REJDYCH, Julia, PODYMA, Katarzyna, ROSOŁOWSKA-ŻAK, Sara, SAMBURA, Maria, SAS, Wiktoria, RYZNAR, Gracja, PIERZCHAŁA, Piotr, MINKOWSKA, Michalina, CHIMIAK, Krystyna and BYLICA, Gabriela. The role of physical exercise in diseases treated with colchicine - an ancient drug with novel clinical applications. Quality in Sport. 2024;15:51771. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.15.51771
https://apcz.umk.pl/QS/article/view/51771

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 26.05.2024. Revised: 20.06.2024. Accepted: 01.07.2024. Published: 05.07.2024.

The role of physical exercise in diseases treated with colchicine - an ancient drug with novel clinical applications

Julia Rejdych, Katarzyna Podyma, Sara Rosołowska-Żak, Maria Sambura, Wiktoria Sas, Gracja Ryznar, Piotr Pierzchała, Michalina Minkowska, Krystyna Chimiak, Gabriela Bylica

Julia Rejdych;
ORCID 0009-0003-7466-7764;
https://orcid.org/0009-0003-7466-7764; julia.rej@gmail.com;
Szpital Miejski nr 4 w Gliwicach, ul. Zygmunta Starego 20, 44-100 Gliwice, Polska.

Katarzyna Podyma;
ORCID 0009-0000-8176-3496;
https://orcid.org/0009-0000-8176-3496; Katarzyna.podyma25@gmail.com
Bonifraterskie Centrum Medyczne sp. z o.o. Szpital Zakonu Bonifratrów pw. Aniołów Stróżów w Katowicach. ul. Ks. Leopolda Markiefki 87; 40-211 Katowice.

Sara Rosołowska-Żak;
ORCID 0009-0003-6202-2475;
https://orcid.org/0009-0003-6202-2475; sararosolowska@gmail.com;
Wojewódzki Szpital Specjalistyczny nr 5 im. św. Barbary w Sosnowcu, Plac Medyków 1, 41-200 Sosnowiec, Polska.

Maria Sambura;
ORCID 0009-0007-5518-1418;
https://orcid.org/0009-0007-5518-1418; maria.e.sambura@gmail.com;
Wojewódzki Szpital Specjalistyczny nr 5 im. św. Barbary w Sosnowcu, Plac Medyków 1, 41-200 Sosnowiec, Polska.

Wiktoria Sas;
ORCID 0009-0006-3487-316X;
https://orcid.org/0009-0006-3487-316X; wsas95178@gmail.com
Powiatowy Zespół Zakładów Opieki Zdrowotnej w Czeladzi , Szpitalna 40, 41-250 Czeladź, Polska.

Gracja Ryznar;
ORCID 0000-0001-6078-0414;
https://orcid.org/0000-0001-6078-0414; gracjaryznar@gmail.com;
Samodzielny Publiczny Zakład Opieki Zdrowotnej Uniwersytecki Szpital Kliniczny im. Wojskowej Akademii Medycznej Uniwersytetu Medycznego w Łodzi – Centralny Szpital Weteranów; ul. Stefana Żeromskiego 113, 90-549 Łódź.

Piotr Pierzchała;
ORCID 0009-0002-8783-742X;
https://orcid.org/0009-0002-8783-742X; p.pierzchala311@gmail.com; Wielospecjalistyczny Szpital Powiatowy S.A. im. dr B. Hagera w Tarnowskich Górach, ul. Pyskowicka 47-51, 42-612 Tarnowskie Góry, Polska.

Michalina Minkowska;
ORCID 0009-0003-9633-256X;
https://orcid.org/0009-0003-9633-256X; m.minkowska95@gmail.com;
Wielospecjalistyczny Szpital Powiatowy S.A. im. dr B. Hagera w Tarnowskich Górach, ul. Pyskowicka 47-51, 42-612 Tarnowskie Góry, Polska.

Krystyna Chimiak;
ORCID 0009-0006-4468-3300;
https://orcid.org/0009-0006-4468-3300; krystynachimiak2@gmail.com;
Zespół Szpitali Miejskich w Chorzowie, Strzelców Bytomskich 11, 41-500 Chorzów, Polska.

