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Twenty shades of the mosaic of autoimmunity

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ABSTRACT

Accelerated, inflammatory atherosclerosis and cardiovascular disease have been associated with several autoimmune diseases including RA, AS, SLE, APS and SSc. Non-invasive, ultrasound- based techniques are suitable for the assessment of preclinical vascular pathophysiology. Multiple vascular and other biomarkers including vitamin D, ferritin, prolactin, suPAR, BNP fragments, oxLDL/β2GPI complexes, anti-Hsp60 and others have been associated with cardiometabolic comorbidities. The control of the underlying inflammatory disease is crucial for minimising cardiovascular risk in autoimmune diseases.

1. Introduction

I think I have known Yehuda forever. Or at least since I was born…

We have always been very close. I always considered him my mentor. He is also a great friend, with some Hungarian roots. I had the opportunity to meet him several times in Hungary, in Israel or just all around the globe. We have invited him to deliver one of his brilliant talks at Hungarian meetings and I was also pleased to attend almost all congresses he organized Fig. 1). For example, the Controversies in Rheumatology and Autoimmunity (CORA) congress series was originally our idea becoming a huge success.

We were also very pleased that in 2008 the Hungarian Association of Rheumatologists elected him as a honorary member. In 2009, the University of Debrecen conferred on him the Doctoris Honoris Causa title (Fig. 2).

In this paper, I would like to thank him for his mentorship and friendship by presenting 25 collaborative encounters we had for the last 20 years. Most of the papers have been published in the field of biomarkers and cardiometabolic comorbidities associated with autoimmune diseases, as well as the effects of therapeutic interventions.

2. Cardiometabolic comorbidities

Accelerated atherosclerosis, as well as increased cardiovascular morbidity and mortality have been associated with several autoimmune diseases. Autoimmunity and systemic inflammation are major drivers of this comorbidity (Fig. 3) [1–3].

We assessed the suitability of ultrasound-based, *non-invasive techniques* for their value in determining abnormal vascular pathophysiology in autoimmune diseases. Endothelium-dependent, flow-mediated vasodilation (FMD) and endothelium-independent, nitroglycerin-mediated vasodilation (NMD) are suitable to detect endothelial dysfunction. Common carotid intima-media thickness (ccIMT) with or without plaque analysis is a marker for overt atherosclerosis. Finally, arterial pulse-wave velocity (PWV) indicates vascular stiffness (Fig. 4) [4].

We were among the first ones to detect abnormal vascular pathophysiology in *rheumatoid arthritis* (RA). Altogether 52 RA patients and 40 matched healthy controls were studied. We assessed ccIMT, FMD and NMD along with numerous immunological and metabolic laboratory markers. FMD was significantly lower in RA compared to controls (5.32 ± 4.66% vs 8.30 ± 3.96%; $p = 0.001$). NMD was preserved in RA. ccIMT was significantly greater in patients with RA vs controls (0.63 ± 0.14 mm vs 0.54 ± 0.15 mm; $p = 0.012$). FMD correlated with serum interferon γ (IFNγ) levels ($R = 0.516$; $p = 0.014$). Patients with RA were divided as "low" (<0.65 mm) vs "high" (>0.65 mm) ccIMT groups, and into "normal" (>5%) vs "impaired" (<5%) FMD subsets. RA patients with high vs low ccIMT had increased serum TNF-α, IL-1, IL-6, IFNγ and CRP and decreased IL-4 and IL-10 levels. Similarly, patients with impaired vs high FMD exerted higher TNF-α, IL-6 and CRP levels. Among metabolic markers, plasma lipoprotein(a) [Lp(a)] correlated with IgM rheumatoid factor (RF) and CRP. Our data suggested that RA was associated with impaired endothelial dysfunction and accelerated atherosclerosis [2].

Vascular *pathophysiology* was also assessed in *ankylosing spondylitis*. Altogether 43 AS patients and 40 matched healthy controls were included in this study. We measured ccIMT, FMD and PWV in relation with numerous clinical parameters and biomarkers. Impaired FMD (6.85 ± 2.98% vs 8.30 ± 3.96%; $p = 0.005$), increased ccIMT (0.65 ± 0.15

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Fig. 1. Professor Yehuda Shoenfeld is awarded the Doctoris Honoris Causa title at the University of Debrecen. Left: the diploma. Right: Professor László Fésüs, Rector of the university hands over the diploma to the awardee.

