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Accelerated Atherosclerosis in Patients with Systemic Lupus Erythematosus and the Role of Selected Adipocytokines in This Process

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Additional information is available at the end of the chapter

Abstract

Systemic lupus erythematosus (SLE) can affect various systems and organs. The most severe forms of the disease affect the kidneys, the central nervous system, and the heart. Cardiac and cardiovascular system diseases are inter alia caused by atherosclerosis, vasculitis, and thromboembolic events. Patients with SLE are at a higher risk of developing accelerated atherosclerosis. This process in SLE patients cannot be explained solely based on classical risk factors. Recently, some adipocytokines/adipokines have been indicated in the development of atherosclerosis, inflammation, and immune processes. It has also been postulated that adipokines might regulate the immune response and hence the atherogenic process. In this work, the factors contributing to accelerated atherosclerosis in SLE patients with special respect to vasculitis/vascular injury are presented, and selected adipocytokines, that is leptin, resistin, and adiponectin, with their relation to atherosclerosis and SLE, are under discussion.

Keywords: systemic lupus erythematosus, pathogenesis, atherosclerosis, adipocytokines, associations

1. Introduction

Systemic lupus erythematosus (SLE) is an organ-nonspecific autoimmune disease, more prevalent in young women than in men. It is characterized by periods of varying activity, sometimes even spontaneous remission. However, there can also be life-threatening disease flares, especially in those patients who undergo incorrect treatment.

The pathogenesis of SLE involves different factors and generally speaking, complex gene-environment interactions [1, 2]. More specifically, abnormal lymphocyte count (T-helper/T-suppressor cell quotient) and defects in T- and B-lymphocyte functions should be emphasized. Ineffective clearance of apoptotic cells [3, 4] and of immune complexes containing host auto-antigens and autoantibodies may also play a role in the development of SLE. Host lipids may contribute to the formation of immune complexes leading to the production of anticardiolipin antibodies [5]. Extracellular DNA molecules generated from apoptotic cells may also contribute to SLE as they promote the origin of anti-DNA autoantibodies, which are characteristic of the disease [6–8]. It should be noted though that the cause of SLE is not fully known.

As already mentioned, SLE is an organ-non-specific autoimmune disease that can affect almost any organ or system; the most severe forms affect the kidneys, the central nervous system, and the heart. Cardiac and cardiovascular system involvement may result from atherosclerosis, vasculitis, and thromboembolic lesions that are known to be interrelated processes [9, 10].

Although SLE patients constitute a small proportion of the population dying from cardiovascular events, they tend to suffer from cardiovascular complications at a young age [11]. Previous studies on SLE-related mortality revealed that early deaths were associated with disease activity and infections, whereas late deaths frequently resulted from atherosclerotic disease [12, 13]. It is noteworthy that these patients often suffer from accelerated atherosclerosis, which is associated inter alia with lipid disturbances, vasculitis, and vascular injury. The latter result from the activity of autoantibodies and immune complexes, which, via the activation of the complement system, lead to autoimmune inflammation of the vascular wall. Long-term side effects of lupus medications may also contribute to the development of cardiovascular disease (CVD) [4, 7, 11, 14, 15].

2. Factors contributing to accelerated atherosclerosis in patients with SLE with special respect to vasculitis/vascular injury

Patients in early stages of SLE rarely exhibit cardiac manifestations. Nevertheless, in over 50% of severe cases, the heart is affected, and the patients suffer from pericarditis, myocarditis, Libman-Sacks endocarditis, pulmonary hypertension, and coronary artery disease (CAD)—the development of which is related to autoimmune processes characteristic of SLE [16].

Among CVD diagnosed in SLE patients, particular attention should be paid to angiopathy, which is due to a chronic inflammatory process within the vascular wall and underlies premature atherosclerosis [17–20]. Atherosclerosis is a progressive disease resulting from a multitude of factors, including altered composition of the extracellular matrix and activation of vascular smooth muscle cells in the arterial walls, which leads to atherosclerotic plaque formation.

Due to modern immunosuppressive therapy, prognosis in SLE patients has markedly improved. However, arterial disease (including CAD) and strokes still account for a large proportion of SLE-related morbidity and mortality, while their pathogenesis has not been fully elucidated [21]. It has been estimated that the incidence of acute coronary syndromes is 50-fold higher

in patients with SLE compared to the control [19, 22–25], while the CAD mortality rate ranges from 3.5 to 15.7% [26]. It should be noted that diagnostic imaging revealed subclinical athero-sclerosis in 30–52% of SLE patients [24, 25, 27, 28].

The mechanisms of accelerated atherosclerosis in SLE patients are not fully understood and remain controversial. Its development cannot be accounted for based on traditional risk factors such as age, male sex, arterial hypertension, abnormalities in serum lipids, smoking, diabetes mellitus, obesity, and abnormal results of laboratory tests including high levels of C-reactive protein (CPR), fibrinogen, and homocysteine [4, 11, 29–34]. Other causative factors that might promote accelerated atherosclerosis should also be considered [35].

