TREATMENT OF HYPERTENSION IN PATIENTS WITH RHEUMATIC DISEASES

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Introduction
Among “rheumatic” diseases rheumatoid arthritis (RA) is the most common immune-inflammatory disorder characterized by symmetric polyarthritis affecting small joints of the hands and feet. In patients with seropositive RA, the disease course is more aggressive, extra-articular manifestations are more frequent and their mortality is increased. Osteoarthritis (OA) is one of the most common causes of disability in adults. It is characterized by cartilage damage of the joints in large joints more often and more frequently involved. Beyond them, gout deserves special attention since it has multiple interactions with hypertension or its treatment.

Hypertension in patients with rheumatoid arthritis
The prevalence of hypertension is substantially (by about 42%) higher in RA than in the average population [1]. Among patients with RA the prevalence of hypertension is estimated to be 52–73% [2, 3], and the proportion of well-controlled patients is much lower, at 13.2%, than in the general population, where it is estimated to be around 30%, but large differences were found in different populations. Both cardiovascular (CV) morbidity and mortality are increased in RA compared to controls, which is only partially attributable to traditional CV risk factors [4, 5], so RA can be characterized as a disease with high CV risk, similarly to diabetes mellitus and chronic kidney diseases. This increased prevalence of hypertension in patients with RA can be explained by several factors: systemic and low-grade inflammation, physical inactivity and medication (e.g. corticosteroids and non-steroidal anti-inflammatory drugs (NSAID)) used for the control of disease activity and its symptoms.

Inflammatory burden plays a pivotal role in the observed excess CV risk [6]. Increased high-sensitivity C-reactive protein (hsCRP) levels representing systemic inflammation are characteristic for patients with RA. Low-grade systemic inflammation can lead to hypertension via several mechanisms: reduction of nitric oxide production in endothelial cells leads to vasodisconformation, increased production of endothelin-1, and platelet activation. Moreover, CRP can activate the renin-angiotensin system (RAS) [7]. As a consequence, systemic vascular resistance is increased in RA while elasticity of small and large arteries is reduced. These processes together with the increased arterial stiffness, also observed in RA, may lead to increased arterial blood pressure [7]. These processes together with the increased arterial stiffness, also observed in RA, may lead to increased arterial blood pressure [7].

Hypertension in patients with osteoarthritis
The prevalence of OA and hypertension significantly increases with growing age. OA and hypertension often coexist in patients. It is very important to highlight that nowadays even patients over 80 years old can benefit from lowering blood pressure [8]. In a large cohort of patients with osteoarthritis, 57.6% were reported to take antihypertensive medication [9]. OA and hypertension often coexist in patients. It is very important to highlight that nowadays even patients over 80 years old can benefit from lowering blood pressure [8].

Sedentary lifestyle caused by OA, and the subsequent overweight, further aggravates this situation. Moreover, pharmacological treatment used for the management of OA (see in RA) is also able to increase blood pressure, as will be discussed later in detail.

Special aspects of the management of hypertension in patients with rheumatic diseases
Non-pharmacological treatment
Risk assessment
Cardiovascular risk stratification should be performed with special consideration in patients suffering from RA. There are several recommendations about how the presence of RA should be considered when categorizing individuals into different CV risk groups.

RA should be regarded as an independent risk factor for hypertension [10]. It was suggested to add “+1” to the total sum of risk factors in RA patients with hypertension [7] when using European Society of Cardiology/European League Against Rheumatism (ESCC/ESR) guidelines [11]. On the other hand, the latest European League Against Rheumatism (EULAR) recommendations for CV risk management compose a subset in RA patients defined if patients meet at least two of the following three criteria:

- disease duration of more than 10 years;
- rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) positivity;
- presence of certain extra-articular manifestations.

For the aforementioned patient population, risk score models should be adapted by applying a 1.5 multiplication factor [12].

Lifestyle modifications
Beyond efforts for the access and maintenance of ideal body weight, regular physical activity, reduction of sodium intake and other dietary considerations, probably the most important recommendation for an RA patient is smoking cessation. There is now clear evidence that several factors (citrullination of autoantigens, changes in cytokine balance, increased risk of infections) link cigarette smoking to the development and more aggressive disease course of RA (predominantly the seropositive form) [13].

