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QUALIFICATION WORK

on the topic: «PHARMACY STUDENTS' AWARENESS OF PHARMACEUTICAL CARE OF PATIENTS WITH HYPERURICEMIA AND GOUT»

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ANNOTATION

Pharmacists play a key role in successful gout management, therefore they should be aware of current recommendations for effective gout treatment and hyperuricemia prevention. The master's thesis is devoted to the study of pharmacy students' awareness of the pharmaceutical care of patients with hyperuricemia and gout. A questionnaire was developed, with the help of which a survey was conducted and the level of awareness of the respondents was assessed.

The total volume of the thesis is 50 pages, it consists of an introduction and 3 chapters and contains 3 tables, 13 figures, and 55 references.

Keywords: pharmacy students, awareness, pharmaceutical care, gout, hyperuricemia

АНОТАЦІЯ

Фармацевти відіграють ключову роль в успішному веденні пацієнтів з подагрою, тому вони повинні знати сучасні рекомендації щодо ефективного лікування подагри та профілактики гіперурикемії. Магістерська робота присвячена вивченню обізнаності студентів-фармацевтів щодо фармацевтичної опіки пацієнтів з подагрою та гіпрурікемією. З цією метою нами розроблена анкета, за допомогою якої проведено анонімне опитування та оцінений рівень обізнаності респондентів.

Загальний обсяг роботи – 50 сторінок, робота складається із вступу та 3 розділів, містить 3 таблиці, 13 рисунків, 55 посилань на літературні джерела.

Ключові слова: студенти-фармацевти, обізнаність, фармацевтична опіка, подагра, гіперурикемія

LIST OF CONTENTS

ABBREVIATION LIST

ACR	–	American College of Rheumatology;
AH	–	arterial hypertension;
COX-2	–	cyclooxygenase-2;
DASH	–	dietary approaches to stop hypertension;
DHB-CHO	–	3,4-dihydroxybenzyl aldehyde;
DHNB	–	3,4-dihydroxy-5-nitrobenzaldehyde;
FDA	–	Food and drug administration;
GI	–	gastrointestinal;
HU	–	hyperuricemia;
IL-1β	–	interleukin-1 beta;
LPS	–	lipopolysaccharide;
MSU	–	monosodium urate;
NADPH	–	nicotinamide adenine dinucleotide phosphate oxidase;
NF-κB	–	nuclear factor κB;
NSAIDs	–	non-steroidal anti-inflammatory drugs;
PBMCs	–	peripheral blood mononuclear cells;
RAS	–	renin-angiotensin system;
ROS	–	reactive oxygen species;
SOD2	–	superoxide dismutase 2;
TNF-α	–	tumor necrosis factor alpha;
UA	–	uric acid;
ULT	–	urate-lowering therapy;
USA	–	United States of America;
XDH	–	xanthine dehydrogenase;
XO	–	xanthine oxidase;
XOR	–	xanthine oxidoreductase.

INTRODUCTION

Relevance of the topic. Hyperuricemia plays a role as one of the key intermediate steps in the development of gout – a monosodium urate monohydrate crystal deposit disease.

Gout is a chronic and debilitating condition that affects millions of people worldwide. Both asymptomatic hyperuricemia and gout are considered elements of purine metabolic disturbances and are usually associated with other metabolic disorders (metabolic syndrome, diabetes mellitus, dyslipidemia, stroke, cardiovascular diseases). As modern society develops, the global incidence of gout and hyperuricemia has also increased, especially in developed countries. Despite the availability of effective treatments, gout remains a significant health concern, with a growing prevalence in many countries.

Gout is a complex disease with a multifactorial etiology that involves genetic, environmental, and lifestyle factors. It typically presents in middle-aged and elderly individuals, with a male predominance. Gout is often associated with other comorbidities, including hypertension, metabolic syndrome, and chronic kidney disease. The disease has a substantial impact on patients' quality of life, with frequent flares of pain and inflammation leading to reduced mobility, work productivity, and social engagement [1, 2].

The management of gout has evolved over time, with several effective therapies available. The mainstay of treatment is the use of urate-lowering agents, which aim to reduce serum uric acid levels and prevent further crystal deposition. Non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are commonly used to manage acute flares, while corticosteroids are reserved for more severe cases. However, despite these treatments, many patients continue to experience recurrent flares, joint damage, and disability.

In recent years, there has been a growing interest in developing new and innovative therapies for gout. These include the use of biological agents that target

specific components of the inflammatory response, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). Other novel therapies include gene therapy, immunomodulatory agents, and the repurposing of existing drugs for gout treatment [1, 2].

The pharmacist plays a key role in gout treatment. Pharmacists are not usually involved in making a diagnosis. However, it is important to know the criteria for acute gouty arthritis if a patient seeks advice from a pharmacy with symptoms indicating it, in order to refer the patient to a doctor for further evaluation. Also, the pharmacist can assist prescribers in optimizing medication selection, performing disease state monitoring, can educate patients about medication benefits, side effects and risks of elevated uric acid, and can improve patient adherence to urate-lowering therapy.

The aim of the study is to evaluate the pharmacy students' awareness of pharmaceutical care for patients with hyperuricemia and gout.

In order to achieve the set goal, it was necessary to solve **the objectives of the study:**

1. To analyze and summarize literature data on the current state of knowledge regarding gout, including its risk factors, clinical manifestations, and the current treatment options.

2. To develop an anonymous survey questionnaire to determine the level of pharmacy students' awareness of the issues of the pharmaceutical care for patients with hyperuricemia and gout.

3. To carry out an anonymous survey of pharmacy students of NUPh using the developed questionnaire.

4. To analyze the respondents' answers and estimate the level of pharmacy students' awareness of the research topic.

The study object – pharmacy students of the National University of Pharmacy.

The study subject – pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout.

The research methods. Sociological (survey by questionnaire), system-analytical, statistical.

The practical significance of the obtained results. The obtained results substantiate the expediency of familiarizing practicing pharmacists and students of special pharmaceutical education with the management of patients with gout. Research results can be considered when revising educational and professional programs and improving the content of educational components.

Approbation of research results and publications. The abstract was published based on the results of the work: Mellouki Hamza, Scientific supervisor: Stepanova S.I. Pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout: Topical issues of new medicines development: Materials of II XXIX International scientific and practical conference of young scientists and students (April 19-21, 2023, Kharkiv). – Kharkiv: NUPh, 2023. P. 373.

Structure and volume. The qualification work contains an introduction, the literature review, 2 chapters of the experimental part, conclusions, and a reference list of used (55 literature sources). The volume of the main text of the work is 52 pages. The work is illustrated with 3 tables and 13 figures.

CHAPTER 1
HYPERURICEMIA AND GOUT: CURRENT PROBLEMS (LITERATURE REVIEW)

Hyperuricemia (HU) is an elevated uric acid level in the blood serum of 360 μmol/l in women and above 420 μmol/l in men due to purine metabolism disorders. This elevated level is the result of increased production, decreased excretion of uric acid, or a combination of both processes. Hyperuricemia is the leading cause of gout and is also related to diabetes, chronic kidney disease, metabolic syndrome, hypertension, stroke, and atherosclerosis [3]. Several recent epidemiological surveys have indicated that the prevalence rates of hyperuricemia among adults in the United States, Australia, and South Korea are 20.1%, 16.6%, and 11.4%, respectively [4, 5, 6]. Moreover, the prevalence of hyperuricemia has increased in recent decades. Asymptomatic UA occurs in 5-8% of the population, while only in 5-20% of them develop gout [7, 8, 9].

Therefore, hyperuricemia has become an important public health problem.

1.1. Hypotheses to account for the mutation of uricase in humans

In most mammals, uric acid is degraded by the enzyme uricase (also known as urate oxidase) to allantoin. During the Miocene epoch (8-20 million years ago) parallel mutations occurred in our hominoid ancestors that, eventually resulting in complete loss of uricase. Unlike the majority of mammals, in humans due to the loss of uricase activity during the evolution. When the enzyme is xanthine oxidase, both uric acid and superoxide anion are produced, whereas the reaction with xanthine dehydrogenase releases uric acid and the reduced form of nicotinamide-adenine dinucleotide. Serum uric acid levels are therefore low (0.5-2.0 mg/dL) in most mammals but humans and the Great Apes have higher uric acid levels than most other mammals (fig.1.1.) [10-13].

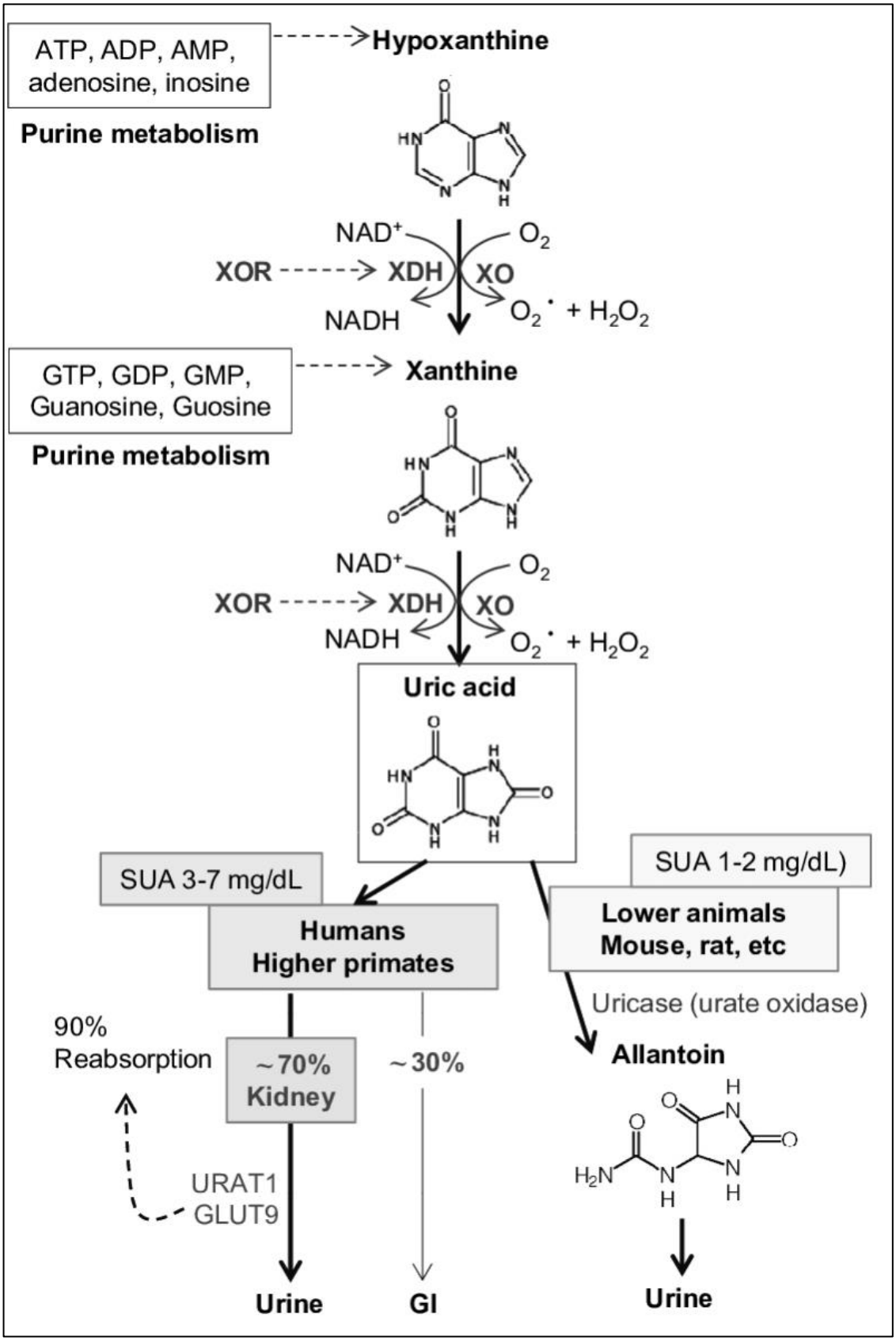


Fig. 1.1. Purine metabolism in humans and lower animals [13].

There are several hypotheses to account for the mutation of uricase in humans and the Great Apes. An early hypothesis was that an increase in serum uric acid level may increase intelligence because it has similarities to other cerebral stimulants, such as caffeine. Perhaps the most favored hypothesis is that the increase in serum uric acid level occurred to provide greater antioxidant activity, and that this may account for the greater longevity of humans and Great Apes compared with most other mammals. Indeed, uric acid is a strong antioxidant, and accounts for much of the antioxidant activity in plasma. An antioxidant hypothesis suggests that the uricase mutation occurred as a consequence of the loss of human ability to synthesize vitamin C approximately 40 to 50 million years ago owing to a mutation in L-gulonolactone oxidase. The mutation may have occurred because the primates of that period were largely fruit-eating and hence were ingesting large quantities of vitamin C, making the mutation harmless. However, later there was a selection advantage for those species that could increase their antioxidants, and this was provided by the uricase mutation. Although the antioxidant hypothesis remains a viable possibility for why the mutation of uricase persisted, an increased uric acid level is not associated with longevity in any species. In fact, in humans, almost all studies show the opposite; higher uric acid levels correlate with an increased death risk. Authors proposed an alternative hypothesis, that the mutation of uricase resulted in increased blood pressure and increased salt sensitivity. It is known that our early hominoid ancestors were on a very low-sodium diet. It is possible that the rapid evolutionary changes may have favored those individuals who could conserve sodium more effectively. In support of this hypothesis is a large amount of literature showing that uric acid levels correlate with blood pressure levels. Also, hyperuricemia caused renal structural changes that resulted in salt sensitivity. Uric acid induces endothelial dysfunction, leading to an acute salt-resistant increase in blood pressure, followed by uric acid-induced arteriolosclerosis of the renal vasculature, in turn leading to persistent salt-sensitive hypertension. The uricase mutation may have been advantageous to our early hominoid ancestors by helping them to maintain blood pressure levels during environmental stress. But in modern

humans, there is evidence that the increase in serum uric acid level may predispose them to cardiovascular disease. In part, this new risk could be attributed to changes in sodium intake because early hominoids were eating only 0.5 g/d of salt compared with the 8 to 10 g/d of salt ingested in developed countries' diets. diets. However, another important consideration is the effect of diet on serum uric acid levels because animals lacking uricase do not regulate serum uric acid levels very effectively. Thus, diets rich in purine increase the gout risk [13].