Fig. 2. Yehuda Shoenfeld at the congress of the Hungarian Association of Rheumatologists in Budapest, 2018 (left) and, together with Professors Gabriella Szűcs and Zoltán Szekanecz at the first CORA congress in Firenze, 2011 (right).

mm vs 0.54 ± 0.15 mm; $p = 0.01$), and higher PWV (8.64 ± 2.44 m/s vs 8.00 ± 1.46 m/s; $p = 0.03$) were found in AS patients compared to controls, respectively. Both ccIMT and PWV correlated with disease duration ($R = 0.559$; $p = 0.013$ and $R = 0.520$; $p = 0.022$, respectively), BASFI ($R = 0.691$; $p = 0.003$ and $R = 0.654$; $p = 0.006$), decreased lumbar spine mobility (R = -0.656; p = 0.006 and R = -0.604; $p = 0.013$), and chest expansion (R = -0.502; $p = 0.047$ and R = -0.613; $p = 0.012$). Thus, AS was associated with impaired endothelial function, as well as with carotid atherosclerosis and increased arterial stiffness [5].

We reviewed cardiovascular manifestations of *antiphospholipid syndrome* (APS). APS is associated with arterial and venous thrombotic events and recurrent fetal loss. in addition, there is increased cardiovascular mortality in APS. Cardiovascular risk is even higher in secondary APS in lupus patients. Antiphospholipid antibodies, lupus anticoagulant, anti-oxLDL and other antibodies have been implicated in vascular events underlying APS. Other cardiac manifestations including valvular disease with thickening and vegetations also occur in APS. In addition, more rarely, ventricular dysfunction, intracardiac thrombi and myxomas, pulmonary hypertension might also exist in APS patients [6].

We have presented data on the pathogenic involvement of *antiphospholipid antibodies* in acute coronary syndrome (ACS). In this study, anti-β2GPI antibodies were significantly more prevalent in ACS compared to healthy controls (14% vs 2%). Serum levels of these APL antibodies were also increased in ACS. Interestingly, anti-β2GPI

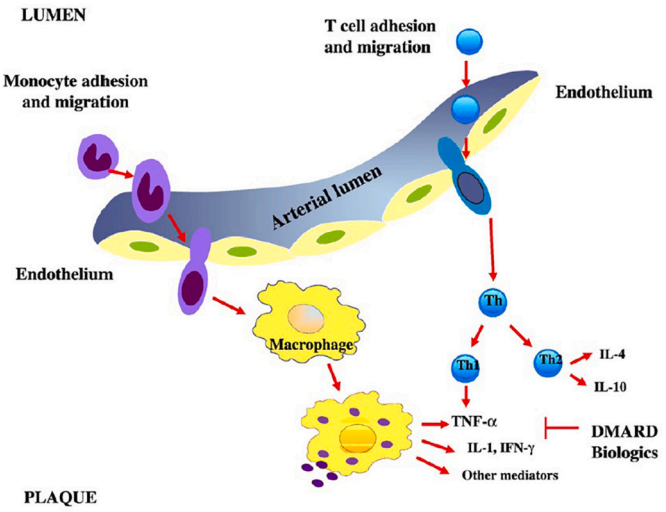

Fig. 3. The role of endothelial cells, macrophages and pro-inflammatory mediators produced by these cells in inflammatory atherosclerosis. Conventional DMARDs and biologics might be cardioprotective by dampeni ng inflammation and disease activity in autoimmune diseases.

antibodies of the IgA isotype were the most relevant for the onset and outcome of ACS. Indeed, anti-β2GPI IgA antibody levels were elevated in unstable angina, as well as myocardial infarction with ST elevation (STEMI). Our results indicated that anti-β2GPI antibodies, primarily those of the IgA isotype, might be involved in the thrombotic events underlying ACS [7].

