Dissertation

Study The Effects of Autoimmune Rheumatic Diseases on Vascular Function

submitted by

Ahmed Mahdy

for the Academic Degree of

Doctor of Medical Science

(Dr. scient. med.)

at the

Medical University of Graz

Physiology Division, Otto Loewi Center of Research in Vascular Biology, Immunity and Inflammation

under the Supervision of

Assoz.-Prof. Priv.-Doz. Andreas Roessler

2021

STATUTORY DECLARATION

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Guidelines of the Medical University of Graz on Good Scientific Practice “.

Graz November 2021

Ahmed Mahdy Hedar

DISCLOSURE

Parts of this thesis have been published in the following open access article:

-Autoimmune Rheumatic Diseases and Vascular Function: The Concept of Autoimmune Atherosclerosis. Ahmed M. Hedar 1,2, Martin H. Stradner 3, Andreas Roessler 1, and Nandu Goswami 1,4.

J. Clin. Med. 2021, 10(19), 4427; https://doi.org/10.3390/jcm10194427.

-A Pilot Study: Hypertension, Endothelial Dysfunction and Retinal Microvasculature in Rheumatic Autoimmune Diseases. Ahmed Mahdy 1,2, Martin Stradner 3, Andreas Roessler 1, Bianca Brix 1, Angelika Lackner 3, Adam Salon 1, and Nandu Goswami 1,4.

J. Clin. Med. 2021, 10(18), 4067; https://doi.org/10.3390/jcm10184067.

1.Physiology Division, Otto Loewi Center of Research in Vascular Biology, Immunity and Inflammation, Medical University of Graz, Neue Stiftingtalstraße 6, 8010 Graz, Austria;
2. Internal Medicine Department, Faculty of Medicine, Ain Shams University, Ramsis Street, Abbassia Square, Cairo 11435, Egypt
3. Rheumatology and Immunology Department, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria
4. Department of Health Sciences, Alma Mater Europaea, Slovenska ulica 17, 2000 Maribor, Slovenia

ACKNOWLEDGEMENTS

First, I would like to thank my teacher, my friend, my father, and, my Professor Nandu Goswami. Without his help and support throughout this period, I would not have finished this thesis. I couldn't forget his support to me, all kinds of support, scientific support, financial support, and, psychological support. I was always felt safe when he was beside me. He was answering all my questions any time I ask him. I cannot find words to express my feeling towards him for what he did for me and what I had got experienced from him for the last two years, and his favor I will not forget it all my life and I hope to return the favor to him one day as I still living.

Second, I want to thank Professor Andreas Roessler, my supervisor and I couldn't forget his support and his advice especially when I need to sign any paper and I couldn't forget his support for me after measurements and his supportive words gave me fuel for more hard work. I did not forget his smile and his emotion which I have always felt what he wants to encourage me to progress.

Third**,** I want to thank professor Martin Stradner, my co-supervisor for the great effort he did with me I will never forget his participation in our study other than he was the main person in recruitments of the patients and control group and explain to the participants the study and measurements and then get their consent to participation in the study, he also became a volunteer and shared in the study when he became one of the healthy control group and underwent blood sample and measurements like the other participant in spite of, he was very tired from his work. Also, I will never forget his role in the revision of our papers before publication and as he helped me a lot with every question I asked. Fourth, I want to thank Ms. Bianca Backer for her help in translating the procedure to the participant plus her great role in obtaining the ethical committee approval and in helping me with any problem I faced during my doctoral study. Also, I want to thank Ms., Angelika Lackner, the research coordinator in the rheumatology department for her effort with recruitments of the patients and control group and arranging with them to attend the clinic at the time of measurements and providing me with the lab results of the participants, in addition, she shared by herself as one of the control group in our measurements and we took blood from her. I want to ask Ruslan for his efforts in doing analysis and statistics of the study

and Adam Salon for his role in taking retinal photos for the participants, small Andy a lab technician for helping us analyze the blood sample, and Joahn, the IT and lab person who helped us a lot in the preservation of the sample in the freezer until need plus his great role in moving the devices for the measurements from Gynecology department to the outpatient's clinic of rheumatology for doing the measurements and then return again which was a great effort from him. Fifth, I want to thank everyone who participates in this study whether patients and control group as without them the study not finished and this important knowledge won't become and without their participation, no paper would be published so, I can find words to express my felling toward them, thank you a lot. Sixth, I want to thank the nearest one in the world for me and I hope if her soul knows what I did and I was hoping to share my success but she died before I finish my dreams, she was my mother, who I never forget her and her support all my life and I hope to give her soul everything I get from my life. Seventh, I want to thank doctoral school ''Translational Molecular and Cellular Biosciences", especially Professor Wolfgang Schreibmayer for all help and his effort with the doctorate students. At the last, I want to thank everyone helped me even if with one letter in this study and I want to say.

"WHO LEARNED ME LETTER IN MY LIFE, I WILL BE SERVANT FOR HIM ALL MY LIFE"

My Greeting

Ahmed Mahdy Hedar

Funding: Doctoral student Ahmed Mahdy Hedar did not received funding from the Medical University of Graz. The Office for Doctoral Studies paid for material and publication of the papers.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACEIs	Angiotensin-converting enzyme inhibitors
ACPA	Anti-citrullinated peptide antibody
ADMA	Asymmetric dimethyl arginine
AIRDs	Autoimmune rheumatic diseases
AL amyloidosis	Primary amyloidosis
ANA	Antinuclear antibodies
Anti-DNA	Anti double-strand antibody
Anti-oxidized LDL	Anti-oxidized Low density lipoprotein antibody
Anti-Ro	Anti-Ro antibody
Anti-La	Anti-La antibody
ARBS	Selective angiotensin receptor blockers
A/V ratio	Arteriole/venule ratio
BMI	Body mass index
CD	Cluster of differentiation
CDAI	Clinical disease activity index
CIMT	Carotid intima-media thickness
CR2	Canon retinal camera 2
CRP	C reactive protein
CRVE	Central retinal artery equivalent

CRVE	Central retinal venular equivalent
CT	Computerized tomography scan
DBP	Diastolic blood pressure
DMARDS	Disease-modified anti-rheumatoid drugs
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren syndrome disease activity index
EULAR	European League Against Rheumatism
FMD	Flow mediated dilation
GFR	Glomerular filtration rate
HDL	High density lipoprotein
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL1	Interleukin-1
IL6	Interleukin- 6
IL10	Interleukin-10
IL-17	Interleukin-17
LDL	Low density lipoprotein
LKH	Landen Krankenhausen
MBP	Mean blood pressure
Mic	Micrometer

MRI	Magnetic resonance imaging
NO	Nitric oxide
NOS	Nitric oxide synthase
PAT	Peripheral arterial tonometry
PiHDL	Pro-inflammatory high density lipoprotein
PET scan	Positron emission topography scan
PSS	Primary Sjögren syndrome
PWV	Pulse wave velocity
R (r)	Correlation coefficient
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SBP	Systolic blood pressure
SD	Standard deviation
SLE	Systemic lupus erythematosus
SPSS	Statistical Package for Social Sciences
TCZ	Tocilizumab
Th1	T helper-1 lymphocytes
TH17	T helper-17 lymphocytes
TNF ά	Tumor necrotic factor alfa
Treg	T regulatory lymphocytes
T8	T lymphocytes cytotoxic 8

VLDL Very low density lipoprotein

LIST OF FIGURES:

LIST OF TABLES

KURZFASSUNG

Hintergrund: Rheumatische Autoimmunkrankheiten, die heute herausfordernde Krankheiten, eine Herausforderung für die Diagnose und eine Herausforderung für die Behandlung sowie eine Herausforderung für die Nachverfolgung der Patienten zur Verbesserung und Heilung darstellen, nehmen jetzt in Inzidenz und Prävalenz zu. Seine Ursachen sind nicht bekannt, aber genetische, umweltbedingte Faktoren spielen eine Rolle und sind an seiner Pathogenese beteiligt. Autoimmune rheumatische Erkrankungen umfassen den Prototyp der Erkrankungen, die rheumatoide Arthritis und systemischer Lupus erythematodes, Sjögren-Syndrom, systemische Sklerose, Myositis, Dermatomyositis und Psoriasis-Arthropathie sind. Die Inzidenz und Prävalenz von Herz-Kreislauf-Erkrankungen bei rheumatischen Autoimmunerkrankungen stieg an und die Sterblichkeit erreichte 30% der Gesamtmortalität aufgrund von Herz-Kreislauf-Erkrankungen. Arteriosklerose gilt weltweit als Hauptursache für Herz-Kreislauf-Erkrankungen. Traditionelle Framingham-Risikofaktoren erklären die Ursachen der Arteriosklerose bei rheumatischen Autoimmunerkrankungen nicht vollständig, so dass andere Ursachen für dieses Ereignis verantwortlich sind, die nicht traditionelle oder nicht klassische Risikofaktoren wie chronische Entzündungen und Medikamente sind. Diese Fall-Kontroll-Studie versucht, den Zusammenhang zwischen chronischen Entzündungen bei rheumatischen Autoimmunerkrankungen und der Gefäßfunktion in Form von Arteriosklerose aufzuzeigen.

Methode: Die Studie war eine Pilotstudie die in der Rheumatologischen Klinik der Medizinischen Universität Graz durchgeführt wurde. Die Studie besteht aus 3 Teilnehmergruppen, die erste Gruppe bestand aus Patienten mit rheumatoider Arthritis (RA) (n = 10), die zweite Gruppe bestand aus Patienten mit primärem Sjögren-Syndrom (PSS) (n = 10) und die dritte Gruppe war gesunde Kontrollen (n = 10). Der systolische Blutdruck (SBP), der diastolische Blutdruck (DBP) und der mittlere Blutdruck (MBP) wurden gemessen. Die Pulswellengeschwindigkeit (PWV) von Femoral-Carotis-Arterien wurde unter Verwendung eines Vicorder-Geräts gemessen. Der Endothelzelldysfunktionsmarker ADMA wurde im Labor mit ELISA gemessen. Der Nachweis der retinalen Mikrovaskulatur erfolgte über eine CR-2-Netzhautkamera, und die Analyse der Netzhautfotos erfolgte unter Verwendung des Mona Reva-Softwareprogramms.

Ergebnisse: Die Studie zeigte, dass die Prävalenz der Hypertonie bei RA-Patienten 80 % beträgt und die Prävalenz der Hypertonie bei PSS-Patienten 40 % beträgt, während die Prävalenz in der Kontrollgruppe nur 20 % betrug. Die Ergebnisse des gemessenen Blutdrucks wurden bei SBP beobachtet (148 ± 16 mmHg bei RA vs. 128 ± 11 mmHg in der Kontrollgruppe; p - 0,007), während 135 ± 16 mmHg bei PSS-Patienten im Vergleich zu 128 ± 11 mmHg in der Kontrollgruppe beobachtet wurden Gruppe p - 0,340. DBP bei RA (77 ± 8 mmHg, im Vergleich zur Kontrolle 67 ± 6 mmHg; p - 0,010). Der DBP bei PSS-Patienten beträgt 72 ± 8 mmHg gegen. 67 ± 6 mmHg in der Kontrollgruppe: p - 0,190. MBP (RA 101 ± 11 mmHg; im Vergleich zu Kontrollkontrollen 88 ±7 mmHg, p = 0,010), während MBP bei PSS-Patienten 93 ± 10 mmHg gegen. 88 ± 7 mmHg in der Kontrollgruppe ohne signifikanten Unterschied betrug: p - 0,240. Der Plasmaspiegel des endothelialen Dysfunktionsmarkers ADMA war bei RA-Patienten (0,45 ± 0,069 ng/ml) im Vergleich zu den Kontrollen (0,38 ± 0,059 ng/ml) mit statistisch signifikanter (p - 0,022) hoch, und der ADMA-Spiegel bei PSS-Patienten Gruppe war (0,43 ± 0,060 ng/ml) im Vergleich zu den Kontrollen (0,38 ± 0,059 ng/ml) ohne statistisch signifikanten Wert. PWV und retinale Mikrovaskulatur zeigten, obwohl sie im Vergleich zur PSS- und Kontrollgruppe einen hohen Anteil an RA aufwiesen, keine statistische Signifikanz.

Schlussfolgerungen: Hypertonie ist bei rheumatologischen Autoimmunerkrankungen im Vergleich zu normalen Menschen sehr häufig und da es keine andere Erklärung für Hypertonie als endotheliale Dysfunktion gibt, gilt Hypertonie als frühes Zeichen einer endothelialen Dysfunktion bei rheumatischen Autoimmunerkrankungen und Hypertonie ist die wichtigste traditionelle Risikofaktor, der zur Arteriosklerose beiträgt. Wir müssen auf Bluthochdruck untersuchen und ihn durch die Kontrolle des Entzündungsprozesses bei rheumatischen Autoimmunerkrankungen behandeln.

Schlüsselwörter: Hypertonie und endotheliale Dysfunktion; ADMA bei Autoimmunerkrankungen; ein frühes Zeichen einer endothelialen Dysfunktion; die Prävalenz von Bluthochdruck bei Autoimmunerkrankungen; PWV bei Autoimmunerkrankungen.

ABSTRACT

Background:

Autoimmune rheumatic diseases (AIRDs) are considered now challenging diseases concerning diagnosis, treatment, and following up the patients. The number of patients is now greatly increasing. AIRDs causes are not known but genetic, environmental factors play a role and participate in its pathogenesis. AIRDs include the prototype of the diseases which are rheumatoid arthritis and other diseases like systemic lupus erythematosus (SLE), Sjögren's syndrome, systemic sclerosis, myositis, dermatomyositis, and Psoriatic arthropathy. The incidence and prevalence of cardiovascular diseases and cardiovascular mortality in AIRDs increased and the mortality reached 30-50 % of all-cause mortality, most cardiovascular diseases developed in AIRDs are due to atherosclerosis which is proven to be the major initiating factor of cardiovascular problems worldwide.

Traditional risk factors like cigarette smoking, male gender, obesity, sedentary lifestyle, diabetes mellitus, and hypertension do not fully explain the causes of atherosclerosis in AIRDs, other causes are responsible for this event which is nontraditional or non-classic risk factors like chronic inflammation and drugs used in treatment. This research depends on a comparison between the diseased patients and healthy control. The major aim is to discuss the effect of the AIRDs characterized by chronic inflammation on the function of the endothelium lining the blood vessels and its relation to the atherosclerosis process.

Method:

A pilot study has been done at the Medical University of Graz in the rheumatology department. The study consists of 3 groups of participants, the group was rheumatoid arthritis (RA) consisting of 10 patients, the second group was primary Sjögren's syndrome (PSS), consisting of 10 patients, and the third group was healthy controls 10 persons. Measuring blood pressure of the participants including, the systolic blood pressure (SBP), mean blood pressure (MBP), and diastolic blood pressure (DBP) was done. Pulse wave velocity (PWV) of femoral-carotid arteries was measured using a Vicorder device. Endothelial cell dysfunction marker Asymmetric dimethylarginine (ADMA) was measured in the lab using ELISA. Detection of retinal blood

vessels (microvasculature) was done by Canon (a CR-2) eye camera, and analysis of the posterior compartment of the eye containing retinal vessels was done using the Mona Reva software program.

Results:

The study showed that:

- The prevalence of hypertension in RA patients is 80%.
- The prevalence of hypertension in PSS patients is 40% while in the control group the prevalence was only 20%.
- The results of blood pressure measurement were seen in SBP (148 ± 16 mmHg in RA while it was 128 ± 11 mmHg in the control group; p value - 0.007).
- SBP was 135 ± 16 mmHg in PSS patients compared to 128 ± 11 mmHg in control group p value - 0.340.
- DBP in RA (77 ± 8 mmHg, while in the control group 67 ± 6 mmHg; p value - 0.010).
- DBP in PSS patients was 72 ± 8 mmHg as compared to 67 ± 6 mmHg in control group: p value - 0.190.
- MBP was in RA group 101 ± 11 mmHg; versus the control controls 88 ±7 mmHg, p value - 0.010.
- MBP in PSS patients was 93 ± 10 mm Hg as compared to 88 ±7 mmHg in the control group with no significant difference: p value - 0.240.
- The plasma level of ADMA (endothelial dysfunction marker)was high in RA group (0.45 ± 0.069 ng/mL) while it was in the control group (0.38 ± 0.059 ng/mL) with statistically significant (p value - 0.022).
- The level of ADMA in PSS patients group was (0.43 ± 0.060 ng/mL) as while ADMA was in the control group (0.38 ± 0.059 ng/mL) with (P value - 0.06) and not reach a statistical significant value.
- PWV and retinal microvasculature although they were high in RA as compared to PSS and control group did not show statistical significance.

Conclusion:

Hypertension is very common in AIRDs if we compared it to normal people and there is no explanation for hypertension other than endothelial dysfunction. So, hypertension is considered the early sign of endothelial dysfunction in AIRDs. Hypertension is considered one of the major risk factors (traditional) which can initiate the atherosclerosis process. We must screen for hypertension and treat it through control of the inflammatory process in AIRDs.

Keywords:

Hypertension as an immune disease - ADMA level in autoimmune diseases-an early sign of endothelial dysfunction - the prevalence of hypertension in autoimmune diseases - PWV in autoimmune diseases- autoimmune atherosclerosis.

1. Introduction

1.1 Autoimmune diseases and atherosclerosis:

Although the improvement of technology, the uses of new devices in the investigation and diagnosis of the diseases, the true reason for atherosclerosis which happens in autoimmune rheumatic disease (AIRDs), has not been understood [1]. Until now all the researches filled to discover the main causes of atherosclerosis in AIRDs, as there are two theories, the first one is well-known factors like age, gender, familial tendency, environmental factors, hypertension, diabetes mellitus, and lifestyle-related factors, all these factors called traditional risk factors.

The second theory in atherosclerosis causes in AIRDs referred to non-traditional risks like chronic inflammation, immune cells, cytokines, and antibodies [1]. In addition, still a debate about the proportion of the contribution of each factor of non-traditional risk in process of atherosclerosis in AIRDs (which one has a major role) [1].

Moreover, there are two types of atherosclerosis, primary atherosclerosis (no clear cause or predisposing factors) which happens with aging. The other type is immune-induced

atherosclerosis, which is called premature atherosclerosis [2]. From a clinical point of view, atherosclerosis (arterial stiffness) is a predisposing factor to vessels diseases and cardiac diseases and a leading cause of death in the general population and also in all autoimmune diseases. Here the study tries to discuss the relationship between the role of chronic inflammation in form of AIRDs, and the pathogenesis of atherosclerosis.

1.2 The challenge of autoimmune rheumatic diseases:

Rheumatic autoimmune diseases, sometimes called connective tissue diseases or collagen diseases are challenged diseases, challenges for diagnosis, challenges for treatment, and challenges for follow-up. They are diseases of unknown causes, but many factors can contribute to them primarily genetic, environmental factors which can initiate or potentiate these diseases. Other factors are considered risk factors like age, food, stress, etc. 5 to 7 % of normal people affecting by collagen diseases [3]. Nowadays, new cases were daily diagnosed as AIRDs.

These diseases have been increasing all over the world, especially in developing worlds, no well-known causes were detected for that increase [4]. Because no clear theories about the pathogenesis of autoimmune diseases are known, this makes these diseases a challenging health problem, plus the physicians find it difficult to diagnose these diseases and AIRDs can remain undiagnosed for many years before diagnosis and in addition, these diseases are difficult to treat [5].

AIRDs start when the human body recognizes its normal antigen as a foreign antigen and attacks them. At this stage, the human body attacks itself and make dysfunctional in the normal physiology and function of the body organs consequently, the pathological process started and the symptoms and sign of the diseases appear [6]. The most dangerous disease as regard mortality in autoimmune diseases family is systemic lupus erythematosus (SLE)(as it is difficult to diagnose usually and is systemic from the start) [7].

The three main causes of death in ARDs come from; number one is the active diseases, number two is infections (due to the use of immunosuppressive drugs), and number three is cardiovascular diseases [8–10]. The rate of morbidity and mortality due to cardiovascular diseases in ARDs became twice or three times morbidity and mortality in the normal population

[11]. It is interesting that 33–50% of all death registered in connective tissue diseases come from heart diseases alone [12,13].

It is well known that every relapsing attack of any disease is dangerous as this aggravates the chronic situation and added more damage. Because of the recurrent relapsing attacks, the outcome of the disease becomes worse, and the mortality due to cardiovascular diseases increases [3].

The releasing cytokines and chemical mediators are considered the cornerstone of chronic inflammation occurring in autoimmune diseases. These chemical mediators aggravate the process of atherosclerosis [14–16], so it is not obvious which factors as tumor necrotic factors (TNF), or Interleukins (ILs) contribute to aggravating the atherosclerosis process. It may come from the inflammatory state of the disease itself or steroids and other immunosuppressive drugs used, or from diseases complications.

1.3 Pathogenesis of autoimmune rheumatic diseases:

The connective tissue (CT) consists of elastin and collagen fibers. The CT is presented in all the organs. Its function is to support the parenchyma of the different organs. Collagen fibers are the main constituent of CT present in multiple organs including blood vessels, sclera, bones, kidneys, lungs, joints, muscles, and skin. In a systemic inflammatory state, all the organs mentioned will be affected throughout the inflammatory process and disease progression.

In the pathogenesis of AIRDs, the immune system recognizes self-antigen as a foreign antigen and attacks it aggressively, initiating the auto-inflammatory process [6]. The attack of the immune system against body organs leads to the release of mediators (cytokines and chemokines), in addition to stimulation of the immune system to release the immune cells (inactive) and conversion from immature to mature lymphocytes (T and B lymphocytes) with the liberation of cytotoxic T cells and release of antibodies from plasma cell (differentiated from B lymphocytes) directed against self-antigens. These events lead to the end-organ failure.

The predisposing causes of autoimmune diseases are an interaction between genetic and environmental factors [6]. Autoimmune diseases depend on T lymphocytes in pathogenesis, acting through activation of (T helper)Th 17 and Th1 cells [18]. In addition, environmental

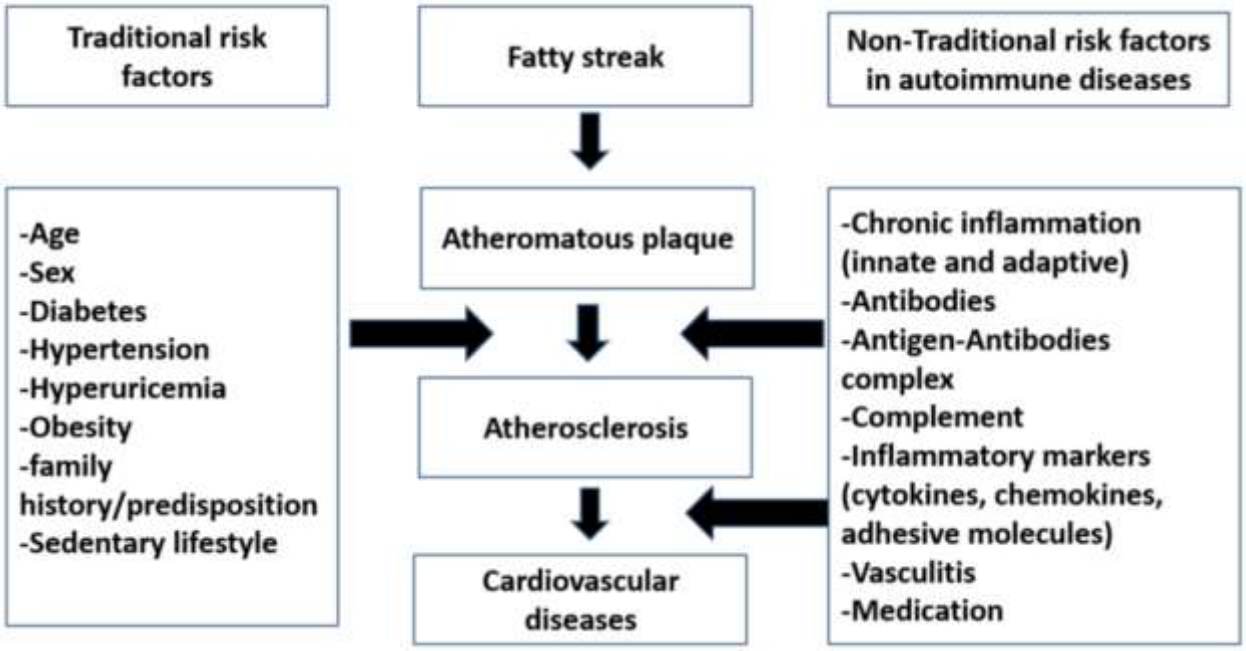
factors may work as super-antigen and encourage the immune system to secret more antibodies against modified self-antigens, these environmental factors include, toxins, ultraviolet radiation, microbes, food additives, and the most important factor in modulating the immune system is the stress which may stimulate the immune system directly and causing autoimmune diseases [18].

