Revmatoidni artritis in ateroskleroza

Rheumatoid Arthritis and Atherosclerosis

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Izvleček

Življenjska doba bolnikov z revmatoidnim artritisom je skrajšana za 3–18 let. Srčnožilni in možgansko-žilni dogodki (srčni infarkt in možganska kap) kot posledica pospešene ateroskleroze so glavni vzrok smrti pri bolnikih z revmatoidnim artritisom. Ateroskleroza je razširjen patološki proces srednje velikih in velikih arterij, ki je odgovoren za kardiovaskularne bolezni. Ateroskleroza ima podobne imunopatofiziološke mehanizme kot avtoimunske bolezni kot je npr. revmatoidni artritis.

Vzrok za zgodnjo aterosklerozo pri revmatoidnem artritisu predstavljajo tako klasični dejavniki tveganja, kakor tudi neklasični dejavniki med katere sodijo nekateri biokemični označevalci (homocistein, cistatin C in lipoproteini) ter dejavniki avtoimunskega vnetja (inflamatorni citokini, adhezijske molekule). Za odkrivanje zgodnje ateroskleroze pri bolnikih z revmatoidnim

Abstract

Life expectancy of rheumatoid arthritis (RA) patients can be reduced by 3–18 years. Cerebrovascular and cardiovascular events (myocardial infarction and stroke) as a consequence of accelerated atherosclerosis are the main cause of death in RA patients. Atherosclerosis is a widespread pathologic process in medium–to–large arteries responsible for cardiovascular diseases. Atherosclerosis shares many similarities in immune–pathophysiological mechanisms with autoimmune inflammatory diseases such as RA.

Classical and non–classical risk factors are the cause for accelerated atherosclerosis in RA patients. Non–classical risk factors include some specific biochemical substances (homocysteine, cystatin C, lipoproteins) as well as inflammatory cytokines and adhesion molecules.

For the diagnosis of accelerated atherosclerosis in RA patients, ultrasound of

artritisom je primerna meritev intime medije notranjih vratnih arterij.
V prispevku so prikazane tudi lastne izkušnje glede diagnostike zgodnje ateroskleroze bolnikov z revmatoidnim artritisom.

internal carotid arteries with measurement of intima media thickness can be employed.
Here, we describe the practical factors involved in the diagnosis of accelerated atherosclerosis in RA patients.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology that can lead to joint destruction, impaired articular function, and physical disability. Invading cells of fibroproliferative tissue express various matrix–degrading enzymes that can destroy bone and cartilage (1).

Life expectancy in RA patients is reduced by 3–10 years. In severe RA, the increased prevalence of mortality is comparable with that found in patients with lymphoma and triple–vessel coronary artery disease. Cerebrovascular diseases and cardiovascular diseases (CVDs) are the main cause of mortality in RA patients (1, 2).

Prevalence of CVD is increasing in prevalence in many populations in the 'developing' world and could become the most common cause of death worldwide (3). Atherosclerosis is a widespread pathologic process of medium–to–large arteries responsible for CVDs such as myocardial infarction (MI) and stroke, which are among the main cause for morbidity and mortality in the western world.

Vascular disease is unquestionably multifactorial in origin and is affected by genetic and lifestyle factors. Independent risk factors for coronary heart disease (CHD) as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel include: age; sex; hypertension; smoking; diabetes mellitus (DM); family history of premature CHD; elevated levels of low–density lipoprotein–cholesterol (LDL–C) in plasma; low levels of high–density lipoprotein–cholesterol ((HDL–C) in plasma. Several prospective epidemiologic studies have suggested that a decrease in the level of HDL–C is a significant independent risk factor for heart disease. Asztalos et al. reported a significant difference in the HDL subpopulation profile of healthy control and CHD patients (3). Plasma lipoproteins have important roles in determining the risk of clinical events, so must be considered for prevention and therapy.

Several studies have demonstrated the importance of various factors on atherosclerosis in RA patients (4). Classical risk factors for atherosclerosis are not sufficient to explain accelerated atherosclerosis in RA patients (5). Atherosclerosis shares many similarities of the immune–pathophysiological response observed in autoimmune diseases (1, 6). Homocysteine has a toxic effect on the endothelium, and stimulates the oxidation ability of LDL lipoproteins. An increased concentration of homocysteine and lipoprotein (a) (Lp (a)) in RA patients has been observed (7). Vasculitis and circular immune complexes could have an impact on the development of atherosclerosis. Inflammatory cytokines seen in active RA can act on endothelial adhesion molecules and accelerate atherosclerosis (4). Several studies have demonstrated that chronic autoimmune inflammation has an impact on destabilisation of atherosclerotic plaques. In macrocytes and mastocytes, activation enzymes are released that lead to collagen degradation in atherosclerotic plaques, resulting in plaque destabilisation (8). Collagen degradation is important in the pathogenesis of RA. Local expression of adhesion molecules such as