Pharmacological treatment
The impact of anti-inflammatory drugs on blood pressure
Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors (coxibs)
Non-selective NSAIDs and coxibs are commonly used both in RA and in OA. In an earlier meta-analysis, including 50 trials, NSAIDs caused an average of 5 mm Hg elevation in systolic blood pressure. The most pronounced increase in blood pressure was observed during treatment with ibuprofen, indomethacin, and naproxen [14]. A more recent systematic review demonstrated a significant increase in mean blood pressure values after at least 4-weeks use of ibuprofen and indomethacin, compared to placebo. After treatment with naproxen, sulindac, nabumetone and diclofenac, blood pressure also increased but the difference did not reach statistical significance. On treatment with ibuprofen, relative risk of development of hypertension was 2.85 (CI: 1.4–5.6). The blood pressure increasing effect of non-selective NSAIDs was more obvious in hypertensive than in normotensive patients [15]. Possible mechanisms in the background can be salt and water retention by decreased prostaglandin production in the renal arteries and subsequently increased antinatriuretic effect in the macula densa, increased peripheral vascular resistance by promoting endothelin-1 and inhibiting vasodilatory prostaglandin synthesis [15].

Several studies have revealed that co-administration of non-selective NSAIDs with diuretics, beta-receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) result in attenuation of the anti-hypertensive effect. Interestingly, this effect cannot be observed with calcium channel blockers (CCBs) [17, 18]. Selective cyclooxygenase-2 inhibitors (coxibs) were developed to decrease the risk of gastrointestinal bleeding in patients who require NSAIDs. However, after a few years it became obvious that coxibs shift the anti-thrombotic-prothrombotic balance in the direction of the prothrombotic way by inhibiting the synthesis of prostacyclin and thereby change the balance between vasodilatory/vasoconstrictor (thromboxane) synthesis in endothelial cells. They markedly increase systolic more than diastolic blood pressure. As a consequence of these processes, they are associated with increased cardiovascular risk (acute coronary syndrome, stroke). Based on the results of a meta-analysis performed of 19 studies, coxibs were found to increase the risk of blood pressure than non-selective NSAIDs or placebo [19]. A meta-analysis showed that rofecoxib (HR: 2.80), a celecoxib (HR: 2.57), ibuprofen (HR: 1.50), diclofenac (HR: 2.40) and other NSAIDs (HR: 1.29) increased CV mortality [20]. This effect was dose-dependent. In another meta-analysis involving 114 clinical studies and data from 16,094 patients, rofecoxib dose-dependent increased the risk of arrhythmia (HR: 2.90), renal impairment (RR: 1.53), peripheral oedema (RR: 0.83) and hypertension (RR: 1.55). On the other hand, in patients treated with celecoxib, the risk of renal dysfunction (RR: 0.61) and hypertension was smaller than in controls [21]. In the largest meta-analysis published so far of 1,028,437 patients, the data showed that the largest increase in CV mortality was found in patients treated with diclofenac (OR:1.91) and COX-2 selective rofecoxib (OR: 1.66), and this deleterious effect of diclofenac was larger than that of rofecoxib. There was a tendency by ibuprofen to increase non-lethal stroke (OR: 1.29). On the other hand, naproxen did not increase CV mortality (OR: 0.84; NS) [22]. These data suggest that none of the NSAIDs are considered to be safe; however, it also became evident that cox-selectivity is not responsible for associated increased CV risk, which is considered as a class effect of this group of drugs. This side effect is related to the baseline CV risk of the patient; in those with higher baseline risk the deleterious side effect of NSAIDs is more pronounced [23].

The cox-2 selectivity is important only for...
having less gastrointestinal bleeding, which is still the most significant side effect of NSAIDs. COXibs are especially unfavourable in patients with heart failure, in whom NSAIDs can no longer change the functional status of heart function and liver cirrhosis. According to the latest findings, among coxibs, only rofecoxib was associated with hypertension, so the class effect for this group of agents is not evident [7].

Extensive research is being conducted in order to generate NO (nitrergic system), which provide the pharmacological effects of the basic molecule (mainly NSAIDs) while releasing NO to neutralize the harmful effects of the original agent [24]. One of these emerging new molecules is naproxeno-n (naproxen joined via a linker to NO), which produces a statistically significant reduction of blood pressure compared to untreated patients [25].

