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FINAL DEGREE PROJECT

GOUT: A NUTRITIONAL AND PHARMACOLOGICAL ANALYSIS

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Main field: ***Nutrition and Bromatology***

Secondary fields: ***Pharmacology and Therapeutic Chemistry and Physiology and Physiopathology***

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Abstract

"La gota és una malaltia crònica, inflamatòria i metabòlica, fortament lligada a altes concentracions d'àcid úric en sèrum (hiperuricèmia). Presenta una deposició de cristalls d'urat sòdic en les articulacions que causen una inflamació, és per això que se la caracteritza com un tipus d'artritis. Tot i que és molt coneguda i té varis fàrmacs pel seu tractament, s'ha vist que la dieta pot jugar un paper fonamental en la gestió de la malaltia. Per tant l'objectiu d'aquest estudi consisteix en determinar si un adequat control de la dieta, té el mateix grau d'impacte que el tractament farmacològic en la gestió de la malaltia. Durant l'estudi, s'ha dut a terme una recerca bibliogràfica en les principals bases de dades, on s'han seleccionat els articles més recents i rellevants. D'aquesta recerca s'ha pogut extreure informació sobre les bases de la gota i les seves causes, en que consisteix el tractament farmacològic actual i quin impacte tenen els diferents tipus d'aliments i dietes en el desenvolupament de la malaltia. També s'ha dut a terme una petita entrevista a un pacient, que s'ha comparat amb la recerca. Finalment s'ha conclòs que un control apropiat de la dieta té un impacte similar al tractament farmacològic, sobretot en la reducció de la hiperuricèmia."

"Gout is a chronic, metabolic, and inflammatory disease, strongly related to high concentrations of serum uric acid. It is characterized by the deposition of monosodium urate crystals in the joint, which provokes an inflammatory process, and that is why it is characterized as a type of arthritis. Despite it being a well-known disease and several drugs being available for its treatment, evidence has shown that the diet plays an important role in gout management. Therefore, the objective of this study is to determine if proper diet control is as effective as the pharmacological treatment for disease management. For this study, bibliographical research has been conducted using the main scientific databases, where the most recent and relevant articles have been selected. The research has provided information on gout basis and its causes, the actual pharmacological treatment, and what impact the diet can have on the disease. Also, a short interview with a patient has been carried out and compared to the research. Overall, this study concludes that proper diet control has a similar impact in comparison to the pharmacological treatment for gout management, especially in hyperuricemia reduction."

Abbreviations

- UA: Uric acid.
- XO: Xanthine oxidase.
- PRPP synthase: Pyrophosphate synthetase.
- HGRPT: Hypoxanthine-guanine phosphoribosyltransferase.
- IMP: Inosine monophosphate.
- GMP: Guanosine monophosphate.
- AMP: Adenosine monophosphate.
- ATP: Adenosine triphosphate.
- URAT1: Urate anion transporter 1.
- OAT: Organic anion transporters.
- SLC2A9: Glucose transporter 9.
- EPA: Eicosapentaenoic acid.
- DHA: Docosahexaenoic acid.
- NSAIDs: Non-steroidal anti-inflammatory drugs.
- COX: Cyclooxygenase.

Integration of different fields

Three important fields of study are discussed throughout this paper: Nutrition and Bromatology, Physiology and Physiopathology, and Pharmacology and Therapeutic Chemistry. The first is important for understanding the nutritional analysis of the disease, where purine concentrations on different types of foods are discussed. Nutrition is also important for the dietary management of the disease and for understanding which is the paper of the exogenous purines in gout. The second, Physiology and Physiopathology, are necessary for the disease presentation, diagnosis, mechanisms, and comorbidities. It also has an important role in uric acid metabolism and inflammation process comprehension. Thirdly, gout has a huge variety of drugs for its treatment, so Pharmacology is necessary to understand how these different drugs work and how they affect the uric acid concentration. These three fields are strongly related. For example, in the pharmacological analysis, physiology and pharmacology are involved, while in the nutritional section, nutrition and physiology are both discussed. Another example would be the treatment and the conclusions, where the research that has been carried out on the three fields comes together.

1. Introduction

Gout is a chronic, metabolic, inflammatory disease characterized by the deposition of monosodium urate crystals in the joints (1). The knees and fingers are the ones most commonly affected. The deposition of these crystals is linked to an increment in uric acid (UA) blood levels, known as hyperuricemia, which has two main causes, a reduction in the excretion of uric acid or an increase in its production.

This disease is characterized as a type of chronic arthritis, which switches between periods of exacerbation, where the patients can experience really painful episodes in the joints, and latency periods where the symptoms disappear. It is important to keep in mind that there are some human behaviors than can precipitate an episode, such as eating or drinking certain types of food, increased alcohol intake, or treatment with certain drugs.

For centuries, gout has been present in human history, known as the main chronic and inflammatory disease. Years ago, it was related to a high social status because wealthy people had access to high purine foods that poorer people did not. These days, people across all social classes can access these different foods types, increasing the impact of gout across society. The purpose of this work is to discuss the basis of the disease and find out which food types have an effect, looking for ones that can be preventative, as well as ones that will be more likely to cause an attack. At the same time, the paper will discuss the treatment of the disease using drugs, as well as via the diet, looking to see if there is any interaction between the foods and the medication.

2. Objectives

Hypothesis: A proper diet control is as effective as the pharmacological treatment for gout management.

Associated objectives:

- Apply correctly the databases.
- Set the basis of the disease.
- Identify which foods are related to the disease and their impact.
- Understand the role of drug treatment in the metabolic processes.

- Evaluate the comorbidities impact on gout management.
- Evaluate the impact of diet on patient health.

3. Methods and Materials

This is a bibliographic research project. The research methods were taught through seminars by the library of the pharmacy faculty from the University of Barcelona (CRAI) as well as the tools used for developing the research. The tools and research methodology include academic access to electronic databases, which provided access to a large number of scientific articles. The principal databases used for this project were PubMed, Scopus, and PMC. Even though most articles were found through these databases, the official web page of the American College of Rheumatology was also an important resource.

The articles were selected due to their matching criteria with the topics of this project. Each one has been read and analyzed carefully. Although the research is based on the most recent information on each topic, some older articles are discussed. This is because they were either considered primary research or they were mentioned in more recent articles. Finally, for the bibliographical development, the reference manager Mendeley was used, and through the tool Mendeley Microsoft Word plugin, the articles had been cited through the document. The bibliography citations follow the Vancouver rules and the scientific citation criteria.

After the bibliographic research has been done, it has been compared with a patient interview, to see if the information found, matches with a real case. The interview had been done face to face with the patient, and specific questions about gout and the patient's health status have been collected. All the information have been collected anonymously and scientifically, and the rules for a patient-pharmacist interview provided on the " Guía Práctica para los Servicios de Atención Farmacéutica en la Farmacia Comunitaria" (2) have been adapted. The questions were highly related to the research topics and helped to understand the concepts discussed in the paper.

4. Results (Research development)

4.1. Pathophysiology

UA is one of the most important concepts to consider when talking about gout and its pathophysiology. UA is a product from the metabolism of endogenous and exogenous purines, the nucleotide bases adenine and guanine, carried out mostly by the liver (3). The exogenous purines come from the diet, while the endogenous are derived from cellular metabolism.

Several enzymes participate in purine metabolism (Figure 1), and a lot of different reactions take place to convert purines to the final product, UA. One of the most important enzymes involved in this process is xanthine oxidase (XO), which converts one of the final products of purine metabolism, hypoxanthine, to UA. This enzyme is one of the main targets for gout therapy. Apart from XO, the enzymes phosphoribosyl pyrophosphate synthetase (PRPP synthase), purine nucleoside phosphorylase and hypoxanthine-guanine phosphoribosyltransferase (HGRPT) are also important because alterations in their activity can cause abnormal acid uric levels.