Similarly, the role of IgG *anti-oxidized LDL* (anti-oxLDL) antibodies in ACS has also been investigated. Anti-oxLDL have been implicated in the development of atherosclerotic plaques. A total of 54 patients with ACS and 41 matched healthy controls were included in this prospective study. Higher IgG anti-oxLDL levels were found in patients with ACS vs controls (22.8 ± 23.3 vs 7.5 ± 5.3 EU/ml; $p < 0.001$). IgG anti-oxLDL concentrations were significantly higher in ACS patients with unstable clinical complications vs those without such complications (30.0 vs 11.7 EU/ml; $p < 0.001$). Serum IgG anti-oxLDL levels also correlated with the subsequent development of unstable coronary events. Levels of anti-oxLDL significantly decreased in response to statin therapy, independently of its lipid-lowering effect [8].

The pathogenesis of *systemic sclerosis* (SSc) includes vasculopathy with endothelial dysfunction. We assessed FMD, NMD and ccIMT in SSc patients compared with healthy controls in order to detect preclinical vascular changes. FMD, but not NMD was significantly impaired in SSc patients compared to healthy controls (4.82 ± 3.76% vs 8.86 ± 3.56%; $p < 0.001$). There was also a tendency of increased ccIMT in SSc patients vs controls (0.67 ± 0.26 mm vs 0.57 ± 0.09; $p = 0.067$). In addition, ccIMT significantly correlated with disease duration ($R = 0.472$; $p = 0.011$). Thus, endothelial dysfunction and possibly manifest carotid atherosclerosis might precede clinical vascular pathology in SSc [9].

We also performed a comparative study on vascular pathophysiology in a mixed population of 101 autoimmune diseases including RA, SSc, PM and APS in comparison to 36 healthy controls. These autoimmune patients exerted impaired FMD (3.7 ± 3.8%), increased ccIMT (0.7 ± 0.2 mm) and increased PWV (9.7 ± 2.4 m/s) vs controls (FMD: 8.4 ± 4.0%; ccIMT: 0.6 ± 0.1 mm; PWV: 8.0 ± 1.5 m/s; $p < 0.05$). We found several correlations between ccIMT, FMD and PWV [10].

All these studies suggest that assessments of arterial stiffness, endothelial dysfunction and carotid atherosclerosis are reproducible and reliable non-invasive techniques for the complex assessment of vascular pathology in autoimmune patients at high risk [2,4,9,10].

3. Biomarkers

We have assessed multiple serum biomarkers including *prolactin*, *ferritin, vitamin D*, as well as the tumor marker *tissue polypeptide antigen* (TPA) in SLE, APS, SSc, RA, polymyositis (PM), dermatomyositis (DM), multiple sclerosis (MS), and autoimmune thyroid diseases. and antiphospholipid syndrome. Hyperprolactinemia was variably detected in 3–24% of PM, SLE, MS, RA and SSc patients. Hyperferritinaemia was observed in 4–23% of SLE, DM, MS and RA patients. In all diseases, most patients had relatively low levels of 25-OH-Vitamin D3. The mean

