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ARE CIRCULATING BLOOD BIOMARKERS FOR INFLAMMATORY RHEUMATIC DISEASES GENDER-DEPENDENT? – SYSTEMATIC REVIEW BASED ON OMICS DATA

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Background: Inflammatory rheumatic diseases (IRDs) are thought to be multifactorial diseases. Female-male ratio in IRDs differs according to the disease¹. In Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) female prevalence is higher opposing to Ankylosing Spondylitis (AS)^{2,3}. Until recently, differences on gender-bias observed in predisposition to IRDs, and to their pathophysiology have been understudied and neglected. Recent research using omics approaches shows that gender-bias is outspread in a diversity of pathologies. The integration of omics results, spite the extremely complex crosstalk among the several biomolecules involved, places these methods at the lead of medical research, overcoming limitations and increasing the forecasts of targeted methodologies⁴⁻⁶.

Objectives: The purpose of this systematic review is to aggregate existing omics results on biomarkers for RA, SLE and AS to raise awareness about whether gender can actually play a role on their profiles.

Methods: Two searches were conducted on PUBMED database (22nd November 2018) with a final output of 81268 articles. Both searches were sorted by best matches and for the second thousandth articles ranked no relevance was found for the aim of this review. The first 1000 articles were further analyzed based on the title, abstract and content. Three articles having relevant results were selected from the first thousand publications. Ten more were identified from the cross-references of both searches. The PICO (P, population; I, intervention; C, comparison; O, outcome) concept was used to perform the analysis according to: Patients: adults (>18 years old) with RA, SLE or AS (SpA); Intervention: any –omic study; Comparison: gender information regarding results; Outcomes: identified genes, proteins or metabolites.

Results: *Dectin-2*, *MCP-1* and *DC-SIGN* polymorphisms were proposed as possible accounts for gender-associated differences in susceptibility to RA⁷. Sex-differentiated and sex-interaction analyses of a GWA study revealed strong evidence of association in both sexes, highlighting links with RA only in one of the genders⁸. Several transcriptomic studies pointed to gender differences on biomarkers profiles for the three diseases. For instance, different expression levels of TNF α , IL-6, IL-17, IL-18, IFN α as well as X or Y chromosome-linked genes were found in SLE and/or AS⁹⁻¹¹. In AS, male patients with syndesmophytes showed higher levels of TNF α and men without syndesmophytes presented higher levels of VEGF, IL-6, TNF α and IL-18 both compared to females-matched¹². In RA patients, microRNAs 222, 532, 98, and 92a were found significantly down regulated in PBMC of female versus male¹³. Six genes displayed a gender-biased expression among male and female SLE patients¹⁴.

Conclusion: Blood biomarkers signatures for the IRDs analyzed in this study have been shown gender-biased. These will contribute for a better understanding of these diseases pathophysiology and probably to different gender approaches regarding diagnosis, monitoring and therapeutic approach.

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ENDOCARDIAL LESIONS IN PATIENTS WITH RHEUMATIC DISEASES: CASE REVIEW

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Background: The infection of a native or prosthetic heart valve usually occurs in patients with structural valvular anomalies that predispose to turbulent flows. Manifestations such as arthralgia, arthritis or back pain appear in up to 40% of patients, which acts as a confounding factor when this infection occurs in patients with rheumatic diseases. On the other hand, in the latter patients, noninfectious endocarditis has been described, which adds even more complexity to the diagnosis.

Objectives: To describe the characteristics of endocardial lesions in patients with rheumatic diseases.

Methods: Patients attending clinics at the Department of Rheumatology were analyzed to determine how many of them required hospitalization for causes directly related to endocardial lesion, from January 2015 until December 2018. The following information was recorded: age, sex, type of rheumatic disease, duration of the disease, immunosuppressive treatment, characteristics of endocardial lesions, complications of endocardial lesions, and cardiovascular risk factors.

Results: All patients were identified from an electronic database. Results regarding to demographic and clinical data are as follows:

Conclusion: The spectrum of endocardial involvement in patients with rheumatic diseases is variable. In this case review, we found lesions of different origin: infectious, thrombotic and tumoral. The appearance of fever of unknown origin in patients with rheumatic diseases, requires ruling out an endocarditis, needing transesophageal echocardiography in case the transthoracic study, which is less sensitive, is negative. It is striking the case of patient 3, a systemic sclerosis with calcinosis in limbs, whose endocardial wart, was studied histologically, revealing in its composition mainly calcium and fibrin. We have not found a bibliographic reference of calcium endocarditis in systemic sclerosis.

In conclusion, patients with rheumatic diseases can develop infectious endocarditis, but also thrombotic valvular vegetations, as well as myxomas whose consequences, from their clinical debut, may pose life-threatening situations for the patient. The presence of fever, stroke or embolic events in these patients should put us on the track of an underlying endocardial involvement.

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	Age	Sex	Rheumatic disease	Baseline Treatment	Endocardial lesions clinical debut	Blood culture	Endocardial lesions	Complications	Clinical evolution
1° case	27	Male	Dermatomyositis	Methotrexate + glucocorticoids	Digital ulcers + Febrile syndrome	Staph. Aureus	Infectious endocarditis	Mitral valve perforation	Resolution after cardiac surgery
2° case	64	Male	Rachialgia	NSAIDS	Febrile syndrome	Strept. Gallolyticus	Infectious endocarditis	-	-
3° case	53	Female	Systemic Sclerosis	Tocilizumab + glucocorticoids	Febrile syndrome	-	Nonbacterial thrombotic endocarditis	Acute ischaemia right lower limb	Resolution after embolectomy
4° case	13	Female	Autoimmune hemolytic anemia	Glucocorticoids, splenectomy	Ischaemic stroke	-	Auricular myxoma	-	Systemic lupus ANA and anti-DNA +
5° case	48	Female	Autoimmune thrombocytopenia	Glucocorticoids	Iliac artery embolism	-	Auricular myxoma	-	Immunologic syndrome secondary to myxoma