This loss, together with UA balance in the kidney, in which the majority of filtered UA is reabsorbed, and the lifestyle and eating habits of developed countries, has led to a high prevalence of HU and its consequences. HU is the primary risk factor for developing gout and this risk increases exponentially when the serum UA levels rise. However, only a minority of those with high UA levels will develop gout [1, 3, 7]. Along with its association with gout, there is increasing evidence of a relationship between HU and hypertension, renal disease, metabolic syndrome, diabetes, cardiovascular disease [10, 14].

1.2. The current view on the pathogenesis of gout

Gout is a chronic systemic metabolic disease caused by genetic and environmental factors, characterized by impaired purine metabolism, which leads to the deposition of monosodium urate (MSU) crystals in various tissues and is manifested by crystal-induced inflammation at the sites of urate fixation (joints, periarticular tissues, internal organs).

According to epidemiology, gout is diagnosed in at least 1-3% of the adult population. The ratio of men and women is 7:1. The peak incidence is observed in men aged 40-50 years, in women – ≥ 60 years [14]. Gout affects 1-2% of adults in developed countries, where it is the most common inflammatory arthritis in men. Epidemiological data are consistent with a rise in the prevalence of gout [15].

Current classic clinical manifestations of gout: gouty arthritis; tophi (deposits of urate crystals in joints, bones, cartilage, soft tissues); gouty nephropathy; nephrolithiasis with urate stones [16].

An acute attack of gout is a paradigm of acute sterile inflammation, as opposed to pyogenic inflammation. Acute gouty inflammation develops as a result of the interaction of MSU microcrystals with neutrophilic granulocytes, monocytes/macrophages and basophilic granulocytes, which leads to the release of inflammatory mediators.

Recent studies suggest that the triggering of interleukin-1 beta (IL-1β) release from leucocytes lies at the heart of a cascade of processes that involves multiple cytokines and mediators. Thus, MSU crystals are triggers of inflammatory mediators:

- cytokines: interleukin-1α and interleukin-6, tumor necrosis factor;
- chemokines: interleukin-8;
- mini-molecules: prostaglandins, histamine;
- fatty acids act as a secondary signal and are necessary for the development of gouty arthritis;

in addition, uric acid crystals activate cyclooxygenase-2 (COX-2), kinases (Syk, p38 MAPK).

Interleukin-1β plays a very important role in the development of gout. Inflammasome promotes the conversion of the inactive form of the mediator pro-interleukin-1β into the active form of interleukin-1β. Inflammasome, a special intracellular complex of proteins that initiates the development of an inflammatory reaction when the cell comes into contact with microorganisms, uric acid crystals, which leads to the transition of pro-inflammatory cytokines to their active state.

The understanding of these mechanisms offers us a novel opportunity to interfere with this inflammatory pathway, and may one day develop more effective therapies for gout. The recent discovery of crystal-induced cytotoxicity offers additional drug targets [17-19].

HU plays a crucial role in the occurrence and development of gout. It has been reported that about a quarter of patients with HU will develop gout [20].

1.3. Asymptomatic hyperuricemia

Asymptomatic hyperuricemia is a term traditionally applied to settings in which the serum urate concentration is elevated but in which neither symptoms nor signs of MSU crystal deposition disease, such as gout, or uric acid renal disease, have occurred. Hyperuricemia is classically defined as a serum urate of more than 420 μmol/l in men or more than 360 μmol/l in women. Asymptomatic hyperuricemia affects approximately 20 % of the general population in the United States of America (USA), with variable rates in other countries [19].

This confirms the importance of hyperuricemia and its prevalence in the population in comparison with clinically defined gout: asymptomatic hyperuricemia is recorded from 10 to 38.7% in various countries of the world [21].

The well accepted consequence of hyperuricemia is an increased risk for gout and kidney stones, and currently, treatment of asymptomatic hyperuricemia is recommended only in people with these established conditions. Yet, people with asymptomatic hyperuricemia are also at risk for developing a variety of other conditions, including hypertension, acute and chronic kidney disease, obesity, metabolic syndrome, fatty liver, diabetes mellitus [19].

Historically asymptomatic hyperuricemia was considered a benign laboratory abnormality with little clinical significance in the absence of gout or kidney stones. Yet, there is increasing evidence that asymptomatic hyperuricemia can predict the development of hypertension, obesity, diabetes mellitus, chronic kidney disease. One potential mechanism by which asymptomatic hyperuricemia may contribute to disease is by stimulating inflammation. While urate has been classically viewed as an anti-oxidant with beneficial effects, more recent studies suggest both crystalline and soluble urate may activate various inflammatory pathways.

UA is an antioxidant that can react with superoxide anion to generate allantoin, peroxynitrite to form triuret, and nitric oxide to form 6-aminouracil. However, the reactions of uric acid with peroxynitrite will also generate the aminocarbonyl radical and the triuretcarbonyl radical. Uric acid will also form radicals when reacted with myeloperoxidase. Moreover, inside the cell uric acid is prooxidative, and this has been shown in cells of various tissues. The mechanism involves the activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) oxidase, and in some cell types, the NADPH oxidase may translocate to the mitochondria. Interestingly, the effect of soluble urate on mononuclear cells is more complex, as priming of peripheral blood mononuclear cells (PBMCs) with urate results in enhanced IL-1β release in response to lipopolysaccharide (LPS), but lesser reactive oxygen species (ROS) release while another study found no statistically significant effects on IL-1β, SOD2 gene transcription nor the total antioxidant capacity of the cell [19].

A number of prospective epidemiological studies have revealed an association between elevated UA levels and the risk of developing cardiovascular complications both in the general population and in patients with arterial hypertension (AH) [22]. An increase in plasma uric acid in patients with untreated hypertension is a predictor of an increased risk of death. The pathogenetic role of hyperuricemia in the development of arterial hypertension and its significance for the development of myocardial infarction and stroke have been proven [23].

There are several mechanisms underlying the association between hyperuricemia and elevated blood pressure. The uric acid molecule is not inert - it induces an inflammatory process, stimulating the release of a number of inflammatory mediators, including those with vasoconstrictor properties. The inflammatory process and ischemia of the renal tissue contribute to the activation of the renin-angiotensin system (RAS), which leads to an increase in blood pressure. Thus, uric acid, directly and indirectly affecting the tubulointerstitial tissue of the kidneys, leads to impaired excretion and the development of HU [24]. The latter stimulates the proliferation of smooth muscle cells, promotes vasoconstriction,

damage to the integrity of the vascular endothelium, the development of endothelial dysfunction, increased arterial stiffness, which also leads to the development of hypertension [25].

The involvement of uric acid in the formation of hypertension is also confirmed by the antihypertensive effect of allopurinol (a drug that reduces uricemia) in patients with untreated hypertension [26]. An increase in its content in the blood is noted in at least 25% of patients with AH [27]. On the other hand, 30% of individuals with hyperuricemia have elevated blood pressure [28]. When hypertension is combined with an increase in the level of uric acid in the blood, the risk of developing cardiovascular diseases increases by 3-5 times [29]. Therefore, the use of antihypertensive drugs that do not cause the appearance of hyperuricemia is important, and in cases where it already occurs, it is necessary the use of drugs that help reduce the level of uric acid in the blood.

1.4. Treatment of established gout

1.4.1. Treatment of acute flares

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in acute gout attacks. There is no evidence for a preference for any one NSAID over others [9], so the choice is based on the patient's prior experience with the drug, concerns about specific symptoms (e.g., nervous system intolerance to indomethacin), and a lower risk of hemostatic problems with a selective cyclooxygenase inhibitor COX-2 drug celecoxib (for example, in patients taking anticoagulants or suffering from thrombocytopenia). Due to the inhibition of prostaglandins, all NSAIDs slow down renal blood flow, maintain salt and water retention, and exacerbate arterial hypertension and the risk of acute heart failure. Whichever NSAID is chosen, treatment of a gout flare usually requires a higher dose (e.g., naproxen 500 twice daily or celecoxib 400 twice daily). Treatment should be continued for the shorter period of time required for complete control of the attack (usually 3-5 days). One of

the supposed benefits of NSAIDs is their intrinsic analgesic activity, which can reduce pain even to the point of complete suppression of inflammation [30-32].

Glucocorticoids are powerful effective anti-inflammatory agents for gout flare-ups. Glucocorticoids and NSAIDs are approximately comparable in terms of effectiveness in the treatment of acute gout attacks. The “2020 American College of Rheumatology guidelines” (2020 ACR guidelines) recommend 0.5 mg/kg prednisolone or equivalent as the starting dose. Prednisolone can be continued at this level until the attack is completely resolved. Use glucocorticoids for as short a period of time as possible, but not too short; because it can lead to a recurrence of the outbreak. Glucocorticoid toxicity is well known, and although the risk of glucocorticoid toxicity is higher with long-term and repeated treatment, even a short course may cause side effects [30-32].

Colchicine is an alkaloid derived from the plant of the Lily family *Colchicum autumnale* L. It acts mainly through the inhibition of microtubule polymerization which affects leukocyte activation, vacuole movement, and cell migration. Colchicine interferes with several inflammatory pathways including adhesion and recruitment of neutrophils, superoxide production, inflammasome activation, the RhoA/Rho effector kinase pathway, the tumor necrosis factor alpha (TNF-α) - induced nuclear factor κB (NF-κB) pathway attenuating the inflammatory response. The currently recommended dose of colchicine for acute flare is 1.2 mgs, followed by 0.6 mgs one hour later. Colchicine must be used with caution, and/or dose adjusted, in patients with chronic kidney disease. After initiating flare treatment with any agent, colchicine may be used adjunctively at a lower daily dose (0.6 mgs once or twice daily) to prevent recurrence [30-33].

A new class of anti-IL1β drugs includes a targeted antibody (canakinumab), a modified receptor (rilonacept), a recombinant receptor antagonist (anakinra). These agents have been shown in phase 2 (anakinra), and phase 3 (canakinumab, rilonacept) studies to be as good as or better than conventional therapy for acute and chronic gout. ILβ-directed therapy has several attractive features, including good tolerability and no likely gastrointestinal (GI), renal or metabolic adverse effects.

Thus, drugs may be particularly appropriate in patients with multiple co-morbidities. Although the cost of biologics is high, acute treatment is brief, such that the cost may be less prohibitive than it initially appears, especially if the duration of hospitalization is shortened as a result. Concerns about infection, relevant when these drugs are used chronically, have not been borne out for short-term use. Canakinumab is approved in Europe for acute gout but was rejected by the Food and Drug Administration (FDA) owing to concerns about the long half-life (26 days) of the drug. In contrast, anakinra has a short half-life (6 hours) and is administered daily for 3–5 days to resolve a flare. The agent is effective and often utilized by many rheumatologists, particularly in hospitalized patients with co-morbidities [30, 34].

1.4.2. Urate-lowering therapy

1.4.2.1. Xanthine oxidase inhibitors

"ACR guidelines 2020" recommend a xanthine oxidase inhibitor, either allopurinol or febuxostat, as the initial urate-lowering therapy agent. Xanthine oxidase inhibitors block the production of urate, and reduce hyperuricemia whether caused by metabolic urate overproduction, or GI or renal urate underexcretion. The catabolism of purine bases and targets of antihyperuricemic agents is shown in Fig.1.2. With prolonged use, xanthine oxidase inhibitors can prevent the deposition of urate and resolve crystals already deposited, including tophi. The rate of crystal dissolution is generally proportional to the degree of urate lowering achieved. Allopurinol is the first-line drug for treating gout. "ACR guidelines 2020" recommend treatment with allopurinol first, and febuxostat only if allopurinol is not tolerated or inadequately effective. Recent studies, were written, support that prolonged urate-lowering can effectively reduce the frequency of attacks [30, 31].