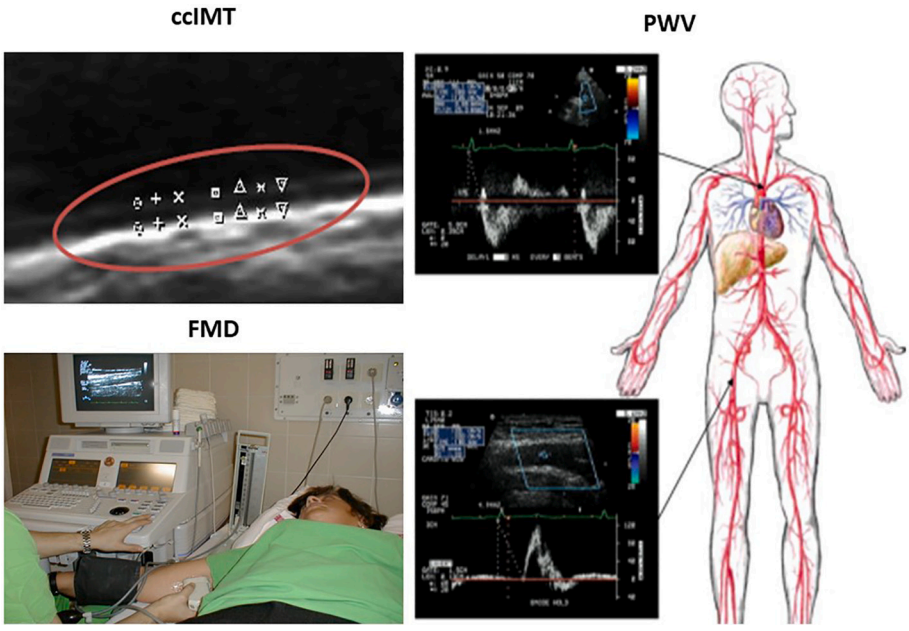

Fig. 4. Ultrasound-based, non-invasive techniques for the assessment of vascular pathophysiology. Common carotid intima-media thickness (ccIMT) is a measure of overt atherosclerosis. The distance between the first and second echogenic line from the lumen compose the ccIMT. Flow-mediated vasodilation (FMD) of the brachial artery is an indicator of endothelial function. It shows the percentage of the dilation of the artery, which is impaired (lower) in the case of endothelial dysfunction. Arterial pulse-wave velocity (PWV) is a marker of vascular stiffness. The distance used for this measurement is between the jugulum and symphysis.

vitamin D levels varied between 9.3 ± 4.4 to 13.7 ± 7.1 ng/mL in the different diseases. The 25- OH-Vitamin D levels <20 ng/mL are regarded as deficient. TPA levels were elevated only in SLE [11].

We then further analysed the role of *vitamin D* in SLE. Altogether 378 patients from several European and Israeli cohorts were pooled and their disease activity was measured by either SLEDAI-2 K or ECLAM scores. Significant negative correlation was demonstrated between serum levels of 25-OH-vitamin D3 and the standardised values of disease activity scores (R = -0.12; $p = 0.018$) [12].

The role of *vitamin D* was also assessed in autoimmune thyroid diseases (AITDs). We compared the levels of 25-OH-vitamin D3 in 50 patients with AITDs, 42 non-AITD patients and 98 healthy controls. The prevalence of vitamin D deficiency (<10 ng/mL) was significantly higher in patients with AITDs compared to healthy individuals (72% vs 31%; $p < 0.001$), as well as in patients with Hashimoto's thyroiditis vs those with non-AITDs (79% vs 52%; $p < 0.05$). Vitamin D deficiency correlated with the presence of antithyroid antibodies ($p = 0.01$) and, non-significantly, with abnormal thyroid function tests ($p = 0.059$) [13].

Vitamin D serum concentrations were also measured in 327 patients with SSc and 141 healthy subjects in association with various clinical and laboratory variables. Lover 25-OH-Vitamin D3 levels were detected in the sera of SSc patients compared to healthy controls (13.5 ± 9.0 ng/mL vs 21.6 ± 9.7 ng/mL; $p < 0.001$). An inverse relationship was found between skin involvement and vitamin D levels. While patients with a Rodnan skin score (RSS) of ≤10 had higher 25-OH-vitamin D3 levels than those with RSS > 10 (17.7 ± 10.4 ng/mL vs 8.0 ± 10.1 ng/mL; $p = 0.02$). Thus, cutaneous fibrosis in SSc might be associated with low vitamin D levels [14].

In another study, *prolactin* was further investigated in SLE. We assessed correlations between hyperprolactinaemia and disease manifestations and activity in a large SLE cohort. Age- and sex-adjusted PRL concentrations were determined in 256 SLE patients. Disease activity was determined by ECLAM or SLEDAI. Hyperprolactinaemia was present in 18% of SLE patients. Such patients had significantly more frequent serositis (40% vs 32%; $p = 0.03$), specifically, pleuritis (33% vs 17%; $p = 0.02$), pericarditis (30% vs 12%; $p = 0.002$), and peritonitis (15% vs 1%; $p = 0.003$). Patients with high PRL levels also more frequently had anaemia (42% vs 26%; $p = 0.02$) and, non-significantly, proteinuria (66% vs 46% $p = 0.06$) [15].