1.4.Autoimmune rheumatic diseases and vascular function (premature atherosclerosis):

The following figure shows the relationship between traditional and nontraditional factors and their effect on the development of atherosclerosis in ARDs:

Figure (1): The relationship between traditional and nontraditional factors and their effect on the development of atherosclerosis in auto-immune diseases

(Reproduced from "Hedar et al, 2021" [220])



Additionally, the previous figure shows the relationship between traditional risk factors including, age, sex, presence of accompanying diseases like diabetes or hypertension, obesity, etc., and nontraditional factors like cytokines, antibodies, immune cells, etc., and their effect on the process of atherosclerosis pathogenesis in rheumatic diseases.

1.4.1. Traditional risk factors in atherosclerosis:

Cardiovascular diseases are one of the most common causes of illness and death in AIRDs [19]. Although the research in the field of cardiovascular diseases and atherosclerosis process is in progress, the true risk factors and precipitating factors that are blamed as the cause of atherosclerosis in autoimmune diseases are not known, and there is a lot of controversy about whether atherosclerosis comes from traditional or non-traditional risk. As mentioned before atherosclerosis is considered the main risk factor in cardiovascular diseases in autoimmune diseases. [12,20].

Diabetes mellitus, dyslipidemia, hypertension, hyperuricemia, age, sedentary lifestyle, male gender, smoking, obesity, and metabolic syndrome, are the common traditional risks [12,21].

The new term, inflammatory cachexia is a term that describes what happens in the body during active inflammation, where there is a state of hypercatabolism in the body due to liberation of many cytokines like IL1, IL6, TNF alpha which acts as fuel to initiate, potentiate, and exaggerate inflammation in rheumatic diseases [22]. Inactive diseases with the release of chemical inflammatory substances (the cytokines, and other chemical mediators), these substances lead to an increase in the normal rate of body metabolism in different ways and cause hypercatabolism of muscle protein and body fats.

Moreover, these mediators lead to loss of appetite (anorexia) and feeling of hotness. All these factors are supposed to decrease body weight (cachexia) [23, 24]. The clinical research has done in this parameter illustrated that there is an increase in the body weight in RA patients during active inflammatory conditions not decreases in the bodyweight [25–27]. However, increasing body weight and obesity which are considered famous risk factors in developing atherosclerosis, obesity has a good prognostic effect on cardiovascular mortality in RA if compared to the mortality that happens to thin, low weight patients. RA patients, with a body mass index (BMI) of more than 30 (obese), have a good outcome in diseases progression and prognosis if compared to patients with low BMI, lower than 20 [28].

“Lipid paradox” is a term used to describe the lipid profile in the active inflammatory condition when all the lipid parameters: including, total cholesterol, low-density lipoprotein (LDL), triglycerides, and high-density lipoprotein (HDL) cholesterol due to the state of increased

burning (hyper catabolism) all the lipid profile decreased, then the lipid profile return to normal or even increased when the active inflammation subsided (Lipid Paradox) [29].

Cigarette smoking is one of the oldest, most common risk- factors in the atheroma formation of great vessels [30]. Smoking contains a lot of toxic substances that initiate inflammation of vascular endothelium (oxidizing agents) and consequently unhealthy endothelium and increases the risk of developing atherosclerosis and arterial vascular diseases in ARDs [31]. On the other hand, the risk will increase if the smoking is combined with the presence of other antibodies like anti-citrullinated peptide antibody (ACPA) or rheumatoid factor (RF) in the circulation (non-traditional risk) [32].

An increase in homocysteine levels in the blood is now considered one of the known classical risk factors in the development of atherosclerotic process and peripheral arterial diseases [33], Hyperhomocysteinemia is considered an important risk factor in the severity and prognosis of cardiovascular events in autoimmune diseases [34].

Metabolic syndrome is one of the most important risk factors in atheroma formation, and although the debate is still present about which has a worse effect on the progression of cardiovascular events in autoimmune diseases, metabolic syndrome is associated with increased risk and disease progression and worst outcome in autoimmune diseases [29,35].

Another factor shared in the development of vascular diseases is hyperuricemia which is well known as part of metabolic syndrome considered a risk factor in ARDs [36].

Insulin resistance as part of prediabetes and an important part of metabolic syndrome may be related to the atherosclerosis process in connective tissue rheumatic diseases [29].

1.4.2. Non (common) traditional risk factors in atherosclerosis:

Now, we will discuss the uncommon risk factors for atheroma formation which means risk factors that are not usually present in the population and defined as risk factors accompanying specific diseases or drugs. In autoimmune diseases, these factors include antibodies, cytokines, drugs side effects, and immune cells (see Figure 2).

The physiological function of the chemical mediator nitric oxide (NO) on endothelial cells is unique and specific for this type of cell. NO is a potent vasodilator and prevents thrombosis and atheroma formation. In the active inflammation with the release of chemical mediators and cytokines, the normal function of NO will be affected and endothelial dysfunction happens. The result is vasoconstriction of blood vessels, endothelial injury, platelets aggregation, immune cells migration, as well as increased tendency to vessel wall thrombosis and atherosclerosis [37].

As the result of finding T cell lymphocytes and B cell lymphocytes in the histopathological analysis of atheroma so both T lymphocytes and B cells lymphocytes share in process of atheroma formation, plus their role in the pathogenesis of all inflammatory diseases [38]. Researchers discovered the role of T lymphocyte cells, in process of atherosclerosis, T helper 1 cells (Th1) [39], and T helper cell 17 (Th17), both of these cells potentiate the process of atheroma formation [14]. The protective role of T lymphocytes comes from T regulatory cells (Treg) which prevent and protect the vessels wall from the process of atherosclerosis [40]. So, the percentage of Th17 lymphocytes to the percentage of regulator T cells can detect to some degree the process of atheroma formation, and also, this percentage is important in the study of new medication used for controlling the disease during clinical trial [39].

Inflammatory cytokine TNF ά is the most important cytokine (chemical mediators) in initiating and maintenance of autoimmune diseases and immune atherosclerosis. Natural TNF ά is released from many immune cells like T cells lymphocytes, macrophages, and in addition to endothelial cells. As TNF ά may initiate the inflammatory process or it potentiates inflammatory states, the medication that antagonizes the effect of TNF ά, Infliximab (TNF ά blocker), plays a critical role in the control of acute inflammation and subsequently active disease management and prognosis [41]. Another cytokine that has an important role in the inflammatory condition and atherosclerosis is IL6, IL6 was found in high concentration in RA patients diagnosed as having atherosclerosis [42]. Also, IL1 was found to participate in the process of atherosclerosis in RA [43].

Antibodies, which are the main pathogenic factor in autoimmune diseases, are an important nontraditional cardiovascular risk in autoimmune atherosclerosis. The researchers found a lot of antibodies that have a role in the atherosclerosis process [44]. The first antibody implicated the process of atherosclerosis in autoimmune diseases as a rheumatoid factor (RF), while its levels in

the plasma increased with arthritis activity and can predict disease prognosis of RA. Also, its titer in the serum is correlated with vascular risk and increased cardiovascular diseases [45,46]. Another antibody needed in the diagnosis and prognosis of RA is anticitrullinated protein antibody (ACPA) is another marker for diagnosis and prognosis, its presences indicate worse prognosis and deformity formation and it was found that has a relation to cardiovascular complication in RA patients [47].

Antinuclear antibodies (ANA) are a group of antibodies related to many autoimmune diseases like SLE, autoimmune hepatitis, scleroderma, and RA, the titer of these antibodies correlates with activity and severity of autoimmune disease, atherosclerosis, and cardiovascular complication [48]. The presence of anti-DNA antibody, which is specific in the diagnosis of SLE disease, was discovered that anti-DNA potentiates cardiovascular-related diseases [49]. Anti-LDL antibodies are one of the new markers in cardiovascular research and they formed against oxidized LDL. The presence of newly discovered anti LDL antibodies in the serum may show an increase in the pathogenesis of atherosclerosis and unhealthy endothelial [50]. Some studies suggested that the presence of anti-oxidized LDL antibodies in the blood may protect against the atherosclerosis process [51, 52]. There are two types of anti-oxidized LDL antibodies, IgG and IgM, the interesting is that IgM has a protective role against atherosclerosis, while IgG potentiates atherosclerosis [50]. Antiphospholipid antibodies are one of the famous antibodies in autoimmune diseases. Whether primary antiphospholipid antibody syndrome or accompany another autoimmune disease (secondary antiphospholipid). Antiphospholipid antibodies are responsible for thrombosis, ischemia, vasculitis, and accelerate all cardiovascular complications [53]. Cryoglobulins are antibodies or immunoglobulins that precipitate at temperature 4 C in vitro, it was found in many autoimmune diseases, like Sjögren's syndrome and SLE, in addition, it associated with hepatitis C virus vascular complication [54]. The presence of Cryoglobulins in the circulation may indicate a sign of worse outcome as it can cause critical symptoms when this globulin agglutinate and obstruct vessels of the peripheral circulation (when the temperature becomes slightly low).

Cryoglobulins precipitate and obstruct the lumen of blood vessels leading to vascular ischemia ranging from critical tissues ischemia up to tissue necrosis and gangrene in addition to vasculitis [55], this vasculitis mostly accelerates endothelial dysfunction [56]. Anti-Ro and anti-La

antibodies are antibodies essential in the diagnosis of some ARDs especially systemic sclerosis in addition to their presence in other autoimmune diseases, some cases of congenital heart block found in neonates of lupus patients may have anti-Ro, and anti-La antibodies in their plasma [57], the researchers described that the presence of anti-Ro antibodies in adults primary Sjögren's syndrome patients may affect the heart and lead to complete heart block [58, 59].

As regards the situation of chronic inflammation, the recent guidelines of the European League Against Rheumatism (EULAR) mentioned that chronic inflammation that presents in rheumatic autoimmune diseases increase the cardiovascular risk by one and a half time more in rheumatic patients if compared to cardiac patients without risk of chronic inflammation; this means that the chronic inflammatory process can consider an independent risk for cardiovascular diseases and equal to hypertension, diabetes.

1.5. Cardiac amyloidosis and relation to rheumatic autoimmune diseases:

Heart failure is one of the most common cardiac diseases. Heart failure has many causes like ischemic, idiopathic (myopathy), preload failure, and afterload failure. The type of heart failure in RA patients is normal cardiac output heart failure or in another term restrictive heart failure (as the heart muscle fibers are good but the problem is the distensibility of the myofibril with an inability to relax [60]. In the old researches, it was thought that ischemic cardiomyopathy present in RA is mostly coronary vessels ischemia (coronary atherosclerosis), later it is discovered that heart failure in patients with RA happens with normal systolic function (normal cardiac output failure), this fact with normal cardiac function and normal ejection fraction could not explain by ischemia of the coronary arteries [60,61].

Restrictive cardiomyopathy is one type of heart disease that leads to restrictive heart failure or normal output heart failure. The restriction of the cardiac muscle is due to a rigid, stiff muscle that happens mostly due to the deposition of substances in the cardiac muscle like iron, or amyloid fibrils. As the result of chronic inflammation that presents in AIRDs, many acute phase reactants and inflammatory proteins are present in the plasma, and these proteins can deposit in organs causing disease of these organs.

The cause of restrictive cardiomyopathy diagnosed in rheumatic diseases may be due to the deposition of heterogeneous acute phase reactants protein fibril in the myocardium [62]. The

deposition of heterogeneous acute phase reactant fibril which showed by light microscopy stained by Hematoxylin and Eosin stain may raise the possibility of Amyloidosis of the heart. The old famous disease of Amyloidosis of cardiac muscles may arise as primary amyloidosis (AL), (which is the most common cause of cardiac amyloidosis), AL is a hematological disease (plasma cell diseases), while secondary amyloidosis, with the interaction and deposition of acute-phase proteins amyloid A, resulted from chronic inflammation (chronic infection and autoimmune diseases) [63]. Primary amyloidosis, as mentioned is a disease of plasma cells, in which the proteins (globulins) most probably can precipitate in the heart muscle and create secondary amyloidosis. The accompanying chronic inflammation globulins can deposit in the liver (the factory of acute-phase proteins) and the kidney (the filter of the blood) leading to enlargement of these organs causing hepatomegaly and kidney causing tubular dysfunction and loss of the proteins in the urine and causing nephrotic syndrome.

Due to the deposition of acute-phase reactant proteins, secondary amyloidosis can be shown in all tissues including the heart muscle [64, 65]. So, the presence of secondary amyloidosis in most AIRDs due to chronic inflammation and (as most AIRDs are not cured but controlled)most of these diseases persist for more than 10 years, the results will be amyloidosis of the heart and an increase in presentation of heart failure which appears to be one of the cardiac cause of mortality in AIRDs especially in RA [62].

1.6. The relationship between hypertension and autoimmune diseases:

Recently, there is a controversy and debate about the issue of the relationship between elevated blood pressure and rheumatic connective tissue diseases. Theoretically, increased blood pressure is supposed to be a common sign in connective tissue diseases, simply due to the stress of the disease. Most studies showed that hypertension presents with a great extent in connective tissue rheumatic diseases and this high percentage is found mostly in the prototype of connective tissue diseases, RA [66]. These papers showed big differences in the diagnosed elevated blood pressure cases in autoimmune diseases [67–71]. Research papers reported that the prevalence of elevated blood pressure in rheumatoid patients is 3–70% [72]. On the other side, another research found that there are no differences in the results of blood pressure recording in rheumatic autoimmune patients as compared to controls [73–78].

Therefore, there is still a debate in the research papers about the most corrected number denoting the percentage of elevated blood pressure in autoimmune diseases [3, 70, and 71]. The questionable issue here is that some study-deny the presence of elevated blood pressure in autoimmune diseases and mentioned that, in rheumatoid arthritis, hypertension is related to aging not to the disease itself [79].

The two major elements of this study, hypertension and autoimmune diseases are influenced by many factors like environmental factors and genetic factors, and the puzzle has still not been resolved and the game of chicken or the egg issue is not being resolved. It was said at first that in the chronic inflammatory condition of AIRDs, the cause of endothelial dysfunction comes from chronic inflammation, chemical mediators, complement fixation, an antigen-antibody reaction which ended by a disturbance in the normal equilibrium of body cytokines then vasoconstriction (disturbance in nitric oxide production), and increased peripheral vascular resistance and finally hypertension.

The other element of the game hypertension started firstly then led to an increase in the mechanical force on the arterial wall with consequent injury of the endothelium lining. This mechanical force starts the shedding of endothelial with the sequence dysfunction of endothelial and loss of endothelial vasodilation ability. The loss of endothelial vasodilator function leads to elevated blood pressure then arterial rigidity (loss of elastic fibers in the artery), stiffness, and atherosclerosis. Relating to this theory, chronic inflammation is a co-factor in endothelial dysfunction [80]. The interesting was that Roman and colleagues despite this information mentioned that there is no difference in the reading of blood pressure between the control group and rheumatoid group in his study [77].

Recently, it is well known that elevated blood pressure is considered the most important and most dangerous traditional cardiovascular risk that can initiate and can fasten the development of arterial rigidity (stiffness) and atheroma formation, and start cardiovascular diseases [21]. Besides hypertension, age is considered the second traditional risk factor that comes after elevated blood pressure and shares in the atheromatous process and subsequent development of cardiovascular events [80]. A major problem in AIRDs is when the patients developed elevated blood pressure, it will be difficult to control if compared to the patients without hypertension [81]. Steroids which are the cornerstone in the treatment of all autoimmune diseases could

exacerbate or start hypertension in these groups of patients due to their effect on salt and water retention [81].

Also, it is well known that the prevalence of hypertension in systemic lupus erythematosus patients is very high, to a greater extent when the kidneys are affected by the disease. Most lupus patients having renal affection including glomerular diseases (glomerulonephritis) or affection of tubular function leads to elevated blood pressure via affection of glomerular filtration rate (ischemia to the glomerulus) and subsequently salt-water retention through activation of the renin-angiotensin system [82–86].

Recently, the new interesting data mentioned that hypertension in the new theories is considered one of the immune diseases, it was found from animals studies that the absence of B lymphocytes (eliminated by treatment with anti-CD 20 antibodies) can control hypertension [87,88]. Also, as mentioned earlier about the relationship between T helper cells and T regulator cells concerning atherosclerosis in autoimmune diseases, an animal study showed that the interchange between the numbers of helper T lymphocytes 1 and helper T lymphocytes 17 as compared to the number of regulator T lymphocytes cells can determine the progress of the blood pressure reading [89,90].

Because the true causes of elevated blood pressure in connective tissue rheumatic diseases are not known until now, the control of elevated blood pressure and hypertension is so difficult in addition to no guidelines specific to deal with elevated blood pressure in connective tissue diseases available [81], plus, one of the interesting issues in medicine is the relation between steroids in inflammatory diseases as regard blood pressure, it is known that steroids produce salt and water retention as most steroids have aldosterone hormone action this leads to increases in blood pressure, but because of its anti-inflammatory effect, the steroids can decrease inflammation and, consequently cytokine production ending by decreasing blood pressure [72, 91]. In recent research, angiotensin-converting enzyme inhibitors (ACEIs) drug family and its relative selective angiotensin receptor blockers (ARBS) have been found to have immunomodulatory function besides their effect on blood vessels as vasodilators, and as mentioned before no specific guidelines for control of hypertension in autoimmune diseases are available so most clinicians use traditional antihypertensive drugs in controlling blood pressure [81,92].

1.7. Rheumatoid arthritis:

The relationship between rheumatoid arthritis and cardiovascular diseases is old and well known. The researcher found practically that the cardiovascular signs may appear before rheumatoid arthritis is diagnosed and these signs are most probably due to accelerated atherosclerosis which accompanies inflammatory conditions [93]. Also, the researcher found that in RA patients cardiovascular events can exacerbate within one year of follow-up, even if the patients without cardiovascular manifestations can have cardiovascular diseases after one-year follow-up [94].

The cardiovascular risk factors in RA are like without RA but the only difference is that chronic inflammation itself consider a risk factor and equals one and a half risk as compared to other risk factors. These traditional risk factors alone couldn't explain cardiovascular events and diseases which happen in RA patients, especially the increased number of patients having premature atherosclerosis within the disease course [95]. The researchers found that 70% of cardiovascular diseases in RA patients presented due to traditional risk factors, while the other one-third of the cases couldn't find clear causes [96, 97].

So, from the above facts appear that about one-third of cardiac events whether coming from premature atherosclerosis and coronary heart diseases or direct affection to cardiac muscle through the inflammatory process, its causes unknown so this percentage most probably coming from non-traditional risk, or we can say it is a combination of classical traditional and nontraditional risk factors [98].

The cardiac clinicians defined the risk of cardiovascular diseases in RA patients like the risk in diabetic (especially myocardial infarction risk) patients this means that the risk of inflammation on the vessels equal the risk of macrovascular complication happen in diabetic patients. Ischemic cardiomyopathy, resulting from coronary arteries atherosclerotic diseases as well as restrictive cardiomyopathy in rheumatoid patients, are common clinical presentations, and also a leading cause of death [99].

Humphreys (2014) mentioned that despite the new technology in the management of rheumatoid arthritis patients and the newer discovery of diseases modified drugs (DMARDs), especially biological DMARDs, the death rate of rheumatoid diseases did not affect by these new drugs in

the last 2 decades [100]. Another researcher Myasoedova (2017) said the opposite although the difference is only 3 years, he suggested that the mortality decreased because of the new medications especially biological drugs which control the inflammation directly through antagonizing the effect of cytokines (TNFά blockers) in the last 20 years [101]. Due to the chronic inflammation in rheumatoid patients and due to the complication of rheumatoid within the cardiovascular system, lung affection, and also kidney problems, the researchers mentioned that the life span of rheumatoid arthritis patients may decrease 10 years or more as compared to healthy group [102].

As mentioned before, the three main predisposing factors to death in connective tissue diseases are cardiovascular diseases, diseases activity, and, infection, in RA, cardiovascular disease is the most important cause of death in rheumatoid patients [103]; it represents about 30% of all mortality in RA. The epidemiological studies showed that the number of people dye with RA is triple the number of death in normal people [104]. The rheumatoid arthritis patients suffering from sudden cardiac death are double the rate of death if compared to healthy persons [48].

The researchers found that there is a high percentage of Senescent T 4 helper (CD4+ CD28)− T lymphocytes in rheumatoid arthritis patients. These types of cells are related to the process of atherosclerosis and the increased amount of CD4+ CD28- was found in rheumatoid arthritis patients having atherosclerosis of carotid arteries with increasing thickness of intima-media [44].

The titer of RF and ACPP is not related only to rheumatoid activity, and prognosis but related also to atherosclerosis and cardiovascular risk [45, 46]. The study of flow-mediated dilatation on rheumatoid arthritis patients shows impairments of brachial artery dilation in response to ischemia [105,106]. In addition, study arterial stiffness in RA patients showed that there are increases in arterial stiffness and sclerosis of big arteries in addition to increased carotid intima-media thickness, all these findings suggesting premature atherosclerosis [107–111].

The biological drugs, used in RA (TNF ά blocker) like Infliximab, work as competitive inhibitors of the TNF ά receptors, so it reverses the effect of TNF ά. IL-6 blocker, Tocilizumab (TCZ) also antagonizes the effect of IL-6 on its receptor site. This category of new biological drugs which act directly on the same receptor of naturally occurring cytokines can treat the

disease symptoms and get a better prognosis, and consequently improve all complications related to the disease like arterial stiffness and improve atherosclerosis outcome [111].

In rheumatoid arthritis patients, although endothelial dysfunction affects the endothelial layer in macrovascular and microvascular circulation, there is no evidence of a relationship between the complications that happen in big or small blood vessels [112].

1.8. Systemic lupus erythematosus:

SLE is one of the most critical rheumatic AIRDs. Systemic lupus is a systemic disease it can affect many organs in the body but the most dangerous organs for mortality are the heart, brain, and kidney, with poor outcomes. Early appearance of SLE at a younger age is usually associated with poor prognosis and death. SLE affects young age ended by death while older age patients have less severe manifestation (the disease can affect any age group) [20]. In the epidemiology of SLE, the disease affects mainly the women, with a male to female ratio of 10:1 (childbearing period), in the older age group this ratio decreases.

SLE, like other autoimmune diseases, pathogenesis comes mainly from the production of autoantibodies that attack healthy tissues. When the immune cells recognize self-antigen as a foreign antigen and start to produce antibodies directed against the nucleus, the disease start. Anti-nuclear antibodies (ANA) and specific anti-double strand antibodies (anti-DNA). ANA is not specific to SLE but its presences in circulation indicate autoimmune diseases, while anti-DNA antibodies are specific to SLE and have a lot of patterns like diffuse, spiked, perinuclear, and scattered.

Immune-complex deposition in blood vessels initiates inflammatory reaction and organ affection [113]. Vasculitis which means inflammation of blood vessels is the cornerstone in lupus pathogenesis and is the initiating point of endothelial dysfunction. The vasculitis is due to the deposition of antigen-antibody (immune complex) in the vessels wall [114,115], however, vasculitis can originate independently of immune-complex deposition by anti-endothelial antibodies [114]. As the blood vessel wall inflammation is settled the endothelial cell becomes not function well (endothelial dysfunction) with the development of a stiff and rigid wall vessel (atherosclerosis) [12, 44].

As still, the controversy about the cause of atherosclerosis in systemic lupus is not clear; it appears that other factors related to the chronic inflammatory conditions and disease progression are the cause of atherosclerosis [20,116], these nontraditional risk factors include antigen-antibody reaction, immune deposition, immunosuppressive drugs used for disease control, and cytokines, especially TNFά. The researchers found that during the analysis of cytokines in lupus patients when comparing between patients with atherosclerosis and patients without atherosclerosis they found that IL10 cytokine is low in lupus with atherosclerosis while was high in the patients who did not have atherosclerosis (IL 10 was protective).

The serum concentration of cytokine IL-6 and cytokine IL-17 was high in SLE patients who developed atherosclerosis. Also, they found that the number of T lymphocytes (T helper cells 17) was lower in lupus patients without atherosclerosis and higher in patients with atherosclerosis. The last finding is that the number of T cell regulators (which protect against atherosclerosis) was higher in patients without atherosclerosis while the number was low in patients with atherosclerosis [40].