It has been suggested that atherosclerosis could be caused by an immune reaction against autoantigens at the endothelial level, which include oxidized low-density lipoprotein (LDL) and heat shock proteins (HSP) 60/65. Endothelial dysfunction plays a key role. It has also been speculated that immune mechanisms might be responsible for conversion of stable to instable plaque with resultant rupture [36].

Thus, it is not surprising that several autoimmune diseases, for example, SLE and antiphos-pholipid syndrome, are considered to raise the risk of CAD [37]; nevertheless, the precise mechanism is yet to be defined [38]. Multiple researchers believe that atherosclerosis is asso-ciated with immune responses [37, 39, 40]; it should be emphasized though that considering atherosclerosis as a solely autoimmune condition would be an oversimplification since meta-bolic disorders and hemodynamic factors are also involved in its development [41].

Although there is a lot of evidence that inflammation plays a central role in atherosclerosis, its pathogenesis is also associated with other risk factors often connected with SLE, that is arterial hypertension (especially renal hypertension), prolonged exposure to high doses of glucocorti-coids (which, apart from having a beneficial anti-inflammatory action, also influence blood pres-sure and glucose metabolism), lupus-associated antiphospholipid syndrome, diabetes mellitus, and hypercholesterolemia [23, 25]. It should be noted that a regimen of ≤ 10 mg prednisone daily is considered safe in this respect [25]; however, the problem of metabolic disorders seen in SLE patients and its relation to glucocorticoid doses has not been satisfactorily elucidated. Contrary to steroids, antimalarial drugs used in SLE patients have a beneficial effect on their lipid profile.

Patients with SLE also exhibit other metabolic disturbances that may promote accelerated ath-erosclerosis and accelerated CAD. These include hypertriglyceridemia, high homocysteine levels, and early menopause [25].

The multifactorial etiology of atherosclerosis makes it difficult to unambiguously determine why SLE patients develop atherosclerotic lesions earlier in life and more frequently than the general population. Researchers are often confronted with inconsistent results [23, 42]; hence, it has been suggested SLE might be considered an independent risk factor for atherosclerosis including CAD [24, 43–45] and CVD [23].

The factors underlying the atherosclerotic process undoubtedly comprise pro-inflammatory cyto-kines, antiphospholipid antibodies, antiendothelial cell antibodies (AECAs), and antineutrophil cytoplasmic antibodies (ANCAs), all acting directly on blood vessels or forming deposits of

immune complexes. Monocyte chemotactic protein-1 (MCP-1) [7] is also involved; its higher concentrations were revealed in the blood of our study participants with mild-to-moderate SLE [46]. Other researchers investigated the relationships between atherosclerotic plaques in the carotid arteries, antiphospholipid antibodies, and peripheral blood leukocyte count, an established indicator of inflammation [25]. There is also a spectrum of vascular abnormalities in SLE, resulting from adverse effects of several drugs or induced by infections, etc. [15].

It is important to note that vascular injury may develop not only due to an inflammatory condition but also as a result of non-inflammatory factors including environmental influences (toxicity, medication, or micro-organisms), neoplastic process, etc. [14]. Vascular disease in SLE patients can occur due to a combination of different pathological processes, for example, atherosclerosis, clotting disorders, and systemic vasculitis associated with vascular wall injury (especially endothelial dysfunction), caused by an autoimmune process [24, 28].

SLE patients most typically exhibit cutaneous vasculitis; systemic vasculitis develops in 10–18% of these patients and, as a life-threatening condition, may require aggressive therapy [14, 15].

Recently, it has been suggested that adipokines might play a causative role in the development of atherosclerosis, inflammatory, and immune processes [47]. These factors, secreted by the white adipose tissue, have autocrine-like actions, locally affecting adipocyte biology. They also act as endocrine factors that regulate systemic processes, for example, food intake, insulin sensitivity, bone growth and energy homeostasis, and affect development of obesity and metabolic syndrome [40, 48]. Adipokines have been indicated in the link between immune response and atherosclerotic process [49].

Since patients with SLE develop metabolic syndrome, insulin resistance, dyslipidemia, or hypertension more frequently than the general population [50–54], the interest in the adipose tissue is justified in the group of rheumatic diseases [55, 56]. Identification of mechanisms common to inflammation and CVD might be of considerable interest especially in the context SLE, which is, potentially, a model disease for gaining a deeper insight into such mechanisms [13]. Generally, the relationship of adipokines to inflammation and coronary atherosclerosis in patients with SLE has not been fully elucidated [57]; for example, it has not been determined whether adiponectin concentrations in SLE result from metabolic disorders or inflammatory processes and nor has it been determined whether adipokine abnormalities associated with connective tissue diseases contribute to disease development or are caused by inflammation induced by other pro-inflammatory factors [58].