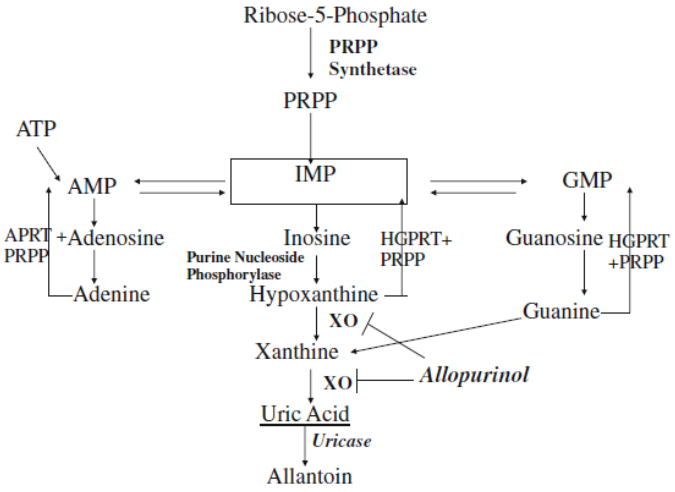

Figure 1: Diagram of purine metabolism

Retrieved From: Fathallah-Shaykh Sahar, T. Cramer Monica. Uric acid and the Kidney. Pediatric nephrology. June 2014, Volume 29. Pages 999-1008. Doi: https://doi.org/10.1007/s00467-013-2549-x

PRPP synthase is involved in the conversion of a sugar metabolite (Ribose-5-Phosphate) to inosine monophosphate (IMP), which is an intermediate between the two purine bases, adenosine, and guanosine. Then purine nucleoside phosphorylase converts that

inosine into hypoxanthine which is the substrate for XO. Meanwhile, HGRPT and APRT (adenosine phosphoribosyltransferase) are part of the purine salvage pathway, which converts the purine bases to guanosine monophosphate (GMP) and adenosine monophosphate (AMP) respectively, molecules that then can be converted to hypoxanthine. Uricase converts UA to a more soluble molecule called allantoin. Unfortunately, in humans uricase is inactive due to a nonsense mutation.

Pathological hyperuricemia occurs when the serum concentration exceeds 408 µmol/L [6.8 mg/dL] (4) and could be due to different reasons. The main one is a reduction in UA excretion and two organs are involved in this process. The first one is the kidney, which is responsible for 66% of the elimination. The other 33% occurs in the gastrointestinal tract (5).

Taking into consideration that UA is not very soluble in aqueous solutions, it is found in physiological fluids as urate, the UA anion. However when this anion leaves the bloodstream and goes to the urine, where the pH changes from 7.3-7.5 to 5.0-6.0, then it switches again to UA, affecting its solubility and transport (3). In the kidney, epithelial membranes exchange UA in both directions, between the interior of the cell and the lumen. This fact is important because an increased absorption or decreased excretion will affect the UA concentration in the bloodstream.

The mechanism that regulates UA excretion is not totally understood, but there are some membrane transporters involved (Figure 2): Urate anion transporter 1 (URAT1) is responsible for the reabsorption of urate after glomerular filtration. Organic anion transporters (OAT1 and OAT3) and glucose transporter 9 (SLC2A9) mediate urate reabsorption from the tubular cells to the circulation (3,6).

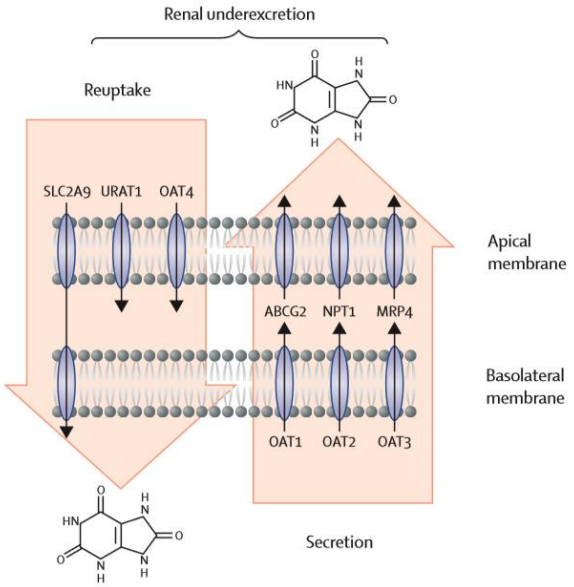

Figure 2: Urate excretion in the kidney

***Retrieved from**: Dalbeth Nicola, Tony R Merriman, K Stamp Lisa. Gout. The Lancelet, Volume 388, 22–28 October 2016, Pages 2039-2052. Doi:* 10.1016/S0140-6736(16)00346-9

Different factors can affect the excretion of UA. An increased exogenous intake can be one of them and it will be discussed later in this paper. Some medications, for example, diuretics, can affect the tubular transport changing the secretion or absorption of UA (3) Changes in the extracellular fluid can also affect the excretion. If extracellular volume increases, it will be detected by the central nervous system (SNC). In response, this will decrease the reuptake and increase the excretion of water and electrolytes as well as UA. Alternatively, if the volume gets reduced it means there will be more reuptake because the SNC detects a lack of liquid, then UA will be reabsorbed.

Another possible cause of an increased UA concentration is enhanced production (3). This normally occurs because there is increased purine degradation in somatic cells, which ends up with more production of UA in the liver. It is usually related to rapid cell proliferation or turnover, for example, leukemias and lymphomas. The increased production can also be related to enzymatic causes linked with the enzymes discussed earlier, PRPP synthase, HGRPT, purine nucleoside phosphorylase or XO. Enzyme activity variations could be a complete deficiency, a partial deficiency, or an increased activity. One example could be a partial or a complete deficiency of HGRPT (called Kelley – Seegmiller syndrome and Lesh-Nyan syndrome respectively). Without this enzyme

guanine cannot be converted back to GMP, letting it go into the salvage metabolic pathway, increasing the UA formation. Another example could be an increased activity of PRPP, making a higher amount of IMP, which is metabolized to UA (Figure 1).

Once UA concentration is high, there is a tendency to develop crystals of urate in the joints. More specifically they are monosodium urate crystals because the uric acid gets combined with sodium ions (4). It is not clear which factors are involved or why the crystal formation occurs, but there are some things that all those who suffer from gout have in common. The first one is hyperuricemia, followed by a drop in the temperature (7). A clear example is the fingers. As a part of the body that is far away from the core, they normally have a lower temperature, which makes it easy for the UA to lose solubility and produce these pathological crystals. Variation in pH may also have an effect, although reports on this topic are not clear. This means that some other factors must be considered. Research suggests that an increase of sodium concentrations increases the probability of urate monosodium crystals formation.

Deposition of urate crystals in the joints results in an inflammatory response, as they are an external and non-recognized agent (Figure 3) (8). This leads to the pathology known as gout. This inflammatory response is initiated by macrophages, which interact with urate crystals and create inflammasomes. This promotes the production of some inflammation factors such as interleukin 1-β (4), and the response is amplified by neutrophils and mast cells. Finally, the tissue is invaded by pro-inflammatory cytokines and prostaglandins. When this happens the first symptoms appear, the most common being arthritis, linked with swelling and erythema in the joint.