Immuno-suppressive drugs like steroids have double effects in the disease progress in autoimmune diseases, for example, the researchers found that high dose corticosteroids can cause salt and water retention and subsequently hypertension, plus causing diabetes and diabetic complications [117], while corticosteroids in a small dose (5 mg), suppress the inflammation and become an anti-inflammatory drug and suppress atherosclerosis process [118]. The other drugs used in the treatment the of system lupus-like hydroxychloroquine, the researchers found it has a protective effect and immunomodulatory and can decrease diseases activity and subsequently decreases all complication.

The problems of coronary arteries in SLE disease are considered the main cause of cardiovascular diseases [119]. It was known that the majority of lupus patients aged between 35–45 years have more risk of developing acute coronary syndrome, weather unstable angina, or myocardial infarction and, with a high percentage of mortality, if the number compared to the normal population [11, 20]. The number of lupus patients developing myocardial infarction is twice in lupus patients as compared to control [119]. The researcher found in a follow-up cohort of patients, the risk of myocardial infarction after 7 years becomes 8 times (in women aged 40 to 49 years) with high mortality [115,120].

Lastly, women with lupus under the age of 45 years have an increased tendency to develop any cardiovascular disease, these diseases like coronary heart diseases, myocarditis, hypertension with renal involvement [121,122], pulmonary embolism, pulmonary vasculitis, pulmonary hypertension, endocarditis, and stroke [123].

As mentioned above, the risk of cardiovascular disease in SLE patients is twice as the normal population of the same age [124]. The mortality due to cardiovascular diseases in lupus may reach 30-40 % of the total death and there is two peak of death, the first peak of mortality is due to disease activity or the side effects of immunosuppressive drugs (infection) or due to renal affection with end-stage renal diseases, these causes of mortality appear in the first 36 months of the disease. The other peak of mortality happens after a long time and is due to chronic inflammation and its complications this time may last up to 20 years from the start of diseases and at this stage, the mortality is mostly due to cardiovascular diseases [20,116]. Aviña–Zubieta (2017) mentioned that death from cardiovascular diseases (myocardial infarction) can present in the first year of the diagnosis and this means the effect of inflammation on the cardiovascular system especially coronary vessels is so aggressive [120].

The reactive hyperemic test flow-mediated dilation (FMD) was found to be impaired in lupus patients; but here the impairment of endothelial dysfunction found was due to traditional risk factors mostly older age patients with other risk diseases like hypertension, elevated blood sugar, and kidney disease [125,126]. Also, research on arterial stiffness in lupus patients showed that the increase in arterial stiffness is related to traditional risk factors hypertension and age, and one of the non-traditional risk factors is glucocorticoid [127–129].

Carotid artery atherosclerosis showed that in young age lupus less than 35 years the percentage was 21%, and the prevalence of atheromatous plaque reached 100% in older age women above 65 years [20,130]. This fact may originate from the aging process or disease activity through these long disease duration or both [20].

1.9. Primary Sjögren's syndrome (PSS):

PSS is one of the systemic (but mild) AIRDs, the disease affects mainly women more than 40 years. PSS is the disease of the exocrine glands mainly the salivary and lacrimal glands. The pathogenesis of the disease is characterized by chronic lymphocytic infiltration, to the salivary

and lacrimal glands then this lymphocytic infiltration leads to chronic inflammation, and at the end destruction of the salivary and lacrimal glands, with an endpoint of dryness of the mouth (xerostomia) and dryness of the eyes (xerophthalmia) [131]. As the PSS is a systemic disease it can affect tissues different from lacrimal and salivary glands, it can affect blood vessels, thyroid, heart, bone, joints, kidney, skin, and lung [132]. The research that discusses the cardiovascular risk in PSS is little but the low number of studies illustrated that PSS affects blood vessels and leads to a state of mild endothelial dysfunction, with subsequent stiffness and rigidity of blood vessels, which ended by subclinical atherosclerosis.

The mild cardiovascular effects which happen in the patients of PSS cannot be explained due to the participation of traditional risk factors alone [133]. Demirci (2016) mentioned that premature atherosclerosis which happens in PSS is due to the use of steroids and abnormal lipid metabolism or may be due to accompanying hypertension, which means that, the inflammation in Sjögren's syndrome is not the cause of mild vascular stiffness and dysfunction of the endothelium [134].

As regards the non-traditional risks in PSS, the researchers showed that the state of mild chronic inflammation which accompanies the disease with the release of different cytokine, and immune complex reactions, could contribute towards vascular dysfunction and atherosclerosis [135]. Oxidized LDL and anti-oxidized LDL antibodies, which their role in the atherosclerosis process not known until now as they are atheroprotective or atherogenic. Anti-oxidized LDL antibodies are low in PSS; on the other hand, anti-oxidized LDL antibodies are high in SLE patients so this controversy in the role of these antibodies indicates that the anti-oxidized LDL antibodies have a major role in the atherosclerosis process [51].

Previously, the main cause of death in PSS was lymphoma as most PSS patients have Non-Hodgkin lymphoma after some time, and the possibility of chronic immune cells activation is predisposed to the development of this type of lymphoma. With increased research related to cardiovascular medicine, cardiovascular diseases became now the main first precipitating factor of mortality in Sjögren patients [136].

As mentioned before, the presence of anti-Ro antibodies in adults with PSS patients may affect the heart and lead to complete heart block [58, 59]; also, PSS can develop atherosclerosis and subsequently coronary heart diseases with its complications [133,134]. The presence of

Cryoglobulins and their agglutination in the vessels of PSS patients and the presence of these globulins with a high concentration in the circulation may indicate a sign of worse outcome as Cryoglobulins can develop severe symptoms due to precipitation in the peripheral circulation (when the temperature becomes slightly low). Cryoglobulins precipitate and obstruct the lumen of blood vessels leading to vascular ischemia ranging from critical tissues ischemia up to tissue necrosis and gangrene in addition to vasculitis [55], this vasculitis mostly accelerates endothelial dysfunction [56].

Thus, control of inflammation by anti-inflammatory drugs can reduce the inflammatory process and subsequently improve the vascular condition and outcome and decrease the risk of atheroma formation [111]. The following table shows some studies that confirm the relationship between rheumatic diseases and the function of the endothelium:

Table (1): Some studies confirming the relationship between rheumatic diseases and the function of the endothelium

Reproduced from (Hedar et al, 2021 [220]).

Author(s)	**Type of research**	**Measurements used**	**Result of the study**	**Comments**
Kerola, et al.,[93]	Review article	Study the outcome of using drugs against inflammation and their effect on endothelial dysfunction using flow-mediated dilation and atheromatous plaque in RA	1. There are good results in endothelial function after using anti-inflammatory drugs for 6-12 month 2. Atheromatous plaque and	The non-traditional risk factors have a role in atherosclerosis in RA patients and need to control these factors for a better outcome as regard

		patients through detection of carotid intima-media thickness	increased thickness of carotid intima-media may be presented before the diagnosis of RA and in the first year after diagnosis	cardiovascular morbidity
Crowson et al. [94]	Review article	Follow up 5638 patients not complained of cardiovascular symptoms and not diagnosed to have cardiac diseases in RA and for early diagnosis of heart diseases	-70% of diagnosed cardiovascular events were related to traditional risk factors and the remaining 30% most probably related to RA	The most important traditional risk factors affecting the cardiovascular system in RA patients are smoking and hypertension
Ruscitti et al., [99]	Prospective cohort study have been done on 347 rheumatoid patients without cardiovascular	The endpoint of the study to detect after follow up 12 months an atheromatous plaque or increase in intima-media	The result of the study showed an increased number of RA patients having atheromatous plaque or	Premature atherosclerosis in RA patients is due to a combination of traditional and nontraditional

	signs to follow up in one year	thickness of the carotid artery	increased carotid intima-media thickness after one year of follow up	risk factors
Maradit-Kremers et al., [104]	Long follow up of 603 patients with RA and age-matched 603 controls group, all the life till death	Follow up rheumatoid patients and control to pick up cardiac diseases (acute coronary syndrome) and sudden cardiac death	Rheumatoid arthritis patients had twice the chance to develop myocardial infarction without symptoms or can develop sudden cardiac death but interestingly not complain of chest pain(angina pectoris) in comparison to normal population throw-out their life	The concept of traditional versus non-traditional risk factors in premature atherosclerosis, the result that common traditional risk(Framingham risk factor) alone couldn't give explanations to the high number of atherosclerosis patients diagnosed with rheumatoid arthritis

Fan, et al., [108]	Cross-section study with 102 patients with RA compared to 46 healthy control group	By ultrasound detection of Brachial artery FMD(endothelial dysfunction), carotid plaque, and carotid intima-media thickness	Results showed endothelial dysfunction and atherosclerosis in the RA group represented by a decrease in FMD results in the rheumatoid group as a comparison to controls. Increased thickness of intima-media in carotid arteries	No significant correlation between endothelial dysfunction and increased thickness of intima in RA patients
Adawi et al.,[109]	A case-control study including forty-fore patients diagnosed as RA in comparison to the normal	Ultrasound detection of flow-mediated dilation in the cubital fossa to detect endothelium dysfunction of brachial artery	Results mentioned that about percentage 85% of the RA patients had premature atherosclerosis in different	Early screening to detect dysfunction of the endothelial and premature atherosclerosis in RA was an important step to avoid

	population		degrees	cardiovascular diseases and complication
Kiss et al., [125]	Cross-section study including sixty-one SLE patients and twenty-six controls group	To measure FMD and CIMT by an ultrasound device	There was a big difference between the diseased group and the control group: FMD reading was lower in SLE than control while CIMT was increased in SLE	Early screening of SLE patients for endothelial dysfunction and premature atherosclerosis
Mak, et al.,[126]	Big cohort consisting of case study versus-control with seventy-one lupus patients and seventy-one normal people and meta-analysis of twenty-five small (case controls)	Detection of Endothelial dysfunction using ultrasound to measure FMD	FMD reading in SLE patients was decreased as compared to healthy controls	It was shown that diabetes mellitus, renal diseases, and hypertension predispose to the development of atheroma in lupus patients

	studies including (1313) patients diagnosed with lupus and 1012 normal population			
Sacre et al., [127]	The study included forty-one lupus patients and thirty-five healthy controls in a cross-sectional study	Carotid-femoral pulse wave velocity to measure arterial stiffness through detection of the speed of wave transmission within the vessels wall	Study results illustrated that there were statistical differences in arterial stiffness between the lupus group and the healthy control group	corticosteroid as an example of non-traditional risk and hypertension as traditional risk, both of them have a greater effect on developing arterial rigidity and atherosclerosis
Thompson et al., [130]	217 female lupus patients followed in the clinic	Zero-point and regular measurement by ultrasound of carotid artery to detect atheromatous plaque of carotid	High incidence of premature atherosclerosis in SLE patients	It is a combination of traditional and non-traditional risk factors for the development of premature

		artery and CIMT		atherosclerosis
Yong, et al., [133]	Meta-analysis and Systematic review including eight studies with 767 patients diagnosed as PSS to detect early endothelial dysfunction, arterial rigidity, and, atheromatous plaque	Using ultrasound device to detect carotid intima-media thickness and arterial stiffness using PWV in PSS patients	The results showed that PSS patients have increased arterial stiffness as detected by pulse wave velocity measurements and increased thickness of the carotid artery in comparison to the normal population	The primary Sjögren's syndrome group of patients developed a moderate degree of arterial stiffness and premature atherosclerosis. We need more research to explore the relationship between risk factors and premature atherosclerosis in PSS
Sezis Demirci, et al., [134]	A case-control study compared 68 healthy controls to 75 PSS patients as regard arterial	Detection of carotid-femoral arterial wall stiffness using pulse wave velocity	Results showed that the speed of pulse wave through the artery in PSS patients was high in comparison to healthy	The cause of arterial stiffness in PSS patients is most probably due to conventional traditional risk factors hypertension,

	stiffness in		controls	and hyperlipidemia in addition to steroidal usage not due to chronic inflammation characterizes the disease

1.10. Endothelial (dys) function and atherosclerosis:

The endothelium layer, the innermost layer of blood vessels which regulates vascular tone, prevents platelet aggregation, keeps smooth laminar blood flow, prevents leucocyte migration, and prevents thrombosis. These physiological functions of the endothelium are carried out by NO which plays an important role in keeping the human body homeostasis. Dysfunction of NO, due to decreased release or decreased action, leads to endothelial injury, loss of normal function of the endothelium, and starting the process of atherosclerosis [137–139].

NO is the main chemical mediator of the endothelium, synthesized by the enzyme nitric oxide synthase (NOS). It uses L-arginine as a substrate for the synthesis of NO. Asymmetricdimethylarginine (ADMA), is the competitive inhibitor of (an analog of L-arginine) the enzyme (NOS). ADMA is naturally presented in the human blood in very low concentrations. The antagonistic action of ADMA is done through competitive inhibition on the same substrate site of the enzyme (NOS) [140,141]. Now all the evidence showed that ADMA is the most important factor in endothelium dysfunction and is responsible for the initiating step in atherosclerosis and cardiovascular events [142,143]. Decreased synthesis or decreased release of nitric oxide was associated with failure of regenerating endothelial and atherosclerosis [144,145].

The term atherosclerosis consists of 2 parts athero and sclerosis. The first part athero is due to the fat deposition within the macrophages plus, the affection of cytokines on intima with

atheromatous plaque formation. Sclerosis means the effect on the media with hypertrophy of muscle layer leads to the increased intima-media thickness in addition to converting of the elastic fiber to collagen fibers resulting in increased rigidity, stiffness, and narrowing of the arteries. Atherosclerosis in old theory was considered a degenerative disease that developed with increasing age. Atherosclerosis now is considered a chronic immune-inflammatory disease and not an inevitable disease because of the presence of immune cells and cytokines in addition to lipoproteins in the cross-section of atherosclerosis [16,146]. This is the new immune theory of atherosclerosis formation and there are many inflammatory factors other than hyperlipidemia associated with its pathogenesis. Abnormal lipid metabolism (oxidation) in new theory in atherosclerosis formation, coming after LDL molecule oxidizes and converted to oxidize LDL and engulfed by macrophages and initiate the inflammatory process[147–151].

The immune system consists of two parts, the innate immune system, and the adaptive immune system. First, The innate represents here in macrophages which shared in the initial step of atherosclerosis through engulfing the oxidized LDL and initiating endothelial dysfunction, through secretion of cytokines and another chemical mediator that lead to hypertrophy of smooth muscle cells in the media ending by atheroma formation, vessel wall rigidity and narrowing [152]. Second, The other arm of the immune system is adaptive which consists of immune cells and antibodies shared in the process of atherosclerosis through B lymphocytes cells and T cell lymphocytes [16,152], either T helper cells (1,17, regulator) or T cytotoxic cells (T8)sharing in atheroma formation [153]. Both B and T cells are present in the cross-section of the plaque with other fat cells (foam cells) and fibrous tissue [154].

At the end of the atherosclerotic process, there is a change of smooth flow of the blood to turbulence blood flow and more inflammatory reaction till at some stage rupture of the plaque, and thrombus formation ended by cardiovascular complications [155]. The following diagram illustrates the pathogenesis of immune-atherosclerosis:

Figure (2) A diagram illustrating the pathogenesis of immune-atherosclerosis

(Reproduced from "Hedar et al, 2021" [220])

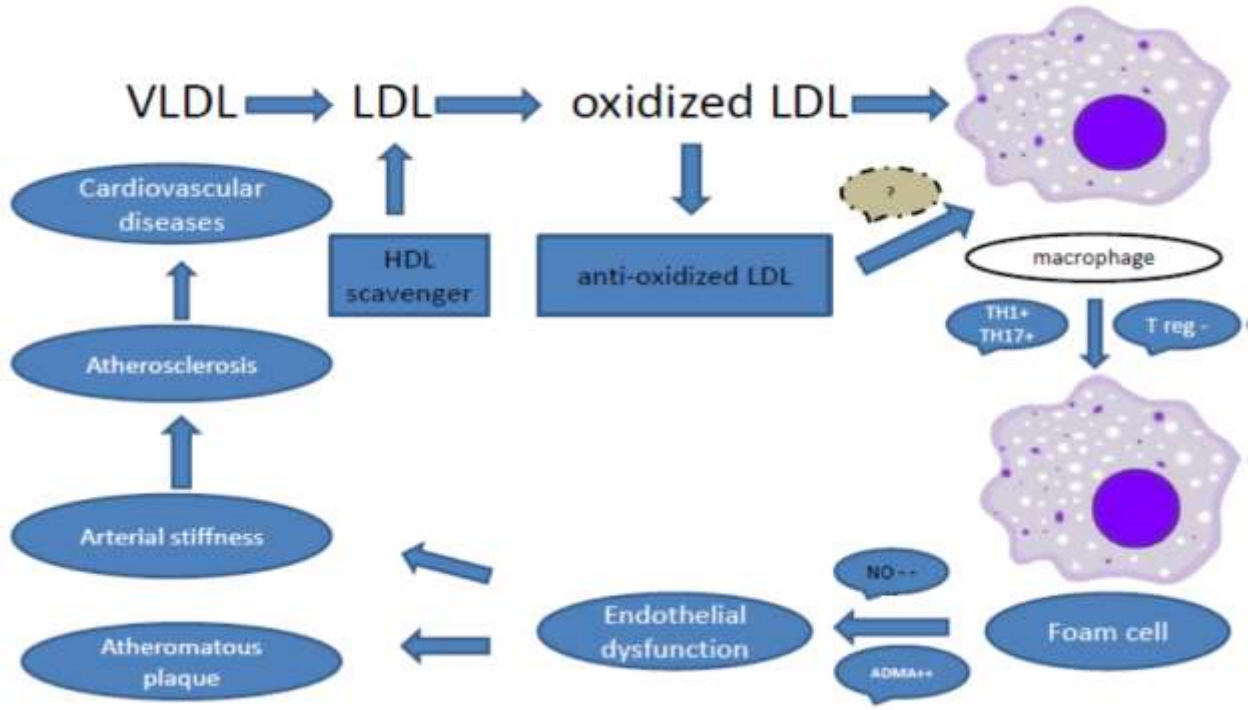


Figure2. Pathogenesis of atherosclerosis based on a possible new theory of autoimmune atherosclerosis. ++ means (stimulate) while −− means (inhibit). Reproduced from (Hedar et al, 2021 [220]).

1.11. Assessment of vascular function:

It is known that the discovery of endothelial dysfunction in the early stage is reversible but late diagnosis becomes unfortunately irreversible changes. So the early detection of endothelial dysfunction through the measurements of vascular function is important before starting cardiovascular diseases and decreasing future morbidity, and mortality [143]. The most fatality comes from heart failure including myocardial infarction, ischemic cardiomyopathy, and the other cause of death coming from cerebral stroke [143].

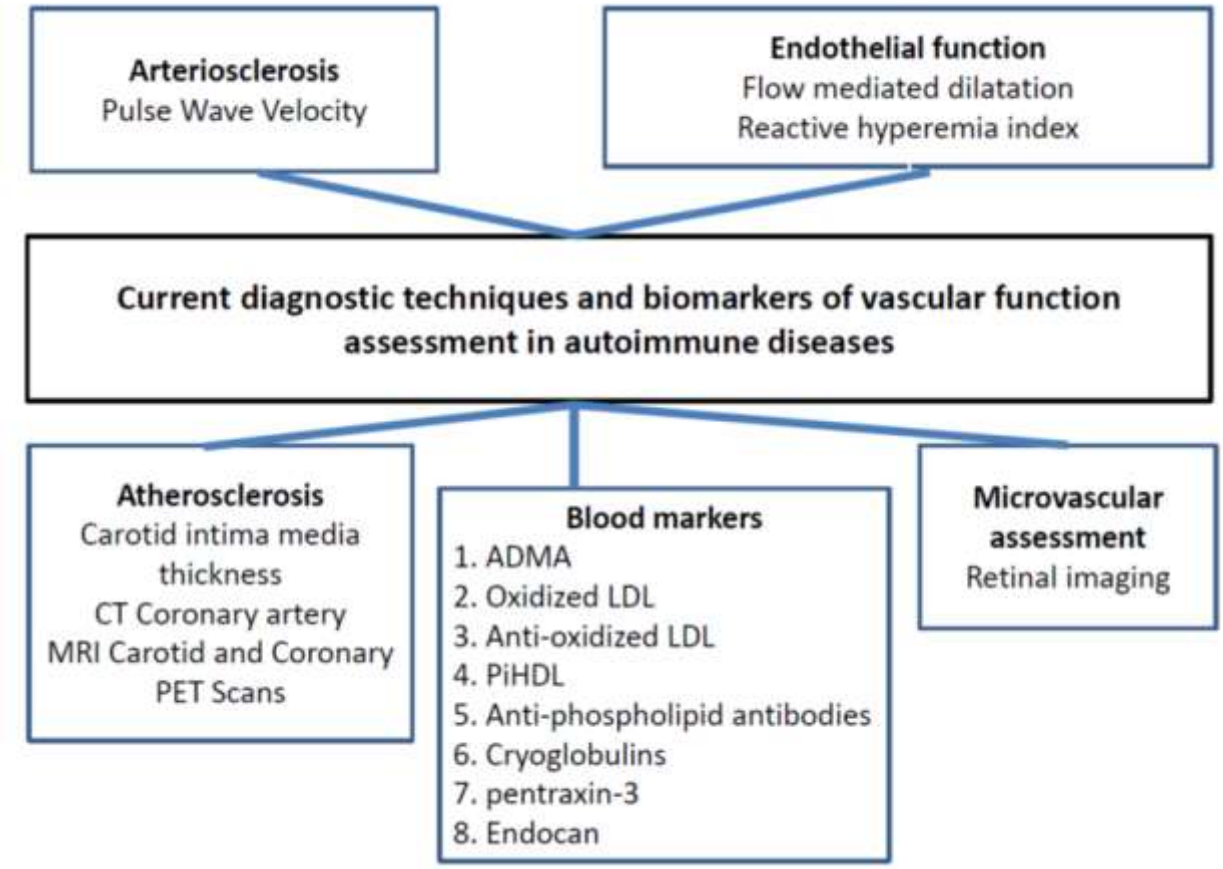
Measurements of vascular function can be done directly through radiological ways to see what happing in the vascular system or can measure indirectly through lab investigations. Radiological investigations are easy to do and non-invasive, while blood markers give us an idea about the function indirect by detection of the specific markers in the serum. The atheromatous plaque and rigid arteries can be assessed by ultrasound devices; neck ultrasound is the most popular way to assess atherosclerosis through detection of Carotid plaque and its intima-media thickness [156].

Atheromatous plaque and carotid intima-media thickness show us the anatomical structure of the vessel, while detection of arterial stiffness and rigidity reflects the arterial function. All these non-invasive methods can detect subclinical atherosclerosis even before cardiovascular disease starts [157,158].

Other than ultrasound many ways and maneuvers can diagnose endothelial health and related vascular function [159]. So, the following figure shows some measurements used in clinical research and practice including some blood biomarkers and radiological investigation for detecting vascular function.

Figure (3): Some measurements used in clinical research and practice including some blood biomarkers and radiological investigation for detecting vascular function.

Reproduced from (Hedar et al, 2021 [220]).



1.11.1. Flow-mediated dilation (FMD):

FMD is considered the most famous and most important way to assess endothelial dysfunction using an ultrasonic assessment device to measure the increase in brachial artery diameter from baseline reading to maximum vessel diameter reaching it after stoppage of circulation in the arm for 5 minutes. This maneuver depends on the state of hyperemia in the brachial artery induced by inflation and deflation of a sphygmomanometer cuff to 200 mmHg or level above systolic reading for 5 min [160–162].

The principle of FMD technique is with stoppage of the circulation for a time, accumulation of different kinds of metabolite like nitric oxide, prostaglandins, and leukotrienes for example, after stoppage point (distal to point of circulation stoppage) then after the return of the circulation to the normal. The effect of accumulated chemical mediators leads to vasodilation of the vessel to compensate for the need for tissues nutrients and oxygen.

In healthy endothelium, the occlusion of the vessel liberates these chemical mediators; these mediators induce dilation of the vessel diameter after the return of circulation to normal. In unhealthy endothelium, there is no dilation or little dilation after the back return of the circulation to normal blood flow, most probably due to low levels of vasodilators nitric oxide. Although FMD is the gold standard non-invasive method to detect endothelial function of the brachial artery [163–165], the technique is operator-dependent, and another disadvantage is stoppage of caffeine and vasodilator drugs for example before the measurement) [166–169].