3. Adipocytokines and their relation to atherosclerosis and systemic lupus erythematosus

White adipose tissue is a loose connective tissue composed of adipocytes and also containing adipocyte precursors, immune system cells fibroblasts, and other cell types [59]. Previously, this tissue had been considered an energy store (triglycerides) but now it is known to produce a number of biologically active substances that act at autocrine, paracrine, and endocrine levels. They regulate homeostasis through regulation of food intake, energy balance, lipid,

and carbohydrate metabolism. They also modulate the insulin effects, angiogenesis, and vascular remodeling, regulate arterial pressure, affect inflammatory processes as well as associated immune response, and have metabolic effects including an impact on the development of atherosclerosis [47, 50, 57, 59–63]. Since the structure of these substances resembles that of the cytokine family, they have been referred to as adipocytokines or adipokines [60]. Their multifunctionality underlies the relationship between white adipose tissue, metabolic disorders, and autoimmune diseases [59]. Actions of selected adipokines are summarized in **Table 1**.

The role of adipokines in atherosclerosis deserves particular attention as they modulate inflammatory processes and initiate its development [60]. Adipokines may constitute a link between impaired insulin sensitivity, obesity, chronic inflammation, and atherosclerosis in patients with SLE [57, 64]. It has been speculated that altered serum/plasma levels of adipokines in SLE might be related to coronary atherosclerosis, insulin resistance, and the inflammatory process [57]; however, these correlations need to be further explored and documented [65]. A deep insight into the mechanisms of adipokine actions would help develop new therapies—also for autoimmune disorders [58, 66].

It is assumed that resistin or leptin have pro-inflammatory and proatherosclerotic effects; they have also been implicated in insulin resistance [57, 67]. Conversely, adiponectin has an inverse association with inflammatory states, atherosclerosis, and insulin resistance [68]; hence, independent of traditional risk factors, low level of adiponectin might also contribute to the development of the abovementioned diseases [57, 69]. However, other studies did not confirm these causative associations [69–71] with respect to total adiponectin levels but only to some adiponectin isoforms determined in the serum [69]. The reported research results are therefore inconsistent.

Resistin plays an important role in the inflammatory process, but its amount in adipocytes is quite small. Greater resistin concentrations have been found in adipose tissue monocytes and macrophages and peripheral blood monocytes [72, 73]. It is also present in neutrophils and is capable of inducing the production of IL-6 and TNFα [42, 74–76]. These facts may indicate pro-inflammatory properties of resistin [73]. Patients with severe inflammatory disease exhibit significant increases in plasma resistin [77]. It is also noteworthy that endothelial cells exhibit sensitivity to resistin.

Resistin	Adiponectin	Leptin
Obesity	Obesity	Insulin resistance
Type 2 diabetes mellitus	Rheumatoid arthritis	Rheumatoid arthritis
Sleep apnea	Degenerative joint disease	Degenerative joint disease
Chronic kidney disease	Diabetes mellitus	Hepatitis
Atherosclerosis	Liver damage	Inflammatory bowel disease
Arthritis	Cardiovascular disease	Sepsis
Nonalcoholic fatty liver disease		Encephalomyelitis
Cardiovascular disease		

Table 1. Relationships between selected adipokines and disease processes in humans.

Although the role of resistin in SLE has not been fully determined [57, 58], its concentrations in the peripheral blood of SLE patients are elevated and have been found to correlate with inflammatory markers, glomerular filtration rate, and glucocorticoid therapy [75, 78]. However, other studies did not reveal significant differences in serum resistin between patients with SLE and control participants [78]. Hence, reports on resistin levels in SLE patients are not consistent and its role remains to be elucidated.

It has been argued that resistin concentrations might be predictive of coronary atherosclerosis, acute coronary events, and associated mortality [74, 78, 79]. It has been hypothesized that resistin secreted from macrophages in atheromas could affect vascular cell function and promote atherosclerosis [80]. Furthermore, it has been suggested that the levels of serum resistin might help determine the severity of myocardial ischemia [81], and its reduction could possibly reduce the risk for CVD [47]. It has also been speculated that this adipokine is more related to the inflammatory process and atherosclerosis than to obesity and insulin resistance [47].

Plasma leptin is known to be proportional to the total amount of adipose tissue, and therefore it is directly related to obesity and associated CVDs including atherosclerosis. Leptin exerts its atherogenic effects via induction of endothelial dysfunction, stimulation of inflammatory response, oxidative stress, platelet aggregation, migration, hypertrophy, and proliferation of vascular smooth muscle cells [82]. It regulates blood pressure and this is probably independent of body adiposity [83]. Plasma leptin concentration correlates with markers of subclinical atherosclerosis such as extracranial carotid intima-media thickness and coronary artery calcification. Beltowski [82] speculates that inhibition of leptin activity might slow down the progression of atherosclerosis in obese individuals with hyperleptinemia.