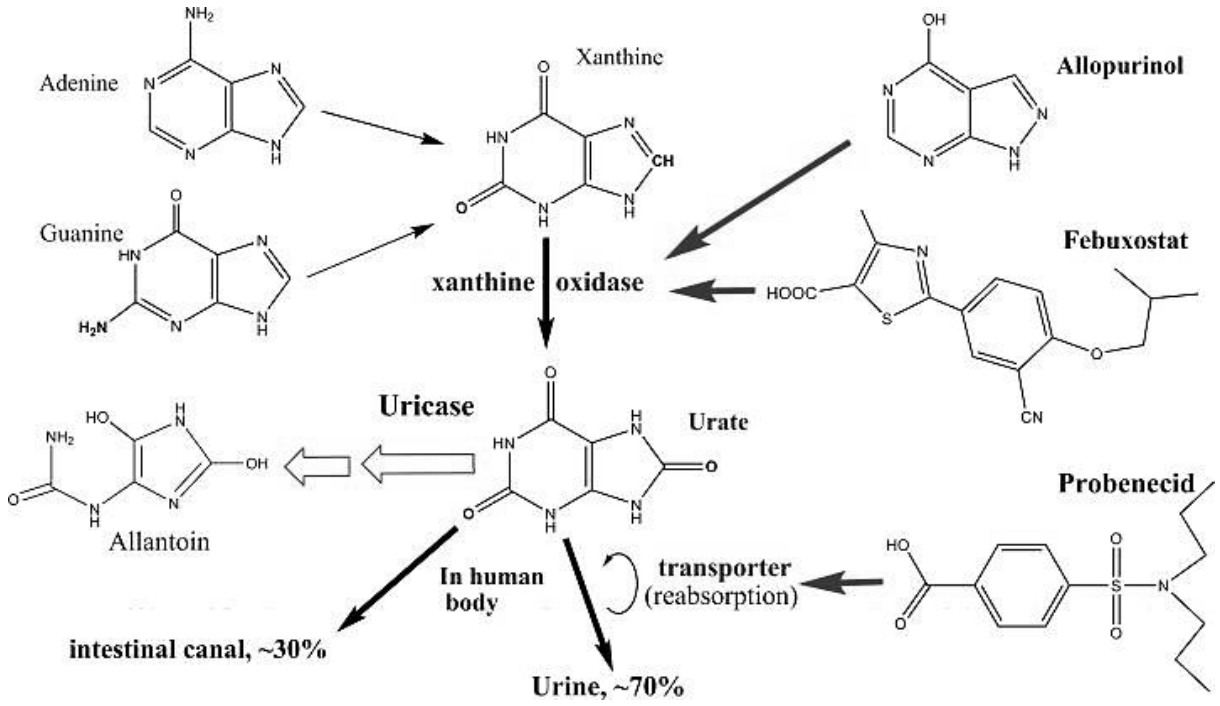


Fig. 1.2. Catabolism of purine bases and targets of antihyperuricemia agents

1.4.2.2. Uricosuric agents

Uricosuric agents inhibit renal transporters including (URAT-1), blocking reabsorption of uric acid from the proximal tubule and promoting urate excretion (Fig.1.2.). There are two FDA-approved uricosuric agents are probenecid and lesinurad. “ACR guidelines 2020” recommend to use probenecid if xanthine oxidase inhibitors are contraindicated or have failed, or as an add-on therapy if needed. Probenecid is modestly effective at lowering serum urate. Lesinurad is a more potent inhibitor of URAT1 than probenecid, and in some patients can result in significant decrements in serum urate [31].

1.4.2.3. Uricase

Raburicase and pegloticase are approved uricase formulations for treating hyperuricemia. They are the third line treatment in those who are intolerant to other medications. Rasburicase, a recombinant fungal enzyme, is used to rapidly lower the

serum urate in the setting of tumor lysis syndrome, but is not generally used in gout due to its immunogenicity. Pegloticase is a recombinant enzyme sourced from nonhuman mammalian genes, decorated with multiple strands of polyethylene glycol intended to reduce its immunogenicity. Pegloticase is FDA-approved for refractory gout treatment. With months of treatment, pegloticase depletes total body urate stores, reduces or halts flares, and resolves tophi in most patients, and can significantly improve quality of life. Treatment with pegloticase for chronic refractory gout is limited by immunogenicity caused by the production of anti-pegloticase antibodies [30, 35].

1.4.2.4. Combination treatment using antihyperuricemic agents with fenofibrate and/or losartan

In selecting an antihypertensive, it is useful to know that losartan is unique among the angiotensin II receptor blockers and antihypertensives in that it has modest uricosuric activity.

Combination therapy of fenofibrate or losartan with antihyperuricemic agents, which included benzbromarone (50 mg once daily) or allopurinol (200 mg twice a day), significantly reduced serum uric acid concentrations in accordance with increased uric acid excretion. A combination of fenofibrate or losartan with antihyperuricaemic agents is a good option for the treatment of gout patients with hypertriglyceridaemia and/or hypertension, though the additional hypouricemic effect may be modest [30, 37].

1.5. Development of new xanthine oxidase inhibitors

Besides the 3-xanthine oxidoreductase (XOR)-inhibitor drugs (allopurinol, febuxostat, and topiroxostat), there are develop new XOR-inhibitor drugs because of the following reasons: current drugs (allopurinol and febuxostat) are associated with certain adverse effects and are not indicated for broad use in patients with

asymptomatic hyperuricemia. Hyperuricemia has been demonstrated to be an independent risk factor for cardiovascular disease, renal diseases, and many other diseases; and long-term control of asymptomatic hyperuricemia may be an effective strategy to prevent/treat these hyperuricemia-related diseases. Thus, there is an urgent need to develop new XOR inhibitors with no or milder adverse effects. In recent years, several synthesized purine analogs were reported to have XOR inhibitory effects (table 1.1). The natural derivatives for the development of novel XOR inhibitors, which could be possible alternatives for allopurinol and febuxostat, or at least in combination therapy to minimize the adverse effects of current drugs, in particular in long-term applications for symptomatic and asymptomatic hyperuricemia-related diseases. We found that 3,4-dihydroxy-5-nitrobenzaldehyde (DHNB), a derivative of natural protocatechuic aldehyde, is a strong XOR-inhibitor in a cell-free system and in a mouse model. DHNB displays potent mixed-type inhibition of XOR and shows an additive effect with allopurinol at low concentrations. In addition, DHNB, but not allopurinol, directly scavenged ROS. DHNB has a different chemical structure from the current clinical XOR-inhibitor drugs, and showed much less toxicity in the mouse model as compared with allopurinol. In a mouse model, a large dose (500 mg/kg) of allopurinol caused high mortality and fur loss of survivors and their offspring; while DHNB did not show any adverse effects at this dose. In fact, natural protocatechuic aldehyde (3,4-Dihydroxybenzyl aldehyde, DHB-CHO) only showed a weak inhibitory effect on XOR activity. DHB-CHO was found in the mushroom *Phellinus linteus*, which has been widely used in China, Japan, and Korea for centuries to treat a broad range of diseases, including gout. *Phellinus linteus* extract showed an XOR inhibitory effect *in vitro*. DHNB showed a much stronger XOR inhibitory effect than DHC-CHO *in vitro*, and has much less toxicity than allopurinol in mice. Thus, DHNB is considered a prime candidate for use as an XOR-inhibitor drug. Further preclinical and clinical studies of DHNB are warranted [38].

Promising hypouricemic drugs are drugs of plant origin. They can combine several mechanisms of influence on SC exchange, as well as cause a favorable anti-

inflammatory, and antioxidant effect, and reduce cardiovascular risks. Numerous xanthine oxidase inhibitors of plant origin are being investigated. Uricosuric effect is characteristic of iridoids (aucubin), hypouricemic - derivatives of hydroxycinnamic acids (4,5-O-dicopheylquinic and lithostermic), coumarins (esculin), flavonoids (acacetin, apigenin, hesperitin, quercetin, kaempferol, luteolin, myricetin, naringenin, puerarin, rutin, formonetin), sesquiterpenoids (stagninol), lignans (phyllantin), a combination of uricosuric and hypouricemic action – coumarins (scopoletin), flavonoids (morin) [38].

Table 1.1.

Recent development of new XOR inhibitors [38]

Compound	Mechanisms	Authors
9-Benzoyl 9-deazaguanines	Purine analogs	Rodrigues M.V. et al., 2016
N-(1,3-Diaryl-3-oxopropyl) amides	Purine analogs	Nepali K. et al., 2011
5,6-Dihydropyrazolo/pyrazolo[1,5-c] quinazoline derivatives	Purine analogs	Kumar D. et al., 2014
Naphthopyrans	Non-purine analogs	Sharma S. et al., 2014]
Thiadiazolopyrimidin-5-ones	Non-purine analogs	Sathisha K.R. et al., 2016
Aryl-2H-pyrazole derivatives	Non-purine analogs	Sun Z.G. et al., 2015
2-Amino-5-alkylidene-thiazol-4-ones	Non-purine analogs	Smelcerovic Z. et al., 2015
2-(Indol-5-yl)thiazoles	Non-purine analogs	Song J.U. et al., 2015
1-Hydroxy/methoxy-4-methyl-2-phenyl-1H-imidazole-5-carboxylic acid derivatives	Non-purine analogs	Chen S. et al., 2015
Riparsaponin	Natural substance	Xu F. et al., 2014
Genistein (4',5,7-Trihydroxyisoflavone)	Natural substance	Lin S. et al., 2015
Morin	Natural substance	Zhang J. et al., 2016
Curcumin analogs	Natural derivatives	Shen L. et al., 2009
Oxidation product of caffeic acid	Natural derivatives	Masuda T. et al., 2014
Aloe-emodin derivatives	Natural derivatives	Shi DH et al., 2014
DHNB (3,4-Dihydroxy-5-nitrobenzaldehyde)	Natural derivatives	Lü JM et al., 2013

1.6. The role of diet in hyperuricemia and gout

Owing to high purine content, substantial consumption of red meat and seafood has been confirmed by a number of studies to be positively correlated with the development of hyperuricemia and gout flares. Fructose, a major constituent of high-fructose corn syrup in sugar-sweetened beverages, can also facilitate ATP depletion through phosphorylation and result in an elevation of circulating uric acid level. A recent meta-analysis including 2 prospective cohort studies has verified the effect of fructose on increasing vulnerability to gout and hyperuricemia. Alcohol intake was also regarded as one of the important precipitating factors for the development or exacerbation of hyperuricemia and gout. Ethanol ingestion has been proven to increase uric acid production by ATP degradation to AMP; furthermore, dehydration and metabolic acidosis associated with alcoholism might contribute to decreased urinary excretion of urate. Along the line, a number of observational studies as well as a meta-analysis have suggested that substantial alcohol consumption may significantly predispose people to gout and hyperuricemia. Based on this published evidence, patients with gout or hyperuricemia are recommended to avoid or limit high-purine organ meat, seafood, alcohol, and high fructose corn syrup-sweetened beverages or foods [39, 40].

It has been pointed out by literature that urinary excretion of uric acid and xanthine was increased after ingestion of dairy products. The low purine content of milk, in combination with the uricosuric effect of casein, may lead to decreased urate concentration. Some studies have observed this urate-lowering effect of dairy products. A randomized clinical trial testified that skim milk powder enriched with glycomacropeptide and G600, standard skim milk powder and lactose powder could all significantly lower serum urate levels, alleviate gouty arthralgia, and reduce the frequency of gout flares over a three-month period. This meta-analysis demonstrated the negative association between dairy products and the risk of gout and hyperuricemia [39, 40].

The current conventional diet for gout focuses on limitation of protein to reduce purine-loading. When the protein intake is reduced, this must be accompanied by a compensatory increase in one or both of the remaining macronutrients (e.g., carbohydrates and fats). There is the risk of increased consumption of foods that are rich in refined carbohydrates (including fructose) and saturated or trans fats. These changes could further exacerbate insulin resistance, leading to higher plasma levels of glucose and lipids, thereby contributing to the development and worsening of metabolic syndrome and its complications in patients with gout.1,6 Furthermore, the long-term therapeutic value of a purine-restricted diet has been questioned due to limited palatability, sustainability, and anti-gout efficacy [41].

That's why, the particular diet that is adapted to an individual should be guided by their concurrent comorbidities and personal preferences. To aid in the personalization of these lifestyle recommendations, there are ongoing efforts to identify phenotypically distinct clusters, or subtypes, of gout based on comorbidities. For example, the DASH diet may be ideal for patients with hypertension and can be implemented with calorie restriction for those who are overweight or obese. For patients who require better lipid or glycemic control, the Mediterranean diet may be most suitable based on improvements in high-density lipoproteins, triglycerides, and markers of insulin resistance [41].

Conclusion for chapter 1

A literature review of gout, its epidemiology, pathophysiology, and management, with a particular focus on the use of novel therapies was carried out. Gout is a well-studied disease for which effective pharmaceutical treatments are available. However, adherence to treatment for gout is low and the underlying causes are complex. In this regard, cooperation between pharmacists and physicians is essential for the practical application of recommendations for the treatment of gout.

CHAPTER 2
MATERIALS AND METHODS OF RESEARCH

2.1. The design of a questionnaire to assess pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout

The structured questionnaire is used to collect data from respondents. consisting of standardized closed questions and predefined answers. This questionnaire type consists of standardized closed questions, that are worded in a specific way, asked in a set sequence and require respondents to choose from a set of predefined answers. When set up correctly, they can enable a large volume of data to be gathered quickly and can provide a really good top-level snapshot of that audience's views, that can be used to support a hypothesis or to inform crucial decisions. When creating the questionnaire, we considered general design concepts, including item creation and analysis, interpretability of terms, assessment of validity and reliability, and specific patient-initiated questions asking during a consultation.

In the study, pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout was assessed using a questionnaire developed by us. First, the questionnaire was pre-tested on a convenience sample of 10 pharmacy students to ensure the reliability and comprehensibility of the content of the questionnaire.

Our research was conducted in February-March 2023. The object of the study were pharmacy students of the National University of Pharmacy. Respondents were selected as a random sample.