1.11.2. Pulse wave velocity (PWV):

PWV is the maneuver used for the assessment of vascular stiffness of big blood vessels. PWV measures the speed of pulse wave transmission across the wall of the blood vessel, as when the vessel walls become rigid the speed of wave transmission will increase, and the reverse when the arterial wall is more elastic the speed of transmission will decrease [170]. The normal speed of transmitted waves across the arterial wall is about 5 to 13 m/s, so the velocity depends on many factors like age, weight, height, and blood pressure.

The diseases that affect collagen and elastic fibers in the arterial wall will affect elasticity and stiffness of the vessels wall and consequently the velocity [52]. One of the most famous devices

for detecting PWV is the Vicorder device which is used to detect arterial stiffness. PWV device needs two-point in the arterial wall to measure the speed of wave transmission between them. The measure between the Carotid artery in the neck and the Femoral artery in the thigh is the best way to measure the velocity between two major arteries. Two sensors are put above the two arteries to detect arterial pulse waves [171].

1.11.3. Carotid intima-media thickness:

The use of an ultrasound device to measure the thickness of intima-media is an easy way to detect endothelial dysfunction (atherosclerosis) [172]. As in the normal anatomy of blood vessels, the thickness of the intima-media is 0.9 mm and the wall is smooth and no plaque is found [164]. When the healthy endothelium loses its function and becomes unhealthy, there is an increase in the thickness of the intima-media layer which can measure easily by ultrasound and also can detect carotid plaque [173].

1.11.4. Retinal Imaging:

Another noninvasive new technique that can be used to assess vascular function in small blood vessels in the retina. Retinal microvasculature can show the relationship between many risk factors and small blood vessels and as we know the retina is the mirror of the brain. These vessels can give an idea about what happens in the brain. Observation of retinal vessels in the previous research showed that venules are not considered only as passive reacting vessels, that change in their diameter occur according to change in the arteriole diameter, the venule represent elements that can respond separately to the changes in the vascular regulation [174].

The researchers showed that dilation of retinal venules can be a sign of inflammation, dysfunction of the endothelial, and also cerebral ischemia. Small narrow retinal arterioles can indicate also dysfunction of the endothelial and most importantly hypertension changes [175]. It is known that an increase in age can affect retina microvasculature [176].

Noninvasive detection of retinal vessels can be done using a digital retinal camera. There are two types of retinal cameras the first one is a portable small retinal camera and the second one is table bounded retinal cameras both of them are designed for taking photos to the eyes (anterior and posterior segments) in a comfortable, quick, and, painless way. Retinal photos which have

been taken by the camera are kept preserved on a computer until analysis of the data is required and the data analysis is done using software programs designed to measure the average diameter of arterioles and venules in the retina.

Through the analysis of retinal photos, the software programs measure the average diameter of the largest six arterioles and the largest six venules running or emerging from retinal branches of ophthalmic artery and veins. The distance that the software used is a zone between one-and half-disc diameter starting from the optic disc margin [177]. The software program shows its results in form of central arteriolar equivalent (CRAE). That means the diameter of retinal arteries is emerging from the ophthalmic artery and central retinal venular equivalent (CRVE) indicating the diameter of retinal veins drain into an ophthalmic vein in micrometer. Also, the program can measure the ratio between the CRAE and CRVE.

1.11.5. Endo-pat test (peripheral arterial tonometry):

A new technique used recently to measure endothelial function in an automated way (not dependent on the skill of the ultra-sonographer). The name of the test is the PAT scan which measures the signal of peripheral arterial tone. This method measured the reactive hyperemia from the terminal phalanges by measuring arterial pulsatile volume changes [178]. It is easy, reliable, accurate, and automatically done, and not dependent on human factors, but is expensive.

1.11.6. Blood markers:

Many blood markers can be used in clinical research and laboratory to assess and measure the function of the endothelial layer directly or indirectly (show Figure 3). Oxidized LDL a new marker that can show us the possibility of atherosclerosis in high-risk patients can be measured in the blood using ELISA. On the other hand, antibodies to oxidized LDL particles can be measured also in the lab [148–151]. They may be protective or harmful on the endothelium and have a role in the process of atherosclerosis (whether IgM or IgG).

Interestingly, it is well known for a long time that high-density lipoprotein (HDL), is the scavenger of the circulation and prevents the atherosclerosis process. HDL is the only beneficial cholesterol in the lipid profile as it works as a scavenger for LDL in the blood, the new interesting knowledge is, when LDL becomes oxidized-LDL, the HDL molecule lost its normal

physiological function as a scavenger for LDL and is converted to another molecule which is pro-inflammatory HDL (PiHDL) [179]. ADMA, which is considered for a long time one of the most unique and important blood markers used to determine endothelial dysfunction, was measured in the lab by ELISA test to show the state of endothelial health [140].

Cryoglobulins is a protein that precipitates at low temperature and can cause vasculitis, it can measure its presence in the blood in vetro in 4 C. it is found to be a good indicator for malignant lymphoma transformation risk in Sjögren's syndrome and also to diagnose vasculitis [180]. Antiphospholipid antibodies whether anticardiolipin antibodies, lupus anticoagulants, are popular markers of vascular endothelium affection, in patients with primary or secondary antiphospholipid antibody syndrome [181].

Pentraxin-3 is now considered one of the inflammatory markers shown to be high in cardiovascular diseases and related AIRDs with cardiac affection [182]. Endocan is also a new mediator of endothelial dysfunction used in the research lab and its presence in the blood in high concentration indicates the presence of atherosclerosis and related cardiovascular events [183,184].

2. Aims of the Research:

The aims of this research are represented by the following points:

- Specifying the relationship between chronic inflammation represented by AIRDs and vascular function.
- Identifying the speed of progress of atherosclerosis in AIRDs.
- Investigating the relationship between endothelial dysfunction and resulting hypertension in AIRDs represented here in rheumatoid arthritis and Sjögren disease and comparing the results to healthy persons.
- Stating the relationship between endothelial dysfunction and hypertension, cause or result. Also, the relationship between traditional and non-traditional cardiovascular risk factors is concerned with the atherosclerosis process in AIRDs.

- Validating the effect of two different diseases on vascular function. RA is the prototype of rheumatological autoimmune diseases with excessive inflammation. It is prolonged disease duration and another disease with mild or moderate inflammation which is PSS.
- The specific aim was to use this data after the assessment of the results of the study for bigger studies with more patients, including with other diseases like SLE.
-
- **The hypothesis of the Research:**
- The hypothesis is presented in the effect of chronic inflammation with the liberation of cytokines and chemical mediators on the function of the endothelium lining of blood vessels. These chemical mediators affect NO secretion and function, in addition to the loss of endothelium regenerating ability and the possibility of atherosclerosis progression due to this endothelial dysfunction.

3. Material and Method

3.1. Design of the Study and Population:

A case-control pilot study involving adults (>18 years) has been done at the Medical University of Graz, at rheumatology clinic with 3 groups from February 2021 to March 2021. Each group consists of 10 patients. The first group was the rheumatoid arthritis group (2 males, eight females, 55 years ±7years, 79kg ±12 kg, only one smoke) and the second group was the primary Sjögren syndrome group (10 females, 52 years ± 8years, 57.5kg ±16 kg, no one smoke) and the third group was the control group (2 males, 8 females, 50 years ±9years, 72.5kg ±9 kg, 3 of them smoke). Only 2 patients of the Sjögren group using steroids in low doses.

The recruitment has done by the rheumatology department and the measurements were done at Landen Krankenhausen (LKH) outpatient's clinic. The patient's database stored in the rheumatology department including all data about the patients was checked and as regards the rheumatoid group, the Disease Activity Index was 3.5 (median) (we used the clinical disease activity index (CDAI), score range between 0–10) and as regard PSS group EULAR Sjögren's syndrome disease activity index (ESSDAI), median 3(0-6).

This was a pilot study, aiming to use data as a basis for sample size calculation in big future studies. The patients had been chosen randomly from those who follow up in the rheumatology clinic. The age-matched control group had been chosen from the person who works in the hospital clinic. All patients had exposed to informed consent after the procedure was explained to them and the blood sample taken for blood analysis of ADMA, serum creatinine, ESR, CRP, lipid profile including cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) level.

3.2. Inclusion / Exclusion criteria:

Male or female adults above 18 years old who were diagnosed with rheumatoid arthritis by the 2010 ACR/EULAR classification criteria and PSS patients who were diagnosed by the 2016 ACR/EULAR classification criteria attending the rheumatology clinic in the Medical University of Graz without any previous history of cardiovascular or cerebrovascular diseases were recruited for the study. Patients (who are ill, have active disease, are not oriented, who are pregnant, or lactating women, having malignancy) were excluded, so the patients who participated in the study were stable, having a good general condition, and not in active diseases state. They come regularly for follow-up in outpatients' clinics.

3.3. Ethical approval:

The study was conducted in accordance with the principles stated in the Declaration of Helsinki as well as local and national regulations in Graz, Austria. Ethical approval for the study was taken from the Ethical Committee unit at the Medical University of Graz under the number (Project identification code: 32-283 ex 19/20). All the measurements were done in accordance with the Declaration of Helsinki of 1964 and modified revision in 2013. The patients had a successful discussion and they have explained carefully the importance of the study and study aims. The maneuver was explained and written informed consent was obtained from participants before sharing into the study.

3.4. Date storage:

The study was adhered to the standards of reporting and was with the roles of the National Data Protection act. Each participant in the study was assigned a code. Patients, control samples, and data were stored.

3.5. Data collection:

During the period between February 2021 and March 2021, the study was done in the rheumatology clinic at the main hospital of the Medical University of Graz, where the room temperature was adjusted at 22-25C and the measurements were done at the same time for 3 days. A paper sheet (manual, original patient information) for every patient contains all information about them as age, gender, weight, height, diagnosis, medication, lifestyle factors (smoking, sports habit, alcohol). Also, this paper contained a manual recording of patients' results and all information about participants.

3.6. Assessment of vascular function

3.6.1. Blood pressure measurements:

Blood pressure was measured in a quiet room using the Vicorder device (SMT medical GmbH & Co.KG, Germany). The Vicorder device was present in the outpatient clinic room with the other device Canon camera, in a separate room different from the room of measurements. After resting off the patients for 10 minutes during which patients have explained the maneuver and consent given. Then, participants were moved to the examination room in the clinic. The Vicorder slandered elastic pressure cuff (7 cm in length) was used to measure blood pressure. The cuff was installed above the right elbow joint (2 inches above the cubital fossa). Mean blood pressure was calculated using internet websites (DBP+ one-third of pulse pressure). Using the software in the connected laptop to start measuring blood pressure and finish with saving of the result. The definition of Hypertension was used as systolic blood pressure more than 140 mmHg or diastolic blood pressure more than 90 mmHg or the patients taking medication for hypertension.

3.6.2. Pulse wave velocity:

Pulse wave velocity is considered a famous way to assess the stiffness of blood vessels as when the artery which contains elastic fiber converts to a rigid tube with hard collagen fiber, this

change affects the wall dispensability and movements and consequently the speed of wave transmission across the vessels wall. Vicorder device which measures the arterial wall stiffness measures the speed of waves transmitted between 2 points through the wall of large arteries, Carotid-Femoral arteries pulse wave velocity is a common way to assess arterial stiffness in cardiovascular research. The Vicorder device was attached to a software program; this software program analyzes the shape of the recorded wave and gives the speed of wave transmission between these two points in m/s. It is an easy non-invasive way to measure arterial stiffness. The first step in the study was for the patient to come to the office in the rheumatology clinic and after about 15- 20 minutes of relaxation after they come. At the office, the patients have explained the study and maneuver and have written consent and sign it. Then, the height, weight, and blood samples were taken for the sake of the measurements in a quiet room in the rheumatology clinic with a temperature adjusted at 22-25 C. The measurement started by measuring the blood pressure of the patient in the right arm, then the patient`s data including weight, height, age, gender were introduced into the software program.

Then a standard 10 cm blood pressure cuff will apply around the upper part of the thigh as high as possible towards the groin and no space between the cuff and femoral artery. After the detection of Carotid artery pulsation in the neck, another sensor (probe) will hold around the neck with its small cuff above the right common Carotid artery pulsation (in the anterior triangle of the neck just medial to sternocleidomastoid muscle). The distance between the 2 arteries (Carotid and Femoral) was measured in cm, then the device started to measure the pulse wave velocity with the progressive successive beat with the feet of the artery pulsation wave, and the software program detect heart rate and best pulse wave to measure the wave velocity, then the reading of the result of PWV, miter per second (m/s) recorded and saved in the program when needed.

3.6.3. Retinal vessels diameter detection:

Canon automated camera (CR-2 Canon automated camera), which is responsible for retinal visualization (posterior segment of the eyes). The camera is connected to the laptop. The patient puts his or her chain on the camera and the examiner tries to adjust the pupil of the patient with the screen until the examiner can see the retina clearly and the patient will fixate his right eye or left eye on a point. The examiner takes a photo to show the optic disc in the center of the photo

and central retinal artery and central retinal vein originated from the optic disc and their nasal and temporal branches.

Then, the photos were stored on the laptop until it was transferred to another computer for photos analysis. Then software program Mona-Riva (VITO, Belgium) was used for analyzing the diameter of the six biggest arterioles and six biggest venules in the retina (within 2 disc space distance from the optic disc margin (standardized), and the result will be given in a form of central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) in micrometer and the software also give what is called A/V ratio which is the percentage of CRA to CRV. Then the results of CRAE and CRVE were stored.

3.6.4. Blood Collection:

After the participants were informed about the study and they signed the consent, then 10mL of venous blood was collected from the left forearm (ante-cubital fossa vein) when the patients were seated. Following that the blood sample was divided into two-part, the first blood samples were analyzed immediately after collection at the routine blood analysis laboratory at the Medical University of Graz main hospital (LKH), Austria. The routine blood test included serum creatinine, erythrocyte sedimentation rate, C reactive protein, lipid profile including cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) level.

Additionally, EDTA mixed blood samples were put in the icebox and transferred to the Medical University of Graz, Department of Physiology, Otto Loewi Research Center. There the blood samples were centrifuged at 1500G for 20 minutes at 4°C. After centrifugation, the superficial part (serum) was obtained and was collected in small tubes then stored at -80°C until used for detection of endothelial dysfunction marker ADMA later. ADMA test was measured using enzyme-linked immunosorbent assay (ELISA), (Immunodiagnostic AG; Bensheim, Germany), and the results were automatically calculated from the ELX800 ELISA reader, and data were obtained. The reference range for the kits was between 0.29 to 0.63 ng/ml.

3.6.5. Data and statistical analysis

Statistical analysis of the data was done by using the software program named: Statistical Package for Social Sciences (SPSS) with (version 26, SPSS Inc.; Chicago, IL, USA). The study

analysis was done using a T-test to compare the rheumatoid group versus the control group and Sjögren's disease groups versus the control group. The data were presented as mean plus or minus slandered deviation (SD). For irregular data (not regularly presented), we used the median plus range. ANOVA and ANOVA – ANCOVA was used in the study to correct the effects of covariates like height, age, and BMI. Additionally, person correlations of the parameters with each other were analyzed also.

The description of statistics was shown as variants, a number, and mean± standard deviation, median, and range. Significant statistical difference was defined as a probability value (p-value) less than 0.05 which was considered mostly as the reference of statistical significance except when the analysis needed an alpha level correction (Benjamini-Hochberg).

The study uses a correlation coefficient (r) factor to indicate the relationship between two variants with results ranging between 1 and minus 1, which means correlation or relation in the same direction(+1) and -1 indicating a proportional correlation in the other direction. 0–0.3 indicate no correlation, 0.4–0.6 indicate moderate correlation, while 0.7–1 indicate a significant correlation between the two variant.

4 . Results:

The result of this study was very effective. I used the patient's database which was available in the rheumatology outpatient clinic at the Medical University of Graz. Uses of evaluating scores in RA was (clinical disease activity index (CDAI, score range 0–10) and, the activity in our study was 3.5 (median). As regards the evaluating score in PSS patients we used (EULAR Sjögren's syndrome disease activity index (ESSDAI, range 0–6) and, it was 3 (median). At the time of measurements, all patients were stable, not distressed, and in good general condition during this visit to the clinic.

The investigated groups consisted of 3 groups, the RA group were 10 patients; there were two males, and eight females, their age was 55 ± 7 years, their weight was 79 kg (median; 57–140), one patient smoke cigarettes, four patients only were taking antihypertensive medication, no one of the patients was taking vasodilators or diuretics to control their blood pressure, (these types of medications couldn't affect the results of measurements as we believe that). All the rheumatoid

group was taking new biological therapy (disease-modified anti-rheumatoid drugs, DMARDS) beside seven patients were taking older DMARDS, Methotrexate.

PSS group was also 10 female patients. Their age was 52 ± 8 years, their weight was 57.5 kg (median (49–145)), no habit of smoking in this group, no one of the patients was known to be hypertensive. The group of PSS patients was not taking any specific drugs only symptomatic medication except only one patient received Cellcept (mycophenolate mofetil), and two patients used small dose prednisolone drug. We believed also these medications were used to control the disease and didn't affect blood pressure readings

The third group was a healthy control group consisting of eight females and two males their age was 50 ± 9 years and their weight was 72.5 kg (median, 60–105). 3 persons in the control group were smoking. Two persons from the control group were known to be hypertensive with diuretics and angiotensin-converting enzyme inhibitors. No one of the participants were taking any anti-inflammatory medication; also, no one was taking any treatment for hyperlipidemia. The following Table below illustrates the information of each group considering that data were shown in form of mean ± Standard deviation. (in some results median and range):

Table (2): General and specific data for the study participants. (Reproduced from "Mahdy et al, 2021" [221]).

Variable	**Control** (n=10; 8 females)	**RA** (n=10;8 females)	**PSS** (n=10;10 females)
Age	Mean 50 ±9Y	Mean 55.3 ±7Y	Mean 52.2 ±8Y
Smoking	3 Smoker 7 Non	1 Smoker 9 Non	10 Non
Weight	Median 72.5 kg (60-105)	Median 79kg (57-140)	Median 57.5kg (49-145)

Disease duration		Median 12(5-43)	Median 5.5(0.5-15)
S. creatinine	Mean 0,79 mg/dl	Mean 0,82 mg/dl	Mean 0,78 mg/dl
SBP	128±10	148±16	135±16
DBP	67±5	77±8	72±8
MBP	87±7	101±10	93±10
ADMA	0,38µmol/l ±0.05	0,45µmol/l ± 0.06	0,43µmol/l ± 0.06
PWV	Mean 8.69m/s ± 1.78	Mean 10.2m/s ± 2.31	Mean 8.74m/s ± 1.64

Consequently, the study showed that the prevalence of hypertension in RA patients is 80%, and the prevalence of hypertension in PSS patients is 40% while in the control group the prevalence was only 20%. The definition of hypertension in the study was SBP more than 140 mmHg and DBP more than 90mmHg or the patient treated for hypertension with medication. The results of blood pressure measurement were seen in SBP (148 ± 16 mmHg in RA vs. 128 ± 11 mmHg in the control group; p-value: 0.007), while 135 ± 16 mmHg was seen in PSS patients' vs 128 ± 11 mmHg in the control group p-value: 0.340. DBP in RA (77 ± 8 mmHg, as compared to the control 67 ± 6 mmHg; p-value: 0.010).

DBP in PSS patients is 72 ± 8 mmHg in vs. 67 ± 6 mmHg in control group: p-value: 0.190. MBP (RA 101 ± 11 mmHg; compared to control controls 88 ±7 mmHg, p-value: 0.010), while MBP in PSS patients was 93 ± 10 mm Hg vs. 88 ±7 mmHg in the control group with no significant difference: p-value: 0.24. But when we compared the autoimmune diseases groups

to the control group we found significant differences in level in the blood pressure (SBP, p-value: 0.02, DBP, p-value 0.01, MBP, p-value: 0.02).

Excluding the cause of elevated blood pressure was kidney diseases; the study found that the serum creatinine level in the blood for all patients was within the normal range plus, the urine analysis of the patients, and glomerular filtration rate (GFR) were also within normal. RA group serum creatinine was (0.82 ± 0.16 mg/dl), PSS group (0.78 ±0.18), control group serum creatinine (0.79 ± 0.04). The result of GFR in the RA group was (82 ± 21 ml/min), the GFR of the PSS group was (90 ± 21 ml/min) while the GFR of the control group was (88 ± 9 ml/min). The study found no correlation between elevated blood pressure and kidney function (0.154) when used serum creatinine as a variable in relation to blood pressure.

The effective finding in the study was the heart rate difference between the three groups. Although all the patients were in a complete state of physical and mental rest and they stayed more than 20 minutes in bed rest but the heart rate was interesting. The heart rate of the rheumatoid group was 76 ± 12 beat/minute, PSS patient's heart rate was 66 ± 11 beat /minute. While the heart rate of the control group was 64 ± 10, this may indicate affection of heart rate in the RA group.

The plasma level of endothelial dysfunction marker ADMA was high in RA (0.45 mole/L ± 0.069 ng/mL) patients as compared to controls (0.38 mole/L ± 0.059 ng/mL), statistically significant (p-value: 0.022), and the level of ADMA in PSS patients group was (0.43 mole/L ± 0.060 ng/mL) as compared to controls (0.38 ± 0.059 ng/mL) with no statistical significant value, as table (2) previously showed.

As regards, other routine lab investigations show: The lipid profile shows: total cholesterol of RA group (268 ±55 mg/dl), PSS group total cholesterol was (182 ±28 mg/dl), control group total cholesterol (228 ± 25 mg/dl), with no statistically significant differences between all groups. Triglyceride level showed in RA group (157 ± 58 mg/dl), PSS group (91 ±32 mg/dl), while control group (177 ± 11 mg/dl). Serum LDL cholesterol showed in RA group (165 ± 50 mg/dl), PSS (104 ± 20 mg/dl), control group (129± 7 mg/dl). HDL cholesterol in RA group (70 ± 14 mg/dl), PSS (63 ±16 mg/dl), control group (73 ± 16 mg/dl).

There was a correlation between age and blood pressure measurements in the diseased group (0.714). That means increasing age is associated with increased blood pressure (the patients were young age) but not in the control group (0.408). ESR result for three groups shown, in the RA group ESR was12 ± 7, while in the PSS group it was 14± 5. CRP test result for diseased groups, was in the RA group 3 ±2, while in the PSS group it was 1.8 ±1.5.

There is no significant correlation were seen between ADMA levels and blood pressure this means that no direct relation between increased ADMA and elevated or decreased blood pressure, and the correlation coefficients were SBP (0.431), DBP (0.178), or MBP (0.321). Also, No correlation coefficient was found between ADMA levels and disease duration, this means that increased disease duration is not associated with an elevated or decreased level of ADMA (0.06). The results showed that there was a negative significant correlation between ADMA and CRAE in the disease group, this means with an increased ADMA(endothelial dysfunction) level the diameter of retinal arterioles will decrease (PSS more than RA) (-0.517).

No correlation between age and ADMA level was seen in the results (0.13); this means increasing age is not associated with endothelial dysfunction, but ADMA level correlates with increasing weight (0.612). As mentioned before that ADMA is considered one of the nephrogenic toxins, there is a correlation between ADMA and creatinine level (0.525). No significant correlation between ADMA level and arterial stiffness (PWV) (0.348), but there was a positive correlation only in PSS as it was observed (0.669) and this means endothelial dysfunction in PSS can associate with arterial stiffness.

Using the Vicoder device to record arterial stiffness between two major arteries carotid and femoral showed that pulse wave velocity results were different between the three groups, the speed of the wave in the RA group was (10.2 ± 2.31 m/s), while the speed of transmission in PSS group was (8.74 ± 1.64 m/s), and the speed in the was control group (8.69 ± 1.78 m/s). As mentioned there are differences in the results, especially between the RA group and the control group but these results did not reach statistical differences between all groups, and also the reading of high PWV was in patients with high blood pressure (Table 2).

As shown by patients with high blood pressure and high PWV, the correlation between blood pressure and PWV showed there is a significant positive correlation between blood pressure

results and pulse wave velocity in the diseased groups and also in the control group. In the RA the correlation was in SBP ($p = 0.02$), but not in DBP ($p = 0.12$), MBP ($p = 0.04$), in PSS group, statistically significant correlations between SBP ($p = 0.003$), DBP ($p = 0.09$), and MBP ($p = 0.01$), these means change in blood pressure associated with change in arterial stiffness. Also, the results of the control group gave significant correlations only in SBP ($p = 0.02$).