There are also data on the involvement of leptin in the immune response [77] and its modulatory effect on monocytes/macrophages, neutrophils, basophils, eosinophils, natural killer cells (NK), and dendritic cells [63, 84]. It has also been indicated in lymphocyte reactivity [85]. As already mentioned, leptin is considered a pro-inflammatory adipokine; therefore, changes in its plasma levels observed in SLE patients are not surprising. Leptin modulates the cardiovascular risk in these patients [86], and several authors have suggested that the adipokine might act as an independent risk factor for CVD [68].

Patients with SLE had higher plasma leptin compared to the control [49, 57, 87, 88], but clinical relevance of leptin level changes in autoimmune disorders remains unclear [87]. Several researchers believe that leptin is involved in the pathogenesis thereof [88, 89]. The evaluation of leptin concentrations in SLE patients with correction for BMI (body mass index) also revealed higher levels in the study group [42]. However, other authors concluded that leptin levels in SLE patients were lower or comparable to those found in healthy controls [90, 91].

Adiponectin, the major product of adipocytes, functions as an autocrine/paracrine factor within the adipose tissue and exerts endocrine effects on distant tissues thus influencing whole-body metabolism [92].

The role of adiponectin in SLE remains controversial. Several researchers observed an increase in adiponectin concentration in SLE patients [57, 91], while others did not find differences compared to the control [50, 58]. However, plasma adiponectin levels tend to be higher in patients with renal SLE in comparison to healthy controls and patients with non-renal SLE [93].

Although the role of adiponectin in SLE pathogenesis has not been fully elucidated [86], higher local and/or systemic concentrations of this adipokine have been noted in chronic inflammatory conditions including SLE [94]. Nevertheless, processes leading to adiponectin levels elevation in chronic inflammatory/autoimmune diseases are still to be clarified [94].

The significance of adiponectin in atherosclerosis also needs clarification [72]. It was postulated that the anti-inflammatory effects of adiponectin were associated with the inhibition of pro-inflammatory cytokines, decreased leukocyte adhesion, and enhanced production of anti-inflammatory cytokines [95]. Adiponectin mediates inhibition of macrophage phagocytosis and decreases the production of IL-6 and TNF. It strongly inhibits B-lymphopoiesis, reduces T-lymphocyte response, and induces the production of anti-inflammatory agents (e.g., IL-10) in human monocytes, macrophages, and dendritic cells [62, 63]. Adiponectin also suppresses monocyte adhesion to endothelial cells as well as migration and proliferation of smooth muscle cells [30]. Hence, it may exert a beneficial effect in the metabolic syndrome and coronary heart disease. Low adiponectin concentrations have been found to enhance insulin resistance and the risk for coronary heart disease. It is noteworthy, though, that, contrary to its protective role with respect to obesity and vascular disease, adiponectin seems to have pro-inflammatory effects in joint diseases [58, 62, 63].

Summing up, it should be noted that metabolic disorders frequently seen in patients with SLE might result from the disease itself or genetic influences/long-term treatment. Patients with SLE also tend to more frequently develop a classic metabolic disease, that is obesity, which is associated with chronic, although not severe, inflammatory conditions. The latter has an impact on insulin resistance-related type 2 diabetes as well as on atherosclerosis and ischemic heart disease.

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References

[1] Hrycek A, Siekiera U, Cieślik P, Szkróbka W. HLA-DRB1 and DQB1 alleles and gene polymorphisms of selected cytokines in systemic lupus erythematosus. Rheumatol Int 2005: 26; 1–6.

[2] Hrycek A, Olszanecka-Glinianowicz M. Pylica płuc z towarzyszącym toczniem rumieniowatym układowym – opis przypadku. Pol Merk Lek 2008: 24; 18–19.

[3] Jasiuk B, Reich A. Znaczenie apoptozy w patogenezie tocznia rumieniowatego układowego. Dermatol Klin 2005: 7; 97–100.

[4] Wade NS, Major AS. The problem of accelerated atherosclerosis in systemic lupus erythematosus: insights into a complex co-morbidity. Thromb Haemost 2011: 106; 849–857.

[5] Jovanović V, Aziz NA, Lim YT, Poh ANA, Chan SJH, Pei EHX, Lew FCH, Shui G, Jenner AM, Bowen L, McKinney EF, Lyons PA, Kemeny MD, Smith KGC, Wenk MR, MacAry PA. Lipid anti-lipid antibody responses correlate with disease activity in systemic lupus erythematosus. PloS One 2013: 8; e55639.

[6] Su K-Y, Pisetsky DS. The role of extracellular DNA in autoimmunity in SLE. Scand J Immunol 2009: 70; 175–183.