The questionnaire developed by us includes the following parts: an explanatory part, which provides information about the tasks and content of the questionnaire, instructions for respondents, and an evaluation part. The evaluation part consists of 31 questions and includes three sections: I – questions on socio-demographic characteristics (age, gender, place of residence, course of study), II – 9 general questions related to the understanding of pharmacy student of the FDI

problem, III – 18 closed questions to assess respondents' knowledge of common FDIs. This section includes FDIs that have been cited in previous studies, some of which may affect serious side effects (grapefruit with atorvastatin, MAOIs with cheese, spironolactone with moderate potassium intake, warfarin with vitamin K supplements, theophylline with excessive amounts of coffee and/or tea), others can significant decrease effectiveness of drugs, especially if specific food is consumed regularly in large quantities or with drugs with a narrow therapeutic index (tetracycline with milk and dairy products, levodopa with protein food). The third section included questions about the effect of consumed beverages on medication and 5 questions to assess knowledge of the appropriate timing of medication intake in relation to food.

Questionnaire

Preface

Dear students! Gout is now regarded as an important medical problem. The urgency of the problem is associated with the high prevalence of the disease among the working population, the disability of patients. We are interested to know your opinion and competence on this issue.

Please take 5-7 minutes of your time to complete the survey. This will help us a lot.

The survey is completely anonymous!

Sincere thanks in advance!

I. General information

1. Please indicate the course of your studies at NUPh
   - 3th course
   - 4th course
   - 5th course
2. Please indicate your age
   - ≤ 21 years
   - 22

- 23
- 24
- 25
- 26
- 27
- 28
- Over 28

3. Please indicate your gender.

- female
- male

4. Please indicate the country of your permanent residence

_____ (open-ended question)

5. Please indicate the course of your studies at NUPh

- 3th course
- 4th course
- 5th course

II. Special part

6. Normal level of uric acid in the blood is an important factor in homeostasis in the human body

- yes
- no
- difficult to answer

7. Uric acid is the end product of metabolism

- purine bases of adenine and guanine
- amino acids
- glucose
- fatty acids

8. The biochemical basis of gout is:

- increase in the concentration of uric acid in the blood
- decrease in the concentration of uric acid in the blood
- increase in the concentration of uric acid in the urine
- decrease in the concentration of uric acid in the urine

– increase in the concentration of urea in the blood
– decrease in the concentration of urea acid in the blood

9. The reasons for the increase in the level of uric acid in the blood is
   – Increased formation of uric acid
   – Insufficient excretion (excretion from the body
   – First and second are correct
10. Uric acid in the human body is formed from purines with the participation of the enzyme
   – COX-1
   – COX-2
   – Xanthine oxidase
   – Phospholipase A2
   – 5-Lipoxygenases
11. Asymptomatic hyperuricemia is
   – increase in the level of uric acid in the blood in the presence of signs of gouty arthritis
   – increase in the level of uric acid in the blood without clinical signs of gouty arthritis
   – increased levels of uric acid in the urine
12. To confirm that a patient has gout or asymptomatic hyperuricemia, a laboratory test should be performed and the following should be determined:
   – level of glycated hemoglobin (HbA1c)
   – serum creatinine level
   – the level of uric acid in the blood
   – serum urea level
   – the level of uric acid in the urine
   – blood glucose level
12. Hyperuricemia is considered when the level of uric acid in the blood serum is higher
   – 260 μmol/l
   – 360 μmol/l
   – 420 μmol/l
   – 650 μmol/l
13. Asymptomatic hyperuricemia is a marker of many pathological processes in the human body
   – yes
   – no

– find it difficult to answer

14. Asymptomatic hyperuricemia is associated with the development of cardiovascular diseases, chronic kidney disease

– yes
– No
– find it difficult to answer

15. Hyperuricemia is considered as a component of the metabolic syndrome

– yes
– no
– find it difficult to answer

16. Hyperuricemia indicates the presence of gout in a patient

– yes, always
– not always
– no
– find it difficult to answer

17. Select drugs that can contribute to the development of hyperuricemia (several answers)

– lisinopril
– febuxostat
– paracetamol
– acetylsalicylic acid (low doses)
– ibuprofen
– hydrochlorothiazide

18. Taking thiazide diuretics may contribute to the development of hyperuricemia

– yes
– no
– difficult to answer

19. Alcohol use is a risk factor for hyperuricemia

– yes
– no
– difficult to answer

20 The main mechanism of action of hypouricemic drugs

– reducing the concentration of uric acid in the blood due to inhibition of its synthesis
– increased excretion of uric acid by the kidneys
– increased excretion of uric acid through the gastrointestinal tract

– anti-inflammatory effect by reducing the synthesis of prostaglandins

21. Basic pathogenetic therapy of patients with gout should be based on
    – suppression of inflammation by prescribing NSAIDs
    – reducing the concentration of uric acid in the blood
    – suppression of inflammation with glucocorticoids
    – appointment of analgesics and chondroprotectors
22. During the period of exacerbation of gout attacks, therapy should be aimed at
    – suppression of inflammation with NSAIDs and colchicine
    – urate-lowering therapy with alopurinol or febuxostat
    – first and second are correct
23. During an attack of acute gouty arthritis apply
    – allopurinol and febuxostat
    – febuxostat and NSAIDs
    – colchicine and NSAIDs
24. Hypouricemic drugs include
    – allopurinol and febuxostat
    – pobenicid and lesinurad
    – diclofenac sodium and celecoxib
    – colchicine and acetylsalicylic acid
    – meloxicam and celecoxib
25. The mechanism of action of allopurinol is to inhibit the enzyme
    – COX-1
    – COX-2
    – xanthine oxidase
    – phospholipase A2
    – 5-lipoxygenase
26. Alopurinol is not recommended during an acute attack of gouty arthritis
    – yes
    – no
27. During an exacerbation of gout and an attack of gouty arthritis, patients should be advised
    – rest and cold in the area of the affected joint
    – rest and warming procedures in the area of the affected joint
    – active movements and gymnastics
28. Pharmacotherapy of asymptomatic hyperuricemia with allopurinol is considered inappropriate
    – yes
    – no

– find it difficult to answer

29. Diet for gout and hyperuricemia should be aimed at
– increased consumption of foods rich in purines
– reduced consumption of foods rich in purines

30. Diet for gout and hyperuricemia should be aimed at
– increased consumption of low-fat dairy products
– reduced consumption of low-fat dairy products

31. Select foods that need to be restricted in the diet of patients with gout in order to normalize purine metabolism (choose as many options as you think are correct):
– legumes (peas, beans)
– seafood (shellfish, etc.)
– offal (liver, kidneys, etc.)
– black pepper
– dairy
– green vegetables
– bread and pastries with bran
– cherries, strawberries

32. Select drinks that need to be limited in the diet of patients with gout in order to normalize purine metabolism (choose as many options as you think are correct):
– fruit juices
– tea coffee
– red wine
– alkaline mineral waters
– grapefruit juice
– drinks containing simple sugars
– milk

2.2. Statistical analysis

The data obtained as a result of the survey were statistically processed using the Excel program, the package of statistical programs STATISTICA 10.0 (StatSoft). Comparative intergroup analysis was performed using Fisher's test φ (if necessary, with Yates correction), the relationship between individual indicators was

based on Spearman's correlation coefficient ρ. A value of $p < 0.05$ was considered statistically significant.

Conclusions for chapter 2

Thus, at the initial stage of the research, a questionnaire was developed to assess the pharmacy student's awareness of pharmaceutical care of patients with hyperuricemia and gout. The questionnaire was first checked by experts and then tested with a pilot study on a convenient sample of 10 students to ensure the content and face validity of the questionnaire. The anonymous questionnaire was distributed among 4th and 5th year pharmacy students of the National University Pharmacy. Descriptive and inferential statistics were performed in this study.

CHAPTER 3
EVALUATION OF PHARMACY STUDENTS' AWARENESS OF PHARMACEUTICAL CARE OF PATIENTS WITH HYPERURICEMIA AND GOUT

3.1. Characteristics of survey respondents

This survey was conducted using the questionnaire developed by us. In order to evaluate the pharmacy students' awareness of FDI, as well as the respondents' attitude to this issue, we collected empirical information during February-March 2023 among pharmacy students in the 4th and 5th years of study in NUPh.

A total of 53 pharmacy students answered the questionnaire, of whom 9 (17.0%) were 4th-year and 44 (83.0%) were 5th-year students. The respondents' characteristic is shown in figure 3.1.

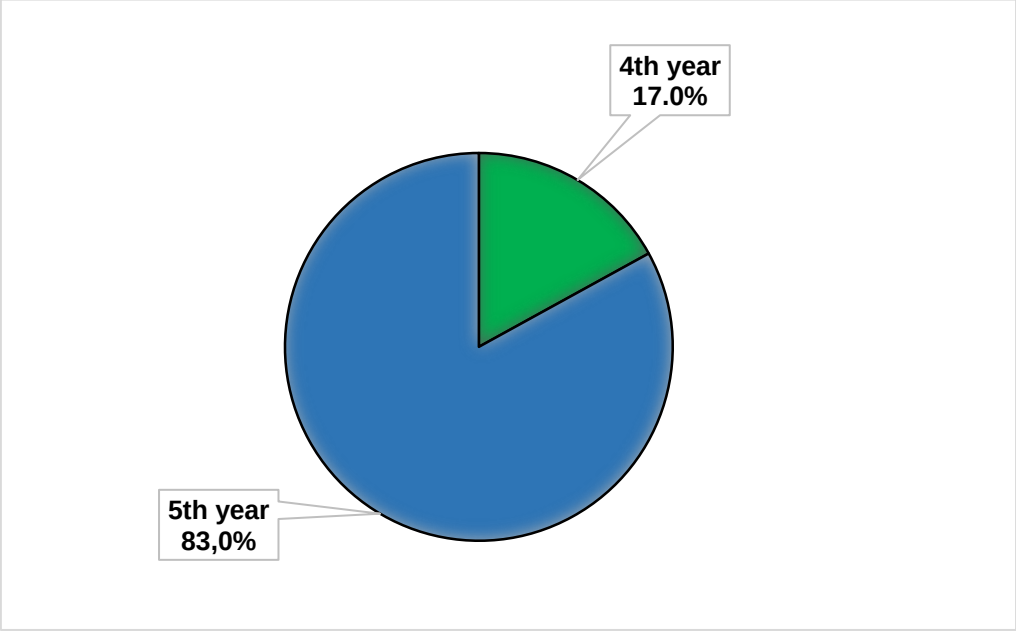


Fig. 3.1. Distribution of the respondents according to year of study

This sample represented mostly the students who are in their final year of university studies. The age of the participants is between 21- and 28 years. Figure

3.2 shows the age distribution of respondents which was as follows: 21 years (5 - 9.4%), 22 years (6-11.3%), 23 years (7-13.2%), 24 years (19 - 35.8%), 25 years (6-11.3%), 26 years (1-1.9%), 27 years (3-5.7%), 28 (3-5.7%). >28 years (3-5.7%). It also found the main age group in the study – 24 years.

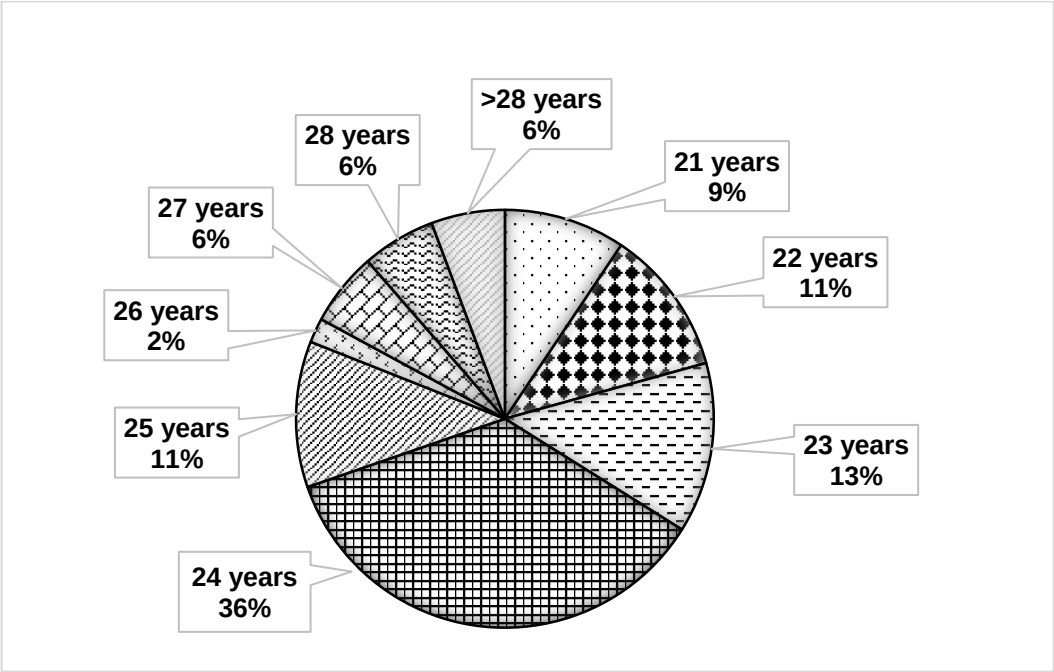


Fig. 3.2. Distribution of the respondents according to their age

40 (81.1%) students named Morocco as their place of permanent residence, 3 (5.7%) students - Ukraine, 3 (5.7%) students - Germany, 1 student each (1.9%) – Lebanon, Egypt, Kuwait, Libya, Portugal, Senegal, Uganda.