Gabriela Bylica;
ORCID 0009-0003-1422-2878;
https://orcid.org/0009-0003-1422-2878 ; gabriela.bylica0@gmail.com;
Zespół Szpitali Miejskich w Chorzowie, Strzelców Bytomskich 11, 41-500 Chorzów, Polska.

Corresponding author: Julia Rejdych, julia.rej@gmail.com
Szpital Miejski nr 4 w Gliwicach, ul. Zygmunta Starego 20, 44-100 Gliwice, Polska.

Abstract

Introduction

Colchicine is a lipid-soluble alkaloid sourced from a plant called Colchicum autumnale(Picture 1.), called the “autumn crocus”.[1] Its use was first mentioned in papyrus placed back in ancient Egypt in 1550 BC. Its characteristics then included alleviation of pain and swelling. Today, colchicine is administered to patients with various diseases, rheumatological like gout, but also Familial Mediterranean Fever. In recent years the alkaloid has been found effective in treatment of atherosclerotic cardiovascular diseases, like acute coronary syndromes, SARS-CoV-2 infections and more. Unequivocally physical exercise

plays a role in diseases treated with colchicine and are complementary actions that patients can undertake for better disease control.

Aim of the study

The study aims to summarize the applications and possible future uses of colchicine in various diseases with special focus on athletes, as well as to outline the role of physical exercise in those illnesses.

Material and methods

We conducted a review of scientific publications published in the years 1974-2024 in English in the PubMed and Google Scholar databases. We used keywords such as "colchicine", “physical exercise” and "cardiovascular disease”.

Conclusions

Colchicine is an ancient drug that is still used in clinical practice with an ongoing search for its new applications. Colchicine treatment is very well established in gout and Familial Mediterranean Fever. The drug is recommended in acute coronary syndromes by the ESC guidelines, furthermore its potential use in other cardiovascular diseases is backed by many scientific studies, including patients who are athletes. Despite a narrow therapeutic window and many interactions with other drugs colchicine is considered a safe and accessible medication. Physical exercise is recommended for many diseases treated with colchicine and plays a vital role in symptom control.

Key words: Colchicine, Gout, Rheumatological disease, Cardiovascular diseases, Acute Coronary Syndrome, Covid-19, Physical exercise, Athletes

Mechanism of action

Colchicine exerts a broad anti-inflammatory effect. Its mechanism is multi-faceted. The most recognized one is the ability of colchicine to bind to tubulins, thus blocking the incorporation into microtubules, an essential component of cytoskeleton. This mechanism makes colchicine a classical antimitotic drug acting to block mitotic cell division in metaphase. In higher

concentrations colchicine causes microtubule depolymerisation resulting in severe toxicity in normal tissues limiting its use in cancer therapies.[2]

Colchicine interferes with the migration of neutrophils to sites of inflammation by disrupting microtubule-dependent processes involved in cell motility and chemotaxis. This inhibition of neutrophil migration helps reduce the inflammatory response associated with conditions like gout, where neutrophil infiltration contributes to tissue damage and pain.[3] Colchicine has been shown to modulate the production and release of inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). By interfering with microtubule-dependent signaling pathways, colchicine can attenuate the activation of inflammatory pathways and reduce the secretion of pro-inflammatory mediators. [3,17] In gout, colchicine can also inhibit the formation and deposition of monosodium urate crystals in joints. Colchicine interferes with the intracellular transport processes involved in crystal formation and deposition, thereby reducing the inflammatory response triggered by these crystals.[4]

Picture 1. Colchicum autumnale - Autumn crocus. [36]

Metabolism and side effects

Colchicine undergoes metabolism primarily in the liver, but also through the kidneys (10-20%) and gut excretion. These metabolism reactions are catalyzed by CYP3A4, P-glycoprotein and CYP2C19 which makes colchicine vulnerable to drug interactions such as those listed in Table 1. Concurrent use of statins and colchicine may increase the risk of myopathy.[5]

Renal impairment significantly increases the risk of colchicine toxicity, as evidenced by various studies. Patients with low estimated glomerular filtration rate (eGFR) have notably higher colchicine exposure, with a more than 5-fold increase observed in patients on hemodialysis compared to those with normal kidney function. According to available data decreased renal elimination may start around eGFR of 60 mL/min and at eGFR below 30mL/min colchicine concentrations increase significantly and may pose a high risk of toxicity. [6,7]