[7] Narshi CB, Giles IP, Rahman A. The endothelium: an interface between autoimmunity and atherosclerosis in systemic lupus erythematosus? Lupus 2011: 20; 5–13.

[8] Hrycek A, Cieślik P. Annexin A5 and anti-annexin antibodies in patients with systemic lupus erythematosus. Rheumatol Int 2012: 32; 1335–1342.

[9] Irzyk K, Ciurzyński M. Zmiany naczyniowe w chorobach układowych tkanki łącznej. Pol Przegl Kardiol 2011: 13; 171–176.

[10] Gęsikowska K, Kandera-Anasz Z, Mielczarek-Palacz A, Sikora J, Machaj I, Smycz M. Toczeń rumieniowaty układowy – ciągle aktualny problem kliniczny i diagnostyczny. Pol Merk Lek 2012: 32; 111–115.

[11] Swacha M, Więsik-Szewczyk E, Olesińska M. Ocena ryzyka sercowo-naczyniowego u chorych na toczeń rumieniowaty układowy – aspekty praktyczne. Reumatologia 2011: 49; 419–425.

[12] Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976: 60; 221–225.

[13] Bruce IN. Atherogenesis and autoimmune disease: the model of lupus. Lupus 2005: 14; 687–690.

[14] Cieślik P, Hrycek A, Kłuciński P. Vasculopathy and vasculitis in systemic lupus erythematosus. Pol Arch Med Wewn 2008: 118; 57–63.

[15] Radic M, Kaliterna DM, Radic J. Vascular manifestations of systemic lupus erythematosus. Neth J Med 2013: 71; 10–16.

[16] de Godoy MF, de Oliveira CM, Fabri VA, de Abreu LC, Valenti VE, Pires AC, Raimundo RD, Figueiredo JL, Bertazzi GRL. Long-term cardiac changes in patients with systemic lupus erythematosus. BMI Res Notes 2013: 6; 171–177.

[17] Escárcega RO, Carrasco MG, Alexandro SF, Jara LJ, Rodriguez JR, Linares LEE, Cervera R. Insulin resistance, chronic inflammatory state and the link with systemic lupus erythematosus related coronary disease. Autoim Rev 2006: 6; 48053.

[18] Płazak W, Gryga K, Dziedzic H, Tomkiewicz-Pająk L, Konieczyńska M, Podolec P, Musiał J. Influence of atorvastatin on coronary calcifications and myocardial perfusion defects in systemic lupus erythematosus patients: prospective, randomized, double-masked, placebo-controled study. Arthritis Res Ther 2011: 13; R117.

[19] Kotlarczyk A, Konarski ł, Matuszczyk A, Misztal K. Wybrane zagadnienia dotyczące układu sercowo-naczyniowego u chorych na toczeń rumieniowaty układowy. Ann Acad Med Siles 2013: 67; 137–141.

[20] Dahl TB, Yndestad A, Skjelland M, Øie E, Dahl A, Michelsen A, Damås JK, Tunheim SH, Ueland T, Smith C, Bendz B, Tonstad S, Gullestad L, Frøland SS, Krohg-Sørensen K, Russell D, Aukrust P, Halvorsen B. Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis. Possible role in inflammation and plaque destabilization. Circulation 2007: 115; 972–980.

[21] Sada K-E, Yamasaki Y, Maruyama M, Sugiyama H, Yamamura M, Maeshima Y, Makino H. Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. J Rheumatol 2006: 33; 1545–1552.

[22] Manzi S, Meilahan EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, D'Agostino RB, Kuller LH. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosu: comparison with the Framingham Study. Am J Epidemiol 1997: 145; 408–415.

[23] Zeller CB, Appenzeller S. Cardiovascular disease in systemic lupus erythematosus: the role of traditional and lupus related risk factors. Curr Cardiol Rev 2008: 4; 116–122.

[24] Pyrpasopoulou A, Chatzimichailidou S, Aslanidis S. Vascular disease in systemic lupus erythematosus. Autoimmune Dis 2012: Article ID 876456, 4 p.

[25] Bruce IN. "Not only…but also": factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology 2005: 44; 1492–1502.

[26] Matsumoto Y, Wakabayashi H, Otsuka F, Inoue K, Takano M, Sada KE, Makino H. Systemic lupus erythematosus complicated with acute myocardial infarction and ischemic colitis. Intern Med 2011: 50; 2669–2673.

[27] Doria A, Shoenfeld Y, Wu R, Gambari PF, Puato M, Ghirardello A, Gilburd B, Carbanese S, Patniak M, Zampieri S, Peter JB, Favaretto E, Laccarino L, Sherer Y, Todesco S, Pauletto P. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2003: 62; 1071–1077.

[28] Croca SA, Rahman A. Imaging assessment of cardiovascular disease in systemic lupus erythematosus. Clin Develop Immunol 2012, Article ID 694143, 7 p.