More than 80% of the students in our survey are Moroccans. Bringing women into the labor market has been a persistent challenge for Morocco. The new constitution and the new family law in 2004 were a great step forward for women's rights domestically and as a model for the broader Muslim world. Across the country, women play a crucial role in socio-economic development despite the fact that there are large inequalities between men and women as far as access to resources is concerned. In the labor market, which is marked by labor and gender division,

women have a growing role in doing their share of farming and of production, small trade, and services. A big gap persists between female and male labor force participation rates. In 2020, the female employment rate in Morocco was 16.7%. In comparison, the male employment rate stood at 62.9%. From a macroeconomic point of view, increasing female labor market participation would improve the country's productive capacity and support growth, while from a microeconomic point of view, it can help women gain a voice in society, leading households to invest more in education [42].

Of these respondents, 33 (62.3%) were male, and 19 (35.8%) were female. One student (1.9%) did not wish to indicate their gender. The survey results are shown in Figure 3.3. Males participated more in this research compared to females. Also, the ratio of males to females is greater in the university.

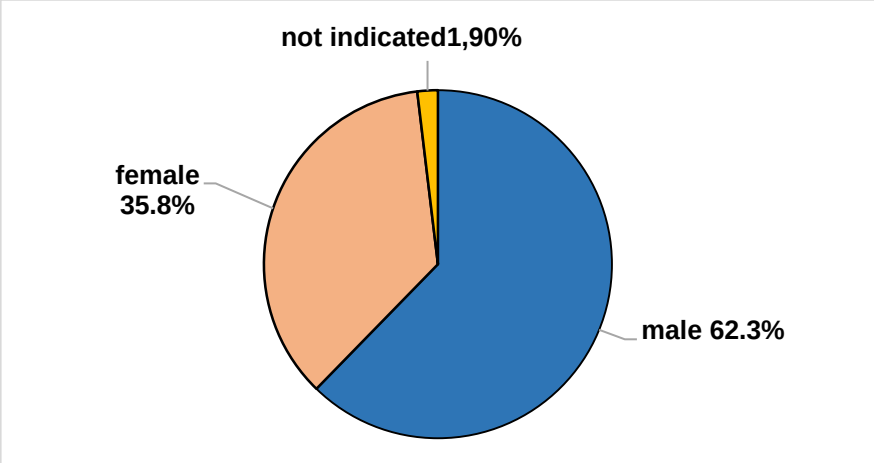


Fig. 3.3. Gender of respondents

An increasingly important problem in pharmacy is the practical application of knowledge gained in the learning process, on the one hand, and the impact of practical work experience on the acquisition and consolidation of skills and knowledge, on the other hand.

Among the respondents, all 5-year students already had experience working in a pharmacy, possibly in the form of an internship, which is provided by the

training program at NUPh. That is, the majority of respondents had little work experience in their specialty.

3.2. Assessment of the hyperuricemia problem from the point of view of pharmacy students

Uric acid is a product of the metabolic breakdown of purine nucleotides (adenine and guanine) of both exogenous and endogenous pools. Usually, mentioning uric acid is associated with the etiological factor of severe inflammatory arthritis (gout) and metabolic syndrome.

Uric acid plays an important role in the human body. More than half of the antioxidant capacity of blood plasma comes from uric acid, which is a strong reactive oxygen species (ROS), peroxynitrite scavenger and antioxidant. It has also been shown that uric acid may play a fundamental role in tissue healing by initiating the inflammatory process required for tissue repair, removal of oxygen free radicals, and mobilization of endothelial progenitor cells. It is required for the induction of type 2 immune responses. These properties may explain the protective potential of uric acid in neurological and infectious diseases.

Low plasma uric acid level is associated with neurological disorders such as Parkinson’s and Alzheimer’s diseases, Pemphigus vulgaris, and other autoimmune disorders, Peroxynitrites and ROS are thought to be responsible for myelin degradation in multiple sclerosis and may be blocked high levels of uric acid. Thus, patients with gout almost never develop multiple sclerosis [43].

Increased uric acid production, impaired renal uric acid excretion, or a combination of the two lead to hyperuricemia. Many studies have shown the relationship between uric acid and different disorders such are obesity, metabolic syndrome, hypertension and coronary artery disease. Serum uric acid concentration is recognized as a very important diagnostic and prognostic factor of many multifactorial disorders [43].

It was interesting to learn how pharmacy students approach the problem of hyperuricemia. 46 (86.8%) respondents consider that normal blood level of uric acid is an important factor in homeostasis in the human body; 4 students (7,5%) – no; and for 3 (5.7%) respondents it was difficult to answer. The results are shown in fig. 3.4.

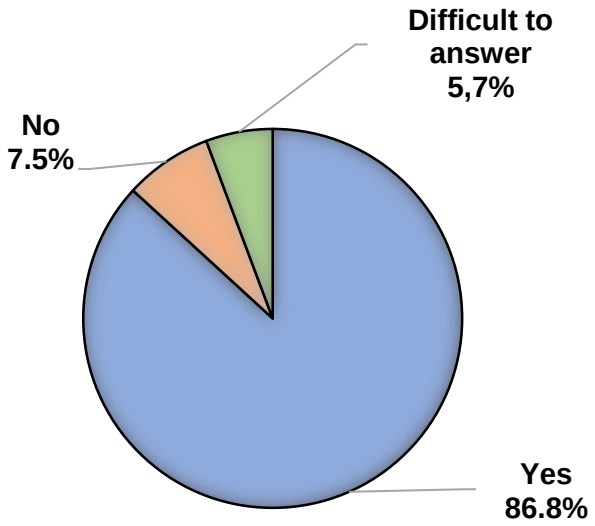


Fig. 3.4. Answers of pharmacy students to the question " Normal level of uric acid in the blood is an important factor in homeostasis in the human body?"

Xanthine oxidase (XO) or xanthine oxidoreductase is a member of an enzyme family known as the molybdenum iron-sulfur flavin hydroxylases. XO is widely distributed throughout various organs including the liver, gut, lung, kidney, heart, brain and plasma with the highest levels being found in the gut and the liver. XO is required to produce uric acid by the breakdown of purine nucleotides.

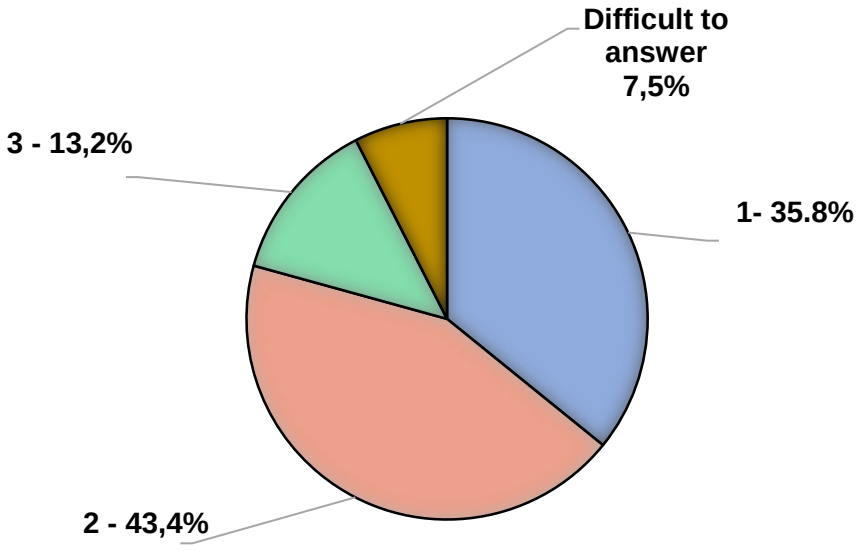
An understanding of the pathophysiology of gout begins with the fact that uric acid, which is only slightly soluble in body fluids, precipitates as monosodium urate crystals in joints, tendons, and other tissues and elicits an inflammatory response. While hyperuricemia is a clear risk factor for gout, local factors have been hypothesized to play a role in crystal formation, such as temperature, pH, mechanical stress, cartilage components, and other synovial and serum factors [44, 45].

The majority of respondents (42 – 79.2%) know that uric acid is the end product of purine metabolism, and 33 (62.2%) pharmacy students answered that in the human body uric acid is formed from the participation of xanthine oxidase. 38 (71.7%) respondents know that pathologically, gout is caused by an increase of blood uric acid levels. As for the reasons for the increase in the blood level of uric acid, 19 (35.8%) students named both an increased uric acid formation and insufficient excretion. 23 (43.4%) respondents considered only increased uric acid formation as the cause, while 7 (13.2%) considered insufficient uric acid excretion, and for 4 (7.5%) students it was difficult to answer. The results are shown in table 3.1 and fig. 3.5.

Table 3.1.

Pharmacy students' knowledge of the biochemical basis of hyperuricemia and gout

Questions	Numbers of answers (%)	
	correct	incorrect
Uric acid is the end product of the metabolism of purine bases of adenine and guanine	42 (79.2%)	11 (20.8%)
The biochemical basis of gout is an increase in the concentration of uric acid in the blood	38 (71.7%)	15 (28.3%)
The reasons for the increase in the blood level of uric acid are increased formation of uric acid and insufficient excretion (excretion from the body)	19 (35.8%)	34 (64.2%)
In the human body uric acid is formed from purines with the participation of the enzyme xanthine oxidase	33 (62.2%)	20 (37.7%)
To confirm whether a patient has gout or asymptomatic hyperuricemia, the blood level of uric acid should be determined	41	12



1 – increased formation of uric acid and insufficient excretion
2 – increased formation of uric acid
3 – insufficient excretion

Fig. 3.5. Distribution of students' answers to the question about the causes of hyperuricemia

The solubility of uric acid at normal physiological pH is generally given at 6.8 mg/dL, with reference ranges for uric acid of 3.5–7.2 mg/dL (210–430 μmol/L) and 2.6–6.0 mg/dL (155–360 μmol/L) in younger men and premenopausal women, respectively. The American College of Rheumatology strongly recommends a treat-to-target management strategy to achieve and maintain serum uric acid of less than 6 mg/dL (< 360 μmol/L) to decrease the risk of gouty flare recurrence and permanent joint damage [31].

Hyperuricemia is a very common biochemical aberration and its prevalence is increasing due to dietary changes, population aging and earlier screenings. Asymptomatic hyperuricemia presents as elevated serum uric acid levels without symptoms or signs of monosodium urate crystal deposition disease. Asymptomatic hyperuricemia affects approximately 21% of the general population and 25% of hospitalized patients in the USA, with variable rates in other countries [46].

Less than half of the respondents (22 – 41.5%) understand the essence of asymptomatic hyperuricemia. 25 (47.2%) students know that hyperuricemia not necessarily induces gout (see table 3.2).

Serum levels of uric acid are positively correlated with individual components of the metabolic syndrome, in particular visceral obesity, and this correlation is stronger when other components are also present [47]. Asymptomatic hyperuricemia is a marker of many pathological processes in the human body and 45 (84.9%) respondents in our survey also think that. 41 (77.4%) students know that hyperuricemia might be a component of the metabolic syndrome. 43 (81.1%) consider that hyperuricemia is associated with the development of cardiovascular diseases and chronic kidney disease (see table 3.2).

To prevent gouty arthritis, cardiovascular disease, and renal failure, the Japanese guidelines for the management of hyperuricemia and gout recommends starting drug urate-lowering therapy for asymptomatic hyperuricemia when serum urate levels increase to > 8.0 mg/dL. However, this approach is not recommended in the United States and Europe. It has been reported that inappropriate administration of such therapy for asymptomatic hyperuricemia is associated with a significant risk of life-threatening side effects [48].

The majority of patients with hyperuricemia are asymptomatic and do not need medical therapy, as they will never develop gout or nephrolithiasis [46].

Pharmacotherapy of asymptomatic hyperuricemia with allopurinol is considered inappropriate and 38 (71.7%) respondents think so.

Table 3.2.

Pharmacy students' knowledge of asymptotic hyperemia and the role of hyperemia in some pathological processes

Questions	Numbers of answers (%)		
	correct	incorrect	difficult to answer
What is asymptomatic hyperuricemia?	22 (41.5%)	31 (58.5%)	-
Asymptomatic hyperuricemia is a marker of many pathological processes in the human body	45 (84.9%)	3 (5.7%)	5 (9.4%)
Asymptomatic hyperuricemia is associated with the development of cardiovascular diseases, chronic kidney disease	43 (81.1%)	7 (13.2%)	3 (5.7%)
Pharmacotherapy of asymptomatic hyperuricemia with allopurinol is considered inappropriate	38 (71.7%)	8 (15.1%)	7 (13.2%)
Hyperuricemia is considered a component of the metabolic syndrome	41 (77.4%)	8 (15.1%)	4 (7.5%)
Hyperuricemia indicates the presence of gout in a patient	25 (47.2%)	27 (50.1%)	1(1.9%)

Drugs play an important role in the pathogenesis of hyperuricemia. They raise serum uric acid level by an increase of uric acid reabsorption and/or decrease in uric acid secretion. Several drugs may also increase uric acid production. Drug-induced hyperuricemia presents an increasingly prevalent problem in clinical practice. Loop diuretics, thiazide diuretics and thiazide-like diuretics are one of the most important causes of secondary hyperuricemia and gout [49].

45 (84.9%) students indicated that taking thiazide diuretics may contribute to the development of hyperuricemia (fig.3.6).

In low dosages (60–300 mg once daily), acetylsalicylic acid reduces uric acid excretion, and may induce hyperuricemia, whereas higher doses are uricosuric [49].

19 (35.8%) respondents answered that acetylsalicylic acid (low doses) also may induce hyperuricemia.