Colchicine use is associated with various side effects and potential toxicity, particularly at higher doses. The most common side effects are gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. These symptoms are often dose-dependent and may necessitate dose adjustments or discontinuation of treatment.[5] In LoDoCo-2 trial 10.5% of patients with chronic coronary disease ended therapy with 0.5mg colchicine due to perceived side effects. [11] According to a metaanalysis conducted by Papageorgiou et al. 12.5% of patients discontinued therapy because of side effects. [38]

Table 1. Drug interactions with colchicine according to Slobodnick A. [16]

Strong CYP3A4 inhibitors	**Moderate CYP3A4 inhibitors**	**P-glycoprotein inhibitors**
Clarithromycin	Cimetidine	Amiodarone
Diltiazem	Ciprofloxacin	Verapamil
Itraconazole,Ketoconazole	Cyclosporine	Carvedilol
Ritonavir	Erythromycin	Itraconazole
Telithromycin	Fluconazole	Ranolazine

In addition to gastrointestinal effects, colchicine can cause hematological abnormalities, including leukopenia, thrombocytopenia, and aplastic anemia, albeit rare. Neurotoxicity, manifesting as peripheral neuropathy and myopathy, has been reported, especially with prolonged use or in patients with renal impairment. [8]

Colchicine in cardiovascular diseases

Colchicine has been found to have a positive effect on patients with various cardiovascular diseases such as pericarditis, atherosclerosis, atrial fibrillations and finally - coronary heart disease. [9] In 2023 ESC Guidelines for the management of acute coronary syndromes low-dose colchicine (0.5mg a day) may be considered if, under optimal therapy, coronary events reoccur. In a COLCOT study which involved 4745 patients with recent ACS colchicine in low doses was corresponding to lower CV deaths, MI, strokes, resuscitated heart arrests or urgent revascularization compared to placebo. [10] The incidents of cardiovascular incidents was also assessed in patients with chronic coronary disease in a randomised, controlled, double blind LoDoCo-2 trial with over 5 thousand patients. The risk of cardiovascular events was significantly lower in patients who received 0.5mg of colchicine daily in comparison to placebo, although the prevalence of death from noncardiovascular causes was higher than placebo group (incidence, 0.7 vs. 0.5 events per 100 person-years; hazard ratio, 1.51; 95% CI, 0.99 to 2.31). Colchicine did not reduce all-cause mortality in patients with chronic coronary disease[11,37]

Colchicine is a first-line treatment used in pericarditis in conjunction with NSAIDS/ASA. According to 2015 ESC guideline for the diagnosis and management of pericardial diseases, the drug is administered orally according to weight: <70kg 0.5mg once a day and ≧70 kg 0.5mg twice a day. In double-blind randomized controlled trials (CORP, ICAP and CORP-2) patients with both acute and recurrent pericarditis have less recurrence and alleviated symptom persistence after 72 hours of treatment.[12]

Colchicine in rheumatological diseases

Colchicine is most recognisably used in gout exacerbation management alongside NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular). According to the 2020 American College of Rheumatology Guideline for the Management of Gout when a patient experiences gout flare it is recommended to use 1.2mg of colchicine orally immediately, and 0.6mg after 1h. It is not advised to use high dose colchicine due to comparable efficacy, but aggravated adverse effects.[13] Similarly according to EULAR due to better availability of the 0.5mg pill in European countries it is advised to use 1.5mg of colchicine at the start of the flare and 0.5mg dose after 1h. Therapy can be continued until the symptoms (pain, swelling, tophi, redness of affected joint) subside, up to 6mg of colchicine in total.[14]

Colchicine drug can be also administered in acute gouty flares prophylaxis concurrently with ULT (urate-lowering therapy).[15]

FMF (Familial Mediterranean Fever) is a genetically driven inflammatory disorder most commonly presented by patients of Mediterranean origin. Symptoms include pain in the abdomen, joints, chest and episodic fevers. A possible mechanism for colchicine use in this disease is targeting increased responsiveness of the inflammasome and accelerated production of IL-1.[16] The efficacy of colchicine in FMF patients was assessed in a double-blind, placebo controlled randomised clinical trial and showed great symptom control, thus this drug is a first line therapy in FMF. [17] Complications of FMF include amyloidosis, most commonly affecting the kidneys, but also gastrointestinal tract, spleen, liver, lungs, and as a result causing end-stage renal failure. [18] Colchicine has been shown to prevent the progression of the aforementioned complications. The factors contributing to adequate control of the complications of the disease are: continuous use rather than interrupted use (adjusted OR 0.15, 95% CI 0.04–0.53), earlier initiation age of colchicine (adjusted OR 0.95, 95% CI 0.90–1.01) and adequate dosage of 1.2-1.8mg/day.[19]