[29] De Leeuw K, Freire B, Smit AJ, Bootsoma H, Kallenberg CG, Bijl M. Traditional and non-traditional risk factors contribute to the development of accelerated atherosclerosis in patients with systemic lupus erythematosus. Lupus 2006: 15; 675–682.

[30] Kahlenberg JM, Kaplan MJ. The interplay of inflammation and cardiovascular disease in systemic lupus erythematosus. Arth Res Ther 2011: 13; 203–213.

[31] Funakubo Asanuma Y. Accelerated atherosclerosis and inflammation in systemic lupus erythematosus. Nihon Rhinsho Meneki Gakkai Kaishi 2012: 35; 470–480.

[32] Skaggs BJ, Hahn BH, McMahon M. The role of the immune system in atherosclerosis: molecules, mechanisms an implications for management of cardiovascular risk and disease in patients with rheumatic diseases. Nat Rev Rheumatol 2012: 8; 214–223.

[33] Vadacca M, Zardi EM, Margiotta D, Rigon A, Cacciapaglia F, Arcarese L, Buzzulini F, Amoroso A, Afeltra A. Leptin, adiponectin and vascular stiffness parameters in women with systemic lupus erythematosus. Intern Emerg Med 2013: 8; 705–712.

[34] Parker B, Urowitz MB, Gladman DD, Lunt M, Bae S-CH et al. Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. Ann Rheum Dis 2013: 72; 1308–1314.

[35] McMahon M, Hahn BH, Skaggs BJ. Systemic lupus erythematosus and cardiovascular disease: prediction and potential for therapeutic intervention. Expert Rev Clin Immunol 2011: 7; 227–241.

[36] Blasi C. The autoimmune origin of atherosclerosis. Atherosclerosis 2008: 201; 17–32

[37] Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, Jara LJ, Abu-Shakra M, Meroni PL, Sherer Y. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation 2005: 112; 3337–3347.

[38] Haque S, Gordon C, Isenberg D, Rahman A, Lanyon P et al. Risk fctors for clinical coronary heart disease in systemic lupus erythematosus: the lupus and atherosclerosis evaluation of risk [LASER] study. J Rheumatol 2010: 37; 322–329.

[39] Shoenfeld Y, Sherer Y, Harats D. Atherosclerosis as an infectious, inflammatory and autoimmune disease. Trends Immunol 2001: 22; 293–295.

[40] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Garcia-Unzueta MT, Berja A, Miranda-Filloy JA, de Matias JM, Gonzalez-Juanatey C, Liorca J. Visfatin is not associated with inflammation or metabolic syndrome in patients with severe rheumatoid arthritis undergoing anti-TNF-α therapy. Clin Exp Rheumatol 2010: 28; 56–62.

[41] Sherer Y, Zinger H, Shoenfeld Y. Atherosclerosis in systemic lupus erythematosus. Autoimmunity 2010: 43; 98–102.

[42] Scotece M, Conde J, Gómez R, López V, Pino J, González A, Lago F, Gómez-Reino JJ, Gualillo O. Role of adipokines in atherosclerosis: interference with cardiovascular complications in rheumatic diseases. Mediators Inflamm 2012: Article ID125458.

[43] Romero-Diaz J, Vargas-Vóracková F, Kimura-Hayama E, Cortázar-Benitez E, Gijón-Mitre R, Criales S, Cabiedes-Contreras J, Iñiguez-Rodriguez Mdel R, Lora-Garcia EA, Núñez-Alvarez C, Liorente L, Aguilar-Salinas C, Sánocha-Guerreo J. Systemic lupus erythematosus risk factors for coronary artery calcifications. Rheumatology 2012: 51; 110–119.

[44] Roman MJ, Shanker B-A, Davis A, Lockshin MD, Sammaritano L, Simantov R, Crow MK, Schwartz JE, Paget SA, Devereux RB, Salmon JE. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Eng J Med 2003: 349; 2399–2406.

[45] Zinger H, Sherer Y, Shoenfeld Y. Atherosclerosis in autoimmune rheumatic diseases-mechanisms and clinical findings. Clin Rev Allerg Immunol 2009: 37; 20–28.

[46] Hrycek E, Franek A, Błaszczak E, Dworak J, Hrycek A. Serum levels of selected chemokines in systemic lupus erythematosus patients. Rheumatol Int 2013: 33; 242–247.

[47] Baran A, Flisiak I, Chodynicka B. Znaczenie wybranych adipokin w łuszczycy. Przegl Dermatol 2011: 98; 422–428.

[48] Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, Mahaney C, Rainwater DL, VandeBerg JL, MacCluer JW, Collier G, Blangero J, Walder K, Jowett JBM. Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. J Clin Endocrinol Metab 2009: 94; 3085–3088.