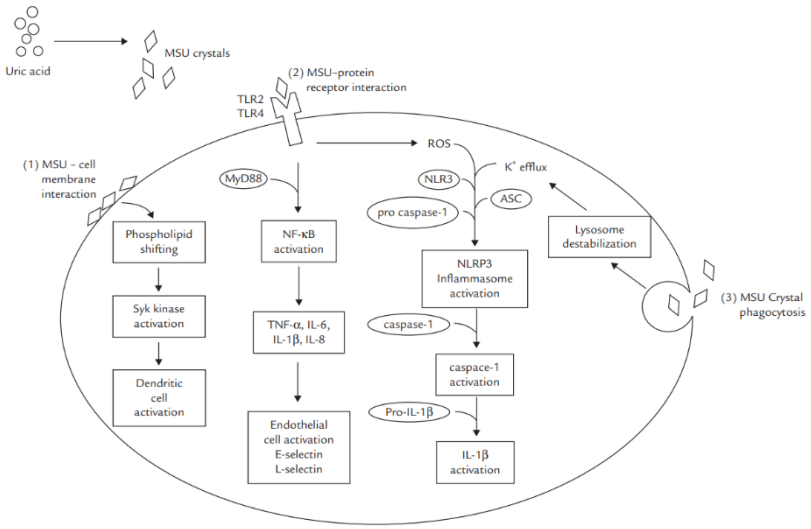

Figure 3: Inflammatory response to urate crystals deposition

Retrieved from: *NicolaDalbeth, Thomas J.Lauterio, Henry R.Wolfe. Mechanism of Action of Colchicine in the Treatment of Gout. Clinical Therapeutics. October 2014. Volume 36. Pages 1465-1479. Doi:* https://doi.org/10.1016/j.clinthera.2014.07.017

4.2. Signs and Symptoms

Gout is characterized by flares that are a painful feeling in the joint where the crystals are formed, related to an acute episode of inflammation (1). The symptoms presented are pain, swelling, heat, redness, and difficulty in moving the affected joint (4). Also, before a flare occurs, the individual can feel discomfort or tingling in the affected zone, normally about 24 hours before the flare occurs. A flare can last for one week or two but can be resolved earlier if the patient uses medications. Examination during a flare will show synovitis, which means an evident joint inflammation, with pain on contact (Figure 4). There is a pronounced tenderness and tendinitis and bursitis can be present. In severe cases, a polyarticular flare (more than one joint affected) can be present and the patient can experience fever. Also, some can have subcutaneous nodules called tophi, but those are normally pain-free (9).

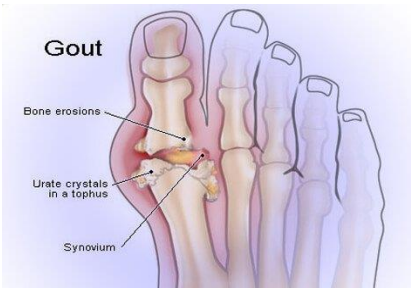

Figure 4: Joint inflamed due to crystal deposition.

Medecinenet [Internet]. San Clemente, 2016. [cited march 14 2020] **Retrieved from**: https://www.medicinenet.com/gout_pictures_slideshow/article.htm

4.3. Diagnosis

An important thing to take into consideration is the existence of risk factors that can always help diagnosis (1); these are described in Table 1 and need to be adjusted by the age of the patient. Proper diagnosis is normally done using the American College of Rheumatology criteria (10). These utilize different options: the first one is the presence of urate crystals in the joint fluid, the second one is the presence of tophi plus urate crystals (determined by laboratory techniques) and the third one is the presence of six or more possible clinical, laboratory and radiological findings (Table 2).

Risks factors	
Alcohol intake	≥ 50g /day
Hypertension	–
Body mass index	≥ 30kg/m^2
Sweetened drinks	≥ 2 drinks /day
Fructose intake	Highest quintile
Meat consumption	Highest quintile
Dairy products consumption	Lowest quintile
Vitamin C intake	< 250 mg

Table 1: Different risk factors related to Gout development

Adapted from: *Roddy E, Doherty M. Epidemiology of gout. Arthritis. Res Ther. 2010;12(6):223.Doi:* 10.1186/ar3199

Different laboratory techniques are used for diagnosis. The main one uses polarizing light microscopy of the synovial fluid or tophus for finding urate crystals, which will appear as needle-shaped in the microscope (4). Testing UA in the blood is also helpful for the diagnosis, but hyperuricemia is not enough by itself to confirm gout. If joint aspiration is not available, it is helpful to use imaging modalities to assist in the diagnosis. Radiography helps to see joint erosion in advanced gout, or ultrasonography might show features of monosodium urate crystal deposition.

Diagnostic criteria for gout	
Presence of characteristic urate crystals in the joint fluids	
Presence of a tophus proven to contain urate crystals by chemical means or polarized light microscopy	
Presence of six or more of the following clinical, laboratory or radiological findings:	Asymmetric swelling within a joint on radiography
	Attack of monoarticular arthritis
	Culture joint fluid negative for microorganisms during an attack of joint inflammation.
	Development of maximal inflammation within one day.
	Hyperuricemia.
	Joint redness.
	More than one attack for acute arthritis
	Pain or redness in the first metatarsophalangeal joint.
	Suspected tophus.
	Subcortical cyst without erosions on radiography.
	Unilateral attack involving first metatarsophalangeal joint.
	Unilateral attack involving tarsal joint.

Table 2: Rules followed to diagnose gout in a patient.

Adapted from: Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum. 1977;20(3):896. Doi: 10.1002/art.1780200320

4.4. Nutritional factors

4.4.1. High purine foods

It has been shown that a diet with a greater intake of meats and seafood is related to a higher level of UA blood concentration and as a consequence, a greater probability of developing gout (11,12). It is important to understand that not all types of meats have the same risk. Pork, beef, and lamb are more harmful than chicken and turkey.

The cause of the increased UA level in blood is twofold. First, there is an increase in exogenous purines, causing the body to produce more UA than normally does. Also, an increase of red meat (pork, beef, lamb) is related to an increase in dietary saturated fat, which is related to a decreased excretion of urate in the kidney (11). The way a diet rich in saturated fats decreases urate excretion is not fully understood, and the data are not clear about it. Some of the hypotheses at the moment are increased retention by the tissues, diminished production of endogenous purines and disturbances of the function of the liver. The metabolism of high-fat diets results in an acidosis and ketosis acidosis situation in the body, which ends up in a decreased in excretion of UA, but this effect

can be balanced with a good carbohydrate and protein intake, but why these effects balance each other are still unclear (11).

However, a high protein diet is not necessarily related to an increased circulating UA and the development of gout. It will also depend on the sources from where this protein comes. For example, if the main source is red meat or seafood there will be a greater possibility of increasing circulating UA concentrations. Also, a higher concentration of purine in food does not necessarily mean that UA blood levels will increase (11). For example, spinach, which has more purines than a raw steak (171mg/100g vs 90.2 mg/100g) (13), does not increase UA levels in serum. So, there are a lot of factors that can affect the relationship between food and its effect on circulating UA concentrations, the quantity of the food, the cooking practice, the type of purines present in the food, and the different bioavailability of the purines are all important. For example, some studies have shown that the process of boiling, steaming or microwaving can reduce the purine content in foods; boiling is the process which decreases purine content the most (14). This happens because boiling makes an extraction of purines from the foods to the water, risen the purine content in the cooking liquid.

4.4.2. Alcohol

There is a well-known relationship between alcohol and gout, but the risk of hyperuricemia and gout varies with the amount and type of alcohol consumed. Is seems that the alcohol affects UA circulating levels by increasing exogenous purines (beer) (11,12), increasing the endogenous production, and decreasing the urate excretion in the kidney. Compared to non-alcoholic diets, the ones which contain beer or liqueur every day are more likely to increase serum urate concentration. Beer has a greater effect than liqueur, and the more of each compound consumed, the higher the risk (15,16). Wine does not appear to be associated with an increase in urate concentration. There is a difference between sexes, since women got higher serum urate levels than men for the same amount of alcohol consumed.

A possible mechanism by which alcohol increases urate is because it increases adenosine triphosphate (ATP) conversion to AMP for alcohol metabolism which ends up in an increased production of UA(12). Another explanation of why beer enhances UA

more than liqueurs is because it contains a large amount of purines, increasing the exogenous intake. Beer yeast contains 2995 mg/ 100mg (13). Another theory about why alcohol decreases UA excretion could be because alcohol is converted to lactic acid in an acute and excessive intake and this acid competes with the excretion of UA in the kidney.