intercellular adhesion molecules (ICAM), E–selectin, endothelin as well as activated T lymphocytes have been found in atherosclerotic plaques and rheumatoid synovia (9). Neoangiogenesis, which is a crucial component of RA, can have a big impact on the development of atherosclerosis (10). An increased percentage of T lymphocytes with receptor expression for interleukin (IL)–2R/CD25 in unstable atherosclerotic plaques has been reported (11). The T lymphocyte subgroup CD4+CD28– has been found in patients with unstable angina pectoris and in patients with RA vasculitis. In patients with unstable angina pectoris, an increased number of T lymphocytes producing interferon (IFN)– and a decreased number of T lymphocytes producing IL–2 and IL–4 were found. The balance between the T–helper (Th)1 (pro–inflammatory) and Th2 (anti–inflammatory) response is lost in both diseases (12). The inflammatory response in angina pectoris is limited by time. With progression from unstable to stable pectoral angina, the autoimmune response is changed from cytolytic Th1 into protective Th2 with immunoglobulin production and inhibition of macrophage activation (13). Myocardial infarction – a consequence of accelerated atherosclerosis – is a major cause of mortality in patients with systemic autoimmune diseases. The reasons for this phenomenon could be the greater number of traditional risk factors for CVDs, corticosteroid treatment, and chronic inflammation. There is no evidence that traditional risk factors have an impact on accelerated atherosclerosis in RA patients. There is no statistical correlation between low–dose corticosteroid treatment and accelerated atherosclerosis in RA patients (4, 14). It appears that chronic inflammation is the main cause for the development of accelerated atherosclerosis in RA patients. A consequence of atherosclerosis in RA patients is early death.

Not only classical risk factors (obesity, hypertension, DM, smoking, increased levels of cholesterol), but also non–classical risk factors (Lp (a), homocysteine, cystatin C) as well as functional tests are being used for the diagnosis of atherosclerosis. Besides stress tests and computer tomography (CT) of coronary arteries for calcium demonstration, ultrasound (US) of carotid arteries has been used for detection of the signs of accelerated atherosclerosis (15).

Patients with coronary artery disease and stable angina pectoris have elevated levels of high–sensitivity C–reactive protein (hs–CRP) and decreased levels of apolipoprotein A1 (apo A1) (16).

MORTALITY OF PATIENTS WITH RA

Patients with inflammatory systemic autoimmune diseases such as RA and systemic lupus erythematosus (SLE) have an increased prevalence of atherosclerosis and, consequently, early cardiovascular death. Life expectancy of RA patients is reduced by 3–18 years for both sexes (14, 17–19). Causes of early death include infections, malignancies as well as diseases of the respiratory tract, gastrointestinal tract, and kidneys (14, 20). The greatest impact on mortality in RA patients is CVDs, which are the cause of death in 52% of subjects (14, 17). Södergren et al. reported that patients with RA had a nearly threefold greater incidence of stroke compared with the general population (21). In RA patients with more aggressive disease and extra–articular involvement, life expectancy is decreased significantly (22). The incidence of coronary artery disease – a complication of atherosclerosis – is increased in RA patients (14). Atherosclerotic cardiovascular complications are the main cause of death in these patients (22).

RISK FACTORS FOR ATHEROSCLEROSIS IN RA PATIENTS

Classical risk factors (Table I)

There is a well–documented association between hypertension and an increased risk of myocardial infarction and stroke (23). In 1994, Wolfe demonstrated that the mean blood pressure has a predictive value on the mortality of RA patients (19). Studies of the prevalence of hypertension in RA patients are rare and results disparate (14).

DM is a well–known risk factor for CVDs. Human leucocyte antigen (HLA)–DR4 has been found in sub-

jects with insulin–dependent DM as well as in RA patients. Despite this observation, the incidence of DM in RA patients is not higher (24).

Cigarette smoking is associated with mortality in patients with CVDs. It also has an important predictive value for mortality in RA patients (19). Cigarette smoking is also a risk factor for the development of RA, especially in individuals carrying the HLA–DRB1 shared epitope (25).

Another well–known risk factor for CVDs is obesity, though Wolfe did not find a significant correlation between body weight and mortality in RA patients (14, 19).

Physical inactivity and sedentary occupations are associated with an increased risk of death due to ischemic heart disease. There is no proof, but we can assume that RA patients are less physically active than the rest of the population. There are no data demonstrating that physical inactivity would predict higher morbidity due to CVDs in RA patients (14, 27).