Even after a kidney transplant patients need to continue the colchicine treatment. According to Livneh, A. et al. development of amyloidosis in a transplanted kidney is inevitable when the administered dose of colchicine is less than 1mg/day, but usually preventable with 1.5mg/day or more.[20] In a proportion of patients inadequate symptom control and resistance to colchicine is observed. A study by Lidar, M. et al. assessed if, on top of oral colchicine use, an intravenous weekly treatment could be helpful. The study revealed a 50% reduction in attack frequency and severity in FMF patients after 3 months of weekly intravenous injections of 1mg colchicine, as well as decrease in analgesic tablets use and erythrocyte sedimentation rate (ESR).[21.22]

The safety of long term intravenous application of colchicine was assessed by Grossman et al. in patients with insufficient symptom control on oral colchicine with maximum tolerated dose of 2-3 mg/day. Monthly rates of abdominal and joint attacks decreased as well as their duration and severity. Additionally, a relatively low number of patients experienced gastrointestinal discomfort and myalgia, but no severe adverse effects have been observed. [23]

The role of physical activity in diseases treated with colchicine

A case report presented by Deligiannis et al. showed a 45-year-old experienced marathon runner who developed myopericarditis during COVID-19 infection treated with colchicine alone. After establishing the diagnosis based on clinical manifestation, ECG, electrocardiography and MRI the patient was treated at home with 1 mg daily of colchicine. A strict ban on exercise lasting 6 months was recommended. After 3 days of the colchicine treatment all of the symptoms subsided. After one month any pathological finding in the ECG and electrocardiography disappeared. After six months MRI and exercise testing did not deviate from norm.[24] Interestingly, damage of the heart in athletes as a result of COVID-19, if based solely on troponin levels, is oftentimes underestimated. [25]

In order to examine the extent of heart damage due to COVID-19 in student athletes a study involving 54 patients ranging from asymptomatic to moderately-symptomatic was conducted. In its findings 39.5% of athletes had pericardial late enhancements with associated pericardial effusion. Although more than 1 in 3 student athletes showed signs of pericardial inflammation there were no patients showing apparent radiological signs of active myocarditis. [26] According to Starekova et al. who examined 145 student athletes with COVID-19 only two patients (1.4%) presented with MRI findings consistent with ongoing myocarditis.[27] These findings rise a question when is the appropriate time for athletes or highly active individuals to return to intensive training regimes after COVID-19. An attempt to answer this question is explored by Phelan et al. viewpoint which is endorsed by the American College of Cardiology Sports and Exercise Cardiology Section. If a patient undergoes asymptomatic COVID-19 infection they should refrain from physical activity for at least 2 weeks starting from a time of positive antigen test. Resuming activities should be conducted in a slow, controlled manner under health professional supervision. For mild to moderate symptoms it is recommended for athletes to return to exercising 2 weeks after symptom resolution. If the patient's condition requires hospitalization further testing, hsTn and cardiac imaging, should be implemented. The experts viewpoint suggest following myocarditis return-to-play guidelines if the athlete does present with abnormal testing. [28]

An interesting fact occurs in athletes regarding upper respiratory tract infections (URTI). The “open window” theory states that high intensity, prolonged exercise creates a transiently suppressed immune system, thus making a gateway for viruses to infect hosts. [29] Low to moderate-intensity activities play a positive role in aforementioned infections, whereas high-

intensity strenuous activities depress our immunity. [30] This could be explained by the reduction of the inflammation and cortisol levels during low intensity training characterized by VO2max <60% or VO2max <37–45% . [31, 32] Contrary, high intensity training (VO2max>70%) can make the athlete more susceptible to infectious diseases due to a suppressed immune system. When a viral infection occurs in athletes (including COVID-19) it is recommended to continue a low intensity training or moderate intensity training (when symptoms are mild) combined with proper nutrition. Sudden cessation of exercise during URTI can further increase muscle catabolism and weaken the immune system. [30]