4.4.3. Fructose and sweetened drinks

Fructose is the only carbohydrate that increases urate blood levels. So consuming soft drinks, which normally have a high concentration of fructose, is related to an increased incidence of hyperuricemia and therefore gout (11,12,17). There is a direct relationship between the number of sodas consumed and the risk of gout which can be more severe depending on the ethnicity. As a example, consumption of soda leads to a 6,89 % greater chance of developing gout in white people but only a 1,48 % greater chance in pacific island's natives (18). These difference between the races is due to the polymorphism in the SLC2A9 gene.

Although soft drinks have a very low amount of purines, they contain is a high fructose concentration. The metabolism of fructose involves high consumption of ATP, which generates AMP in the liver, which will be finally metabolized to UA. Besides, there is an indirect factor which can increase UA levels, because a higher fructose intake is related to insulin resistance. It increases the glucose concentration in the blood, making the body generate more insulin, which decreases the UA kidney excretion. The insulin effect on UA excretion is not completely understood, is it not clear if it inhibits UA secretion in the tubule or increases UA reabsorption at the tubular level (19). The main theory right now suggests that insulin changes the extracellular volume near the blood vessels surrounding the tubules, affecting UA excretion.

Other foods, which also can have high fructose concentrations are fruit juices, apples, or acid fruits (mandarin or oranges). There is a significant relationship between juice consumption and gout risk and the same applies to apples and oranges (20). However, the risk is lower than sweetened beverages (21). The data are not clear about the number of fructose calories necessary to cause an increase in the circulating urate, so more research must be done in this area.

4.4.4. Low-fat Dairy products

Dairy products have a very low amount of purines, for example, milk has no detectable purines(13). These products are related to lower levels of urate in the blood, in a comparison between a dairy-free diet and dairy inclusive diet, the first one increases the UA levels. Also the intake of milk at least once a day decreases significantly the incidence of gout (22).

Dairy consumption decreases the urate levels because of the uricosuric effect of milk protein in the kidney. Milk contains orotic acid (11), which competes with the urate for the kidney transporter URAT 1, reducing urate reuptake, which means there will be more excretion of UA. Also, dairy protein and fat can module the inflammatory response to monosodium urate crystals, they may have a similar effect as colchicine, a drug that will be discussed later in this paper.

4.4.5. Coffee/Tea

There appears to be an inverse relationship between coffee intake and blood urate levels. However, the studies do not show any difference between decaffeinated coffee and normal coffee, so a compound in this beverage other than caffeine has to be responsible for this effect(11,12,23). Tea, by the way, seems not to be related to urate serum concentrations. It is important to consider that more research has to be done because the data are not sufficient.

4.4.6. Vegetables and fiber:

Vegetables are linked with lower UA levels, maybe because they increase UA kidney excretion, but data are not clear(12). Fiber intake also has an inverse relationship with urate serum concentrations. These could be because fiber reduces nutrient absorption in the gut, making a decreased intake of exogenous purines. When fiber arrives in the gastrointestinal tract, it increases the rate of passage, which could potentially decrease digestion and nutrient absorption(24).

4.5. Anti-inflammatory nutrition

Even though foods can increase or decrease circulating UA levels, there is another characteristic that should be considered, the anti-inflammatory effect. The fact that some foods can have some anti-inflammatories properties, can help to reduce flares frequencies.

4.5.1. Omega 3 fatty acids, EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid)

As is discussed above in this paper, seafood and bluefish have a high content in purines, increasing the risk of high levels of circulating UA (12,13). However, these foods also contain EPA and DHA, fatty acids with anti-inflammatory properties (25). These two fatty acids regulate genes, which are involved in multiple processes, including inflammation. To notice the therapeutic effect of EPA and DHA is important to administrate enough of these two compounds to make the dose effective (25).

These Omega-3 fatty acids regulate the signaling pathways and genes expression of immune cells, for example, a study of the Nutrients journal says that the administration of EPA and DHA in lipopolysaccharide-stimulated THP-1 macrophages, induce changes in the gene expression that may protect macrophages from an excessive inflammatory response (25). However, this is not the only mechanism related to inflammation reduction. They also showed a rapid and selective inhibition effect on the NLRP-3 inflammasome, through G protein-coupled receptors (26).

Knowing the possible action mechanisms, is clear that omega-3 fatty acids help reducing inflammation (25,26). But, the source of EPA and DHA also contains a great number of purines, so an evaluation of fatty fish intake must be considered (11–13). As it appears in an article of the American College of rheumatology, while the consumption of fatty fish helps reducing flare attacks, the omega-3 fatty acids supplements did not (26). These differences between the main source and the supplements could be because the supplements, don't reach the same dose as fish does (26). Despite fatty fish reduces the

possibility of flare attacks, if they are consumed in a rich purine diet, they can increase the possibility of high UA blood levels, because of its rich purine content (11–13,25,26).

4.5.2. Turmeric

Turmeric or curcumin is a spice that comes from the rhizome of the plant *Curcuma Long*a and it has been recognized with different medical properties, thanks to its major polyphenol, curcumin (27). It aids modulating de inflammatory response, oxidative stress and metabolic syndrome, characteristics which can make this spice helpful for the flare attacks (27,28). The anti-inflammatory mechanism of curcumin is based on blocking the activation of the nuclear factor- KB (NF-KB), which regulates the expression of the tumor necrosis factor α (TNF-α), an important mediator on the inflammatory process (27). The activation of NF-KB can occur through multiple ways including oxidative stress, that is why curcumin is helpful against this process (27).

For these different properties, curcumin has seen to be useful during osteoarthritis and that is why it can be useful for chronic arthritis pathologies. There is a study from the Baqiyatallah University of Medical Sciences that had made a randomized double-blind placebo-controlled trial (28). The study shows a significant reduction of pain, and an improvement in joint function, in the treatment group compared with the placebo ones. The treatment consisted of a daily dose of 500 mg curcuminoid with 5 mg of piperine for 6 weeks (28). It is important to consider that these improvements were not related to a decrease in the circulating cytokines, they were related to the changes in the synovial cytokines, for this reason, it is possible, that curcumin effects are more related to a local anti-inflammatory effect rather than a systemic one (29). Another study shows that curcumin could have the same beneficial effects as non-steroidal anti-inflammatory drugs (NSAIDs) have (30). Even though the effects of the drug were faster than curcumin, for long term administration, they show similar outcomes. This is the reason why curcumin could be a proper substitute for NSAIDs, especially when these drugs cause severe gastrointestinal effects (30).

Therefore, curcumin has perfect properties to deal with inflammation, there is an inconvenient related to it, its low bioavailability (27,28). It has poor absorption, rapid metabolism, and rapid elimination. However, there are some different agents which can

help this bioavailability to increase, for example, piperine, the major component of black pepper (28). By blocking the curcumin metabolic pathway, piperine enhances curcumin bioavailability (27). That is why in the study discussed above, they add 5 mg of piperine to the curcumin complex. Despite its low Bioavailability, there is no discussion that turmeric presents multiple medical properties, and it helps to reduce the oxidative stress and inflammation, which makes this spice important to consider for gout treatment. (27–30).

4.5.3. Vitamin C

Vitamin C or ascorbic acid is an essential nutrient that we can find in numerous fruits and vegetables, besides that, this substance also presents two beneficial effects in gout patients (20). Vitamin C had shown the trait of increasing UA excretion through urine, reducing the serum UA. This effect is due to the vitamin C transporters (SLC23A1, SLC23A2) can modify URAT1 (responsible of UA reabsorption) activity in the proximal tubular cells, even the mechanism is not fully understood, the proximity of these transporters in the apical membrane of the proximal tubular cells, suggest that they can interact with each other (20). The other beneficial effect is blocking the pro-oxidative stress of fructose and UA, which is a source of inflammation (20,31). Vitamin C as an antioxidant substance acts neutralizing free radicals of the oxidative stress by being an electron donor (20,31).

Looking at the action mechanisms, Vitamin C can be considered on diet management for gout. However, as it is discussed on the omega 3 fatty acids, the vitamin C source also can be a problem, because fruits and juices are known to have a high fructose content, which is prejudicial for gout management as is discussed above (11,12,20), that's why, a risk-benefit for each food should be examined, choosing the sources that have less fructose and more Vitamin C, for example, broccoli (31).