[49] McMahon M, Skaggs B, Sahakian L, Grossman J, FritzGerald J, Ragavendra N,Charles-Schoeman CH, Chernishof M, Gorn A, Witztum JL, Wong WK, Weisman M, Wallace DJ, La Cava A, Hahn BH. High plasma leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus, and are associated with inflammatory oxidized lipids. Ann Rheum Dis 2011: 70; 1619–1624.

[50] Vadacca M, Margiotta D, Rigon A, Cacciapaglia F, Coppolino G, Amoroso A, Afeltra A. Adipokines and systemic lupus erythematosus: relationships with metabolic syndrome and cardiovascular disease risk factors. J Rheumatol 2009: 36; 295–297.

[51] Chung CP, Avales I, Oeser A, Gebretsodik T, Shintani A, Raggi P, Stein CM. High prevalence of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristics and cardiovascular risk factors. Ann Rheum Dis 2007: 66; 208–214.

[52] Bultink IEM, Turkstra F, Diamant M, Dijkmans BAC, Voskuyl AE. Prevalence of and risk factors for the metabolic syndrome in women with systemic lupus erythematosus. Clin Exp Rheumatol 2008: 26; 32–38.

[53] Tellels R, Lanna C, Ferreira G, Ribeiro A. Metabolic syndrome in patients with systemic lupus erythematosus: association with traditional risk factors for coronary heart disease and lupus characteristics. Lupus 2010: 19; 803–809.

[54] dos Santos FMM, Borges MC, Telles RW, Correia MITD, Lanna CCD. Excess weight and associated risk factors in patients with systemic lupus erythematosus. Rheumatol Int 2013: 33; 681–688.

[55] Gómez R, Conde J, Scotece M, Gómez-Reino J, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? Nat Rev Rheumatol 2011: 7; 528–536.

[56] Barbosa VS, Rêgo J, da Silva NA. Possible role of adipokines in systemic lupus erythematosus and rheumatoid arthritis. Rev Bras Rheumatol 2012: 52; 271–287.

[57] Chung CP, Long AG, Solus JF, Rho YH, Oeser A, Raggi P, Stein M. Adipocytokines in systemic lupus erythematosus: relationships to inflammation, insulin resistance and coronary atherosclerosis. Lupus 2009: 18; 799–806.

[58] Krysiak R, Handzlik-Orlik G, Okopień B. The role of adipokines in connective tissue diseases. Eur J Nutr 2012: 51; 513–528.

[59] Olewicz-Gawlik A, Dańczak-Pazdrowska A, Klama K, Mackiewicz S, Silny W, Hrycaj P. Rola adipokin w patogenezie twardziny układowej – badania własne i przegląd literatury. Reumatologia 2009: 47; 329–331.

[60] Szadkowska A. Adipokiny w Miażdżyca u Dzieci i Młodzieży. Redakcja Mirosława Urban. Wydawca Cornetis 2007r.

[61] Juge-Aubry CHE, Henrichot E, Meier CHA. Adipose tissue: a regulator of inflammation. Best Pract Res Clin Endocrinol Metab 2005: 19; 547–566.

[62] Lago F, Dieguez C, Gómez-Reino J, Gualillo O. The emerging role of adipokines as mediators of inflammation and immune responses. Cytokine Growth Factor Rev 2007: 18; 313–325.

[63] Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nature Publishing Group. Nat Clin Pract Rheumatol 2007: 3; 716–724.

[64] Niedzwiedzka-Rystwej P, Deptuła W. Tkanka tłuszczowa a układ odpornościowy. Allergia Astma Immunol 2009: 15; 101–105.

[65] Al M, Ng L, Tyrrell P, Bargman J, Bradley T, Silverman E. Adipokines as novel biomarkers to pediatric systemic lupus erythematosus. Rheumatology 2009: 48; 497–501.

[66] Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nature Publishing Group. Nat Rev Immunol 2006: 6; 773–783.

[67] Guzik TJ, Mangalat D, Korbut R. Adipokines – novel link between inflammation and vascular function? J Physiol Pharmacol 2006: 57; 505–528.

[68] Wu Z, Zhao S. Adipocyte: a potential target for the treatment of atherosclerosis. Med Hypoth 2006: 67; 82–86.

[69] Baessler A, Schlossbauer S, Stark K, Strack CH, Riegger G, Schunkert H, Hengstenberg C, Fischer M. Adiponectin multimetric forms but not total adiponectin levels are associated with myocardial infarction in non-diabetic men. J Atheroscler Thromb 2011: 18; 616–627.

[70] Lawlor DA, Davey Smith G, Ebrahim S, Thompson S, Sattor N. Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women. J Clin Endocrinol Metab 2005: 90; 5677–5683.

[71] Khalili P, Flyvbjerg A, Frystyk J, Lundin F, Jundle J, Engstrom, Nilsson PM. Total adiponectins does not predict cardiovascular events in middle-aged men in a prospective long-term follow-up study. Diab Metab 2010: 31; 137–143.