As mentioned before that age has no correlation with the ADMA, here there was a significant correlation between increasing age and arterial stiffness (PWV) in all the three groups together. That means, with increasing age, arterial stiffness will happen due to replace of elastin by collagen fibers($r = 0.703$). The results showed that PWV did not depend on diseases duration (may be the activity of the diseases) so no correlation between disease duration and arterial stiffness (PWV) was found ($r = 0.179$).

The results of retinal photos analysis by the Mona Reva software program showed RA group the diameter of CRAE (138 mics ± 6, $p = 0.125$), in the PSS patients group (146 mics ± 17, $p = 0.58$) and the control group (151 mics ± 21). This analysis of retinal arteriole showed no statistically significant differences in the diameter of arteriole between the diseased groups and healthy controls, but the diameter of CRAE in RA patients is low (constricted), as compared to the healthy group and also PSS group. As regards the analysis of CRVE, there was no difference in retinal vein diameter between the diseased and healthy groups. The following table shows statistical differences between the diseases group RA and PSS and the control group. All the results were compared to the control group:

Table (3): Statistical differences between diseases (group RA, PSS, and control group)

Reproduced from (Mahdy et al, 2021 [221]).

variant	RA	PSS	RA+PSS
SBP	0.007	0.340	0.023
DBP	0.01	0.19	0.01

MBP	0.01	0.24	0.02
ADMA	0.02	0.06	0.02
PWV	0.07	0.48	0.18

Moreover, a study of the correlation between the groups showed that there was a significant negative correlation between CRAE and ADMA (-0.517) this means an increase in ADMA (endothelial dysfunction) will be accompanied by decreased retinal vessels diameter. Weight (-0.482) increased weight, the vessels diameter will decrease. BP (-0.465), increase blood pressure will decrease the diameter (brain microvascular autoregulation). height (-0.578). These results were seen only with CRAE in the diseased group, not the control group. Regarding the lipid profile, no correlations were found between cholesterol level values and all the other parameters. This means no relation of cholesterol and blood pressure (0.252), also no correlation between endothelial dysfunction (ADMA) and cholesterol level (-0.105), cholesterol level and arterial stiffness (PWV), no correlation (0.13), cholesterol level, and CRAE (0.17) no correlation was seen.

5. Discussion:

This study tried to compare AIRDs represented here by RA and PSS patients to healthy people (the study did not compare between RA which is a very common disease with high incidence and prevalence against another less common disease PSS with fewer data). The study here was aiming to compare complications of chronic inflammation that happens in these diseases to the normal population.

Until now, there is still no evidence about the true number of AIRDs suffering from hypertension and the relationship between chronic inflammation and vascular changes in AIRDs. The study tried to resolve this debate and reach conclusive results and add important and interesting data in this field of research. I hope to use these data to plane more large studies in the near future and although the study was a pilot study with a small number of participants, the study found statistically significant differences between the three groups and tried to resolve the issue

between researchers if, hypertension primary is responsible for endothelial dysfunction and arteriosclerosis or the chronic inflammation leads to endothelial dysfunction then hypertension.

As the study stated that the prevalence was 80% in the RA group and hypertension prevalence was 40% in PSS while hypertension was 20% in the healthy matched control group. So, the high prevalence of hypertension in both diseased groups, and, as no explanation for hypertension was appeared other than endothelial dysfunction, so that most probably endothelial dysfunction which resulted from chronic inflammation is responsible for hypertension. Consequently, hypertension is responsible for premature atherosclerosis presented in AIRDs.

The study showed that elevated plasma ADMA levels in diseased groups accompanied by high blood pressure, especially in RA patients and these results confirmed that there was associated endothelial dysfunction in the patients' groups. At the time of examination, the results of arterial stiffness and retinal small vasculature not showed effects on the macro- or microvascular system. The study used PWV to measure the arterial stiffness and asses macrovascular function and used a Canon camera to assess microvascular function in the retina represented here by CRAE and CRVE.

As mentioned before the true percentage of hypertension in AIRDs is unknown. Some studies reported that there is a difference between diseases and control with varying degrees, and other studies showed no difference in the percentage of hypertension between the diseased and healthy groups. [185,186,187], others mentioned that the prevalence of hypertension may be high but it is underestimated [188].

The mechanism of hypertension in AIRDs is most commonly due to the effect of chronic inflammation on the endothelial cells, as well as a state of chronic vasculitis present due to immune-complex deposition or vasculitis in situ affecting endothelium and decreasing release of potent vasodilator NO ending by vasoconstriction and elevated blood pressure [189]. The elevated blood pressure may be due to medications like steroids or nonsteroidal anti-inflammatory drugs [190].

The other important question does hypertension as a mechanical force is responsible for endothelial injury by shearing stress and affects endothelial cell lining leading to dysfunction of the endothelium with loss of vasodilator function (NO) [191]. Or, the chronic inflammation in

AIRDs is responsible for endothelial dysfunction with loss of vasodilator capability of the endothelium accompanied by hypertension, then progress to arterial stiffness and premature atherosclerosis [192–194].

Several studies have tried to resolve this controversy and reach conclusive results without success. Konukoglu and Uzun mentioned that in their research that they did not reach to conclusive opinion as inflammation cause hypertension or hypertension cause inflammation [195]. Kim Lauper and colleagues' opinion was, due to chronic inflammation in autoimmune diseases there is an affection of inflammation on lipid metabolism and consequently atherosclerosis process and then blood pressure reading changes, which mean hypertension in AIRDs is primarily due to abnormal lipid metabolism.

Here the prevalence of hypertension was higher than most studies have done before. One research was done by Roman and his colleagues and they found only 18% of the patients had hypertension [196].

In another study, Han and his colleagues did a large cohort study and they found that the percentage of hypertension in their cohort was 34% in the RA patients group while the prevalence was 23% in the controls group [197]. Maxime Dougados in his research with his research colleagues found that the hypertension prevalence in the rheumatoid arthritis group was 11% [198], while Roman and colleagues again in another study did one year before his previous study [196], he reported the prevalence of hypertension was only 3% [199]. Another study showed nearly the same results as our study, Chung and his research colleagues mentioned that the prevalence of hypertension was 73% [200].

Without proceeding with any statistical results, Panoulas and his colleagues reported that hypertension was very common in AIRDs but unfortunately remains underestimated [201]. Here in my study, I think the differences in the results of blood pressure measurements in all these studies may be related to number one, the human skills in measuring blood pressure and second to the number of diseased patients recruited in every study, the third reason may be the definition of hypertension used by every study (In this study, Hypertension was defined as patients taking antihypertensive drugs or having a previous reading of persistently elevated blood pressure and did not take medication or systolic blood pressure higher than 140 mmHg and diastolic blood

pressure was more than 90 mmHg during study measurements), the fourth reason is the ethnicity of the patients recruited, the fifth is the diseases duration and diseases activity which reflects the general condition of the patients (relapse or remission), and time of measurements before or after the antihypertensive medication intake.

Other studies simply reported that the difference in the blood pressure reading in the rheumatoid group and the presence of hypertension in RA is not due to the disease but due to the advancing age of the patients [200,202,203], but in our study, there was no significant correlation between age changes and blood pressure measurements in the healthy group. The results of this small study were significant, as the study added some knowledge to the literature as regards the prevalence of hypertension in AIRDs.

The results of this study were confirmed by the same results of Rossi and his colleagues. Their results showed that endothelial dysfunction was the cause of hypertension [204], but on the other hand, Shimbo and his colleagues had another opinion as they mentioned that hypertension was the cause of endothelial dysfunction not a result of it [205]. Taddei and his research colleagues showed in their study that hypertension is not a cause of endothelial dysfunction [206].

But, we still need another research to confirm our results with a big number of the patients and also to confirm who comes first hypertension or endothelial dysfunction and our thought which consider that, endothelial dysfunction is the cause of hypertension in AIRDs because of finding high levels of ADMA in the diseased groups. These results confirmed our hypothesis that hypertension present in AIRDs most probably comes from chronic inflammation.

The following question needs to be answered, Is atherosclerosis, that happens in AIRDs, due to nontraditional risk factors including chronic inflammation, drugs used in the treatment of AIRDs ?. Or is it due to traditional risk factors like hypercholesterolemia, age, hypertension, and male sex. All studies discussing the relation between AIRDs and atherosclerosis concentrate on traditional and nontraditional risk factors affecting the progress of the atherosclerosis process and these studies compare between traditional factors themselves which one has a great role and which one has a minor role in atherogenesis (especially hypertension and age).

The results of arterial stiffness are aimed at measuring the PWV changes in AIRDs. The study showed that, by the time of measurements, there was an increase in PWV for rheumatoid patients

as compared to the healthy control group; however, these results did not reach statistical significance values. Interestingly, the patients who expressed higher arterial wave speed were also having elevated blood pressure, so the question here is whether levels of higher PWV were due to previously elevated blood pressure or related to chronic inflammation?, the study recommended both answers were true, and the inflammation cause elevated blood pressure (hypertension) and consequently hypertension causing an increase in speed of pulse wave across the arterial wall (arterial stiffness).

Most, if not all the other studies have shown that there is a high prevalence of arterial stiffness in RA patients [207]. Kocabay and his research colleagues mentioned in their study that high speed of pulse waves across the arterial wave due to arterial stiffness has been found in some AIRDs like Bechet's disease, SLE, and RA patients [208]. Wang and his research colleagues had on SLE patients a meta-analysis, the meta-analysis also showed an increased arterial stiffness done by PWV [209]. Another research have done by Awalia and his research colleagues showed that the rate and progress of arterial stiffness of the blood vessels seen in RA is not related to the disease duration but related to the degree of disease activity, that means, greater the activity and inflammatory status of the disease, greater the arterial wall rigidity and stiffness and these reflected on the symptoms and sign [210].

While Dzieza-Grudnik and his research colleagues found that no difference was presented in PWV and arterial stiffness in active rheumatoid arthritis with short disease duration [211]. Our study did not find any difference in arterial stiffness between PSS patients and the control group at the time of measurements, Sabio and research colleagues showed that there was an increase in arterial stiffness (PWV) reading in PSS patients [212]. On the other hand, Atzeni and his research team found that there was no difference in arterial stiffness between PSS patients and the control group [213]. Another meta-analysis has done by Yong and his research team in the PSS patients and they found a high prevalence of PWV and arterial stiffness was seen in these groups of patients [214]. As the study did not find at the time of examination, there were any differences in PWVs and arterial stiffness in the primary Sjögren group as compared to the control group.

The difference between this study and others is in the results. For example, the duration of the diseases was short (median 5 years) and the other studies use different age groups and different

disease duration plus here the age of the participant was slightly younger and maybe the difference in the ethnicity of patients recruitment or the degree of disease activity or disease duration [199].

Regarding the results of ADMA in the plasma, this study supposes that there was a high level of endothelial dysfunctional marker ADMA in the rheumatoid group and also in the Sjögren's group as compared to healthy control. Nearly all the studies have done discussing the relationship between autoimmune diseases and ADMA were positive results [213]. For example, the study results were similar to Erre and his research colleagues as they mentioned that ADMA was high in their study, they did a meta-analysis that included many studies and they confirmed that there was a higher ADMA level in autoimmune diseases as compared to controls [215]. This means that all the autoimmune diseases show some degree of abnormal function of the endothelial cells due to chronic inflammatory situations.

As we know the researches that discussed the relation between retinal microvasculature and other diseases or even risk factors for the diseases is low and in the field of autoimmune diseases and retinal vessels diameter, it was only a few studies that discussed this issue, especially the relationship between RA and PSS and retinal vessels diameter. Although most studies discussed the retinal vessels whether arteriole or venule mentioned that the venules are often passive structure follow changes in the arteriole but the interesting finding was one study showed that the retinal venular diameter did not follow the arterial changes and there was an increase in venular diameter (CRVE) in the rheumatoid group, this changes may be due to the effect of chronic inflammation on retinal venules [216].

Moreover, Van Doornum and his research colleagues found a change in venular diameter in rheumatoid diseases as compared to a normal healthy person with wider retinal venular diameter but not in CRAE [217]. In this study, by the time of examination, the study did not find any significant statistical differences in the retinal vessel diameter (CRAE, CRVE) between the diseased groups, RA and PSS, and the control group. However, the study found that the diameter of retinal arteriole (CRAE) in the RA group was smaller than the diameter in the Sjögren's syndrome and also the control group.

The results of smaller retinal arteriolar diameter in the RA group have been found in the patients with elevated blood pressure reading, so the decreases in the diameter of CRAE were available in the rheumatoid group was most probably due to the elevation in blood pressure. The explanation of this phenomenon is most probably because of elevated blood pressure on brain vessels. As we know high blood pressure can affect brain (retinal) microcirculation to produce vasoconstriction and consequently smaller arterioles to keep a constant blood supply to the brain. So, the effect of elevated blood pressure on the retinal vessels is greater than the effect of inflammation in decreasing the diameter of arterioles [218].

In the future, other studies are needed to explore the relation between retinal vessels diameter and other diseases to show the effect of these diseases on the microvascular circulation easily as the scientist mentioned before-the retina is the mirror of the brain-.

As a result, the debate about the real prevalence of hypertension in AIRDs is still available and, as mentioned, the prevalence of hypertension is very high up to critical numbers in our study(nearly all the RA patients who participated in the study had hypertension). And as the study found, the age of the patients was younger as compared to control and the prevalence of hypertension in Austria was low especially at this age level. In addition, as there was no cause explaining the elevation in blood pressure in the patients (as kidney function was within normal range and no steroids drugs were used by the patients), thus finally, no definite cause of elevated blood pressure in this patients group other than abnormal endothelial cell function (endothelial dysfunction) as shown by elevation of blood endothelial dysfunction markers ADMA level in the diseased groups.

No guidelines were available in the treatment of hypertension in autoimmune diseases, so the clinicians use the traditional antihypertensive medication to control blood pressure in autoimmune diseases suffering from hypertension [200].

5.1. Limitations of the Research:

Although a low number of patients participated in this study because of the Coronavirus pandemic, the study got excellent results. So, we will use the pilot study data which we got as a basis for calculating a bigger study with more patients and other autoimmune diseases in future

epidemiological studies discussing the relation between vascular dys (function) and autoimmune diseases.

6. Conclusions and future directions:

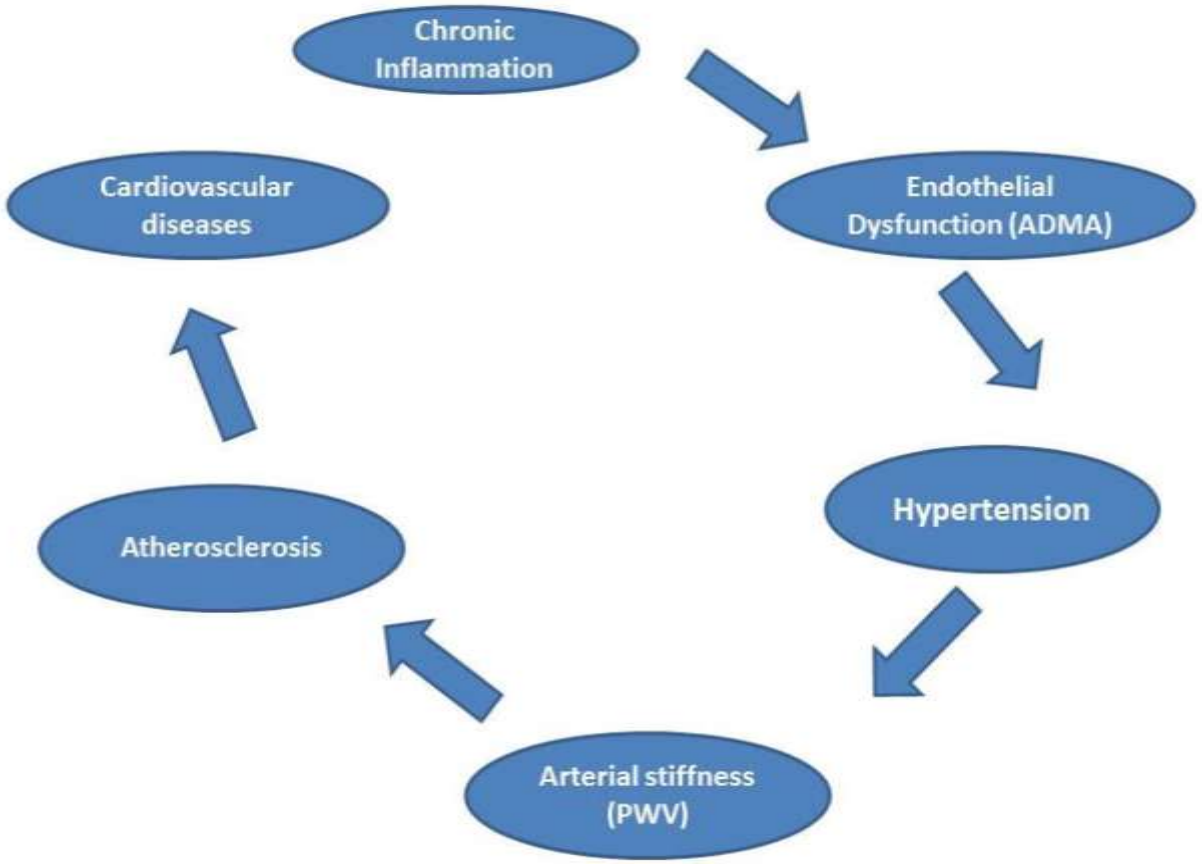
The relationship between autoimmune diseases and the function of the vascular system is very complicated. Due to the chronic inflammatory process which distinguishes the autoimmune diseases, this inflammation will affect endothelial cells lining the blood vessels then the endothelial cells will lose their normal regenerating power and consequently homeostasis function with disturbance in the equilibrium between chemical mediators they release. These changes in cytokines and chemical mediators lead to vasoconstrictor due to loss of NO and its vasodilator function.

Based on the results of the study and as mentioned before about the debate among researchers about the contribution of traditional and nontraditional risk factors in process of atherosclerosis and which factor has a major role in this process and which factor had less participation in the process of atherosclerosis, the study suggested that nontraditional risk factors, represented here in chronic inflammation, initiate the process of premature atherosclerosis through one of the traditional risk factors which are hypertension. Hypertension is considered the major and most important traditional risk that helps to begin the process of premature atherosclerosis and the presence of hypertension in AIRDs is considered an early sign of atherosclerosis [219].

Technically, hypertension as mechanical force leads to shearing and injury of endothelium cells. This process potentiates the inflammatory process in the endothelium with the remodeling of blood vessels and as the inflammatory process continues with active disease, the vicious circle persists. Injury with more inflammation, more endothelial dysfunction, and more rigidity and stiffness of blood vessels end by premature atherosclerosis. To summarize, the following figure illustrates the pathway of premature atherosclerosis and the relationship between chronic inflammation and the cardiovascular system:

Figure (4): The Relationship between Chronic Inflammation and Cardiovascular System.

(Reproduced from "Mahdy et al, 2021" [221])



In conclusion, the study recommends detection of elevated blood pressure is important, and also the management of hypertension is another goal facing the clinicians. So the early detection of hypertension through screening is very important to prevent atherosclerosis and consequently cardiovascular diseases in AIRDs.

Future studies will be needed in the field of chronic inflammation and cardiovascular diseases to confirm the relationship between the inflammatory process and premature atherosclerosis. Also, other AIRDs that have a major effect on vessel wall structure as scleroderma patients could be

included in future studies. These studies should be in many inflammatory diseases (infectious and non-infectious) like rheumatoid arthritis, primary Sjögren's syndrome, systemic lupus erythematous (as hypertension and glomerular diseases are very common in lupus and the inflammation is great.

As I hope to use the results of this pilot study as a reference for a bigger study and because of the high statistical difference between the diseased group and control group and as the difference in elevated blood pressure variant was high between the RA group and control group, when we do sample size for comparing two proportion for big study, we will found that the minimal number of the patients needed is a small number for example: with a confidence level of 95% and power of 80%, we need 7 patients for each group. With confidence level of 99% and power of 80%, we need 11 patients in every group.

7. Bibliography

1. Frostegård, J. Atherosclerosis in Patients with Autoimmune Disorders. Arter. Thromb. Vasc. Biol. 2005, 25, 1776–1785, doi:10.1161/01.atv.0000174800.78362.ec.

2. Sima, P.; Vannucci, L.; Vetvicka, V. Atherosclerosis as autoimmune disease. Ann. Transl. Med. 2018, 6, 116, doi:10.21037/atm.2018.02.02. (In English)

3. Symmons, D.; Gabriel, S.E. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat. Rev. Rheumatol. 2011, 7, 399–408, doi:10.1038/nrrheum.2011.75. (In English)

4. Fairweather, D.; Rose, N.R. Women and Autoimmune Diseases1. Emerg. Infect. Dis. 2004, 10, 2005–2011, doi:10.3201/eid1011.040367. (In English)

5. Saccucci, M.; Di Carlo, G.; Bossù, M.; Giovarruscio, F.; Salucci, A.; Polimeni, A. Autoimmune Diseases and Their Manifestations on Oral Cavity: Diagnosis and Clinical Management. J. Immunol. Res. 2018, 2018, 6061825, doi:10.1155/2018/6061825. (In English)

6. Sinha, A.; Lopez, M.; McDevitt, H. Autoimmune diseases: The failure of self-tolerance. Science 1990, 248, 1380–1388, doi:10.1126/science.1972595. (In English)

7. Amador-Patarroyo, M.J.; Rodriguez-Rodriguez, A.; Montoya-Ortiz, G. How Does Age at Onset Influence the Outcome of Autoimmune Diseases? Autoimmune Dis. 2011, 2012, 1–7, doi:10.1155/2012/251730. (In English)

8. Di Franco, B.L.M.; Lucchino, B.; Spaziante, M.; Iannuccelli, C.; Valesini, G.; Iaiani, G. Lung Infections in Systemic Rheumatic Disease: Focus on Opportunistic Infections. Int. J. Mol. Sci. 2017, 18, 293, doi:10.3390/ijms18020293. (In English)

9. Villa-Forte, A.; Mandell, B.F. Cardiovascular disorders and rheumatic disease. Rev. Española de Cardiol. 2011, 64, 809–817, doi:10.1016/j.recesp.2011.05.009. (In Spanish)

10. Mehta, B.; Pedro, S.; Ozen, G.; Kalil, A.; Wolfe, F.; Mikuls, T.; Michaud, K. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: A US national cohort study. RMD Open 2019, 5, e000935, doi:10.1136/rmdopen-2019-000935. (In English)

11. Manzi, S.; Meilahn, E.N.; Rairie, J.E.; Conte, C.G.; Medsger, T.A.; Jansen-McWilliams, L.; D'Agostino, R.B.; Kuller, L.H. Agespecific Incidence Rates of Myocardial Infarction and Angina in Women with Systemic Lupus Erythematosus: Comparison with the Framingham Study. Am. J. Epidemiol. 1997, 145, 408–415, doi:10.1093/oxfordjournals.aje.a009122. (In English)

12. Amaya-Amaya, J.; Montoya-Sánchez, L.; Rojas-Villarraga, A. Cardiovascular Involvement in Autoimmune Diseases. BioMed Res. Int. 2014, 2014, 367359, doi:10.1155/2014/367359. (In English)

13. Buleu, F.; Sirbu, E.; Caraba, A.; Dragan, S. Heart Involvement in Inflammatory Rheumatic Diseases: A Systematic Literature Review. Medicina 2019, 55, 249, doi:10.3390/medicina55060249. (In English)

14. Szekanecz, Z.; Kerekes, G.; Végh, E.; Kardos, Z.; Baráth, Z.; Tamási, L.; Shoenfeld, Y. Autoimmune atherosclerosis in 3D: How it develops, how to diagnose and what to do. Autoimmun. Rev. 2016, 15, 756–769, doi:10.1016/j.autrev.2016.03.014.