4.5.4. Cherries

This fruit, according to different articles, had appeared to be related to lower UA circulating levels and a gout flares reduction (32). Cherry presents an anti-inflammatory mechanism, it inhibits cyclooxygenase 1 and 2 due to anthocyanin, a flavonoid present in the cherry extract (32,33). The extract also appears to reduce urate crystals stimulated

inflammatory cytokines in affected joints (33). Another important cherry effect is the capacity of lowering serum urate, by inhibiting XO (32,33).

Despite the mechanisms are promising, data is not significant enough, and more research should be done, especially in the serum urate-lowering capacity (33). Another aspect that must be considered about cherries, is that they present vitamin C, and as it is discussed above, it is another important compound for gout management. In resume, although more research is needed, cherries may be helpful for gout management in both stages, flare attacks, and urate-lowering therapies (32,33).

4.6. Pharmacological analysis

For gout treatment, two scenarios have to be considered, the acute treatment which involves the flares, and the long term one, which uses urate-lowering drugs (1). The flare treatment includes corticosteroids, colchicine, and NSAIDs (non-steroidal anti-inflammatory drug). In the acute case, the treatment should start as soon as possible when a flare appears, and patients need an action plan and easy access to the drugs to make the attack last as few days as possible. Long term treatment is only recommended for people whose flares have become chronic (more than 2 flares a year) or have tophi present, or patients with other comorbidities, for example, chronic kidney disease. Having hyperuricemia, but no other symptoms is not enough to include the urate-lowering therapy (4).

The urate-lowering therapy target is to reach 6 mg/dL of circulating urate in the blood (10). At this serum concentration, monosodium urate crystals will be more likely to dissolve. An important consideration of this therapy is that it can precipitate flares when it is introduced, due to mechanisms that will be discussed later in this paper. The recommendation for avoiding this problem is doing prophylaxis with anti-inflammatories for 6 months before the urate-lowering therapy starts (34).

Long term therapy should start after a flare occurs, and then last till the desired urate concentration (6 mg/dL) in serum is achieved. Normally it takes between three to six months. After this time if, there has not been any symptoms, the patient can stop taking

the medication. In case any of the symptoms of a flare occurs, the prescription should be continued indefinitely (4). A worrying problem with this therapy is that it has a very low adherence (10-46%) (35) , so it is important to make the patient aware of the disease and urate levels. Patient's understanding of the chronic nature of the disease is essential to successful gout management.

4.6.1. Urate lowering drugs

Allopurinol

Allopurinol is a first-line therapy, which means it is the first option to give to a patient. It is also a "predrug", so bioactivation is required. This means that the allopurinol metabolite oxypurinol is the one that makes the pharmacological action. Oxypurinol is an XO inhibitor, that blocks the last 2 reactions of purine metabolism. Allopurinol is normally excreted by the kidney and there are no contraindications, although some individuals have a sensitivity to it. The dosing varies between 50-900 mg/ day, but for doses above normal (300 mg/day) should be monitored (4). It has some interactions but the most important one is with diuretics, which can increase the possibility of allopurinol hypersensitivity syndrome. Patients with a decreased renal function should not take it for reasons explained later in this paper. There is a study that found that allopurinol can also reduce XO expression, but more research is needed (36).

Febuxostat

Febuxostat is also a first-line treatment for gout and it also inhibits XO (Figure 5). Although it has been shown to be more effective than allopurinol to decrease the serum concentration of urate, it is not more effective in reducing the flare frequency. This drug is metabolized in the liver by conjugation with glucuronic acid or by oxidation (3). There is no other side effect except for possible hypersensitivity. Both, allopurinol and febuxostat, can cause acute attacks at the start of the treatment, since it takes a long time for the drugs to control urate levels (34).

Probenecid

Probenecid does not inhibit any enzyme, it is a diuretic that increases the urinary excretion (Figure 5) of UA by inhibition of a tubular anion transporter, which is involved

in urate reuptake (37). It specifically inhibits the URAT and OAT transporters (Figure 2). It is metabolized in the liver by conjugation and excreted for the kidneys. Normally, it is used as a second-line treatment because it has a lot of drug interactions, making it dangerous if combined with other drugs (ex: methotrexate), which could result in severe toxicity. It can be used in combination with XO inhibitors if they are not enough for lowering serum urate levels. One important side effect is that it can make UA stones in the kidney, so a high fluid intake is important, to avoid this problem (37).

Benzbromarone

Benzbromarone increases renal urate excretion by inhibition of the tubular transporter URAT 1, blocking urate reabsorption. Its indication is the same as probenecid. It is metabolized in the liver and is mainly excreted in bile and feces (4,38). It is strongly contraindicated in patients with excess of alcohol intake and liver diseases for metabolic reasons. It also presents numerous interactions with other drugs, for example, warfarin (it increases the anticoagulant effect), and also with fluconazole and rifampicin (38). As side effects it can also produce kidney stones, so high liquid intake is recommended. As a uricosuric, it is more powerful than probenecid, being effective in patients that have decreased filtration rates. However, it is not used because of the possible hepatotoxicity that it presents.

Pegloticase

Pegloticase is an intravenous drug. It is an exogenous uricase, that will convert UA to its more soluble metabolite allantoin (Figure 1) that is excreted by the kidney (39). Due to the administration form and possible side effects, it is a third-line treatment and is only used in refractory gout, where the other treatments have failed. The dose is 8 mg every two weeks and is administrated by a rheumatologist. It cannot be used at the same time as other urate-lowering therapies. It presents important side effects such as immunogenic effects or infusion reactions (39) .

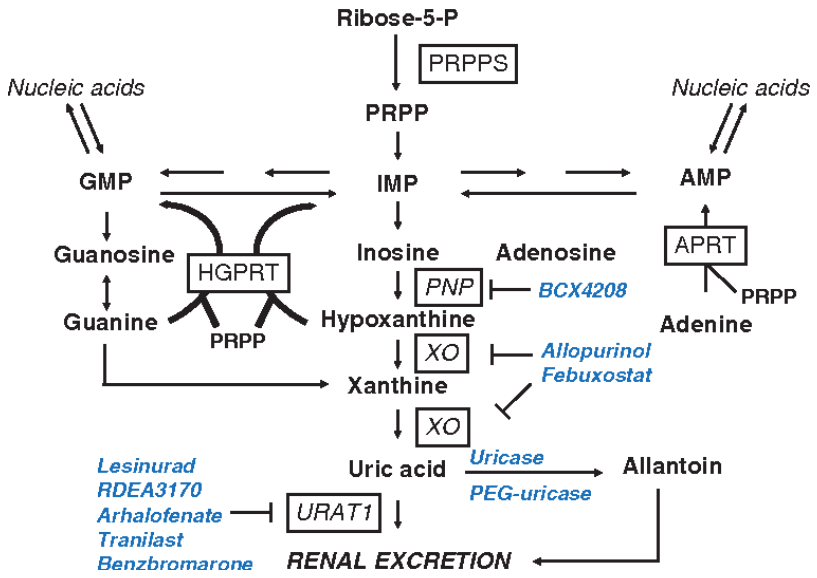

Figure 5: Action places of gout drugs.