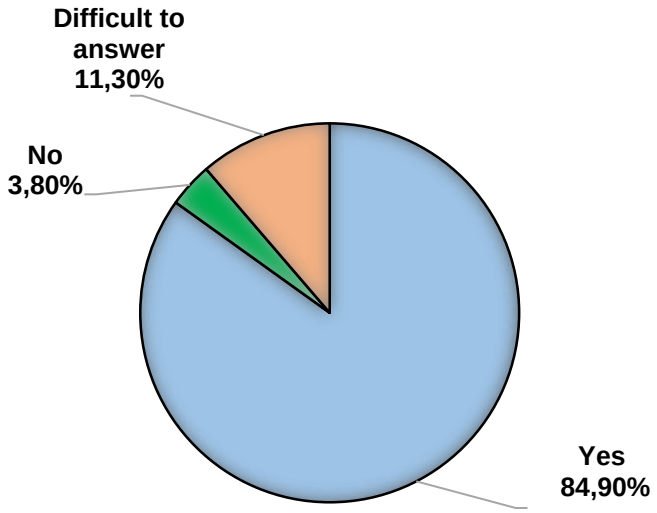


Fig. 3.6. Answers of pharmacy students to the question "Taking thiazide diuretics may contribute to the development of hyperuricemia"

Xanthine oxidase inhibitors (allopurinol or febuxostat) are the drugs of choice for urate-lowering therapy and achieving a target plasma level of UA <360 μmol/l. The dose should be titrated based on the safety of the drug and at the same time as reducing the incidence of gout attacks. Appropriate monitoring of UA levels and toxicity should also be carried out [31].

In our survey, 29 (54.7%) students consider that baseline gout therapy should include the hypouricemic drugs allopurinol or febuxostat. 23 (43.4%) respondents think that the main drugs are NSAIDs, 2 (3.8%) – glucocorticoids (fig.3.7).

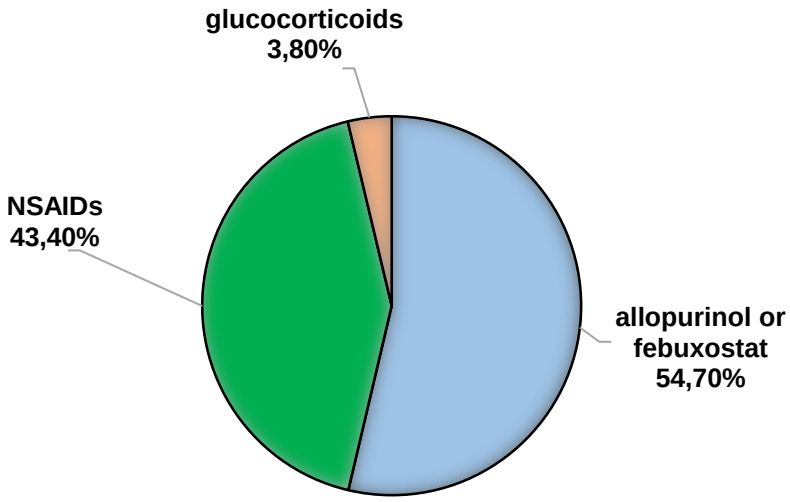


Fig. 3.7. Answers of pharmacy students to the question about basic pathogenetic therapy of patients with gout.

Colchicine, NSAIDs, and glucocorticoids are first-line therapy in patients with acute gout. The choice of drug is based on the preferences of the patient and the doctor, and considering comorbidity (especially the presence of chronic diseases of the kidneys and digestive tract). A long-term treatment of up to 7-10 days may be needed.

So, during the period of exacerbation of gout attacks, therapy should be aimed at inflammation suppression with NSAIDs and colchicine, and only 18 (34.0%) students agree with this statement, 24 (45.3%) respondents spoke in favor of hypouricemic therapy, 10 (18.9%) students think that it is necessary to combine anti-inflammatory and hypouricemic therapy (fig.3.8).

Although 35 (66.0%) students confirmed that allopurinol is not recommended during an exacerbation of gout and an attack of gouty arthritis. 9 (17.0%) respondents think that it is possible, and 9 (17.0%) – refrain from choosing.

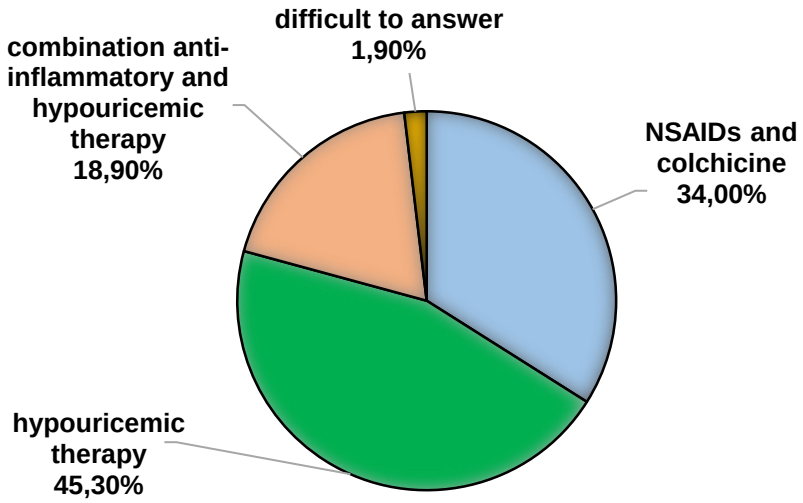


Fig. 3.8. Answers of pharmacy students to the question about the main direction of therapy during the exacerbation of gout attacks

There are also risk factors for the development of gout, such as high-purine foods, which cause an excess of substrate for UA synthesis in the body. In addition, it should be remembered that fatty foods disrupt the urate excretion by the kidneys.

Urate production is accelerated by purine-rich diets, and endogenous purine production. Foods rich in purine include all meats but specifically organ meats (kidneys, liver, “sweet bread”), game meats, and some seafood (anchovies, herring, scallops). A proper choice of the type legume with a smaller purine content is important.

High fructose oral intake over several days is associated with increased uric acid concentration. Fructose is strongly associated with hyperuricemia and an increased risk of gout in both genders. Fructose increases intracellular and circulating uric acid levels due to increased nucleotide turnover and nucleotide synthesis. Fructose may induce an increase in blood lactate concentration, which blocks urate excretion and results in hyperuricemia. It may also increase the risk of insulin resistance [49].

The pharmacy students were asked to choose the foods to limit gout (several sources). Respondents noted that patients with gout should limit purine-rich foods

such as: legumes (32 answers – 60.1%), seafood (26 answers – 49.1%) offal (26 answers - 49.1%), meat (19% - 35.8%) (fig.3.9).

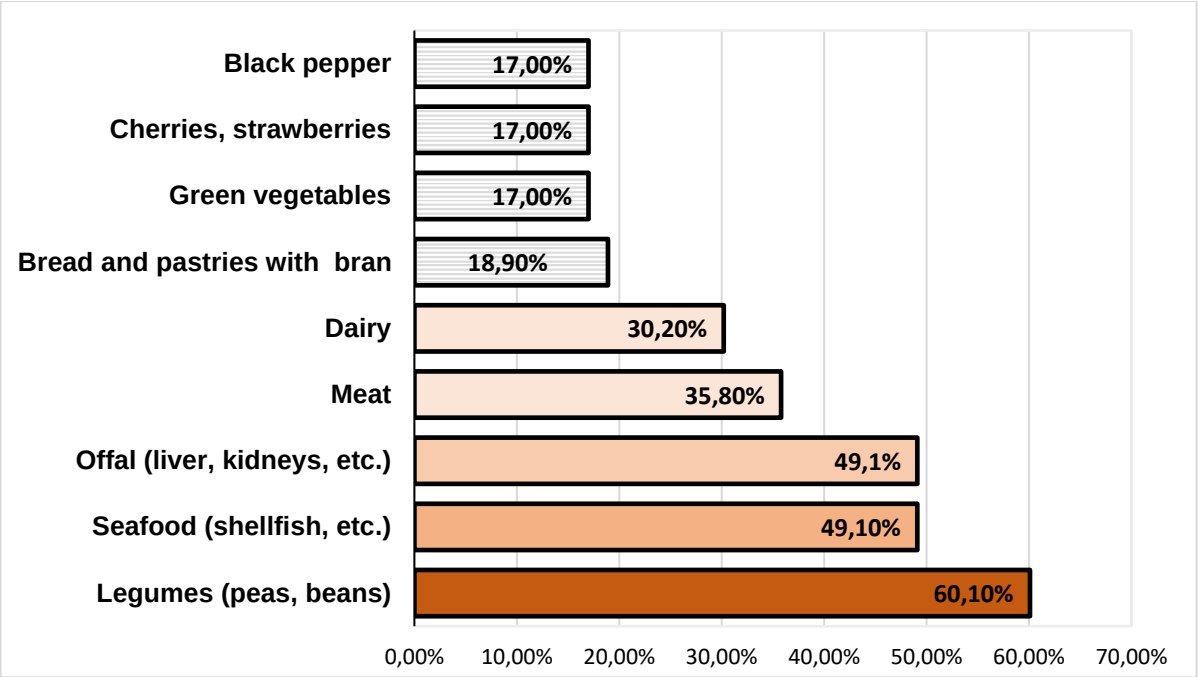


Fig. 3.9. The respondents' choice of foods that need to be restricted in the diet of patients with gout

16 (30.2%) students chose dairy products among the foods that need to be restricted in the diet of patients with gout. But as is known, low-fat milk and low-fat yogurt are excellent foods for gout sufferers because of their low purine content and ability to lower gout risk.

9 (17.0%) respondents consider that it is necessary to limit the consumption of cherries and strawberries intake, the same number of students think that it is necessary to limit green vegetable intake, 10 (18.9%) – bread and pastries with bran. Vitamin C-rich foods, such as cherries, strawberries and green vegetables, show some evidence of potentially reducing gout attacks. These foods must be considered as a part of a healthy diet.

Conducted researches did not find an association between the consumption of purine-rich vegetables and plasma urate and gout. Therefore, the question arises

whether it is appropriate to limit the consumption of vegetables rich in purines, such as asparagus, cauliflower, beans, lentils and spinach, in patients with gout [39].

Most of the students correctly chose the foods to be restricted for gout. However, some students gave wrong answers.

Other possible causes of hyperuricemia include excessive alcohol consumption. Alcohol, being metabolized to lactic acid, prevents the excretion of urates. The most dangerous are strong alcoholic drinks and beer. Beer, which is purine-rich, increases uric acid levels by decreasing kidney excretion.

49 (92.5%) respondents consider that alcohol use is a risk factor for hyperuricemia (fig. 3.10).

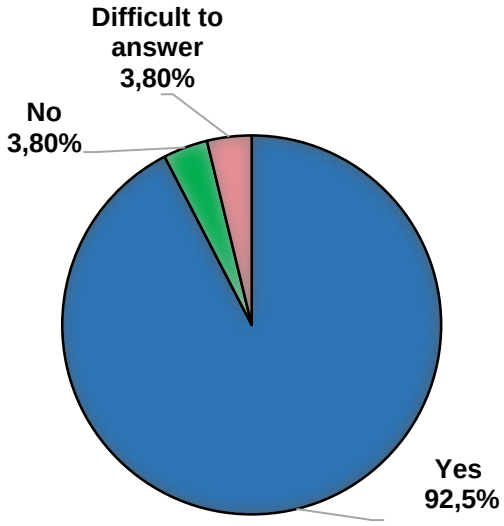


Fig. 3.10. Answers of pharmacy students to the question "Alcohol use is a risk factor for hyperuricemia "

Many sugar-sweetened juices can increase the gout risk. There has been some evidence from some studies that high fructose in fruit juices may be associated with a higher risk of gout. Fructose is added to soft drinks, but it occurs naturally in fruit juices. So, drinking too much fruit juice could be as risky as drinking a sugary soft drink. Several studies have found an increased gout risk from sugar-sweetened drinks. This link has been found in both men and women. Current evidences are insufficient to validate the association between coffee consumption and a lower risk

of HU. Unfortunately, the effect described above for coffee does not apply to tea. But other research shows that increasing coffee intake can actually trigger gout attacks.

The students were asked to choose drinks from the proposed list, that need to be limited in the diet of patients with gout in order to normalize purine metabolism (fig. 3.11).