15. Fatkhullina, A.R.; Peshkova, I.O.; Koltsova, E.K. The role of cytokines in the development of atherosclerosis. Biochemistry 2016, 81, 1358–1370, doi:10.1134/s0006297916110134. (In English)

16. Ross, R. Atherosclerosis—An Inflammatory Disease. N. Engl. J. Med. 1999, 340, 115–126, doi:10.1056/nejm199901143400207. (In English)

17. Mayadas, T.N.; Tsokos, G.C.; Tsuboi, N. Mechanisms of Immune Complex–Mediated Neutrophil Recruitment and Tissue Injury. Circulation 2009, 120, 2012–2024, doi:10.1161/circulationaha.108.771170. (In English)

18. Jörg, S.; Grohme, D.A.; Erzler, M.; Binsfeld, M.; Haghikia, A.; Müller, D.N.; Linker, R.A.; Kleinewietfeld, M. Environmental factors in autoimmune diseases and their role in multiple sclerosis. Cell. Mol. Life Sci. 2016, 73, 4611–4622, doi:10.1007/s00018- 016-2311-1. (In English)

19. Giannelou, M.; Mavragani, C.P. Cardiovascular disease in systemic lupus erythematosus: A comprehensive update. J. Autoimmun. 2017, 82, 1–12, doi:10.1016/j.jaut.2017.05.008. (In English)

20. Teixeira, V.; Tam, L.-S. Novel Insights in Systemic Lupus Erythematosus and Atherosclerosis. Front. Med. 2018, 4, 262, doi:10.3389/fmed.2017.00262. (In English)

21. Hajar, R. Risk factors for coronary artery disease: Historical perspectives. Heart Views 2017, 18, 109–114, doi:10.4103/heartviews.heartviews_106_17. (In English)

22. Masuko, K. Rheumatoid Cachexia Revisited: A Metabolic Co-Morbidity in Rheumatoid Arthritis. Front. Nutr. 2014, 1, 20, doi:10.3389/fnut.2014.00020. (In English)

23. Pérez-Baos, S.; Prieto-Potin, I.; Roman-Blas, J.A.; Pernaute, O.S.; Largo, R.; Herrero-Beaumont, G. Mediators and Patterns of Muscle Loss in Chronic Systemic Inflammation. Front. Physiol. 2018, 9, 409, doi:10.3389/fphys.2018.00409. (In English)

24. Londhe, P.; Guttridge, D.C. Inflammation induced loss of skeletal muscle. Bone 2015, 80, 131–142, doi:10.1016/j.bone.2015.03.015. (In English)

25. Klaasen, R.; Wijbrandts, C.A.; Gerlag, D.M.; Tak, P.P. Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum. 2010, 63, 359–364, doi:10.1002/art.30136. (In English)

26. García-Poma, A.; Segami, M.I.; Mora, C.S.; Ugarte-Gil, M.F.; Terrazas, H.N.; Rhor, E.A.; García, E.; Ramos, M.P.; Alva, M.; Castañeda, I.; et al. Obesity is independently associated with impaired quality of life in patients with rheumatoid arthritis. Clin. Rheumatol. 2007, 26, 1831–1835, doi:10.1007/s10067-007-0583-4. (In English)

27. de Resende Guimarães, M.F.B.; Rodrigues, C.E.M.; Gomes, K.W.P.; Machado, C.; Brenol, C.V.; Krampe, S.F.; De Andrade, N.P.B.; Kakehasi, A.M. High prevalence of obesity in rheumatoid arthritis patients: Association with disease activity, hypertension, dyslipidemia and diabetes, a multi-center study. Adv. Rheumatol. 2019, 59, 44–49, doi:10.1186/s42358-019-0089-1. (In English)

28. van der Helm-van Mil, A.H.M.; Van Der Kooij, S.M.; Allaart, C.F.; Toes, R.; Huizinga, T.W.J. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann. Rheum. Dis. 2008, 67, 769– 774, doi:10.1136/ard.2007.078832. (In English)

29. Kerekes, G.; Nurmohamed, M.T.; González-Gay, M.A.; Seres, I.; Paragh, G.; Kardos, Z.; Baráth, Z.; Tamási, L.; Soltész, P.; Szekanecz, Z. Rheumatoid arthritis and metabolic syndrome. Nat. Rev. Rheumatol. 2014, 10, 691–696, doi:10.1038/nrrheum.2014.121.

30. Zhu, J.; Nelson, K.; Toth, J.; Muscat, J.E. Nicotine dependence as an independent risk factor for atherosclerosis in the National Lung Screening Trial. BMC Public Health 2019, 19, 103, doi:10.1186/s12889-019-6419-8. (In English)

31. Mahmoudi, M.; Aslani, S.; Fadaei, R.; Jamshidi, A.R. New insights to the mechanisms underlying atherosclerosis in rheumatoid arthritis. Int. J. Rheum. Dis. 2017, 20, 287–297, doi:10.1111/1756-185x.12999. (In English)

32. Spinelli, F.R.; Pecani, A.; Ciciarello, F.; Colasanti, T.; Di Franco, M.; Miranda, F.; Conti, F.; Valesini, G.; Alessandri, C. Association between antibodies to carbamylated proteins and

subclinical atherosclerosis in rheumatoid arthritis patients. BMC Musculoskelet. Disord. 2017, 18, 214, doi:10.1186/s12891-017-1563-8. (In English)

33. Tinelli, C.; DI Pino, A.; Ficulle, E.; Marcelli, S.; Feligioni, M. Hyperhomocysteinemia as a Risk Factor and Potential Nutraceutical Target for Certain Pathologies. Front. Nutr. 2019, 6, 49, doi:10.3389/fnut.2019.00049. (In English)

34. Lazzerini, P.E.; Capecchi, P.L.; Selvi, E.; Lorenzini, S.; Bisogno, S.; Galeazzi, M.; Pasini, F.L. Hyperhomocysteinemia, inflammation and autoimmunity. Autoimmun. Rev. 2007, 6, 503–509, doi:10.1016/j.autrev.2007.03.008. (In English)

35. Mok, C.C. Metabolic syndrome and systemic lupus erythematosus: The connection. Expert Rev. Clin. Immunol. 2019, 15, 765–775, doi:10.1080/1744666X.2019.1620601. (In English)

36. Meek, I.L.; Vonkeman, H.E.; Van De Laar, M.A. Hyperuricaemia: A marker of increased cardiovascular risk in rheumatic patients: Analysis of the ACT-CVD cohort. BMC Musculoskelet. Disord. 2014, 15, 174, doi:10.1186/1471-2474-15-174. (In English)

37. Skeoch, S.; Bruce, I.N. Atherosclerosis in rheumatoid arthritis: Is it all about inflammation? Nat. Rev. Rheumatol. 2015, 11, 390– 400, doi:10.1038/nrrheum.2015.40. (In English)

38. Sherer, Y.; Shoenfeld, Y. Mechanisms of Disease: Atherosclerosis in autoimmune diseases. Nat. Clin. Pr. Rheumatol. 2006, 2, 99– 106, doi:10.1038/ncprheum0092. (In English)

39. Kobezda, T.; Ghassemi-Nejad, S.; Mikecz, K.; Glant, T.T.; Szekanecz, Z. Of mice and men: How animal models advance our understanding of T-cell function in RA. Nat. Rev. Rheumatol. 2014, 10, 160–170, doi:10.1038/nrrheum.2013.205. (In English)

40. Mengya, Z.; Hanyou, M.; Dong, L.; Xiaohong, L.; Lihua, Z. Th17/Treg imbalance induced by increased incidence of atherosclerosis in patients with Systemic Lupus Erythematosus (SLE). Clin. Rheumatol. 2013, 32, 1045–1052, doi:10.1007/s10067-013-2237- . (In English)

41. Li, P.; Zheng, Y.; Chen, X. Drugs for Autoimmune Inflammatory Diseases: From Small Molecule Compounds to Anti-TNF Biologics. Front. Pharmacol. 2017, 8, 460, doi:10.3389/fphar.2017.00460. (In English)

42. Kerekes, G.; Szekanecz, Z.; Dér, H.; Sándor, Z.; Lakos, G.; Muszbek, L.; Csipö, I.; Sipka, S.; Seres, I.; Paragh, G.; et al. Endothelial dysfunction and atherosclerosis in rheumatoid arthritis: A multiparametric analysis using imaging techniques and laboratory markers of inflammation and autoimmunity. J. Rheumatol. 2008, 35, 398–406. (In English)

43. Matsuura, E.; Atzeni, F.; Sarzi-Puttini, P.; Turiel, M.; Lopez, L.R.; Nurmohamed, M.T. Is atherosclerosis an autoimmune disease? BMC Med. 2014, 12, 47, doi:10.1186/1741-7015-12-47. (In English)

44. Sanjadi, M.; Sichanie, Z.R.; Totonchi, H.; Karami, J.; Rezaei, R.; Aslani, S. Atherosclerosis and autoimmunity: A growing relationship. Int. J. Rheum. Dis. 2018, 21, 908–921, doi:10.1111/1756-185x.13309. (In English)

45. Bugatti, S.; Manzo, A.; Montecucco, C.; Caporali, R.F. The Clinical Value of Autoantibodies in Rheumatoid Arthritis. Front. Med. 2018, 5, 339, doi:10.3389/fmed.2018.00339. (In English)

46. Westerlind, H.; Rönnelid, J.; Hansson, M.; Alfredsson, L.; Mathsson-Alm, L.; Serre, G.; Cornillet, M.; Holmdahl, R.; Jakobsson, P.; Skriner, K.; et al. Anti–Citrullinated Protein Antibody Specificities, Rheumatoid Factor Isotypes, and Incident Cardiovascular Events in Patients With Rheumatoid Arthritis. Arthritis Rheumatol. 2020, 72, 1658–1667, doi:10.1002/art.41381. (In English)

47. Majka, D.S.; Vu, T.-H.T.; Pope, R.M.; Teodorescu, M.; Karlson, E.W.; Liu, K.; Chang, R.W. Association of Rheumatoid Factors With Subclinical and Clinical Atherosclerosis in African American Women: The Multiethnic Study of Atherosclerosis. Arthritis Rheum. 2016, 69, 166–174, doi:10.1002/acr.22930. (In English)

48. Pertovaara, M.; Kähönen, M.; Juonala, M.; Laitinen, T.; Taittonen, L.; Lehtimäki, T.; Viikari, J.S.A.; Raitakari, O.T.; Hurme, M. Autoimmunity and atherosclerosis: The presence of antinuclear antibodies is associated with decreased carotid elasticity in young women. The Cardiovascular Risk in Young Finns Study. Rheumatology 2009, 48, 1553–1556, doi:10.1093/rheumatology/ kep288. (In English)

49. Didier, K.; Bolko, L.; Giusti, D.; Toquet, S.; Robbins, A.; Antonicelli, F.; Servettaz, A. Autoantibodies Associated With Connective Tissue Diseases: What Meaning for Clinicians? Front. Immunol. 2018, 9, 541, doi:10.3389/fimmu.2018.00541. (In English)

50. Ames, P.R.J.; Alves, J.D.; Lopez, L.R.; Gentile, F.; Margarita, A.; Pizzella, L.; Batuca, J.; Scenna, G.; Brancaccio, V.; Matsuura, E. Antibodies Against β2-Glycoprotein I Complexed With an Oxidised Lipoprotein Relate to Intima Thickening of Carotid Arteries in Primary Antiphospholipid Syndrome. Clin. Dev. Immunol. 2006, 13, 1–9, doi:10.1080/17402520600554930. (In English)

51. Cinoku, I.; Mavragani, C.P.; Tellis, C.C.; Nezos, A.; Tselepis, A.D.; Moutsopoulos, H.M. Autoantibodies to ox-LDL in Sjögren's syndrome: Are they atheroprotective? Clin. Exp. Rheumatol. 2018, 36 (Suppl. 112), 61–67. (In English)

52. Lopez, L.R.; Salazar-Paramo, M.; Palafox-Sanchez, C.; Hurley, B.L.; Matsuura, E.; La Torre, I.G.-D. Oxidized low-density lipoprotein and β2-glycoprotein I in patients with systemic lupus erythematosus and increased carotid intima-media thickness: Implications in autoimmune-mediated atherosclerosis. Lupus 2006, 15, 80–86, doi:10.1191/0961203306lu2267oa. (In English)

53. Sciascia, S.; Amigo, M.-C.; Roccatello, D.; Khamashta, M. Diagnosing antiphospholipid syndrome: 'extra-criteria' manifestations and technical advances. Nat. Rev. Rheumatol. 2017, 13, 548–560, doi:10.1038/nrrheum.2017.124. (In English)

54. Napodano, C.; Gulli, F.; Rapaccini, G.L.; Marino, M.; Basile, U. Cryoglobulins: Identification, classification, and novel biomarkers of mysterious proteins. Adv. Clin. Chem. 2021, 104: 299–340, doi:10.1016/bs.acc.2020.09.006. (In English)

55. Ragab, G.; Hussein, M.A. Vasculitic syndromes in hepatitis C virus: A review. J. Adv. Res. 2017, 8, 99–111, doi:10.1016/j.jare.2016.11.002. (In English)

56. Filer, A.; Gardner-Medwin, J.M.; Thambyrajah, J.; Raza, K.; Carruthers, D.M.; Stevens, R.J.; Liu, L.; Lowe, S.E.; Townend, J.; Bacon, P.A. Diffuse endothelial dysfunction is common to ANCA associated systemic vasculitis and polyarteritis nodosa. Ann. Rheum. Dis. 2003, 62, 162–167, doi:10.1136/ard.62.2.162. (In English)

57. Miranda-Carús, M.-E.; Askanase, A.D.; Clancy, R.M.; Di Donato, F.; Chou, T.-M.; Libera, M.R.; Chan, E.K.L.; Buyon, J.P. Anti- SSA/Ro and Anti-SSB/La Autoantibodies Bind the Surface of Apoptotic Fetal Cardiocytes and Promote Secretion of TNF-α by Macrophages. J. Immunol. 2000, 165, 5345–5351, doi:10.4049/jimmunol.165.9.5345. (In English)

58. Jobling, K.; Rajabally, H.; Ng, W.-F. Anti-Ro antibodies and complete heart block in adults with Sjögren's syndrome. Eur. J. Rheumatol. 2018, 5, 194–196, doi:10.5152/eurjrheum.2018.18019. (In English)

59. Sung, M.J.; Park, S.-H.; Kim, S.-K.; Lee, Y.-S.; Park, C.-Y.; Choe, J.-Y. Complete Atrioventricular Block in Adult Sjögren's Syndrome with Anti-Ro Autoantibody. Korean J. Intern. Med. 2011, 26, 213–215, doi:10.3904/kjim.2011.26.2.213. (In English)

60. Schau, T.; Gottwald, M.; Arbach, O.; Seifert, M.; Schöpp, M.; Neuß, M.; Butter, C.; Zänker, M. Increased Prevalence of Diastolic Heart Failure in Patients with Rheumatoid Arthritis Correlates with Active Disease, but Not with Treatment Type. J. Rheumatol. 2015, 42, 2029–2037, doi:10.3899/jrheum.141647. (In English)

61. Mantel, Ä .; Holmqvist, M.; Andersson, D.C.; Lund, L.H.; Askling, J. Association Between Rheumatoid Arthritis and Risk of Ischemic and Nonischemic Heart Failure. J. Am. Coll. Cardiol. 2017, 69, 1275–1285, doi:10.1016/j.jacc.2016.12.033. (In English)

62. Davis, J.M.; Lin, G.; Oh, J.K.; Crowson, C.S.; Achenbach, S.J.; Therneau, T.M.; Matteson, E.L.; Rodeheffer, R.J.; Gabriel, S.E. Fiveyear changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population. Int. J. Cardiol. 2017, 240, 379–385, doi:10.1016/j.ijcard.2017.03.108. (In English)

63. Falk, R.H.; Comenzo, R.L.; Skinner, M. The Systemic Amyloidoses. New Engl. J. Med. 1997, 337, 898–909, doi:10.1056/nejm199709253371306. (In English)

64. Beydoun, S.R.; Rison, R.A.; Commins, D. Secondary amyloidosis as a life-ending event in multifocal motor neuropathy. Muscle Nerve 2001, 24, 1396–1402, doi:10.1002/mus.1162. (In English)

65. Stather, D.; Ford, S.; Kisilevsky, R. Sarcoid, amyloid, and acute myocardial failure. Mod. Pathol. 1998, 11, 901–904. (In English)

66. Siebert, S.; Lyall, D.M.; Mackay, D.F.; Porter, D.; McInnes, I.B.; Sattar, N.; Pell, J.P. Characteristics of rheumatoid arthritis and its association with major comorbid conditions: Cross-sectional study of 502 649 UK Biobank participants. RMD Open 2016, 2, e000267, doi:10.1136/rmdopen-2016-000267. (In English)

67. Chung, C.P.; Oeser, A.; Solus, J.F.; Avalos, I.; Gebretsadik, T.; Shintani, A.; Raggi, P.; Sokka, T.; Pincus, T.; Stein, C.M. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis 2008, 196, 756–763, doi:10.1016/j.atherosclerosis.2007.01.004. (In English)

68. Gerli, R.; Sherer, Y.; Vaudo, G.; Schillaci, G.; Gilburd, B.; Giordano, A.; Bocci, E.B.; Allegrucci, R.; Marchesi, S.; Mannarino, E.; et al. Early Atherosclerosis in Rheumatoid Arthritis: Effects of Smoking on Thickness of the Carotid Artery Intima Media. Ann. New York Acad. Sci. 2005, 1051, 281–290, doi:10.1196/annals.1361.069. (In English)

69. Han, C.; Robinson, D.W.; Hackett, M.V.; Paramore, L.C.; Fraeman, K.H.; Bala, M.V. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J. Rheumatol. 2006, 33, 2167–2172. (In English)

70. Panoulas, V.F.; Douglas, K.M.J.; Milionis, H.J.; Stavropoulos-Kalinglou, A.; Nightingale, P.; Kita, M.D.; Tselios, A.L.; Metsios, G.S.; Elisaf, M.; Kitas, G.D. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis.

Rheumatology 2007, 46, 1477–1482, doi:10.1093/rheumatology/kem169. (In English)

71. Agca, R.; Heslinga, S.C.; Van Halm, V.P.; Nurmohamed, M.T. Atherosclerotic cardiovascular disease in patients with chronic inflammatory joint disorders. Heart 2016, 102, 790–795, doi:10.1136/heartjnl-2015-307838. (In English)

72. Panoulas, V.F.; Metsios, G.S.; Pace, A.V.; John, H.; Treharne, G.; Banks, M.J.; Kitas, G. Hypertension in rheumatoid arthritis. Rheumatology 2008, 47, 1286–1298, doi:10.1093/rheumatology/ken159. (In English)

73. Karvounaris, S.A.; Sidiropoulos, P.I.; Papadakis, J.A.; Spanakis, E.K.; Bertsias, G.K.; Kritikos, H.D.; Ganotakis, E.; Boumpas, D.T. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: A retrospective, cross-sectional, controlled, study. Ann. Rheum. Dis. 2006, 66, 28–33, doi:10.1136/ard.2006.053488. (In English)

74. Dessein, P.H.; Stanwix, A.E.; Joffe, B.I. Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: Acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. Arthritis Res. 2002, 4, R5, doi:10.1186/ar428. (In English)

75. Roman, M.J.; Moeller, E.; Davis, A.; Paget, S.A.; Crow, M.K.; Lockshin, M.D.; Sammaritano, L.; Devereux, R.B.; Schwartz, J.; Levine, D.M.; et al. Preclinical Carotid Atherosclerosis in Patients with Rheumatoid Arthritis. Ann. Intern. Med. 2006, 144, 249– 256, doi:10.7326/0003-4819-144-4-200602210-00006. (In English)

76. La Montagna, G.; Cacciapuoti, F.; Buono, R.; Manzella, D.; Mennillo, G.A.; Arciello, A.; Valentini, G.; Paolisso, G. Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Diabetes Vasc. Dis. Res. 2007, 4, 130–135, doi:10.3132/dvdr.2007.031. (In English)

77. Roman, M.J.; Devereux, R.B.; Schwartz, J.; Lockshin, M.D.; Paget, S.A.; Davis, A.; Crow, M.K.; Sammaritano, L.; Levine, D.M.; Shankar, B.-A.; et al. Arterial Stiffness in Chronic Inflammatory Diseases. Hypertension 2005, 46, 194–199, doi:10.1161/01.hyp.0000168055.89955.db. (In English)

78. Solomon, D.H.; Curhan, G.C.; Rimm, E.B.; Cannuscio, C.C.; Karlson, E.W. Cardiovascular risk factors in women with and without rheumatoid arthritis. Arthritis Rheum. 2004, 50, 3444–3449, doi:10.1002/art.20636. (In English)

79. Manavathongchai, S.; Bian, A.; Rho, Y.H.; Oeser, A.; Solus, J.F.; Gebretsadik, T.; Shintani, A.; Stein, C.M. Inflammation and Hypertension in Rheumatoid Arthritis. J. Rheumatol. 2013, 40, 1806–1811, doi:10.3899/jrheum.130394. (In English)

80. Ecobici, M.; Stoicescu, C. Arterial Stiffness and Hypertension–Which Comes First? MAEDICA–a J. Clin. Med. 12, 184–190. (In English)

81. Wolf, V.L.; Ryan, M.J. Autoimmune Disease-Associated Hypertension. Curr. Hypertens. Rep. 2019, 21, 1–9, doi:10.1007/s11906- 019-0914-2. (In English)

82. Shaharir, S.S.; Mustafar, R.; Mohd, R.; Said, M.S.M.; Gafor, H.A.; Said, M.S.M. Persistent hypertension in lupus nephritis and the associated risk factors. Clin. Rheumatol. 2014, 34, 93–97, doi:10.1007/s10067-014-2802-0. (In English)

83. Bruce, I.N.; Urowitz, M.B.; Gladman, D.D.; Ibañez, D.; Steiner, G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: The Toronto Risk Factor Study. Arthritis Rheum. 2003, 48, 3159–3167, doi:10.1002/art.11296. (In English)

84. Sabio, J.M.; Vargas-Hitos, J.A.; Navarrete-Navarrete, N.; Mediavilla, J.D.; Jiménez-Jáimez, J.; Díaz-Chamorro, A.; Jiménez- Alonso, J. Prevalence of and Factors Associated with Hypertension in Young and Old Women with Systemic Lupus Erythematosus. J. Rheumatol. 2011, 38, 1026–1032, doi:10.3899/jrheum.101132. (In English)

85. Ballocca, F.; D'Ascenzo, F.; Moretti, C.; Omedè, P.; Cerrato, E.; Barbero, U.; Abbate, A.; Bertero, M.T.; Biondi-Zoccai, G.; Gaita, F. Predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): A systematic review and metaanalysis. Eur. J. Prev. Cardiol. 2015, 22, 1435–1441, doi:10.1177/2047487314546826. (In English)

86. Sabio, J.M.; Vargas-Hitos, J.A.; Martínez-Bordonado, J.; Navarrete-Navarrete, N.; Díaz-Chamorro, A.; Olvera-Porcel, C.; Jiménez- Alonso, J. Cumulated organ damage is associated with arterial stiffness in women with systemic lupus erythematosus irrespective of renal function. Clin. Exp. Rheumatol. 2016, 34, 53–57. (In English)

87. Harrison, D.G. The Immune System in Hypertension. Trans. Am. Clin. Clim. Assoc. 2014, 125, 130–140. (In English)

88. Drummond, G.R.; Vinh, A.; Guzik, T.J.; Sobey, C.G. Immune mechanisms of hypertension. Nat. Rev. Immunol. 2019, 19, 517–532, doi:10.1038/s41577-019-0160-5. (In English)

89. Chen, S.; Agrawal, D.K. Dysregulation of T cell Subsets in the Pathogenesis of Hypertension. Curr. Hypertens. Rep. 2015, 17, 1– 10, doi:10.1007/s11906-014-0521-1. (In English)

90. Rodriguez-Iturbe, B.; Pons, H.; Johnson, R.J. Role of the Immune System in Hypertension. Physiol. Rev. 2017, 97, 1127–1164, doi:10.1152/physrev.00031.2016. (In English)

91. Bartoloni, E.; Alunno, A.; Santoboni, G.; Gerli, R. Beneficial cardiovascular effects of low-dose glucocorticoid therapy in inflammatory rheumatic diseases. J. Rheumatol. 2012, 39, 1758–1760, doi:10.3899/jrheum.120192. (In English)

92. Taylor, E.B.; Wolf, V.L.; Dent, E.; Ryan, M.J. Mechanisms of hypertension in autoimmune rheumatic diseases. Br. J. Pharmacol. 2019, 176, 1897–1913, doi:10.1111/bph.14604. (In English)

93. Kerola, A.; Kauppi, M.; Kerola, T.; Nieminen, T. How early in the course of rheumatoid arthritis does the excess cardiovascular risk appear? Ann. Rheum. Dis. 2012, 71, 1606–1615, doi:10.1136/annrheumdis-2012-201334. (In English)

94. Crowson, C.S.; Rollefstad, S.; Ikdahl, E.; Kitas, G.D.; Van Riel, P.; Gabriel, S.E.; Matteson, E.L.; Kvien, T.K.; Douglas, K.; Sandoo, A.; et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann. Rheum. Dis. 2018, 77, 48–54, doi:10.1136/annrheumdis-2017-211735. (In English)

95. Sarmiento-Monroy, J.C.; Amaya-Amaya, J.; Espinosa-Serna, J.S.; Herrera-Diaz, C.; Anaya, J.-M.; Rojas-Villarraga, A. Cardiovascular Disease in Rheumatoid Arthritis: A Systematic Literature Review in Latin America. Arthritis 2012, 2012, 371909, doi:10.1155/2012/371909. (In English)

96. Balagopal, P.B.; De Ferranti, S.D.; Cook, S.; Daniels, S.R.; Gidding, S.S.; Hayman, L.L.; McCrindle, B.W.; Mietus-Snyder, M.; Steinberger, J. Nontraditional Risk Factors and Biomarkers for Cardiovascular Disease: Mechanistic, Research, and Clinical Considerations for Youth. Circulation 2011, 123, 2749–2769, doi:10.1161/cir.0b013e31821c7c64. (In English)

97. Sandoo, A.; Carroll, D.; Metsios, G.S.; Kitas, G.D.; Van Zanten, J.J.V. The association between microvascular and macrovascular endothelial function in patients with rheumatoid arthritis: A cross-sectional study. Arthritis Res. Ther. 2011, 13, R99, doi:10.1186/ar3374. (In English)

98. Wibetoe, G.; Sexton, J.; Ikdahl, E.; Rollefstad, S.; Kitas, G.D.; Van Riel, P.; Gabriel, S.; Kvien, T.K.; Douglas, K.; Sandoo, A.; et al. Prediction of cardiovascular events in rheumatoid arthritis using risk age calculations: Evaluation of concordance across risk age models. Arthritis Res. 2020, 22, 90, doi:10.1186/s13075-020-02178-z. (In English)

99. Ruscitti, P.; Cipriani, P.; Masedu, F.; Romano, S.; Berardicurti, O.; Liakouli, V.; Carubbi, F.; Di Benedetto, P.; Alvaro, S.; Penco, M.; et al. Increased Cardiovascular Events and Subclinical Atherosclerosis in Rheumatoid Arthritis Patients: 1 Year Prospective Single Centre Study. PLoS ONE 2017, 12, e0170108, doi:10.1371/journal.pone.0170108. (In English)

100. Humphreys, J.H.; Warner, A.; Chipping, J.; Marshall, T.; Lunt, M.; Symmons, D.P.M.; Verstappen, S.M.M. Mortality Trends in Patients with Early Rheumatoid Arthritis Over 20 Years: Results From the Norfolk Arthritis Register. Arthritis Rheum. 2014, 66, 1296–1301, doi:10.1002/acr.22296. (In English)

101. Myasoedova, E.; Gabriel, S.E.; Matteson, E.L.; Davis, J.M.; Therneau, T.M.; Crowson, C.S. Decreased Cardiovascular Mortality in Patients with Incident Rheumatoid Arthritis (RA) in Recent Years: Dawn of a New Era in Cardiovascular Disease in RA? J. Rheumatol. 2017, 44, 732–739, doi:10.3899/jrheum.161154. (In English)

102. Chehata, J.C.; Hassell, A.B.; Clarke, S.A.; Mattey, D.L.; Jones, M.A.; Jones, P.W.; Dawes, P.T. Mortality in rheumatoid arthritis: Relationship to single and composite measures of disease activity. Rheumatology 2001, 40, 447–452, doi:10.1093/rheumatology/ 40.4.447.