***Retrieved from**: Richette Pascal, Garay Ricardo. Novel discovery strategies for gout. Expert opinion on Drug discovery. Dec 2012. Volume 8. Pages 183-189. Doi*: 10.1517/17460441.2013.742061

4.6.2. Acute Gout treatment

Colchicine

Colchicine is used in both therapies, urate-lowering therapy, and flare treatment. The mechanism of action is the prevention of microtubules assembly which will inhibit the inflammatory response to the urate crystals deposition (Figure 3) (8). Because microtubule assembly is present in the majority of inflammatory processes, the utilization of colchicine is being studied in other inflammatory chronic diseases (1). Colchicine is used to prevent gout flares at 0,6 to 1,2 mg of dose, but drug administration is quite particular: when a flare occurs, the patient should start with 1.2 mg initially, followed by 0.6 mg after 1 hour. The maximum dose is 1.2 mg a day, though this can change if the patient has kidney disease (4). Also, it has important interactions with CYP 4503A4 and P glycoprotein inhibitors (for example diltiazem and ciclosporin respectively). As side effects this drug presents reversible axonal neuromyopathy (8). Patients should take care if any symptoms or signs appear then and discontinue the treatment if it is necessary.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are the first-line treatment when a flare occurs. The most common one is indomethacin, but other ones, for example, naproxen or ibuprofen are good too. The mechanism of action is by inhibiting the enzymes cyclooxygenase 1 (COX 1) and cyclooxygenase 2 (COX 2) (40). The first one is a gastrointestinal protector enzyme and the second one modulates the inflammatory response. The inhibition of COX1 will cause gastrointestinal side effects, and the inhibition of COX2 has the main therapeutic effect. There are some COX2 specific inhibitors, but they do not seem to be more effective than the nonspecific ones. Any NSAID is given at its max dose when an attack appears and is continued one or two days after the symptoms have disappeared. For example, indomethacin, should be taken 50 mg three times per day. This drug could be contraindicated if the patient has any kidney disease, cardiovascular problems or gastrointestinal diseases, due to the side effects that this type of drug can present (40). As secondary effects, there is the gastrointestinal damage due to the lack of prostaglandin production in the stomach. Another secondary effect is an increase in cardiovascular disease by increasing blood pressure and lowering kidney function, especially in long terms treatments (40).

Corticosteroids

These drugs are not a first-line treatment and are an alternative for patients who cannot take colchicine or NSAIDs or have several comorbidities. The mechanism of action is the same as endogenous steroids, they react with type 3 steroid receptor, which will produce an anti-inflammatory response. When there are only one or two joints affected, intraarticular corticosteroids could be effective. If not, normally oral prednisolone is the one used, at the dose of 35 mg/day (1). The principal side effect is the corticosteroid rebound, that can happen when the patient stopped taking the medication, so the dose must be decreased slowly to avoid side effects.

4.7. Gout and comorbidities

It has been noticed that gout is associated with different comorbidities like heart and renal diseases, which a lot of times are highly related to hyperuricemia. These comorbidities are one of the most important causes of death for gout patients (36). Also, the prevalence of metabolic syndrome, related to gout disease is high, frequently the patients show hypertension, abdominal obesity (body max index and waist circumference elevated), Type 2 diabetes and hypertriglyceridemia. The presence of these signs is higher in gout patients compared to non-gout individuals (41).

Asymptomatic hyperuricemia can cause other effects in the body apart from gout (1,4). It can cause the metabolic syndrome mentioned above and renal arteriosclerosis, which means the deposition of fatty molecules in the vascular walls, making the passage narrower, and the blood will have difficulties to circulate. Other effects that a higher blood UA concentration can make to the body are decreasing nitric oxide production by limiting enzyme activity, activating the renin-angiotensin system, and increasing insulin resistance, which will end up increasing the cardiovascular risk (42).

Cardiovascular mortality increases with gout due to the high levels of UA in blood and the inflammation produced for crystal deposition (41). Gout medication does not help this problem because NSAIDs and diuretic side effects are related to cardiovascular problems (34). As said before hyperuricemia is one of the most important factors related with the increased cardiovascular risk. There are many different studies that support a relation between high circulating UA levels and an increased frequency of cardiovascular death: stroke, atrial fibrillation, and heart failure (42).

Another factor to consider with cardiovascular disease is XO enzyme. As it is a redox enzyme it can produce free radicals (Figure 6). With a normal enzyme function, this should not be a problem but with increased activity, for example, more purine metabolism, it can end up creating more free oxygen species (42). These radicals will cause damage due to oxidative stress in the vascular endothelia and the inhibition of NO

production. However, is it unclear for the moment if this problem is due to an increased XO activity or due to an increased circulation of soluble UA(42).

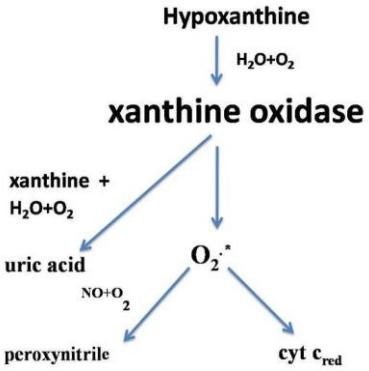

Figure 6: XO mechanism, and production of oxygen free radicals.

Retrieved from: Pathak, Khanin & Rahman, Syed & Bhagawati, Sudhansu. (2017). Chemical Science Review and Letters An Overview of Antioxidant and free Radicals-A Review Article. 2017. 242-251.URL: https://www.researchgate.net/publication/319483353

There is a high prevalence of chronic kidney disease (CKD) in gout patients. The main problem with this comorbidity is that it will decrease urate excretion in urine, increasing the probability of originating gout. In addition the risk of end-stage renal failure is higher in gout patients because different problems can appear (36,41). These include accumulation of monosodium urate crystals in renal tubules, the possibility of kidney stones or the possible renal toxicity of elevated levels of UA (41).

Comorbidities affect gout management, and gout affects the management of the other diseases. A clear example is aspirin, which is cardioprotective but at the same time increases uricemia. At the same time, drug treatment of hypertension is related to an increased risk of developing gout (beta-blockers, angiotensin converter enzyme inhibitors, and some tubular loop diuretics)(42). However, insulin-lowering drugs and dyslipidemia management drugs present benefits for gout patients since they have urate-lowering effects (19).

The other way around, colchicine and NSAIDs are not recommended in patients with renal failure and steroids cannot be given to patients with metabolic syndrome, hypertension or diabetes mellitus type 2 (41). Also, colchicine and statins (a drug used

for the treatment of dyslipidemias) should not be given together in patients with renal failure because of a metabolic interaction (they compete for the same metabolic enzyme)(10).

There are some interactions with urate-lowering therapy too. For example, furosemide, a drug used in heart failure, decreases the allopurinol hypouricemic effects, by blocking the allopurinol reduction of XO expression (a new mechanism just found) (10,36). In the case of chronic kidney disease, allopurinol dose should be considered because it can cause serious cutaneous skin reactions, but reducing the dose for avoiding skin reactions, it will difficult to reach the desired uricemia levels. The normal procedure then dictates a switch to febuxostat (36).

4.8. Dietary management of gout

Although there are well documented pharmacological treatments for gout, the role of the diet for management is basic to properly control this disease. Diet is a key factor for patients to have an improvement in quality of life and to minimize the pharmacological treatments and their side effects. Historically, diet control was based on cutting high purine foods out of the diet, reducing the amount of exogenous purine intake (12). But as is already discussed in this paper, there are many other factors which can affect UA and not all the rich purine foods affect uricemia the same way (12–14). Also, is it important to look to at the type of purines present in each food (adenine, guanine, hypoxanthine, and xanthine), because adenine and particularly hypoxanthine are known to be more uricogenic, than guanine and xanthine (43).

Right now, most nutrition guidelines or recommendations focus on different aspects of food and liquid intake. In general, there are common factors which are present in gout diets, limiting or avoidance of alcohol; losing weight if the person is obese (as it is said before high-fat levels in the body increases the metabolic syndrome and uricemia levels); reducing the fructose intake by sweetened drinks (sodas) and juices (17); reducing purine intake from red meats and seafood; including dairy products, particularly low fat; and maybe introducing vitamin C supplementation (44).

There are also recommendations that will impact a flare development. The patient should avoid alcohol, drink water (between 8-16 cups)/day and consume less than 170 mg of meat a day as well as avoiding seafood (43). Then as a protein source, eggs (0 mg/ 100mg of purine content), low-fat dairy and tofu (20 mg/100mg) should be considered (13). On the other hand, there are long term recommendations, which include weight loss and daily exercise, increasing protein from plants, fruits, and whole grains, one or two servings of low-fat dairy daily, decreasing or eliminating beer, liqueur, and high fructose beverages and finally consider drinking coffee and taking vitamin C (43).