Physical exercise can be an additional action for patients suffering from rheumatic diseases such as gout. Long lasting submaximal exercise can reduce or maintain the levels of uric acid. In the acute phase of gout physiotherapy can maintain or increase range of motion and regain muscle strength. Physical inactivity can worsen the symptoms of the disease which ultimately, if left untreated, can cause a disability. [33] According to Schlesinger et al. physically active patients had over 12 times less gout flares per year and 2.8 times decreased pain perception after 4 weeks of standard treatment. [34] In rheumatoid arthritis home-based exercise programs were assessed in various randomised controlled trials which suggested a reduced pain and improved function of patients. To conclude, physical exercise plays a vital role in diseases treated with colchicine and should be prescribed alongside pharmacotherapy. [35]

Colchicine in COVID-19

In the ongoing pursuit of effective treatments against SARS-CoV-2 infections, colchicine as an anti-inflammatory drug that is well-tolerated and inexpensive, has been extensively studied as a potential adjuvant medication for managing COVID-19 infections. Severe COVID-19 mostly presented as an ARDS (acute respiratory distress syndrome) and it has been linked to a cytokine storm syndrome, which involves a hyperinflammation due to significant increase in cytokine productions such as interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrosis- (TNF-).[39] Colchicine was seen as a promising medication because it acts on multiple targets related to inflammation in COVID-19. [40] According to a meta-analysis by Hariyanto et al. which involved 5778 patients, adding colchicine treatment may reduce both severity and mortality of the disease.[41] Contrary, according to a meta-analysis by Rachma et al. colchicine did not reduce mortality nor the need for mechanical ventilation or cardiovascular events. [39] To summarise, colchicine as part of COVID-19 treatments presents inconclusive information.

Conclusions and discussion

Colchicine is a well studied drug that is effective in treatment of certain cardiovascular and rheumatological diseases. More studies are needed to assess if the drug is applicable in the context of athletes and highly active individuals. Colchicine was studied in the context of COVID-19 disease, but the results are inconclusive, further research is needed. Physical exercise can be helpful in treatment of upper respiratory tract infections. Side effects and withdrawal from treatment with colchicine should be discussed with a patient.

Disclosure:

The authors declare that they have no financial or non-financial conflicts of interest that could be perceived as influencing the interpretation of the research findings or the content of this manuscript. This work was conducted independently without any external funding or support.

Author's contribution

Conceptualization: Julia Rejdych

Methodology: Katarzyna Podyma

Software: Wiktoria Sas

Check: Gracja Ryznar, Piotr Pierzchała, Michalina Minkowska

Formal Analysis: Michalina Minkowska

Investigation: Julia Rejdych

Resources: Sara Rosołowska-Żak, Maria Sambura

Data Curation: Sara Rosołowska-Żak

Writing -Rough Preparation: Krystyna Chimiak, Gabriela Bylica

Writing -Review and Editing: Sara Rosołowska-Żak

Visualization: Wiktoria Sas

Supervision: Katarzyna Podyma

Project Administration: Julia Rejdych

All authors have read and agreed with the published version of the manuscript.

Receiving funding: no funding was received.

Disclosures: No disclosures.

Financial support: No financial support was received.

Conflict of interest: The authors declare no conflict of interest.