103. Sarzi-Puttini, P.; Atzeni, F.; Gerli, R.; Bartoloni, E.; Doria, A.; Barskova, T.; Matucci-Cerinic, M.; Sitia, S.; Tomasoni, L.; Turiel, M. Cardiac involvement in systemic rheumatic diseases: An update. Autoimmun. Rev. 2010, 9, 849–852, doi:10.1016/j.autrev. 2010.08.002. (In English)

104. Maradit-Kremers, H.; Crowson, C.S.; Nicola, P.J.M.Z.; Ballman, K.; Jacobsen, S.; Gabriel, S.E. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: A population-based cohort study. Arthritis Rheum. 2005, 52, 402–411,doi:10.1002/art.20853. (In English)

105. Taverner, D.; Paredes, S.; Ferré, R.; Masana, L.; Castro, A.; Vallvé, J.-C. Assessment of arterial stiffness variables in patients with rheumatoid arthritis: A mediation analysis. Sci. Rep. 2019, 9, 4543, doi:10.1038/s41598-019-41069-5. (In English)

106. Awalia, A.; Satyadi, S.; Wibisono, S.; Soeroso, J. AB0296 ARTERIAL STIFFNESS IN RHEUMATOID ARTHRITIS PATIENTS: DO DISEASE ACTIVITY AND DURATION OF ILLNESS MATTER? Abstr. Accept. Publ. 2019, 78, 1608, doi:10.1136/annrheumdis- 2019-eular.3407.

107. Cem, O.; Askin, A.; Yasar, K.; Ozgul Ucar, E.; Izzet Selcuk, P.; Fulya, D.; Kubilay, S.; Huseyin, T. Clinical significance of aortic stiffness, carotid inti-ma-media thickness and serum osteoprotegerin level in rheumatoid arthritis patients. Egypt. Rheumatol. 2019, 41, 111–115.

108. Fan, C.; Zhang, Z.; Mei, Y.; Wu, C.; Shen, B. Impaired brachial artery flow-mediated dilation and increased carotid intima-media thickness in rheumatoid arthritis patients. Chin. Med J. 2012, 125, 832–837. (In English)

109. Adawi, M.; Watad, A.; Bragazzi, N.L.; Amital, H.; Saaida, G.; Sirchan, R.; Blum, A.; Golan, S.; Rizak, S.; Arnon, B. Endothelial function in rheumatoid arthritis. Qjm: Int. J. Med. 2018, 111, 243–247, doi:10.1093/qjmed/hcy010. (In English)

110. Dimitroulas, T.; Hodson, J.; Sandoo, A.; Sm-ith, J.; Kitas, G.D. Endothelial injury in rheumatoid arthritis: A crosstalk between dimethylarginines and systemic inflammation. Arthritis Res. 2017, 19, 32, doi:10.1186/s13075-017-1232-1. (In English)

111. Wong, M.; Oakley, S.P.; Young, L.; Jiang, B.Y.; Wierzbicki, A.; Panayi, G.; Chowienczyk, P.; Kirkham, B. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. Ann. Rheum. Dis. 2008, 68, 1277–1284, doi:10.1136/ard.2007.086157. (In

English)

112. González, L.A.; Toloza, S.M.; Alarcón, G.S. Impact of Race and Ethnicity in the Course and Outcome of Systemic Lupus Erythematosus. Rheum. Dis. Clin. North. Am. 2014, 40, 433–454, doi:10.1016/j.rdc.2014.04.001. (In English)

113. Ghiggeri, G.M.; D'Alessandro, M.; Bartolomeo, D.; Degl'Innocenti, M.L.; Magnasco, A.; Lugani, F.; Prunotto, M.; Bruschi, M. An Update on Antibodies to Necleosome Components as Biomarkers of Sistemic Lupus Erythematosus and of Lupus Flares. Int. J. Mol. Sci. 2019, 20, 5799, doi:10.3390/ijms20225799. (In English)

114. Mula, R.V.R.; Machiah, D.; Holland, L.; Wang, X.; Parihar, H.; Sharma, A.C.; Selvaraj, P.; Shashidharamurthy, R. Immune Complex- Induced, Nitric Oxide-Mediated Vascular Endothelial Cell Death by Phagocytes Is Prevented with Decoy FcγReceptors. PLoS ONE 2016, 11, e0153620, doi:10.1371/journal.pone.0153620. (In English)

115. Selzer, F.; Sutton-Tyrrell, K.; Fitzgerald, S.; Tracy, R.; Kuller, L.; Manzi, S. Vascular Stiffness in Women With Systemic Lupus Erythematosus. Hypertension 2001, 37, 1075–1082, doi:10.1161/01.hyp.37.4.1075. (In English)

116. Urowitz, M.B.; Bookman, A.A.; Koehler, B.E.; Gordon, D.A.; Smythe, H.A.; Ogryzlo, M.A. The bimodal mortality pattern of systemic lupus erythematosus. Am. J. Med. 1976, 60, 221–225, doi:10.1016/0002-9343(76)90431-9. (In English)

117. Coutinho, A.E.; Chapman, K.E. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol. Cell. Endocrinol. 2011, 335, 2–13, doi:10.1016/j.mce.2010.04.005. (In English)

118. van der Sluis, R.J.; Hoekstra, M. Glucocorticoids are active players and therapeutic targets in atherosclerotic cardiovascular disease. Mol. Cell. Endocrinol. 2020, 504, 110728, doi:10.1016/j.mce.2020.110728. (In English)

119. Zeller, C.B.; Appenzeller, S. Cardiovascular Disease in Systemic Lupus Erythematosus: The Role of Traditional and Lupus Related Risk Factors. Curr. Cardiol. Rev. 2008, 4, 116–122, doi:10.2174/157340308784245775. (In English)

120. Aviña-Zubieta, J.A.; To, F.; Vostretsova, K.; De Vera, M.; Sayre, E.C.; Esdaile, J.M. Risk of Myocardial Infarction and Stroke in Newly Diagnosed Systemic Lupus Erythematosus: A General Population-Based Study. Arthritis Rheum. 2017, 69, 849–856, doi:10.1002/acr.23018. (In English)

121. Svensson, C.; Eriksson, P.; Zachrisson, H.; Sjöwall, C. High-Frequency Ultrasound of Multiple Arterial Areas Reveals Increased Intima Media Thickness, Vessel Wall Appearance, and Atherosclerotic Plaques in Systemic Lupus Erythematosus. Front. Med. 2020, 7, 581336, doi:10.3389/fmed.2020.581336. (In English)

122. Ward, M.M. Premature morbidity from cardiovascular and cerebro-vascular diseases in women with systemic lupus erythematosus. Arthritis Rheum. 1999, 42, 338–346, doi:10.1002/1529-0131(199902)42:23.0.Co;2-u. (In English)

123. Schoenfeld, S.R.; Kasturi, S.; Costenbader, K.H. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: A systematic review. Semin. Arthritis Rheum. 2013, 43, 77–95, doi:10.1016/j.semarthrit.2012.12.002. (In English)

124. Kostopoulou, M.; Nikolopoulos, D.; Parodis, I.; Bertsias, G. Cardiovascular Disease in Systemic Lupus Erythematosus: Recent data on epidemiology, risk factors and prevention. Curr. Vasc. Pharmacol. 2020, 18, 1, doi:10.2174/1570161118666191227101636. (In English)

125. Kiss, E.; Soltesz, P.; Der, H.; Kocsis, Z.; Tarr, T.; Bhattoa, H.; Shoenfeld, Y.; Szegedi, G. Reduced flow-mediated vasodilation as a marker for cardiovascular complications in lupus patients. J. Autoimmun. 2006, 27, 211–217, doi:10.1016/j.jaut.2006.09.008. (In English)

126. Mak, A.; Kow, N.Y.; Schwarz, H.; Gong, L.; Tay, S.H.; Ling, L.H. Endothelial dysfunction in systemic lupus erythematosus–a case-control study and an updated meta-analysis and meta-regression. Sci. Rep. 2017, 7, 1–10, doi:10.1038/s41598-017-07574-1. (In English)

127. Sacre, K.; Escoubet, B.; Pasquet, B.; Chauveheid, M.-P.; Zennaro, M.-C.; Tubach, F.; Papo, T. Increased Arterial Stiffness in Systemic Lupus Erythematosus (SLE) Patients at Low Risk for Cardiovascular Disease: A Cross-Sectional Controlled Study. PLoS ONE 2014, 9, e94511, doi:10.1371/journal.pone.0094511. (In English)

128. Ding, F.M.; Li, M.; Yang, X.; Ye, Y.; Kang, L.; Pang, H.; Wang, Q.; Xu, D.; Zeng, X.; Zhang, S. Accelerated Age-Related Arterial Stiffness in Systemic Lupus Erythematosus Patients. JCR: J. Clin. Rheumatol. 2016, 22, 426–433, doi:10.1097/rhu.0000000000000432. (In English)

129. Mendoza-Pinto, C.; Rojas-Villarraga, A.; Molano-González, N.; García-Carrasco, M.; Munguía-Realpozo, P.; Etchegaray-Morales, I.; Morales-Sánchez, H.; Berra-Romani, R.; Cervera, R. Endothelial dysfunction and arterial stiffness in patients with systemic lupus erythematosus: A systematic review and meta-analysis. Atherosclerosis 2020, 297, 55–63, doi:10.1016/j.atherosclerosis. 2020.01.028. (In English)

130. Thompson, T.; Sutton-Tyrrell, K.; Wildman, R.P.; Kao, A.; Fitzgerald, S.G.; Shook, B.; Tracy, R.P.; Kuller, L.H.; Brockwell, S.; Manzi, S. Progression of carotid intima-media thickness and plaque in women with systemic lupus erythematosus. Arthritis Rheum. 2008, 58, 835–842, doi:10.1002/art.23196. (In English)

131. Hayashi, T. Dysfunction of Lacrimal and Salivary Glands in Sjögren's Syndrome: Nonimmunologic Injury in Preinflammatory Phase and Mouse Model. J. Biomed. Biotechnol. 2011, 2011, 1–15, doi:10.1155/2011/407031. (In English)

132. Fauchais, A.-L.; Ouattara, B.; Gondran, G.; Lalloué, F.; Petit, D.; Ly, K.H.; Lambert, M.; Launay, D.; Loustaud-Ratti, V.; Bezanahari, H.; et al. Articular manifestations in primary Sjogren's syndrome: Clinical significance and prognosis of 188 patients. Rheumatology 2010, 49, 1164–1172, doi:10.1093/rheumatology/keq047. (In English)

133. Yong, W.C.; Sanguankeo, A.; Upala, S. Association between primary Sjogren's syndrome, arterial stiffness, and subclinical atherosclerosis: A systematic review and meta-analysis. Clin. Rheumatol. 2019, 38, 447–455, doi:10.1007/s10067-018-4265-1. (In English)

134. Demirci, M.S.; Karabulut, G.; Gungor, O.; Celtik, A.; Ok, E.; Kabasakal, Y. Is There an Increased Arterial Stiffness in Patients with Primary Sjögren's Syndrome? Intern. Med. 2016, 55, 455–459, doi:10.2169/internalmedicine.55.3472. (In English)

135. Ramos-Casals, M.; Tzioufas, A.G.; Font, J. Primary Sjogren's syndrome: New clinical and therapeutic concepts. Ann. Rheum. Dis. 2004, 64, 347–354, doi:10.1136/ard.2004.025676. (In English)

136. Chiu, Y.-H.; Chung, C.-H.; Lin, K.-T.; Lin, C.-S.; Chen, J.-H.; Chen, H.-C.; Huang, R.-Y.; Wu, C.-T.; Liu, F.-C.; Chien, W.-C. Predictable biomarkers of developing lymphoma in patients with Sjögren syndrome: A nationwide population-based cohort study. Oncotarget 2017, 8, 50098–50108, doi:10.18632/oncotarget.15100. (In English)

137. Verma, S.; Anderson, T.J. Fundamentals of Endothelial Function for the Clinical Cardiologist. Circulation 2002, 105, 546–549, doi:10.1161/hc0502.104540. (In English)

138. Pyke, K.E.; Tschakovsky, M.E.; Bandi, E.; Bernareggi, A.; Grandolfo, M.; Mozzetta, C.; Augusti-Tocco, G.; Ruzzier, F.; Lorenzon, P. The relationship between shear stress and flow-mediated dilatation: Implications for the assessment of endothelial function. J. Physiol. 2005, 568, 357–369, doi:10.1113/jphysiol.2005.089755. (In English)

139. Liao, J.K. Linking endothelial dysfunction with endothelial cell activation. J. Clin. Investig. 2013, 123, 540–541, doi:10.1172/jci66843. (In English)

140. Böger, R.H. Asymmetric Dimethylarginine, an Endogenous Inhibitor of Nitric Oxide Synthase, Explains the “L-Arginine Paradox” and Acts as a Novel Cardiovascular Risk Factor. J. Nutr. 2004, 134, 2842S–2847S, doi:10.1093/jn/134.10.2842s. (In English)

141. Vanholder, R.; De Smet, R.; Glorieux, G.; Argilés, A.; Baurmeister, U.; Brunet, P.; Clark, W.; Cohen, G.; De Deyn, P.P.; Deppisch, R.; et al. Review on uremic toxins: Classification, concentration, and interindividual variability. Kidney Int. 2003, 63, 1934–1943, doi:10.1046/j.1523-1755.2003.00924.x. (In English)

142. Giannotti, G.; Landmesser, U. Endothelial Dysfunction as an Early Sign of Atherosclerosis. Herz 2007, 32, 568–572, doi:10.1007/s00059-007-3073-1. (In English)

143. Nkeh-Chungag, B.N.; Goswami, N.; Engwa, G.A.; Sewani-Rusike, C.R.; Mbombela, V.; Webster, I.; de Boever, P.; Kessler, H.H.; Stelzl, E.; Strijdom, H. Relationship between endothelial function, an-tiretroviral treatment and cardiovascular risk factors in HIV patients of African descent in South africa: A cross-sectional study. J. Clin. Med. 2021, 10, 392.

144. Goswami, N.; Fredriksen, P.M.; Lundin, K.E.A.; Agu, C.; Elias, S.O.; Motaung, K.S.; Brix, B.; Cvirn, G.; Sourij, H.; Stelzl, E.; et al. COVID-19 and its effects on endothelium in HIV-

positive patients in sub-Saharan Africa: Cardiometabolic risk, thrombosis and vascular function (ENDOCOVID STUDY). BMC Infect. Dis. 2021, 21, 1–11, doi:10.1186/s12879-021-06426-8.

145. Leone, A.; Moncada, S.; Vallance, P.; Calver, A.; Collier, J. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet 1992, 339, 572–575, doi:10.1016/0140-6736(92)90865-z. (In English)

146. Xu, H.; Jiang, J.; Chen, W.; Li, W.; Chen, Z. Vascular Macrophages in Atherosclerosis. J. Immunol. Res. 2019, 2019, 1–14, doi:10.1155/2019/4354786. (In English)

147. Itabe, H.; Obama, T.; Kato, R. The Dynamics of Oxidized LDL during Atherogenesis. J. Lipids 2011, 2011, 1–9,doi:10.1155/2011/418313. (In English)

148. Shimoni, S.; Bar, I.; Zilberman, L.; George, J. Autoantibodies to Oxidized Low-Density Lipoprotein in Patients with Aortic Regurgitation: Association with Aortic Diameter Size. Cardiology 2014, 128, 54–61, doi:10.1159/000357835. (In English)

149. Shoenfeld, Y.; Wu, R.; Dearing, L.D.; Matsuura, E. Are Anti–Oxidized Low-Density Lipoprotein Antibodies Pathogenic or Protective? Circulation 2004, 110, 2552–2558, doi:10.1161/01.cir.0000143225.07377.ea. (In English)

150. Van den Berg, V.J.; Vroegindewey, M.M.; Kardys, I.; Boersma, E.; Haskard, D.; Hartley, A.; Khamis, R. Anti-Oxidized LDL Antibodies and Coronary Artery Disease: A Systematic Review. Antioxidants 2019, 8, 484, doi:10.3390/antiox8100484. (In English)

151. Charach, G.; Rabinovich, A.; Argov, O.; Weintraub, M.; Charach, L.; Ayzenberg, O.; George., J. Anti-oxidized low-density lipoprotein antibodies in chronic heart failure. World J. Cardiol. 2012, 4, 302–308, doi:10.4330/wjc.v4.i11.302. (In English)

152. Hansson, G.K. Inflammation, Atherosclerosis, and Coronary Artery Disease. New Engl. J. Med. 2005, 352, 1685–1695, doi:10.1056/nejmra043430. (In English)

153. Shimokama, T.; Haraoka, S.; Watanabe, T. Immunohistochemical and ultrastructural demon-stration of the lymphocyte-macrophage interaction in human aortic intima. Mod. Pathol. 1999, 4, 101–107. (In English)

154. Boyle, J.J. Association of coronary plaque rupture and atherosclerotic in-flammation. J. Pathol. 1997, 181, 93–99, doi:10.1002/(sici)1096-9896(199701)181:13.0.Co;2-h. (In English)

155. Lee, W.H.; Ko, Y.H.; Kim, D.I.; Lee, B.B.; Park, J.E. Prevalence of Foam Cells and Helper–T cells in Atherosclerotic Plaques of Korean Patients with Carotid Atheroma. Korean J. Intern. Med. 2000, 15, 117–121, doi:10.3904/kjim.2000.15.2.117. (In English)

156. O'Leary, D.H.; Polak, J.F.; Wolfson, S.K.; Bond, M.G.; Bommer, W.; Sheth, S.; Psaty, B.M.; Sharrett, A.R.; Manolio, T.A. Use of

sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. CHS Collaborative Research Group. Stroke 1991, 22, 1155–1163, doi:10.1161/01.str.22.9.1155. (In English)

157. Letswalo, B.P.; Schmid-Zalaudek, K.; Brix, B.; Matjuda, E.N.; Klosz, F.; Obernhumer, N.; Gaisl, M.; Engwa, G.A.; Sewani-Rusike, C.; Fredriksen, P.M.; et al. Cardiometabolic risk factors and early indicators of vascular dysfunction: A cross-sectional cohort study in South African adolescents. BMJ Open 2021, 11, e042955, doi:10.1136/bmjopen-2020-042955.

158. Matjuda, E.; Engwa, G.; Anye, S.; Nkeh-Chungag, B.; Goswami, N. Cardiovascular Risk Factors and Their Relationship with Vascular Dysfunction in South African Children of African Ancestry. J. Clin. Med. 2021, 10, 354, doi:10.3390/jcm10020354.

159. Dorogovtsev, V.; Yankevich, D.; Goswami, N. Effects of an Innovative Head-Up Tilt Protocol on Blood Pressure and Arterial Stiffness Changes. J. Clin. Med. 2021, 10, 1198, doi:10.3390/jcm10061198.

160. Brix, B.; Apich, G.; Ure, C.; Roessler, A.; Goswami, N. Physical therapy affects endothelial function in lymphedema patients. Lymphology 2020, 53, 109–117.

161. Strijdom, H.; De Boever, P.; Nawrot, T.; Goswami, N. HIV/AIDS: Emerging threat to cardiovascular health in sub-Saharan Africa. South. Afr. Med. J. 2016, 106, 537, doi:10.7196/samj.2016.v106i6.10721.

162. Vaes, A.W.; Spruit, M.A.; Theunis, J.; Goswami, N.; Vanfleteren, L.E.; Franssen, F.M.; Wouters, E.F.; De Boever, P. Endothelial function in patients with chronic obstructive

pulmonary disease: A systematic review of studies using flow mediated dilatation. Expert Rev. Respir. Med. 2017, 11, 1–11, doi:10.1080/17476348.2017.1389277.

163. Marincowitz, C.; Webster, I.; Westcott, C.; Goswami, N.; De Boever, P.; Seidel, G.; Strijdom, H. Vascular health assessment with flow-mediated dilatation and retinal image analysis: A pilot study in an adult population from Cape Town. Cardiovasc J. Afr 2020, 31, 1–8.

164. Louwies, T.; Panis, L.I.; Alders, T.; Bonné, K.; Goswami, N.; Nawrot, T.S.; Dendale, P.; de Boever, P. Microvascular reactivity in rehabilitating car-diac patients based on measurements of retinal blood vessel diameters. Microvasc. Res. 2019, 124, 25–29.

165. Marincowitz, C.; Genis, A.; Goswami, N.; De Boever, P.; Nawrot, T.; Strijdom, H. Vascular endothelial dysfunction in the wake of HIV and ART. FEBS J. 2019, 286, 1256–1270, doi:10.1111/febs.14657.

166. Strijdom, H.; De Boever, P.; Walzl, G.; Essop, M.F.; Nawrot, T.S.; Webster, I.; Westcott, C.; Mashele, N.; Everson, F.; Malherbe, S.T.; et al. Cardiovascular risk and endothelial function in people living with HIV/AIDS: Design of the multi-site, longitudinal EndoAfrica study in the Western Cape Province of South Africa. BMC Infect. Dis. 2017, 17, 41, doi:10.1186/s12879-016-2158-y.