4.8.1. Low-purine diet

Low purine diet was the first diet introduced in gout management because it decreases circulating UA levels 1-2 mg/dL (11). But nowadays, they are not used anymore because of increased fat and carbohydrate intake, which can increase comorbidity problems. Also, there are some foods which have a high level of purines, for example, some vegetables and legumes, but are not related with an increase in uricemia and risk of gout. They would be avoided in this type of diet just because of the high concentration of purines that they contain (43).

4.8.2. Plant-based diet

This type of diet is based on consumption of whole grains, legumes, fruits, and vegetables. Considering that vegetables with high purine content do not affect uricemia in the same way animal purine does, there is no need to exclude high purine content vegetable and legumes (43,44). In beans, vegetables, and soy products, more than 60% of the purine type is adenine and guanine while in the animal products more than 50% is hypoxanthine (43). Vegetarians always show lower UA in circulation than the non-vegetarians. Ironically a vegan diet might be expected to have lower UA levels than a vegetarian diet, but it shows a higher uricemia than a nonvegetarian diet (13). This is related to the fact that in a vegan diet there is no consumption of dairy products, which helps to reduce the uricemia, as explained before (45). Plant based diets are not only worth it for the management of gout and hyperuricemia but they also works for gout comorbidities and are one of the principal components of the dietary approaches to stop hypertension (44) .

4.8.3. Weight-loss diet

Obesity is related to high levels of uricemia, this relationship could be due to multiple factors such as an increment of the oxygen demand, an increase of endogenous purines because of the synthesis of fatty acids and a reduction in renal urate excretion (11). One study on coronary artery disease risk development in young adults showed that overweight people are 3 to 9 times more likely to develop hyperuricemia(46). Loss of fat mass is directly relating to reaching the desired UA levels in the blood, so weight loss diets must be considered. The hypouricemic effect of weight loss depends on the amount of weight loss and the initial uricemia (47). In common with plant-based diet, it also will help to deal with cardiovascular and kidney diseases.

4.9. Patient interview analysis

(Interview available in the Annex)

Interview: The patient is a 58 years old Caucasian man, from Spain, 76 kg weight and 1,60m tall, follows the Mediterranean diet with some excesses sometimes. As well as gout, he presents other comorbidities such as over-weight (BMI = 76 kg / 1, 60m^2 = 29,6) and moderate hypertension.

The content of the interview, in general matches with the content of this paper. There are slight variations in some topics since that every patient is different, and fitting everyone into the same characteristics for a disease is almost impossible. The patient characteristics (age, ethnicity, comorbidities and weight) also match with the gout patient prototype (1).

The patient looks well informed about gout and he explains quite well the disease in his own words. Even if there are some conceptual mistakes, the general idea of the disease is clear. However, the concept of the chronic nature of the disease does not appear in his definition. As said before in this paper, communicating this concept to the patients is basic to assure a good treatment adherence (35). The year of diagnosis and symptoms described in the interview are the ones expected considering the information provided

by this paper, despite the description of the first attack, which the patient already said was unusual.

The interview description of flares is also the one expected. The treatment helps to reduce the time a flare lasts, and also the patient can feel when an attack would start in the next few hours. Interestingly there are not consistent periods between flares. It is a random process, which means that variations in food intake or metabolic changes, could be responsible. The patient only takes medication for the flares, which means that he has no problems controlling the UA blood levels, because he does not need therapy with urate-lowering drugs.

The eating habits of this patient follow the Mediterranean diet, which is considered one of the best diets in the world (48), and it is probably what helped the patient to avoid the urate-lowering drugs. He is aware that there are some foods which are negatively related with gout, he relates it to an attack and not the increase of the UA levels, which is the main consequence.

He has taken some foods out of the diet: beer, sweetened drinks, and red meat. The patient had introduced these changes 6 months ago and has not experienced any flare, so probably there is a positive relation between these two situations. An important factor, which the patient talks about and is not discussed in this paper, is to have regular eating hours. He says before he started to control eating times, the flares were more common, so maybe some research on this topic is worth considering.

5. Conclusions

Different topics related with gout have been discussed in this paper, allowing for an overall analysis of the disease. This study has provided a general analysis and overview of gout establishing the key points for understanding the disease, its consequences, and the different ways to treat it.

1. Databases have been properly applied during the project. All the different tools and research methods have followed the directions given, and only reliable sources have been consulted. The article selection criteria have been developed properly, and only the most relevant articles and sources have been selected. Finally, using the reference manager Mendeley and following the Vancouver citation rules, the references have been properly cited and managed.

2. Gout is a disease that involves a large number of different mechanisms and metabolic pathways. Different systems in the body take part; the liver, the kidney, the gut and the joints (1). These characteristics mean that even though the disease has been documented and studied for years, there are still some parts that require more research. This will allow for a better awareness of the signs and symptoms of the disease, simplifying the complex diagnoses that are used right now, allowing for an improved treatment.

3. Food plays a basic, yet important role in gout management, treatment and prevention (12). A proper control of the diet helps to reduce UA levels, as well as manage gout comorbidities. On one hand, not all the foods which have a high purine content end up increasing the UA blood levels, it depends on the cooking practice used and the type of purine presented. On the other hand, if a food contains no purines it does not mean it would not affect the UA levels, as seen with soft drinks. There are many other foods that help to reduce UA circulating levels by different mechanisms, for example, dairy products and coffee. Finally, the anti-inflammatory properties of some foods should be considered to reduce flare frequencies, making diet management also helpful for acute gout.

4. Gout drug treatment can be separated into two big families; urate-lowering therapy and acute gout treatment (4). Both use different drugs which act in different ways. Although the drugs used right now are effective in reducing a flare period or decreasing the UA circulating levels, further research needs be carried out into the treatment of the disease. This is because gout is a chronic disease, which means there is no cure at the moment.

5. Comorbidities are important factors to consider in gout management (36). Metabolic syndrome, cardiovascular disease, and kidney disease are related to gout and high UA levels. The main problem with these different co-existing diseases is the interactions between them and their treatments. This is one of the reasons why treatment via the diet is important for gout.

6. Gout is a chronic, metabolic, and inflammatory disease related to different comorbidities and different recommendations will help its management. These include; keeping the patient well informed about the disease and its consequences, properly analyzing any other health problems the patient may present and how they would affect gout management ,if pharmacological treatment is necessary choose the most appropriate one based on the patient health status, and finally, looking into the dietary habits of the patient and make the necessary corrections to achieve appropriate UA serum levels.

In conclusion, all the associated objectives for this project had been achieved. The hypothesis of the paper appeared to be partially confirmed. As it is discussed, diet appears to be as important as drug treatments for reducing serum UA, presenting strong evidence that proper control in food intake could be as effective as urate-lowering drugs. Despite the anti-inflammatory properties of some foods that can reduce flare frequencies, when a flare attack occurs, it seems that pharmacological treatment is needed since food response is not quick enough. This seems to make drug treatment more effective for flares.

References

1. Hainer BL, Matheson E, Travis Wilkes R. Diagnosis, treatment, and prevention of gout. Am Fam Physician. 2014;90(12):831–836.

2. Aliaga AM, Álvarez de Toledo F, Baena MI, Faus MJ, Gascón MP, Gastelurrutia MÁ, et al. Foro AF-FC.. Guía Práctica para los Servicios de Atención Farmacéutica en la Farmacia Comunitaria. Consejo General de Colegios Oficiales de Farmacéuticos. 2010. 54 p.

3. Fathallah-Shaykh Sahar TCM. Uric acid and the kidney. Pediatr Nephrol. 29:999–1008.

4. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016;388(10055):2039–2052.