Total cholesterol is related to the risk of suffering from CHD. HDL–C is a major anti–atherogenic lipoprotein. Studies have shown a powerful inverse association between levels of HDL–C and Apo A–1 and the risk of vascular disease. The usual profile is for HDL–C levels to be low in rheumatic disease associated with systemic inflammation (and triglycerides to be high), though inter–study variations have been noted. High levels of LDL–C and low levels of HDL–C are well–known risk factors for atherosclerosis (28).

RA patients with severe disease activity have significantly decreased levels of LDL–C and HDL–C compared with patients with minimal disease activity. As disease activity decreases, RA patients undergo normalisation of almost all serum lipid concentrations (29). Recently, Myasoedova et al. reported a significant decrease in levels of total cholesterol and LDL during the 5.5 years before the onset of RA in RA patients in comparison with non–RA–subjects (30).

Non–classical risk factors (Table I)

Lp (a) is a recognised independent risk factor for atherosclerotic CVD. Early studies demonstrated that Lp (a) plays a potential part in thrombogenesis by interfering with several steps in the fibrinolytic pathway. Recently, new biological functions have been assigned to Lp (a), including activation of various cell types that have important roles in atherogenesis. Lp (a) is an atherogenic lipoprotein and is present in atherosclerotic (but not in normal) vessel walls (31). The effects of the inflammatory process on Lp (a) metabolism are unclear (32). It has been suggested that increased synthesis and/or decreased destruction of Lp (a) or changes in Lp (a) distribution between intravascular and extravascular regions may cause dyslipoproteinemia in RA, and that in inflammation, Lp(a) synthesis is increased in the liver in much the same way as other acute–phase reactants (32). Until now, no correlation between Lp (a) and mortality of RA patients has been established.

Another factor that has been associated with chronic heart disease is an elevated concentration of homocysteine in plasma. Wilcken and Wilcken demonstrated that patients with coronary artery disease suffered more often from abnormal homocysteine metabolism than controls (33). Schneede et al. reported that hyperhomocysteinemia is commonly observed in RA and is not necessarily dependent upon methotrexate (MTX) use (34). Lazzerini et al. found that homocysteine concentrations in the synovial fluid from RA patients were significantly higher than those from control subjects with osteoarthritis (35). Woolf and Manore found elevated concentrations of homocysteine the plasma of older women with RA (36).

Cystatin C has been shown to be elevated in the synovial fluid of patients with RA compared with patients with other joint diseases. Renal function is an important determinant of coronary atherosclerosis, and serum level of cystatin C is a novel, accurate measure of the glomerular filtration rate and a predictor of cardiovascular events and mortality, as stated by Maahs et al. Serum concentrations of cystatin C have been demonstrated to better predict CVD events than serum concentrations of creatinine (37).

Risk factors correlated with disease activity (Table I)

RA is an inflammatory disease in which many factors of the autoimmune inflammatory response can be observded. CRP, pro–inflammatory cytokines and adhesion molecules (ICAM and vascular cell adhesion molecule (VCAM)) are proof of an inflammatory response. Huo et al. found elevated levels of ICAM and VCAM in patients with angina pectoris. VCAM is one of the most important adhesion molecules involved in monocyte recruitment to atherosclerotic lesions, as well as for the initiation and progression of atherosclerotic disease (38).

Rosenau and colleagues stated that atherosclerosis is also an inflammatory condition associated with higher levels of hs–CRP. They found that patients with proven coronary disease and elevated inflammatory activity according to hs–CRP levels exhibited increased thrombogenic activity, with higher fibrinogen concentrations. CRP is an acute–phase reactant synthesised in the liver in direct response to circulating levels of IL–6 (18). CRP is a marker for underlying systemic inflammation. Pai et al. found tumour necrosis factor (TNF) α and IL–6 to be important for some risk factors for CVD: DM, hypertension, CRP levels, and low concentrations of HDL–C (39). Heinrich et al. showed that CRP concentrations were significantly related to atherosclerosis in the coronary, peripheral and carotid arteries (40). Raised CRP levels predict the mortality of CHD or the risk of future myocardial infarction or stroke (39). Rosenau and Pahor found that elevation of serum levels of hs–CRP within the normal range was a strong predictor of atherosclerosis. In addition to being a useful biomarker for subclinical inflammation and cardiovascular risk, CRP may play a part in the inflammation of atherosclerosis itself (18, 41).