The role of *ferritin* in SLE has also been further elucidated. Ferritin levels were measured in 274 SLE serum samples. Disease activity was determined by ECLAM or SLEDAI. Hyperferritinaemia was found in 18.6% of SLE patients. When compared to subjects with normal ferritin levels, a significantly greater proportion of patients with hyperferritinaemia had thrombocytopenia (15.4% vs 33.3%; $p = 0.003$) and lupus anticoagulant (11.3% vs 29.0%, $p = 0.01$). Moreover, patients with elevated ferritin levels also had higher total anti-cardiolipin (99.7 ± 36.9 GPI vs 30.9 ± 17.3 GPI; $p = 0.02$) and IgM anti-cardiolipin levels (75.3 ± 35.7 GPI vs 9.3 ± 10.3 GPI; $p = 0.02$). The ECLAM score significantly correlated with hyperferritinaemia ($p = 0.04$). Thus, in SLE, hyperferritinaemia might be an early marker for secondary APS development [16].

Both *ferritin* and *prolactin* levels were investigated in 150 multiple sclerosis (MS) patients and 100 matched healthy volunteers. Hyperprolactinaemia was documented in 6.7%, while hyperprolactinaemia in 8% of MS patients ($p < 0.01$ and $p = 0.02$ vs controls, respectively). Hyperprolactinaemia was associated with the secondary-progressive type of MS in female patients ($p = 0.05$), while hyperferritinaemia correlated with male gender ($p = 0.03$) and with the relapsing-progressive type of the disease ($p = 0.02$). Thus, these biomarkers might be associated with gender and clinical type of MS [17].

4. Therapeutic interventions

In autoimmune diseases, disease activity and autoimmunity are the major drivers for comorbidities mentioned above, as well as the production of various vascular and metabolic biomarkers (Fig. 3) [1,3,4,18]. Logically, therapeutic interventions including targeted therapies that dampen disease activity might also have effects on these comorbidities [1,3]. We have summarized data on the effects of biologics on the vasculature in RA (Fig. 3) [1,3].

In one study, we assessed the effects of *rituximab* on FMD, ccIMT, and lipid profile in RA. Five female RA patients received two infusions of 1000 mg rituximab IV. Assessments were performed at baseline, as well as at weeks 2, 6, and 16 after the first infusion. Rituximab treatment resulted in a rapid and sustained improvement in FMD. The mean improvement was 30%, 22%, and 81% at weeks 2, 6, and 16, respectively compared to baseline. RTX had little effect on atherosclerosis (ccIMT) within this relatively short period of time. However, we observed 10%, 9%, and 2% decreases in ccIMT at weeks 2, 6, and 16, respectively vs baseline. Rituximab therapy resulted in 3–11% decrease in total cholesterol (TC), as well as 14–35% increase in HDL-C levels. Thus, two infusions of rituximab exerted early and sustained favourable effects on endothelial dysfunction, as well as plasma lipids [19].

We also investigated the effects of one-year *anti-TNF* (etanercept or certolizumab pegol) therapy on the production of soluble vascular biomarkers in a mixed cohort of RA and AS patients. In 53 anti-TNF-treated RA and AS patients, we determined circulating oxLDL/β2GPI complex (AtherOx), anti-Hsp60 IgG, and B-type natriuretic peptide (BNP) 8–29 fragment and soluble urokinase plasminogen activator receptor (suPAR) levels. We also prospectively assessed FMD, ccIMT and PWV in these patients. TNF-α inhibition significantly decreased oxLDL/β2GPI complex levels after 12 months vs baseline (0.20 ± 0.11 vs 0.24 ± 0.10 U/mL; $p = 0.014$). The suPAR levels decreased only in patients with critically high (>9 ng/mL) suPAR levels at baseline ($p = 0.04$). In RA, BNP levels were higher in RF/ACPA seropositive vs seronegative patients ($p < 0.05$). Serum levels of these vascular biomarkers variably correlated with lipids, ACPA, IgM RF and CRP ($p < 0.05$). Moreover, ccIMT positively correlated with BNP, and PWV with suPAR and anti-Hsp60, whereas FMD inversely associated with anti-Hsp60 ($p < 0.05$). In RM-ANOVA analysis, disease activity supported the effects of anti-TNF treatment on 12-month changes in oxLDL/β2GPI complex levels. Thus, these biomarkers might be involved in the pathogenesis of atherosclerosis and cardiovascular disease underlying RA/AS. TNF inhibition variably affects the release of oxLDL/β2GPI complexes, suPAR, and BNP [20].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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