Bibliography

1. Angelidis C, Kotsialou Z, Kossyvakis C, et al. Colchicine Pharmacokinetics and Mechanism of Action. *Current Pharmaceutical Design*. 2018;24(6):659-663. doi:10.2174/1381612824666180123110042
2. Leung YY, Yao Hui LL, Kraus VB. Colchicine—Update on mechanisms of action and therapeutic uses. *Seminars in Arthritis and Rheumatism*. 2015;45(3):341-350. doi:10.1016/j.semarthrit.2015.06.013
3. Ben-Chetrit E, Bergmann S, Sood R. Mechanism of the anti-inflammatory effect of colchicine in rheumatic diseases: a possible new outlook through microarray analysis. *Rheumatology*. 2005;45(3):274-282. doi:10.1093/rheumatology/kei140
4. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of Action of Colchicine in the Treatment of Gout. *Clinical Therapeutics*. 2014;36(10):1465-1479. doi:10.1016/j.clinthera.2014.07.017
5. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. *Clinical Toxicology*. 2010;48(5):407-414. doi:10.3109/15563650.2010.495348
6. Hansten PD, Tan MS, Horn JR, et al. Colchicine Drug Interaction Errors and Misunderstandings: Recommendations for Improved Evidence-Based Management. *Drug Safety*. 2022;46(3):223-242. doi:10.1007/s40264-022-01265-1
7. Robinson PC, Terkeltaub R, Pillinger MH, et al. Consensus Statement Regarding the Efficacy and Safety of Long-Term Low-Dose Colchicine in Gout and Cardiovascular Disease. *The American Journal of Medicine*. 2022;135(1):32-38. doi:10.1016/j.amjmed.2021.07.025
8. Harris R, Marx G, Gillett M, Kark A, Arunanthy S. Colchicine-induced bone marrow suppression: treatment with granulocyte colony-stimulating factor. *The Journal of Emergency Medicine*. 2000;18(4):435-440. doi:10.1016/s0736-4679(00)00160-8
9. Imazio M, Nidorf M. Colchicine and the heart. *European Heart Journal*. 2021;42(28):2745-2760. doi:10.1093/eurheartj/ehab221
10. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal*. 2023;44(38):3720-3826. doi:10.1093/eurheartj/ehad191
11. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *New England Journal of Medicine*. 2020;383(19):1838-1847.

doi:10.1056/nejmoa2021372

12. Imazio M. Colchicine for Recurrent Pericarditis (CORP). *Annals of Internal Medicine*. 2011;155(7):409. doi:10.7326/0003-4819-155-7-201110040-00359

13. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care & Research*. 2020;72(6):744-760. doi:10.1002/acr.24180

14. Leczenie napadu dny moczanowej. Medycyna Praktyczna dla lekarzy. Accessed May 5, 2024. https://www.mp.pl/reumatologia/wytyczne/284440,leczenie-napadu-dny-moczanowej

15. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Annals of the Rheumatic Diseases*. 2016;76(1):29-42. doi:10.1136/annrheumdis-2016-209707

16. Slobodnick A, Shah B, Krasnokutsky S, Pillinger MH. Update on colchicine, 2017. *Rheumatology*. 2017;57(suppl_1):i4-i11. doi:10.1093/rheumatology/kex453

17. Dinarello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW. Colchicine Therapy for Familial Mediterranean Fever. *New England Journal of Medicine*. 1974;291(18):934-937. doi:10.1056/nejm197410312911804

18. Bhatt H, Cascella M. Familial Mediterranean Fever. *StatPearls*. Published online July 31, 2023.

19. Sevoyan MK, Sarkisian TF, Beglaryan AA, Shahsuvaryan GR, Armenian HK. Prevention of Amyloidosis in Familial Mediterranean Fever with Colchicine: A Case-Control Study in Armenia. *Medical Principles and Practice*. 2009;18(6):441-446. doi:10.1159/000235892

20. Livneh A, Zemer D, Siegal B, Laor A, Sohar E, Pras M. Colchicine Prevents Kidney Transplant Amyloidosis in Familial Mediterranean Fever. *Nephron*. 1992;60(4):418-422. doi:10.1159/000186801

21. Lidar M, Kedem R, Langevitz P, Pras M, Livneh A. Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. *The Journal of rheumatology*. 2003;30(12):2620-2623.

22. Surma S, Basiak M, Romańczyk M, Filipiak KJ, Okopień B. Colchicine — From rheumatology to the new kid on the block: Coronary syndromes and COVID-19. *Cardiology Journal*. 2023;30(2):297-311. doi:10.5603/cj.a2021.0123

23. Grossman C, Farberov I, Feld O, Livneh A, Ben-Zvi I. Efficacy and safety of long-term treatment with intravenous colchicine for familial Mediterranean fever (FMF) refractory

to oral colchicine. *Rheumatology International*. 2019;39(3):517-523. doi:10.1007/s00296-018-04237-w

24. Deligiannis A, Dervisopoulou E, Kouidi E. Usefulness of colchicine for Covid-19 myopericarditis in athletes. A case report and review of the literature. *Case Reports and Reviews*. 2021;2(1). doi:10.33425/2693-1516.1015

25. Schellhorn P, Klingel K, Burgstahler C. Return to sports after COVID-19 infection. *European Heart Journal*. 2020;41(46):4382-4384. doi:10.1093/eurheartj/ehaa448