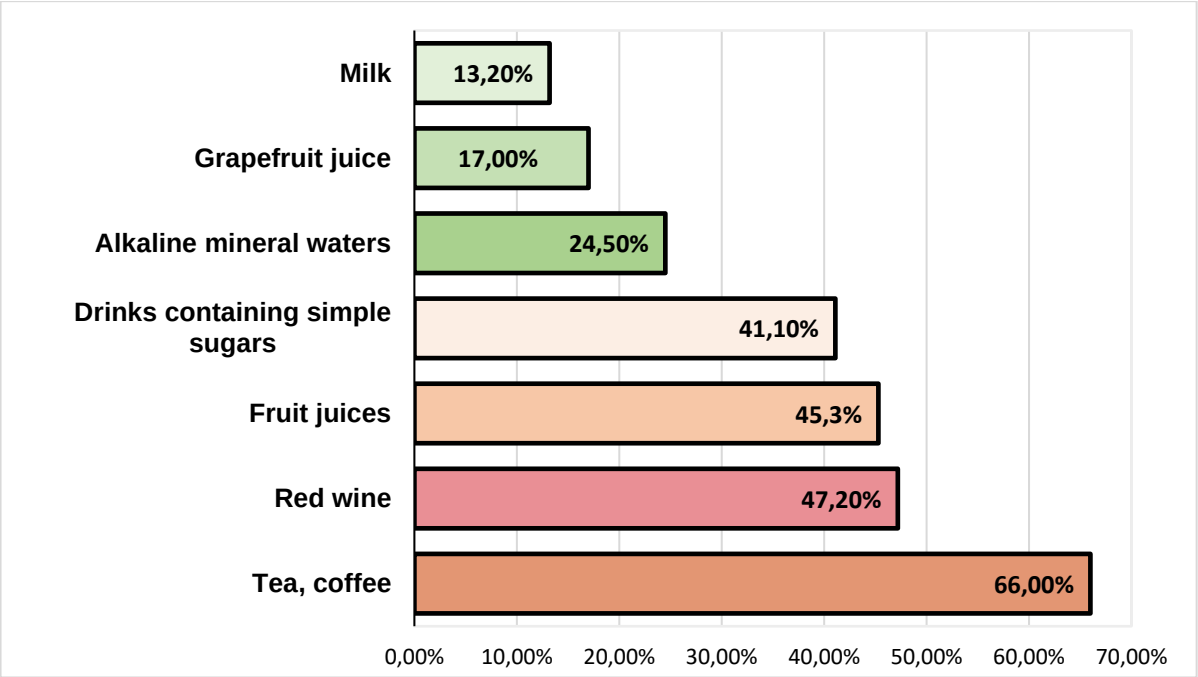


Fig. 3.11. The respondents' choice of drinks which need to be restricted in the diet of patients with gout

Patients should be strongly encouraged to lead a healthy lifestyle, including weight loss, regular exercise, and avoidance of smoking, alcohol, and sugary drinks. Treatment of gout requires a lifestyle that reduces the risk of modifiable factors such as hyperlipidemia, hypertension, hyperglycemia, obesity and smoking.

Conclusions for chapter 3

1. To assess pharmacy students’ knowledge, a survey was conducted using a 32-question questionnaire about gout management.

2. A total of 53 pharmacy students studying at the Pharmaceutical faculty and the Faculty for foreign citizens' education of the National University of Pharmacy took part in our survey.
3. As the survey has shown, 87 % of the pharmacy students consider that normal blood level of uric acid is an important factor in homeostasis in the human body.
4. Most students understand gout biochemical mechanisms and hyperuricemia association with cardiovascular diseases, obesity, diabetes, and metabolic syndrome.
5. The main aim of gout treatment is to reduce serum uric acid levels to an established target. 54.7% of students consider that baseline gout therapy should include hypouricemic drugs. Optimal management of acute gout includes anti-inflammatory drugs NSAIDs, and only 34.0% of students agree with this statement, 45.3% of respondents spoke in favor of hypouricemic therapy, and 18.9% of students think that it is necessary to combine anti-inflammatory and hypouricemic therapy.
6. Purine-rich foods, fructose and alcohol play an important role in hyperuricemia pathogenesis. Most of the students correctly chose the foods to be restricted for gout.
7. The obtained results indicate the inadequacy of pharmacy students' knowledge on some issues concerning therapeutic approaches in gout treatment and set the goal of further consideration of the research results when revising educational and professional programs and improving the content of educational components. An educational intervention to train pharmacy students is effective to increase pharmacist knowledge on the management of gout.
8. The results can be used to develop appropriate educational interventions to promote knowledge on the management of gout among pharmacists and other healthcare professionals.

CONCLUSIONS

1. A literature review of gout, its epidemiology, pathophysiology, and management, with a particular focus on the use of novel therapies was carried out.
2. To assess the pharmacy students' knowledge, a survey was conducted using the 32-question questionnaire on gout management.
3. A total of 53 students of the National University of Pharmacy took part in our survey. After professional education, they will carry out pharmaceutical care and consult patients on various issues, including gout management.
4. As the survey has shown, 87 % of pharmacy students consider that a normal uric acid blood level is an important factor in homeostasis in the human body.
5. Most students understand the gout biochemical mechanisms and hyperuricemia association with cardiovascular diseases, obesity, diabetes, and metabolic syndrome.
6. The main aim of gout treatment is to reduce serum uric acid levels to an established target. 54.7% of students consider that baseline gout therapy should include hypouricemic drugs. Optimal management of acute gout includes anti-inflammatory drugs NSAIDs, and only 34.0% of students agree with this statement, 45.3% of respondents spoke in favor of hypouricemic therapy, and 18.9% of students think that it is necessary to combine anti-inflammatory and hypouricemic therapy.
7. Purine-rich foods, fructose and alcohol play an important role in hyperuricemia pathogenesis. Most of the students correctly chose the foods to be restricted for gout.
8. The obtained results indicate the inadequacy of pharmacy students' knowledge on some issues concerning therapeutic approaches in gout treatment and set the goal of further consideration of the research results when revising educational and professional programs and improving the content of educational components. An educational intervention to train pharmacy students is effective to increase pharmacist knowledge on the management of gout.

9. The results can be used to develop appropriate educational interventions to promote knowledge on the management of gout among pharmacists and other healthcare professionals.

REFERENCES

1. The global burden of gout: estimates from the Global Burden of Disease 2010 study / Smith E., Hoy D., Cross M. et al. *Ann Rheum Dis.* 2014. Vol. 73. P. 1470-1476.
2. Li R., Yu K., Li C. Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review. *Asia Pac J ClinNutr*. 2018 Vol. 27, № 6. P. 1344-1356.
3. Mortada I. Hyperuricemia, type 2 diabetes mellitus, and hypertension: an emerging association. *Curr Hypertens Rep*. 2017. Vol. 19, № 9. P. 1-5.
4. Contemporary Prevalence of Gout and Hyperuricemia in the United States and Decadal Trends: The National Health and Nutrition Examination Survey, 2007–2016 / Chen-Xu M., Yokose C., Rai SK. et al. *Arthritis Rheumatol.* 2019. Vol. 71, № 6. P. 991-999.
5. Prevalence and associations of gout and hyperuricaemia: results from an Australian population-based study. Ting K, Gill TK, Keen H, Tucker GR, Hill CL. *Intern Med J.* 2016. Vol. 46, № 5. P. 566-573.
6. Kim Y., Kang J., Kim G.T. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. *Clin Rheumatol*. 2018. Vol. 37, № 9. P. 2529-2538.
7. Roddy E., Choi H.K. Epidemiology of gout. *Rheum Dis Clin North Am*. 2014. Vol. 40, № 2. P. 155-75.
8. Review of Hyperuricemia as New Marker for Metabolic Syndrome / L. Billiet et al. *ISRN Rheumatol*. 2014. Vol. 2014. P. 1-7.
9. Association of dietary patterns with blood uric acid concentration and hyperuricemia in northern Chinese adults / M. Zhou et al. *Nutr J.* 2022. Vol. 21, № 42. P. 1-10.
10. Phylogenetic Articulation of Uric Acid Evolution in Mammals and How It Informs a Therapeutic Uricase / Z. Li et al. *Molecular Biology and Evolution*. 2022. Vol. 39, № 1. P. 1-8.
11. Jung Hwan Park, Yong-Il Jo, and Jong-Ho Lee Renal effects of uric acid: hyperuricemia and hypouricemia. *Korean J Intern Med*. 2020. 35. № 6. P. 1291-1304.
12. Uric Acid, Evolution and Primitive Cultures / R. J. Johnson et al. *Semin Nephrol*. 2005. 25, № 1. P. 3-8.
13. Chen C., Lü J.-M., Yao Q. Hyperuricemia-related diseases and xanthine oxidoreductase (XOR) inhibitors: An overview. *Med Sci Monit*. 2016. Vol. 22. P. 2501-2512.

14. Шуба Н.М. Гіперурикемія – мультиморбідна патологія в ревматології *УКр. Ревматологічний журнал*. 2013. № 52, № 2. С. 14-22.
15. Bardin T., Richette P. Épidémiologie et génétique de la goutte. *La Presse Médicale*, 2011. Vol. 40, № 9. P. 830–835.
16. Gouty arthropathy: review of clinical manifestations and treatment, with emphasis on imaging / J. S. Weaver et al. *J. Clin Med.* 2022. 11, № 1. P. 1-28.
17. Busso N., So A. Gout. Mechanisms of inflammation in gout. *Arthritis Res Ther*. 2010. 12, № 2. P. 1-8.
18. Desai J., Steiger S., Anders H.-J. Molecular Pathophysiology of Gout. *Trends in Molecular Medicine*. 2017. 23, № 8. P. 756-768.
19. Asymptomatic Hyperuricemia – a silent activator of the innate immune system / L. A. B. Joosten, T.O. Crisan, P. Bjornstad, R. J. Johnson *Nat Rev Rheumatol*. 2020. 16, № 2. P. 75-86.
20. Nian Y.-L., You C.-G. Susceptibility genes of hyperuricemia and gout. *Hereditas*. 2022. Vol. 159, № 30. P. 1-11.
21. Дзяк Г.В., Коваленко В.Н., Хомазюк Т.А. Подагра: взгляд в будущее. К.: МОРИОН, 2020. 192 с.
22. Gagliardi A.C., Miname M.H., Santos R.D. Uric acid: a marker of increased cardiovascular risk. *Atherosclerosis*. 2009. Vol. 202. P. 11-17.
23. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence (abstract) / J. Sundstrom et al. *Hypertension*. 2005. Vol. 45. P. 28-33.
24. Uric acid and inflammatory markers / Ruggiero C., Cherubini A., Ble A. et al. *Eur. Heart J.* 2006. Vol. 27. P. 1174-1181.
25. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system / D.B. Corry. et al. *J. Hypertens*. 2008. Vol. 26. P. 269-275
26. Feig D.I., Soletsky B., Johnson R.J. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA*. 2008. Vol. 300. P. 924-932.
27. Serum uric acid in essential hypertension: an indicator of renal vascular involment / F.H. Messerli et al. *Ann. Intern. Med*. 1993. Vol. 93. P. 817-821
28. Lin K.C., Lin H.Y., Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. *J. Rheumatol*. 2000. Vol. 27. P. 1501-1505.
29. Uric acid and hypertension / Daniel I. Feig, Duk-Hee Kang, Takahiko Nakagawa et al. *Current Hypertension Reports*. 2006. Vol. 8. P. 111-115.
30. Pillinger M. H., Mandell B. F. Therapeutic approaches in the treatment of gout. *Seminars in Arthritis and Rheumatism*. 2020. Vol. 50, № 3. P. 24-30.

31. 2020 American College of Rheumatology Guideline for the Management of Gout / J. D. FitzGerald et al. *Arthritis Care Res* (Hoboken). 2020. Vol. 72, № 6. P. 744-760.
32. 2016 updated EULAR evidence-based recommendations for the management of gout / P. Richette et al. *Ann Rheum Dis.* 2017. Vol.76, № 1. P. 29-42.
33. Update on colchicine, 2017 / A. Slobodnick. *Rheumatology*. 2018. 57, № 1. P. 4-11.
34. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial / C.A. Janssen et al. Rheumatology. 2019. Vol. 58. P. 1344-1352.
35. Mandell B.F., Yeo A.E., Lipsky P.E. Tophus resolution in patients with chronic refractory gout who have persistent urate-lowering responses to pegloticase. *Arthritis Res Ther.* 2018. Vol. 20, №1. P. 286.
36. Uricases as therapeutic agents to treat refractory gout: Current states and future directions / X.Yang et al. *Drug Dev Res.* 2012. 73, № 2. P. 66-72.
37. Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism / S. Takahashi et al. *Ann Rheum Dis*. 2003. Vol. 62, № 6. P. 572-575.
38. Chen C., Lü J.-M., Yao Q. Hyperuricemia-Related Diseases and Xanthine Oxidoreductase (XOR) Inhibitors: An Overview. *Med Sci Monit*. 2016. 22. P. 2501-2512.
39. The association of dietary intake of purinerich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study / L. Zgaga et al. *PLoS One*. 2012. Vol. 7, № 6. P. 1-8.
40. Li R., Yu K., Li C. Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review *Asia Pac J ClinNutr*. 2018. Vol. 27, № 6. 1344-1356.
41. Yokose C., McCormick N., Choi H. K. The role of diet in hyperuricemia and gout. *Curr Opin Rheumatol*. 2021. Vol. 33, № 2. P. 135-144.
42. Female employment rate in Morocco 2012-2020. Published by Statista Research Department, Apr 26, 2023 URL : https://www.statista.com/statistics/1266084/female-employment-rate-in-morocco/ (date of access: 20.03.23).
43. El Ridia R., Tallima H. Physiological functions and pathogenic potential of uric acid: A review. *J Adv Res.* 2017. Vol. 8, № 5. P. 487-493.
44. George J., Struthers A. D. Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. *Vasc Health Risk Manag*. 2009. Vol. 5. P. 265-272.
45. Martillo M. A., Nazzal L., Crittenden D. B. The Crystallization of Monosodium. Urate *Curr Rheumatol Rep*. 2014. Vol. 16, № 2: 400.

46. George C., Minter D.A. Hyperuricemia. 2023. URL : https://www.ncbi.nlm.nih.gov/books/NBK459218 (date of access: 20.03.23).
47. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome / W. Baldwin et al. *Diabete.s* 2011. Vol. 60, № 4. P. 1258-1269.
48. Shin D.H. To treat or not to treat asymptomatic hyperuricemia in chronic kidney disease *Kidney Res Clin Pract*. 2019. Vol. 38, № 3. P. 257-259.
49. Drug-induced hyperuricaemia and gout / C. B. Salemet al. *Rheumatology*. 2017. Vol. 56, № 5. P. 679-688.