Risk factors correlated with medications (Table I)

Glucocorticoid (GK) treatment has an impact on lipid levels, insulin resistance, blood pressure, and haemostasis. Elevated levels of cholesterol and lipoprotein have been found in patients being treated with GK for longer periods of time. Regular systemic treatment with GK could be associated with an increase in the incidence of major CVD (42). No correlation between GK therapy and CHD mortality in RA patients has been found, in contrast to results in patients with SLE (14).

There have been some disagreements on the impact of classical disease–modifying anti–rheumatic drugs (cDMARDs) such as gold salts, d–penicillamine, cyclosporine, leflunomide, MTX and azathioprine on the incidence of CHD (14, 43). Chloroquine decreased the concentrations of cholesterol, triglyceride and very–low–density lipoprotein (VLDL) in the sera of RA patients. A recently published study showed no evidence of an increased risk of CVD in patients receiving MTX (43).

Table 1: *Risk factors for accelerated atherosclerosis in RA patients*

Classical risk factors	BMI, smoking, blood sugar, blood pressure, lipids
Non–classical risk factors	Homocysteine, lipoproteins
Risk factors correlated with disease activity	ESR, CRP, RF
Medication	Glucocorticoids, cDMARDs
Cytokines and adhesion molecules	IL–2, IL–6, TNF–α, ICAM, VCAM

BMI = body mass index, ESR = erythrocyte sedimentation rate, CRP = C–reactive protein, RF = rheumatoid factor, DMARD = disease–modifying antirheumatic drugs, IL = interleukin, TNF–α= tumour necrosis factor, ICAM = intercellular adhesion molecule, VCAM = vascular cell adhesion molecule.

DIAGNOSIS OF ATHEROSCLEROSIS

As well as classical and non–classical risk factors, imaging methods are used to detect accelerated atherosclerosis. Contrast radiography and CT of coronary arteries are used to detect plaques. Magnetic resonance imaging (MRI) of carotid and peripheral arteries can also be done (44). MRI spectroscopy can be used to detect cholesteryl esters in vessel walls. Most of these examinations carry some risks or are not universally available. In recent decades, ultrasound of the carotid arteries has become very important because it is a use-

ful tool for the detection and monitoring of changes in intima–medial thickness (IMT), allowing for evaluation of changes in arterial walls. Measurement of the IMT of carotid plaques using B–mode ultrasound is a non–invasive and reproducible method for evaluation and follow–up of atherosclerotic complications.

High–resolution B–mode ultrasonography in combination with colour Doppler ultrasound is being used. Ultrasonographic assessment of common carotid atherosclerosis is a feasible, reliable, valid, and cost–effective method for population studies and clinical trials of the progression and regression of atherosclerosis (15, 45). IMT values measured using ultrasound correlate closely with direct measurement of local and systemic atherosclerotic burden in pathology studies (45).

CONCLUSIONS

Increased IMT as an indicator of asymptomatic atherosclerosis and higher incidence of plaques in RA patients has been observed in some studies as well as in studies undertaken in our centre (41, 46, 47, 48). Classical risk factors have some impact on the development of atherosclerosis, but autoimmune disease itself is the reason for accelerated atherosclerosis in female RA patients. TNF and IL–6 are pro–inflammatory cytokines and indicators of autoimmune inflammation, whereas cellular adhesion molecules reflect vascular cellular injury and endothelial dysfunction. Together they demonstrate the importance of pro–inflammatory cytokines on accelerated atherosclerosis in autoimmune inflammation such as in RA (41, 46, 47). Early intervention and control of disease activity may reduce the risk of atherosclerosis and cardiovascular events in patients with RA (49 – 50). It is not only the activity but also the duration of the disease and patients' age that are important for atherosclerotic changes in RA patients.

Patients with RA have a marked increase in carotid atherosclerosis that is independent of traditional risk factors. Once the concept of enhanced atherosclerosis in autoimmune disease (primarily in RA) becomes more widespread, several preventive and diagnostic measures should be used widely. RA patients are at risk of enhanced atherosclerosis and consequently coronary artery disease, so preventive measures should be taken to avoid or control classical risk factors. In addition, an active diagnostic approach to detect subclinical atheroma should be considered because primary prevention with statins and aspirin might be required. Carotid ultrasonography is a simple and inexpensive way of identifying preclinical atherosclerosis in this population. Finally, appropriate control of RA does not only mean long–term remission and control of disease activity, but also prevention of the number one–killer among RA patients: coronary artery disease.

Many patients in studies undertaken in our centre received aggressive therapy, and additional questions remain that cannot be answered here. Would the appearance of IMT and plaques increase even more without such therapy? Would more effective therapies reduce IMT? Even so, the data suggest that control of disease activity might reduce IMT and plaque appearance in RA – an illness that affects 1% of the population. More prospective longitudinal studies are necessary to answer these questions.

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