167. Harris, R.A.; Nishiyama, S.K.; Wray, D.W.; Richardson, R.S. Ultrasound Assessment of Flow-Mediated Dilation. Hypertension 2010, 55, 1075–1085, doi:10.1161/hypertensionaha.110.150821. (In English)

168. Bots, M.L.; Westerink, J.H.D.M.; Rabelink, T.; De Koning, E.J. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: Effects of technical aspects of the FMD measurement on the FMD response. Eur. Heart J. 2004, 26, 363–368, doi:10.1093/eurheartj/ehi017. (In English)

169. Celermajer, D.; Sorensen, K.; Gooch, V.; Spiegelhalter, D.; Miller, O.; Sullivan, I.; Lloyd, J.; Deanfield, J. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992, 340, 1111–1115, doi:10.1016/0140- 6736(92)93147-f. (In English)

170. Asmar, R.; Benetos, A.; Topouchian, J.; Laurent, P.; Pannier, B.; Brisac, A.-M.; Target, R.; Levy, B.I. Assessment of Arterial Distensibility by Automatic Pulse Wave Velocity Measurement. Hypertension 1995, 26, 485–490, doi:10.1161/01.hyp.26.3.485. (In English)

171. Kis, E.; Cseprekál, O.; Kerti, A.; Salvi, P.; Benetos, A.; Tisler, A.; Szabó, A.; Tulassay, T.; Reusz, G.S. Measurement of pulse wave velocity in children and young adults: A comparative study using three different devices. Hypertens. Res. 2011, 34, 1197–1202, doi:10.1038/hr.2011.103. (In English)

172. Campuzano, R.; Moya, J.L.; García-Lledó, A.; Tomas, J.P.; Ruiz, S.; Megías, A.; Balaguer, J.; Asín, E. Endothelial dysfunction, intima–media thickness and coronary reserve in relation to risk factors and Framingham score in patients without clinical atherosclerosis. J. Hypertens. 2006, 24, 1581–1588, doi:10.1097/01.hjh.0000239294.17636.27. (In English)

173. Paul, J.; Shaw, K.; Dasgupta, S.; Ghosh, M.K. Measurement of intima media thickness of carotid artery by B-mode ultrasound in healthy people of India and Bangladesh, and relation of age and sex with carotid artery intima media thickness: An observational study. J. Cardiovasc. Dis. Res. 2012, 3, 128–131, doi:10.4103/0975-3583.95367. (In English)

174. Wang, Y.L.; Hui, Y.N.; Guo, B.; Ma, J.X. Strengthening tight junctions of retinal microvascular endothelial cells by pericytes under normoxia and hypoxia involving angiopoietin-1 signal way. Eye 2007, 21, 1501–1510, doi:10.1038/sj.eye.6702716. (In English)

175. Hughes, A.D.; Wong, T.Y.; Witt, N.; Evans, R.; Thom, S.A.M.; Klein, B.E.; Chaturvedi, N.; Klein, R. Determinants of retinal microvascular architecture in normal subjects. Microcirculation 2009, 16, 159–166, doi:10.1080/10739680802353868. (In English)

176. Wong, T.Y.; Klein, R.; Klein, B.E.K.; Meuer, S.M.; Hubbard, L.D. Retinal Vessel Diameters and Their Associations with Age and Blood Pressure. Investig. Opthalmology Vis. Sci. 2003, 44, 4644–4650, 4644–4650, doi:10.1167/iovs.03-0079. (In English)

177. Kawasaki, R.; Tielsch, J.; Wang, J.J.; Wong, T.Y.; Mitchell, P.; Tano, Y.; Tominaga, M.; Oizumi, T.; Daimon, M.; Kato, T.; et al. The metabolic syndrome and retinal microvascular signs in a Japanese population: The Funagata study. Br. J. Ophthalmol. 2007, 92, 161–166, doi:10.1136/bjo.2007.127449. (In English)

178. Goswami, N.; Gorur, P.; Pilsl, U.; Anyaehie, B.; Green, D.A.; Bondarenko, O.; Roessler, A.; Hinghofer-Szalkay, H.G. Effect of Orthostasis on Endothelial Function: A Gender Comparative Study. PLoS ONE 2013, 8, e71655, doi:10.1371/journal. pone.0071655. (In English)

179. Van Lenten, B.J.; Hama, S.Y.; De Beer, F.C.; Stafforini, D.M.; McIntyre, T.M.; Prescott, S.M.; La Du, B.N.; Fogelman, A.M.; Navab, M. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J. Clin. Investig. 1995, 96, 2758–2767, doi:10.1172/jci118345. (In English)

180. Retamozo, S.; Gheitasi, H.; Quartuccio, L.; Kostov, B.; Corazza, L.; Bové, A.; Almirall, A.S.; Gandía, M.; Ramos-Casals, M.; De Vita, S.; et al. Cryoglobulinaemic vasculitis at diagnosis predicts mortality in primary Sjögren syndrome: Analysis of 515 patients. Rheumatology 2016, 55, 1443–1451, doi:10.1093/rheumatology/kew194. (In English)

181. Funke, A.; Danowski, A.; de Andrade, D.C.O.; Rêgo, J.; Levy, R.A. A importância de reconhecer a síndrome antifosfolípide na medicina vascular. J. Vasc. Bras. 2017, 16, 140–149.

182. Ristagno, G.; Fumagalli, F.; Bottazzi, B.; Mantovani, A.; Olivari, D.; Novelli, D.; Latini, R. Pentraxin 3 in Cardiovascular Disease. Front. Immunol. 2019, 10, 823, doi:10.3389/fimmu.2019.00823.

183. Kali, A.; Shetty, K.R. Endocan: A novel circulating proteoglycan. Indian J. Pharmacol. 2014, 46, 579–583, doi:10.4103/0253- 7613.144891. (In English)

184. Balta, S.; Mikhailidis, D.P.; Demirkol, S.; Ozturk, C.; Celik, T.; Iyisoy, A. Endocan: A novel inflammatory indicator in cardiovascular disease? Atherosclerosis 2015, 243, 339–343, doi:10.1016/j.atherosclerosis.2015.09.030.

185. Panoulas, V.F.; Metsios, G.S.; Pace, A.V.; John, H.; Treharne, G.; Banks, M.J.; Kitas, G. Hypertension in rheumatoid arthritis. Rheumatology 2008, 47, 1286–1298. [CrossRef]

186. Karvounaris, S.; Sidiropoulos, P.; Papadakis, J.; Spanakis, E.K.; Bertsias, G.K.; Kritikos, H.D.; Ganotakis, E.; Boumpas, D.T. Metabolic syndrome is common among middle-to-older

aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: A retrospective, cross-sectional, controlled, study. Ann. Rheum. Dis. 2006, 66, 28–33. [CrossRef]

187. Solomon, D.H.; Curhan, G.C.; Rimm, E.B.; Cannuscio, C.C.; Karlson, E.W. Cardiovascular risk factors in women with and without rheumatoid arthritis. Arthritis Rheum. 2004, 50, 3444–3449. [CrossRef] [PubMed]

188. Wolf, V.L.; Ryan, M.J. Autoimmune Disease-Associated Hypertension. Curr. Hypertens. Rep. 2019, 21, 10. [CrossRef] [PubMed]

189. Morrison, A.; Ramey, D.R.; Van Adelsberg, J.; Watson, D.J. Systematic review of trials of the effect of continued use of oral non-selective NSAIDs on blood pressure and hypertension. Curr. Med. Res. Opin. 2007, 23, 2395–2404. [CrossRef] [PubMed]

190. Panoulas, V.F.; Douglas, K.M.J.; Stavropoulos-Kalinoglou, A.; Metsios, G.S.; Nightingale, P.; Kita, M.D.; Elisaf, M.; Kitas, G. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology 2008, 47, 72–75. [CrossRef]

191. Barbieri, M.; Ferrucci, L.; Corsi, A.M.; Macchi, C.; Lauretani, F.; Bonafè, M.; Olivieri, F.; Giovagnetti, S.; Franceschi, C.; Paolisso, G. Is chronic inflammation a determinant of blood pressure in the elderly? Am. J. Hypertens. 2003, 16, 537–543. [CrossRef]

192. Steyers, C.M., III; Miller, J.F., Jr. Endothelial Dysfunction in Chronic Inflammatory Diseases. Int. J. Mol. Sci. 2014, 15, 11324–11349. [CrossRef]

193. Xavier, C.; Vera, B. Chronic Inflammatory Diseases and Endothelial Dysfunction. Aging Dis. 2016, 7, 81–89. [CrossRef]

194. Dharmashankar, K.; Widlansky, M.E. Vascular Endothelial Function and Hypertension: Insights and Directions. Curr. Hypertens. Rep. 2010, 12, 448–455. [CrossRef]

195. Konukoglu, D.; Uzun, H. Endothelial Dysfunction and Hypertension. In Hypertension: From Basic Research to Clinical Practice; Islam, M.S., Ed.; Springer International Publishing: Cham, Switzerland, 2017; pp. 511–540.

196. Roman, M.J.; Moeller, E.; Davis, A.; Paget, S.A.; Crow, M.K.; Lockshin, M.D.; Sammaritano, L.; Devereux, R.B.; Schwartz, J.; Levine, D.M.; et al. Preclinical Carotid Atherosclerosis in Patients with Rheumatoid Arthritis. Ann. Intern. Med. 2006, 144, 249–256. [CrossRef]

197. Han, C.; Robinson, D.W.; Hackett, M.V.; Paramore, L.C.; Fraeman, K.H.; Bala, M.V. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J. Rheumatol. 2006, 33, 2167–2172. [PubMed]

198. Dougados, M.; Soubrier, M.; Antunez, A.; Balint, P.; Balsa, A.; Buch, M.; Casado, G.; Detert, J.; Elzorkany, B.; Emery, P.; et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: Results of an international, cross-sectional study (COMORA). Ann. Rheum. Dis. 2014, 73, 62–68. [CrossRef]

199. Roman, M.J.; Devereux, R.B.; Schwartz, J.; Lockshin, M.D.; Paget, S.A.; Davis, A.; Crow, M.K.; Sammaritano, L.; Levine, D.M.; Shankar, B.-A.; et al. Arterial Stiffness in Chronic Inflammatory Diseases. Hypertension 2005, 46, 194–199. [CrossRef]

200. Chung, C.P.; Oeser, A.; Solus, J.F.; Avalos, I.; Gebretsadik, T.; Shintani, A.; Raggi, P.; Sokka, T.; Pincus, T.; Stein, C.M. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis 2008, 196, 756–763. [CrossRef] [PubMed]

201. Panoulas, V.F.; Metsios, G.S.; Pace, A.V.; John, H.; Treharne, G.; Banks, M.J.; Kitas, G. Hypertension in rheumatoid arthritis. Rheumatology 2008, 47, 1286–1298. [CrossRef]

202. Del Rincón, I.D.; Williams, K.; Stern, M.P.; Freeman, G.L.; Escalante, A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001, 44, 2737–2745. [CrossRef]

203. Dessein, P.H.; Joffe, B.; Singh, S. Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. Arthritis Res. Ther. 2005, 7, R634–R643. [CrossRef] [PubMed]

204. Rossi, R.; Chiurlia, E.; Nuzzo, A.; Cioni, E.; Origliani, G.; Modena, M.G. Flow-mediated vasodilation and the risk of developing hypertension in healthy postmenopausal women. J. Am. Coll. Cardiol. 2004, 44, 1636–1640. [CrossRef]

205. Shimbo, D.; Muntner, P.; Mann, D.; Viera, A.J.; Homma, S.; Polak, J.F.; Barr, R.G.; Herrington, D.; Shea, S. Endothelial Dysfunction and the Risk of Hypertension: The multi-ethnic study of atherosclerosis. Hypertension 2010, 55, 1210–1216. [CrossRef] [PubMed]

206. Taddei, S.; Bruno, R.M. Endothelial dysfunction in hypertension: Achievements and open questions. J. Hypertens. 2016, 34, 8. [CrossRef]

207. Mäki-Petäjä, K.M.; Hall, F.C.; Booth, A.D.; Wallace, S.M.; Yasmin; Bearcroft, P.W.; Harish, S.; Furlong, A.; McEniery, C.M.; Brown, J.; et al. Rheumatoid Arthritis Is Associated with Increased Aortic Pulse-Wave Velocity, Which Is Reduced by Anti–Tumor Necrosis Factor-Therapy. Circulation 2006, 114, 1185–1192. [CrossRef] [PubMed]

208. Kocabay, G.; Hasdemir, H.; Yildiz, M. Evaluation of pulse wave velocity in systemic lupus erythematosus, rheumatoid arthritis and Behçet's disease. J. Cardiol. 2012, 59, 72–77. [CrossRef]

209. Wang, P.; Mao, Y.-M.; Zhao, C.-N.; Liu, L.-N.; Li, X.-M.; Li, X.-P.; Pan, H.-F. Increased Pulse Wave Velocity in Systemic Lupus Erythematosus: A Meta-Analysis. Angiology 2017, 69, 228–235. [CrossRef]

210. Awalia, A.; Satyadi, S.; Wibisono, S.; Soeroso, J. AB0296 Arterial stiffness in rheumatoid arthritis patients: Do disease activity and duration of illness matter? Ann. Rheum. Dis. 2019, 78, 1608. [CrossRef]

211. Dzie˙za-Grudnik, A.; Sulicka, J.; Strach, M.; Siga, O.; Klimek, E.; Korkosz, M.; Grodzicki, T. Arterial stiffness is not increased in patients with short duration rheumatoid arthritis and ankylosing spondylitis. Blood Press. 2016, 26, 115–121. [CrossRef] [PubMed]

212. Sabio, J.M.; Sánchez-Berná, I.; Martínez-Bordonado, J.; Vargas-Hitos, J.A.; Navarrete-Navarrete, N.; Ruiz, M.E.; Jiménez-Alonso, J. Prevalence of and Factors Associated with

Increased Arterial Stiffness in Patients with Primary Sjögren's Syndrome. Arthritis Care Res. 2014, 67, 554–562. [CrossRef] [PubMed]

213. Atzeni, F.; Sarzi-Puttini, P.; Gianturco, L.; Signorello, M.C.; Boccassini, L.; Ricci, C.; Colonna, V.D.G.; Turiel, M. New Parameters for Identifying Subclinical Atherosclerosis in Patients with Primary SjöGren's Syndrome: A Pilot Study. Clin. Exp. Rheumatol. 2014, 32, 361–368. [CrossRef] [PubMed]

214. Yong, W.C.; Sanguankeo, A.; Upala, S. Association between primary Sjogren's syndrome, arterial stiffness, and subclinical atherosclerosis: A systematic review and meta-analysis. Clin. Rheumatol. 2019, 38, 447–455. [CrossRef]

215. Erre, G.L.; Mangoni, A.A.; Castagna, F.; Paliogiannis, P.; Carru, C.; Passiu, G.; Zinellu, A. Meta-Analysis of Asymmetric Dimethylarginine Concentrations in Rheumatic Diseases. Sci. Rep. 2019, 9, 5426. [CrossRef]

216. Okada, M.; Wong, T.Y.; Kawasaki, R.; Baharuddin, N.B.; Colville, D.; Buchanan, R.; Savige, J. Retinal Venular Calibre is Increased in Patients with Autoimmune Rheumatic Disease: A Case-Control Study. Curr. Eye Res. 2012, 38, 685–690. [CrossRef]

217. Van Doornum, S.; Strickland, G.; Kawasaki, R.; Xie, J.; Wicks, I.P.; Hodgson, L.A.B.; Wong, T.Y. Retinal vascular calibre is altered in patients with rheumatoid arthritis: A biomarker of disease activity and cardiovascular risk? Rheumatology 2011, 50, 939–943.[CrossRef]

218. Dervenis, N.; Coleman, A.L.; Harris, A.; Wilson, M.R.; Yu, F.; Anastasopoulos, E.; Founti, P.; Pappas, T.; Kilintzis, V.; Topouzis, F. Factors Associated with Retinal Vessel Diameters in an Elderly Population: The Thessaloniki Eye Study. Investig. Opthalmol. Vis. Sci. 2019, 60, 2208–2217. [CrossRef]

219. Vaes, A.W.; Spruit, M.A.; Theunis, J.; Goswami, N.; Vanfleteren, L.E.; Franssen, F.M.; Wouters, E.F.; De Boever, P. Endothelial function in patients with chronic obstructive pulmonary disease: A systematic review of studies using flow mediated dilatation. Expert Rev. Respir. Med. 2017, 11, 1021–1031. [CrossRef] [PubMed]

220. Hedar, A.M.; Stradner, M.H.; Roessler, A.; Goswami, N. Autoimmune Rheumatic Diseases and Vascular Function: The Concept of Autoimmune Atherosclerosis. J. Clin. Med. 2021, 10, 4427. https://doi.org/10.3390/jcm10194427.

221. Mahdy, A.; Stradner, M.; Roessler, A.; Brix, B.; Lackner, A.; Salon, A.; Goswami, N. A Pilot Study: Hypertension, Endothelial Dysfunction and Retinal Microvasculature in Rheumatic Autoimmune Diseases. J. Clin. Med. 2021, 10, 4067. https://doi.org/10.3390/jcm10184067.

8. Supplemental tables

Table 1: shows the some papers that discuss the relationship between the rheumatic diseases and function of the endothelium

Author(s)	**Type of research**	**Measurements used**	**Result of the study**	**Comments**
Kerola, et al.,[93]	Review article	Study the outcome of using drugs against inflammation and their effect on endothelial dysfunction using flow-mediated dilation and atheromatous plaque in RA patients through detection of carotid intima-	1. There are good results in endothelial function after using anti-inflammatory drugs for 6-12 month 2. Atheromatous plaque and increased thickness of carotid intima-	The non-traditional risk factors have a role in atherosclerosis in RA patients and need to control these factors for a better outcome as regard cardiovascular morbidity

		media thickness	media may be presented before the diagnosis of RA and in the first year after diagnosis	
Crowson et al. [94]	Review article	Follow up 5638 patients not complained of cardiovascular symptoms and not diagnosed to have cardiac diseases in RA and for early diagnosis of heart diseases	-70% of diagnosed cardiovascular events were related to traditional risk factors and the remaining 30% most probably related to RA	The most important traditional risk factors affecting the cardiovascular system in RA patients are smoking and hypertension
Ruscitti et al., [99]	Prospective cohort study have been done on 347 rheumatoid patients without cardiovascular signs to follow up in one year	The endpoint of the study to detect after follow up 12 months an atheromatous plaque or increase in intima-media thickness of the carotid artery	The result of the study showed an increased number of RA patients having atheromatous plaque or increased carotid intima-media	Premature atherosclerosis in RA patients is due to a combination of traditional and nontraditional risk factors

			thickness after one year of follow up	
Maradit-Kremers et al., [104]	Long follow up of 603 patients with RA and age-matched 603 controls group, all the life till death	Follow up rheumatoid patients and control to pick up cardiac diseases (acute coronary syndrome) and sudden cardiac death	Rheumatoid arthritis patients had twice the chance to develop myocardial infarction without symptoms or can develop sudden cardiac death but interestingly not complain of chest pain(angina pectoris) in comparison to normal population throw-out their life	The concept of traditional versus non-traditional risk factors in premature atherosclerosis, the result that common traditional risk(Framingham risk factor) alone couldn't give explanations to the high number of atherosclerosis patients diagnosed with rheumatoid arthritis
Fan, et al., [108]	Cross-section study with 102 patients with	By ultrasound detection of Brachial artery	Results showed endothelial dysfunction	No significant correlation between

	RA compared to 46 healthy control group	FMD(endothelial dysfunction), carotid plaque, and carotid intima-media thickness	and atherosclerosis in the RA group represented by a decrease in FMD results in the rheumatoid group as a comparison to controls. Increased thickness of intima-media in carotid arteries	endothelial dysfunction and increased thickness of intima in RA patients
Adawi et al.,[109]	A case-control study including forty-fore patients diagnosed as RA in comparison to the normal population	Ultrasound detection of flow-mediated dilation in the cubital fossa to detect endothelium dysfunction of brachial artery	Results mentioned that about percentage 85% of the RA patients had premature atherosclerosis in different degrees	Early screening to detect dysfunction of the endothelial and premature atherosclerosis in RA was an important step to avoid cardiovascular diseases and complication

Kiss et al., [125]	Cross-section study including sixty-one SLE patients and twenty-six controls group	To measure FMD and CIMT by an ultrasound device	There was a big difference between the diseased group and the control group: FMD reading was lower in SLE than control while CIMT was increased in SLE	Early screening of SLE patients for endothelial dysfunction and premature atherosclerosis
Mak, et al.,[126]	Big cohort consisting of case study versus-control with seventy-one lupus patients and seventy-one normal people and meta-analysis of twenty-five small (case controls) studies including (1313) patients	Detection of Endothelial dysfunction using ultrasound to measure FMD	FMD reading in SLE patients was decreased as compared to healthy controls	It was shown that diabetes mellitus, renal diseases, and hypertension predispose to the development of atheroma in lupus patients

	diagnosed with lupus and 1012 normal population			
Sacre et al., [127]	The study included forty-one lupus patients and thirty-five healthy controls in a cross-sectional study	Carotid-femoral pulse wave velocity to measure arterial stiffness through detection of the speed of wave transmission within the vessels wall	Study results illustrated that there were statistical differences in arterial stiffness between the lupus group and the healthy control group	corticosteroid as an example of non-traditional risk and hypertension as traditional risk, both of them have a greater effect on developing arterial rigidity and atherosclerosis
Thompson et al., [130]	217 female lupus patients followed in the clinic	Zero-point and regular measurement by ultrasound of carotid artery to detect atheromatous plaque of carotid artery and CIMT	High incidence of premature atherosclerosis in SLE patients	It is a combination of traditional and non-traditional risk factors for the development of premature atherosclerosis
Yong, et al.,	Meta-analysis	Using ultrasound	The results	The primary

[133]	and Systematic review including eight studies with 767 patients diagnosed as PSS to detect early endothelial dysfunction, arterial rigidity, and, atheromatous plaque	device to detect carotid intima-media thickness and arterial stiffness using PWV in PSS patients	showed that PSS patients have increased arterial stiffness as detected by pulse wave velocity measurements and increased thickness of the carotid artery in comparison to the normal population	Sjögren's syndrome group of patients developed a moderate degree of arterial stiffness and premature atherosclerosis. We need more research to explore the relationship between risk factors and premature atherosclerosis in PSS
Sezis Demirci, et al., [134]	A case-control study compared 68 healthy controls to 75 PSS patients as regard arterial stiffness in	Detection of carotid-femoral arterial wall stiffness using pulse wave velocity	Results showed that the speed of pulse wave through the artery in PSS patients was high in comparison to healthy controls	The cause of arterial stiffness in PSS patients is most probably due to conventional traditional risk factors hypertension, and hyperlipidemia in addition to

				steroidal usage not due to chronic inflammation characterizes the disease

Table2. Showing general and specific data for the study participants groups. Data were shown in form of mean ± Standard deviation. (in some results median and range).

Variable	**Control** (n=10; 8 females)	**RA** (n=10;8 females)	**PSS** (n=10;10 females)
Age	Mean 50 ±9Y	Mean 55.3 ±7Y	Mean 52.2 ±8Y
Smoking	3 Smoker 7 Non	1 Smoker 9 Non	10 Non
Weight	Median 72.5 kg (60-105)	Median 79kg (57-140)	Median 57.5kg (49-145)
Disease duration		Median 12(5-43)	Median 5.5(0.5-15)
S. creatinine	Mean 0,79 mg/dl	Mean 0,82 mg/dl	Mean 0,78 mg/dl
SBP	128±10	148±16	135±16
DBP	67±5	77±8	72±8
MBP	87±7	101±10	93±10
ADMA	0,38µmol/l ±0.05	0,45µmol/l ± 0.06	0,43µmol/l ± 0.06
PWV	Mean 8.69m/s ± 1.78	Mean 10.2m/s ± 2.31	Mean 8.74m/s ± 1.64

Table 3: statistical differences between diseases group and control group, RA and PSS as regard blood pressure, PWV, and ADMA. All the results as compared to the control group

variant	RA	PSS	RA+PSS
SBP	0.007	0.340	0.023
DBP	0.01	0.19	0.01
MBP	0.01	0.24	0.02
ADMA	0.02	0.06	0.02
PWV	0.07	0.48	0.18