APPENDICES

Appendix A


НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
СЕРТИФІКАТ УЧАСНИКА
Цим засвідчується, що
Mellouki Hamza
Scientific supervisor: Stepanova S.I.
брав(ла) участь у роботі
XXIX Міжнародної науково-практичної конференції молодих вчених та студентів
«АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»
В.о. ректора
Національного фармацевтичного
університету
Алла КОТВІЦЬКА
19-21 квітня 2023 р, м. Харків

Appendix B

XXIX Міжнародна науково-практична конференція молодих вчених та студентів
«АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»

PHARMACY STUDENTS' AWARENESS OF PHARMACEUTICAL CARE OF PATIENTS WITH HYPERURICEMIA AND GOUT

Mellouki Hamza
Scientific supervisor: Stepanova S.I.
National University of Pharmacy, Kharkiv, Ukraine
hmaza.mellouki@gmail.com

Introduction. Hyperuricemia (HU) is an elevated uric acid level in the blood serum of 360 μmol/l in women and above 420 μmol/l in men due to purine metabolism disorders. This elevated level is the result of increased production, decreased excretion of uric acid, or a combination of both processes. Hyperuricemia is the leading cause of gout and is also related to diabetes, chronic kidney disease, metabolic syndrome, hypertension, stroke, and atherosclerosis. Several recent epidemiological surveys have indicated that the prevalence rates of hyperuricemia among adults in the United States, Australia, and South Korea are 20.1%, 16.6%, and 11.4%, respectively. Moreover, the prevalence of hyperuricemia has increased in recent decades. Asymptomatic HU occurs in 5-8% of the population, while only in 5-20% of them develop gout. Therefore, hyperuricemia has become an important public health problem. The role of the pharmacist is very important for the interprofessional management of gout.

Aim of our study is to assess the awareness of pharmacy students on pharmaceutical care of patients with hyperuricemia and gout.

Materials and methods. To study the awareness of pharmacy students of the National university of pharmacy we conducted the survey using a questionnaire developed by us.

Results and discussion. The questionnaire includes: an explanatory part, which provides information about the objectives of the survey, and an evaluation part, consisting of 33 questions on the socio-demographic characteristics of the respondents and questions to assess the general knowledge necessary to advise pharmacy visitors.

As the survey has showed, the pharmacy students know the general issues of managing patients with gout or asymptomatic HU. Respondents associate the elevated level of blood uric acid not only with gout but also with health conditions such as heart disease, diabetes, and kidney disease. Most students know that the dietary strategy for hyperuricemia is to reduce the intake of purine-rich foods.

Conclusions. There is evidence that pharmacists can play a significant role in optimizing gout care. Through patient education and collaboration with prescribers, pharmacists can help reduce the overall burden of gout-related disease. A concerted effort is needed to improve the quality of care and quality of life in patients with gout. Interventions targeting quality of care have the potential to not only improve standard of care, but also improve the health-related quality of life in patients with gout.

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of Pharmacology and Pharmacotherapy
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Pharmacology and
Pharmacotherapy

_____

Sergey Shtrygol'
«21» of September 2022

ASSIGNMENT

FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Hamza MELLOUKI

1. Topic of qualification work: «Pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout», supervisor of qualification work: Svitlana STEPANOVA, PhD, assoc. prof. approved by order of NUPh from "06" of February 2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: april 2023.

3. Outgoing data for qualification work: publications devoted to the current state of knowledge regarding gout, including its risk factors, clinical manifestations, and the potential of new and emerging therapies for the treatment of gout, including urate-lowering agents, anti-inflammatory drugs, and biologic therapies.

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
to analyze and summarize literature data on the current state of knowledge regarding gout and hyperuricemia; based on advanced European guidelines for the gout management to develop a questionnaire; to conduct an anonymous survey, analyze respondents' answers and determine the level of pharmacy students' awareness in the researched issue
5. List of graphic material (with exact indication of the required drawings):
tables – 3, figures – 13

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Svetlana STEPANOVA, associate professor of higher education institution the department of pharmacology and pharmacotherapy	Svetlana STEPANOVA, 21.09.2022	Hamza MELLOUKI, 21.09.2022
2	Svetlana STEPANOVA, associate professor of higher education institution the department of pharmacology and pharmacotherapy	Svetlana STEPANOVA, 01.11.2022	Hamza MELLOUKI 01.11.2022
3	Svetlana STEPANOVA, associate professor of higher education institution the department of pharmacology and pharmacotherapy	Svetlana STEPANOVA, 12.12.2022	Hamza MELLOUKI 12.12.2022

7. Date of issue of the assignment: "21" of September 2022

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Issuance of a task for qualification work; definition of the topic of the work, the goal and task of the research; establishing the object and subject of research; drawing up a calendar plan for work execution	September-October 2022	**done**
2.	Search, analytical processing and accumulation of information sources, practical materials in traditional bibliographic systems and on the Internet; selection of research methods	October-November 2022	**done**
3.	Development of a questionnaire and conducting a survey	November-December 2022	**done**
4.	Evaluation of answers to an anonymous questionnaire among pharmacy students regarding the awareness of food-drug interaction	January 2023	**done**
5.	Analysis, generalization and systematization of acquired knowledge, skills and information; assessment of scientific novelty and practical significance of the work	February-March 2023	**done**
6.	Preparation of the manuscript, editing and formatting of the qualification work; preparation of the accompanying documents and submission of work to the Examination Committee of the NUPh.	March-April 2023	**done**

An applicant of higher education _____ Hamza MELLOUKI

Supervisor of qualification work _____ Svetlana STEPANOVA

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі фармакології та фармакотерапії**				
Меллоукі Хамза	Обізнаність студентів-фармацевтів щодо фармацевтичної опіки пацієнтів з гіперурикемією та подагрою	Pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout	Доц. Степанова С.І.	Проф. Міщенко О.Я.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар громадян

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу щодо академічного плагіату у кваліфікаційній роботі здобувача вищої освіти

№ 113320 від « 12 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Меллоукі Хамза, 5 курсу, англ-08 групи, спеціальності 226 Фармація, промислова фармація, на тему: «Обізнаність студентів-фармацевтів щодо фармацевтичної опіки пацієнтів з гіперурикемією та подагрою / Pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
професор **Інна ВЛАДИМИРОВА**

6%
28%

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work for the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Hamza MELLOUKI

on the topic: «Pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout»

Relevance of the topic. Gout is the most common form of inflammatory arthritis and is caused by chronic elevation of serum uric acid levels above the saturation point for monosodium urate crystal formation. The prevalence of gout has been increasing. This disease is diagnosed in at least 1–3% of the adult population. Recent studies suggest that patients' lack of knowledge about the disease and treatment options, combined with healthcare practitioners' lack of familiarity with clinical practice guidelines, represent significant barriers to optimal gout treatment. In addition, most patients with gout are elderly and may have comorbidities, such as cardiovascular disease and/or renal impairment, which can further complicate treatment choices for both acute and chronic gout. There is evidence that pharmacists can play a significant role in optimizing the care of this population. Through patient education and collaboration with prescribers, pharmacists may help to decrease the overall disease burden associated with gout.

Practical value of conclusions, recommendations, and their validity. The practical value of the results of qualification work is obtaining information that can be considered to modify educational and professional programs and improving the content of educational components.

Assessment of work. The literature review is written analytically, in compliance with the requirements of scientific style and the text contains correct references to other authors. The chosen research methods are generally accepted and adequate to the goal and task. The data were processed using traditional statistical methods. A sufficient amount of empirical data for analysis was obtained, and

experimental data were carefully analyzed. The results of the research were analyzed and summarized in comparison with the data of scientific literature, further perspectives and directions of work were highlighted. The work is relevant, meets the requirements and has practical and scientific value. The list of resources consists of 55 sites. Approbation of research results took place on April 19-21, 2023 at the XXIX International scientific and practical conference of young scientists and students «Topical issues of new medicines development» (Kharkov, Ukraine).

General conclusion and recommendations on admission to defend. The work is performed in full, designed in accordance with the current requirements for the qualification works at the National University of Pharmacy, and can be recommended for submission to the State Examination Commission for further defense.

Scientific supervisor _____ Svetlana STEPANOVA

«4» of April 2023

Ф А 2.2.1-32-356

REVIEW

for the qualification work for the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Hamza MELLOUKI

on the topic: «Pharmacy students' awareness of pharmaceutical care of patients with hyperuricemia and gout»

Relevance of the topic. Gout is a chronic and debilitating condition that affects millions of people worldwide. It is a type of arthritis caused by the accumulation of uric acid crystals in the joints, which leads to inflammation, pain, and stiffness. Despite the availability of effective treatments, gout remains a significant health concern, with a growing prevalence in many countries. Pharmacists are able to collaborate in the optimization of gout management. When treating gout, pharmacists can use their in-depth understanding of medicines and their interactions, helping to ensure a clear management pathway. The pharmacist is the bridge between doctors and patients who counsels and advises the patient to maximize the effect of the drugs and minimize their adverse effects. Pharmacists can also support patients in other ways: addressing acute flares; providing patient education; reiterating the importance of ongoing treatment adherence.

Thus, understanding the current recommendations for the effective treatment of gout and hyperuricemia prevention is crucial for pharmacists to ensure optimal patient management.

Theoretical level of work. The theoretical provisions of the qualification work are related to actual problems in the field of pharmaceutical care during the dispensing of drugs. The author of the work conducted a comprehensive analysis of theoretical material on the subject of research. The thesis provides the author's opinion regarding the analyzed provisions and proper argumentation of the author's position. The correct references are given to the used literary sources of information.

Author's suggestions on the research topic. The author has developed a questionnaire that can be used to assess the level of knowledge of pharmacists and other healthcare professionals about gout management.

Practical value of conclusions, recommendations, and their validity. The obtained results indicate the inadequacy of pharmacy students' knowledge on a number of issues of the research topic and set the goal of further consideration of the research results when revising educational and professional programs and improving the content of educational components. The conclusions are well-founded and correspond to the purpose and objectives of the research. The results obtained can be used by education and healthcare professionals to develop appropriate educational interventions to promote knowledge of gout management among pharmacists and other healthcare professionals.

Disadvantages of work. No significant shortcomings were identified in the work, however, it can be noted: individual grammatical, stylistic, and technical errors; These do not fundamentally change the assessment of the work and do not reduce its scientific and practical significance.

General conclusion and assessment of the work. The scientific work is done according to the requirements for qualification work in NUPh and can be recommended for defense.

Reviewer _____ prof. Oksana MISHCHENKO

«10» of April 2023

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВЯ УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
Витяг з протоколу № 14
від 11 квітня 2023 року
м. Харків
засідання кафедри фармакології та фармакотерапії

ПРИСУТНІ: зав. каф. проф. Штриголь С.Ю., проф. Кіреєв І.В., проф. Деримедвідь Л.В, проф. Бутко Я.О., доц. Бєлік Г.В., доц. Рябова О.О., доц. Жаботинська Н.В., доц. Куценко Т.О., доц. Таран А.В., доц. Матвійчук А.В., доц. Степанова С.І., ас. Кононенко А.В., ас. Толмачова К.С., ас. Цеменко К.В., Адлер Б.А., Чубар`ян Ю.І., Барзак Д.Т., Краснораменська О.В., Шульга Ю.М., Рубан Я.В., Суровцева Д.О., Леонова Я.І., Заворотько Д.І., Вороніна А.О., Давидов Е.М., Шостенко К.В., Дібт Шараф Еддін, Жудат Ікрам, Алауі Абдаллауі Яссін, Буррус Ахлам, Ель Хамді Мохаммед, Меллоукі Хамза, Іфтахі Яссін, Карім Ашраф, Айнау Умайма, Елбадауі Хажар, Ель Хайель Хаджар, Толбі Ель Мехді, Беналлал Зінеб, Бенсаід Мохаммед, Ел-Жамаі Сальма, Ельбахаджі Раіхана, Бензід Ясіне, Кадді Каутар.

ПОРЯДОК ДЕННИЙ:
Розгляд кваліфікаційних робіт здобувачів вищої освіти для подання робіт до Екзаменаційної комісії.

СЛУХАЛИ:
Здобувача вищої освіти Меллоукі Хамзу зі звітом про проведену наукову діяльність за темою кваліфікаційної роботи: «Обізнаність студентів-фармацевтів щодо фармацевтичної опіки пацієнтів з гіперурикемією та подагрою».

УХВАЛИЛИ:
Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Меллоукі Хамза допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри фармакології
та фармакотерапії, проф. _____ Штриголь С.Ю.
Секретар кафедри фармакології
та фармакотерапії, ас. _____ Кононенко А.В.

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Хамза МЕЛЛОУКІ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Обізнаність студентів-фармацевтів щодо фармацевтичної опіки пацієнтів з гіперурикемією та подагрою»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Хамза МЕЛЛОУКІ у повному обсязі виконала кваліфікаційну роботу. За актуальністю, методичним рівнем, теоретичним та практичним значенням, об'ємом виконаних досліджень кваліфікаційна робота відповідає вимогам і допускається до захисту в Екзаменаційній комісії.

Керівник кваліфікаційної роботи

_____ Світлана СТЕПАНОВА

«04» квітня 2023 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Хамза МЕЛЛОУКІ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри
фармакології та фармакотерапії

_____ Сергій ШТРИГОЛЬ

«11» квітня 2023 року

Qualification work was defended
of Examination commission on the
« ___ »__of June__ 2023
with the grade _____
Head of the State Examination commission,
DPharmSc, Professor
_____ / Oleh SHPYCHAK /