26. Brito D, Meester S, Yanamala N, et al. High Prevalence of Pericardial Involvement in College Student Athletes Recovering From COVID-19. *JACC: Cardiovascular Imaging*. 2021;14(3):541-555. doi:10.1016/j.jcmg.2020.10.023

27. Starekova J, Bluemke DA, Bradham WS, et al. Evaluation for Myocarditis in Competitive Student Athletes Recovering From Coronavirus Disease 2019 With Cardiac Magnetic Resonance Imaging. *JAMA Cardiology*. 2021;6(8):945. doi:10.1001/jamacardio.2020.7444

28. Phelan D, Kim JH, Chung EH. A Game Plan for the Resumption of Sport and Exercise After Coronavirus Disease 2019 (COVID-19) Infection. *JAMA Cardiology*. 2020;5(10):1085. doi:10.1001/jamacardio.2020.2136

29. Aoi W, Naito Y. Immune Function, Nutrition, and Exercise. In: *Nutrition and Enhanced Sports Performance*. Elsevier; 2019:83-95. Accessed May 12, 2024. http://dx.doi.org/10.1016/b978-0-12-813922-6.00007-2

30. Agha-Alinejad H, Ahmadi Hekmatikar AH, Ruhee RT, et al. A Guide to Different Intensities of Exercise, Vaccination, and Sports Nutrition in the Course of Preparing Elite Athletes for the Management of Upper Respiratory Infections during the COVID-19 Pandemic: A Narrative Review. *International Journal of Environmental Research and Public Health*. 2022;19(3):1888. doi:10.3390/ijerph19031888

31. Steensberg A, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *American Journal of Physiology-Endocrinology and Metabolism*. 2003;285(2):E433-E437. doi:10.1152/ajpendo.00074.2003

32. Rose GL, Skinner TL, Mielke GI, Schaumberg MA. The effect of exercise intensity on chronic inflammation: A systematic review and meta-analysis. *Journal of Science and Medicine in Sport*. 2021;24(4):345-351. doi:10.1016/j.jsams.2020.10.004

33. Shinde S, Shah S. Impact of physical activity on gouty arthritis: A systematic review. *D Y Patil Journal of Health Sciences*. 2021;9(4):140. doi:10.4103/dypj.dypj_65_21

34. Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute

gouty arthritis. *The Journal of rheumatology*. 2002;29(2):331-334.

35. Gwinnutt JM, Wieczorek M, Cavalli G, et al. Effects of physical exercise and body weight on disease-specific outcomes of people with rheumatic and musculoskeletal diseases (RMDs): systematic reviews and meta-analyses informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. *RMD Open*. 2022;8(1):e002168. doi:10.1136/rmdopen-2021-002168

36. Anna M. Accessed May 2, 2024. https://plantura.garden/uk/flowers-perennials/autumn-crocus/autumn-crocus-overview

37. Efficacy and Safety of Colchicine in Patients With Chronic Stable Coronary Disease. American College of Cardiology. Accessed May 9, 2024. https://www.acc.org/Latest-in-Cardiology/Articles/2020/10/30/15/06/Efficacy-and-Safety-of-Colchicine-in-Patients-With-Chronic-Stable-Coronary-Disease

38. Papageorgiou N, Briasoulis A, Lazaros G, Imazio M, Tousoulis D. Colchicine for prevention and treatment of cardiac diseases: A meta-analysis. *Cardiovascular Therapeutics*. 2016;35(1):10-18. doi:10.1111/1755-5922.12226

39. Rachma B, Putra PYP, Putri DAE, Zulaifah Z, Prameswari AS. Colchicine as adjuvant therapy in COVID-19 patients: a meta-analysis. *International Journal of Public Health Science (IJPHS)*. 2022;11(4):1458. doi:10.11591/ijphs.v11i4.21837

40. Vitiello A, Ferrara F. Colchicine and SARS-CoV-2: Management of the hyperinflammatory state. *Respiratory Medicine*. 2021;178:106322. doi:10.1016/j.rmed.2021.106322

41. Hariyanto TI, Halim DA, Jodhinata C, Yanto TA, Kurniawan A. Colchicine treatment can improve outcomes of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Clinical and Experimental Pharmacology and Physiology*. 2021;48(6):823-830. doi:10.1111/1440-1681.13488