55.6	0.9	-0.209	0.2	1.00	0.98-1.01	0.6
Missing	1								
Leukocytes >5.85x10^9/l ‡									
Yes	105	**38.1**	**23.6-54.0**		-0.014	0.9	**1.02**	**1.00-1.03**	**0.03**
No	108	**31.9**	**20.7-50.4**	**0.008**	-0.096	0.3	1.00	0.98-1.01	0.6
Missing	4								

*P-value for associations in age, sex, race, waist, log leukocytes and cardiovascular drug use adjusted linear regression models; †p-value for associations in log Framingham score, race, log glomerular filtration rate, waist and log leukocytes adjusted logistic regression models; ‡Groups divided by median value amongst all patients; ¶Included dyslipidaemia, hypertension, smoking and diabetes (5,7-10).

Significant associations are shown in bold. cIMT: carotid intima-media thickness; SD: standard deviation; RA: rheumatoid arthritis; IQR: interquartile range; OR: odds ratio; CI: confidence intervals; BMI: body mass index; MetS: metabolic syndrome; CDAI: Clinical Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor.

ing disease-modifying agents for rheumatic disease and, hence, had established RA (5, 7-10). No exclusion criteria were applied. As the production and effects of adipokines on cardiovascular risk depend on (patho) physiological context (5, 8-10), we also determined whether the presence of conventional and nonconventional cardiovascular risk factors modified resistin concentrations and their associations with atherosclerosis. The Human Research Ethics Committee (Medical) from the University of the Witwatersrand in Johannesburg, South Africa approved the protocol and each participant gave informed written consent.

Carotid ultrasound measurement and its reproducibility in our setting were previously reported (7). Carotid artery plaque was defined according to the Mannheim criteria (7). Resistin concentrations were measured in serum using a solid-phase sandwich enzyme-linked immunosorbant assay (Quantikine® JS. R&D Systems, Inc., Minneapolis, MN, USA). The lower detection limit was 0.026 ng/ml and the inter- and intra-assay coefficients of variation were 8.4% and 4.7%, respectively.

The baseline recorded characteristics in the present cohort have been reported (5).

The mean (SD) cIMT and plaque prevalence were 0.709 (0.109) mm and 40.6%, respectively.

Resistin concentrations in all patients and relevant subgroups are given in Table I. Resistin concentrations were larger in patients with compared to those without a leukocyte count above the median value amongst all patients, independent of potential confounders or/and mediators (5).

Table I also shows the independent relationships of resistin concentrations with cIMT and plaque. In all patients and the different subgroups, resistin concentrations were not related to cIMT. However, in patients with a leukocyte count above the median, resistin concentrations were independently associated with carotid artery plaque. In the respective logistic regression models, replacement of the leukocyte count by C-reactive protein concentrations or the Clinical Disease Activity Index did not materially alter the results (OR (95% CI)=1.02 (1.00-1.03), p=0.04 for both models). The leukocyte count and C-reactive protein concentrations were strongly correlated (R=0.275, p<0.0001). Nevertheless, when patients were stratified by the median C-reactive protein level, no independent associations were found between resistin concentrations and atherosclerosis in the respective subgroups.

Whereas in our previous study, resistin concentrations were associated with endothelial activation amongst patients with conventional cardiovascular risk factors, long standing disease or clinically evident joint damage (5), a relationship of resistin with plaque was not found in the respective groups in the present investigation. This indicates that whereas resistin may be involved in early atherogenesis, this adipokine may not contribute to advanced atherosclerosis amongst RA patients with the respective characteristics.

In conclusion, the leukocyte count is independently associated with increased resistin concentrations and additionally modifies the relationship of resistin concentrations with plaque in RA. The present study supports the paradigm in which resistin contributes to the link between inflammation and enhanced cardiovascular risk in RA (5). The potential role of resistin in enhanced cardiovascular risk and its stratification in RA merits further study.

P.H. DESSEIN, *MD, FCP (SA), FRCP (UK), PhD*[1]
L. TSANG[1]
A.J. WOODIWISS, *PhD*[1]
H.-C. HSU, *MBBCh, FCP (SA)*[1]
G.R. NORTON, *MBBCh, PhD*[2]
A. SOLOMON, *FCP (SA)*[3]

P. Dessein and A.Solomon made an equal contributed to the manuscript.

[1]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [2]Nephrology Department, Milpark Hospital, Johannesburg, South Africa; [3]Department of Rheumatology, Charlotte Maxeke Johannesburg Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

Address correspondence to:
Patrick Dessein, P.O. Box 1012, Melville 2109, Johannesburg, South Africa.
E-mail: dessein@telkomsa.net

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