In the latest EULAR recommendations, two opposite ways are mentioned about how GCs influence CV risk in patients with RA: at first, due to their well-known harmful effects on lipids, glucose tolerance and obesity, corticosteroids could elevate CV risk, and secondly, they can even decrease it by suppressing inflammation and decreasing pain [12].

**References**


4. Concomitant medication of patients must be carefully assessed before the start of treatment of patients with rheumatic diseases since they can influence the treatment of hypertension, or on the effects of antihypertensive medication during treatment with DMARDs. Biological therapies may increase plasma cyclosporin levels. Reduction of the dose or withdrawal of cyclosporin may be possible if hypertension becomes treatment-resistant [7,27].

5. Biological therapies

Although there are few observations so far, no evidence exists to suggest any impact on hypertension, or on the effects of antihypertensive medication during treatment with TNFα-blocking agents (TNFα--blocking agents). Moreover, the potential future of the anti-human IL-6 receptor antibody tocilizumab has been suggested to treat recalcitrant hypertension [28].

**The impact of antihypertensive drugs on rheumatic diseases**

Concomitant medication of patients must be carefully assessed before the initiation of any antihypertensive treatment. Patients with RA have increased sympathetic activity, which may result in high plasma renin activity. Therefore, antihypertensive treatment with ACEIs seems to be reasonable. Moreover, ACEIs suppress proinflammatory mediators such as reactive oxygen species (ROS) and CRP, and promote the expression of some anti-inflammatory factors [29].

**Gout**

Gout is characterized by severely painful inflammatory attacks caused by the accumulation of monosodium urate monohydrate crystals in the joints and their surroundings. The development of crystal deposits in the affected joints is triggered by high serum uric acid levels. A typical acute gout attack often involves the first metatarsophalangeal joint, which is known as podagra. However, gouty arthritis can occur in other joints including the ankles, knees, elbows, wrists and fingers. Symptoms of acute attacks are represented by rapid onset of intense pain, accompanied by local swelling, warmth and hyperemia. The increased level of uric acid is the result of a disturbed purine metabolism. Hyperuricaemia can be of primary or secondary origin, and both can be caused by underlying metabolic dysfunction as well as by increased production of uric acid or decreased renal excretion of uric acid. The actual mechanism of gout formation is still incompletely understood, but the crystallization of urate is promoted by high serum uric acid levels. A typical acute gout attack most often occurs unilaterally, coinciding with increased dietary intake or physical stress. The development of crystal deposits in the affected joints is followed by tissue edema, necrosis and acute inflammation, leading to the development of crystal deposits in the joints and their surroundings. The development of crystal deposits in the affected joints is triggered by high serum uric acid levels. A typical acute gout attack often involves the first metatarsophalangeal joint, which is known as podagra. However, gouty arthritis can occur in other joints including the ankles, knees, elbows, wrists and fingers. Symptoms of acute attacks are represented by rapid onset of intense pain, accompanied by local swelling, warmth and hyperemia. The increased level of uric acid is the result of a disturbed purine metabolism. Hyperuricaemia can be of primary or secondary origin, and both can be caused by underlying metabolic dysfunction as well as by increased production of uric acid or decreased renal excretion of uric acid. The actual mechanism of gout formation is still incompletely understood, but the crystallization of urate is promoted by high serum uric acid levels. A typical acute gout attack most often occurs unilaterally, coinciding with increased dietary intake or physical stress. The development of crystal deposits in the affected joints is triggered by high serum uric acid levels. A typical acute gout attack often involves the first metatarsophalangeal joint, which is known as podagra. However, gouty arthritis can occur in other joints including the ankles, knees, elbows, wrists and fingers. Symptoms of acute attacks are represented by rapid onset of intense pain, accompanied by local swelling, warmth and hyperemia. The increased level of uric acid is the result of a disturbed purine metabolism. Hyperuricaemia can be of primary or secondary origin, and both can be caused by underlying metabolic dysfunction as well as by increased production of uric acid or decreased renal excretion of uric acid. The actual mechanism of gout formation is still incompletely understood, but the crystallization of urate is promoted by high serum uric acid levels. A typical acute gout attack most often occurs unilaterally, coinciding with increased dietary intake...