[72] Miranda-Filloy JA, López-Mejias R, Genre F, Carnero-López B, Ochoa R, Diaz de Terán T, González-Juanatey C, Blanco R, González-Gay MA. Adiponectin and resistin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. Clin Exp Rheumatol 2013: 31; 365–371.

[73] Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin an adipokine with potent proinflammatory properties. J Immunol 2005: 174; 5789–5795.

[74] Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 2005: 111; 932–939.

[75] Almehed K, d'Elia HF, Bokarewa M, Carlsten H. Role of resistin as a marker of inflammation in systemic lupus erythematosus. Ann Res Ther 2008: 10; 1–9.

[76] Johnston A, Arnadottir S, Gudjonsson JE, Aphale A, Sigmarsdottir AA, Gunnarsson SJ, Steinsson JT, Elder JT, Valdimarsson H. Obesity in psoriasis; leptin and resistin as mediators of cutaneous inflammation. Br J Dermatol 2008: 159; 342–350.

[77] Kumor-Kisielewska A, Kierszniewska-Stępień D, Pietras T, Kroczyńska-Bednarek J, Kurmanowska Z, Antczak A, Górski P. Assessment of leptin and resistin levels in patients with chronic obstructive pulmonary disease. Pol Arch Med Wewn 2013: 123; 215–220.

[78] Baker JF, Morales M, Qatanani M, Cucchira A, Nackos E, Lazar MA, Teff K, von Feldt JM. Resistin levels in lupus and association with disease-specific measures, insulin resistance, and coronary calcification. J Rheumatol 2011: 38; 2369–2375.

[79] Fiková M, Haluzik M, Gay S, Šenolt L. The role of resistin as a reulator of inflammation: implications for various human pathologies. Clin Immunol 2009: 133; 157–170.

[80] Jung HS, Park KH, Cho YM, Chung SS, Cho HJ, Cho SY, Kim SJ, Kim SY, Lee HK, Park KS. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res 2006: 69: 76–85.

[81] Zheng H, Xu H, Xie N, Huang J, Fang H, Luo M. Association of serum resistin with peripheral arterial disease. Pol Arch Med Wewn 2013: 123; 680–685.

[82] Beltowski J. Leptin and atherosclerosis. Atherosclerosis 2006: 189; 47–60.

[83] Beltowski J. Role of leptin in blood pressure regulation and arterial hypertension. J Hypertens 2006: 24; 789–801.

[84] Matarese G, Maschos S, Mantzoros CS. Leptin in immunology. J Immunol 2005: 174; 3137–3142.

[85] Lord GM, Matarese G, Howard JK, Baker RJ, Blooms SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 1998: 394; 897–901.

[86] Scotece M, Conde J, Gómez R, López V, Lago F, Gómez-Reino J, Gualillo O. Beyond fat mass: exploring the role of adipokines in rheumatic diseases. Sci World J 2011: 11; 1932–1947.

[87] Garcia-Gonzalez A, Gonzalez-Lopez L, Valera-Gonzalez IC, Gardona-Muñoz EG, Salazar-Parmo M, González-Ortiz M, Martinez-Abundis E, Gamez-Nawa JI. Serum leptin levels in women with systemic lupus erythematosus. Rheumatol Int 2002: 22; 138–141.

[88] Xu W-D, Zhang M, Zhang Y-J, Liu S-S, Pan H-F, Ye DQ. Association between leptin and systemic lupus erythematosus. Rheumatol Int 2014: 34; 559–563.

[89] Otero M, Lago R, Gomez R, Dieguez C, Lago F, Gómez-Reino J, Gualillo O. Towards a pro-inflammatory and immunomodulatory emergin role of leptin. Rheumatology 2006: 45; 944–950.

[90] De Sanctis JB, Zabaleta M, Bianco NE, Garmendia JV, Rivas L. Serum adipokine levels in patients with systemic lupus erythematosus. Autoimmunity 2009: 42; 272–274.

[91] Wisłowska M, Rok M, Stępień K, Kuklo-Kowalska A. Serum leptin in systemic lupus erythematosus. Rheumatol Int 2008: 28; 467–473.

[92] Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular diseases. Curr Opin Lipidol 2007: 18; 263–270.

[93] Rovin BH, Song H, Herbert LA, Nadasdy T, Nadasdy G, Birmingham DJ, Yu CY, Nagaraja HN. Plasma, urine and renal expression of adiponectin in human systemic lupus erythematosus. Kidney Intern 2005: 68; 1825–1833.

[94] Fantuzzi G. Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol 2008: 121; 326–330.

[95] Song H, Chan J, Rovin BH. Induction of chemokine expression by adiponectin in vitro is isoform dependent. Transl Res 2009: 54; 18–26.