5. Mandal AK, Mount DB. The Molecular Physiology of Uric Acid Homeostasis. Annu Rev Physiol. 2015;77(1):323–345.

6. Wright AF, Rudan I, Hastie ND, Campbell H. A complexity of urate transporters. Kidney Int [Internet]. 2010;78(5):446–452. Available from: http://dx.doi.org/10.1038/ki.2010.206

7. Loeb JN. The influence of temperature on the solubility of monosodium urate. Arthritis Rheum. 1972;15(2):189–192.

8. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of action of colchicine in the treatment of gout. Clin Ther [Internet]. 2014;36(10):1465–1479. Available from: http://dx.doi.org/10.1016/j.clinthera.2014.07.017

9. Aati O, Taylor WJ, Siegert RJ, Horne A, House ME, Tan P, et al. Development of a patient-reported outcome measure of tophus burden: the Tophus Impact Questionnaire (TIQ-20). Ann Rheum Dis [Internet]. 2015 º1;74(12):2144-2150. Available from: http://ard.bmj.com/content/74/12/2144.abstract

10. Khanna D. ACR Guidelines: 2012 American College of Rheumatology Guidelines for Management of Gout Part I: Am Coll Rheumatol [Internet]. 2012;7(10):3842–3845. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3683400%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC368044

11. Álvarez-Lario B, Alonso-Valdivielso JL. Hiperuricemia y gota: El papel de la dieta. Nutr Hosp. 2014;29(4):760–770.

12. Beyl RN, Hughes L, Morgan S. Update on Importance of Diet in Gout. Am J Med [Internet]. 2016 Nov 1;129(11):1153–1158. Available from: https://www.amjmed.com/article/S0002-9343(16)30723-9/fulltext

13. Kaneko K, Aoyagi Y, Fukuuchi T, Inazawa K, Yamaoka N. Total purine and purine base content of common foodstuffs for facilitating nutritional therapy for gout and hyperuricemia. Biol Pharm Bull. 2014;37(5):709–721.

14. Li T, Ren L, Wang D, Song M, Li Q, Li J. Optimization of extraction conditions and determination of purine content in marine fish during boiling. PeerJ. 2019;2019(5):1–23.

15. Choi HK, Curhan G. Beer, liquor, and wine consumption and serum uric acid level: The Third National Health and Nutrition Examination Survey. Arthritis Care Res. 2004;51(6):1023–1029.

16. Neogi T, Chen C, Niu J, Chaisson C, Hunter DJ, Zhang Y. Alcohol quantity and type on risk of recurrent gout attacks: An internet-based case-crossover study. Am J Med [Internet]. 2014;127(4):311–318. Available from: http://dx.doi.org/10.1016/j.amjmed.2013.12.019

17. Ayoub-Charette S, Liu Q, Khan TA, Au-Yeung F, Blanco Mejia S, De Souza RJ, et al. Important food sources of fructose-containing sugars and incident gout: A systematic review and meta-analysis of prospective cohort studies. BMJ Open. 2019;9(5).

18. Batt C, Phipps-Green AJ, Black MA, Cadzow M, Merriman ME, Topless R, et al. Sugar-sweetened beverage consumption: A risk factor for prevalent gout with SLC2A9 genotype-specific effects on serum urate and risk of gout. Ann Rheum Dis. 2014;73(12):2101–2106.

19. Toyoki D, Shibata S, Kuribayashi-Okuma E, Xu N, Ishizawa K, Hosoyamada M, et al. Insulin stimulates uric acid reabsorption via regulating urate transporter 1 and ATP-binding cassette subfamily G member 2. Am J Physiol - Ren Physiol. 2017;313(3):826–834.

20. Nakagawa T, Lanaspa MA, Johnson RJ. The effects of fruit consumption in patients with hyperuricaemia or gout. Rheumatol (United Kingdom). 2019;58(7):1133–1141.

21. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: Prospective cohort study. Bmj. 2008;336(7639):309–312.

22. Zgaga L, Theodoratou E, Kyle J, Farrington SM, Agakov F, Tenesa A, et al. The association of dietary intake of purine-rich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study. PLoS One. 2012;7(6):1–8.

23. Choi HK, Curhan G. Coffee, tea, and caffeine consumption and serum uric acid level: The Third National Health and Nutrition Examination Survey. Arthritis Care Res. 2007;57(5):816–821.

24. Lyu LC, Hsu CY, Yeh CY, Lee MS, Huang SH, Chen CL. A case-control study of the association of diet and obesity with gout in Taiwan. Am J Clin Nutr. 2003;78(4):690–701.

25. Allam-Ndoul B, Guénard F, Barbier O, Vohl MC. A study of the differential effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on gene expression profiles of stimulated thp-1 macrophages. Nutrients. 2017;9(5):7–10.

26. Zhang MA, Zhang Y, Terkeltaub R, Chen C, Neogi T. Effect of Dietary and Supplemental Omega-3 Polyunsaturated Fatty Acids on Risk of Recurrent Gout Flares. Arthritis Rheumatol. 2019;71(9):1580–1586.

27. Hewlings S, Kalman D. Curcumin: A Review of Its' Effects on Human Health. Foods. 2017;6(10):92.

28. Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A. Curcuminoid treatment for knee osteoarthritis: A randomized double-blind placebo-controlled trial. Phyther Res. 2014;28(11):1625–1631.

29. Panahi Y, Hosseini MS, Khalili N, Naimi E, Simental-Mendía LE, Majeed M, et al. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomed Pharmacother [Internet]. 2016;82:578–582. Available from: http://dx.doi.org/10.1016/j.biopha.2016.05.037

30. Mazzolani F, Togni S. Oral administration of a curcumin-phospholipid delivery system for

the treatment of central serous chorioretinopathy: A 12-month follow-up study. Clin Ophthalmol. 2013;7:939–945.

31. Ellulu MS, Rahmat A, Patimah I, Khaza'Ai H, Abed Y. Effect of vitamin C on inflammation and metabolic markers in hypertensive and/or diabetic obese adults: A randomized controlled trial. Drug Des Devel Ther. 2015;9:3405–3412.

32. Collins MW, Saag KG, Singh JA. Is there a role for cherries in the management of gout? Ther Adv Musculoskelet Dis. 2019;11:1-16.

33. Chen PE, Liu CY, Chien WH, Chien CW, Tung TH. Effectiveness of Cherries in Reducing Uric Acid and Gout: A Systematic Review. Evidence-based Complement Altern Med. 2019;2019:1-7.

34. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American college of rheumatology guidelines for management of gout. part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res. 2012;64(10):1447–1461.

35. De Vera MA, Marcotte G, Rai S, Galo JS, Bhole V. Medication adherence in gout: A systematic review. Arthritis Care Res. 2014;66(10):1551–1559.

36. Ankli B, Berger CT, Haeni N, Kyburz D, Hügle T, So AKL, et al. The target uric acid level in multimorbid patients with gout is difficult to achieve: data from a longitudinal Swiss single-centre cohort. Swiss Med Wkly. 2019;149:w20121.

37. Silverman W, Locovei S, Dahl G. Probenecid, a gout remedy, inhibits pannexin 1 channels. Am J Physiol - Cell Physiol. 2008;295(3):761–767.

38. Lee MHH, Graham GG, Williams KM, Day RO. A benefit-risk assessment of benzbromarone in the treatment of gout: Was its withdrawal from the market in the best interest of patients? Drug Saf. 2008;31(8):643–665.

39. Becker MA, Baraf HSB, Yood RA, Dillon A, Vázquez-Mellado J, Ottery FD, et al. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. Ann Rheum Dis. 2013;72(9):1469–1474.

40. Van Durme CMPG, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RBM. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev. 2014;2014(9).

41. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med [Internet]. 2012;125(7):679-687. Available from: http://dx.doi.org/10.1016/j.amjmed.2011.09.033

42. Palmer TM, Nordestgaard BG, Benn M, Tybjarg-Hansen A, Smith GD, Lawlor DA, et al. Association of plasma uric acid with ischaemic heart disease and blood pressure: Mendelian randomization analysis of two large cohorts. BMJ. 2013;347(7919):1–10.

43. Nielsen SM, Zobbe K, Kristensen LE, Christensen R. Nutritional recommendations for gout: An update from clinical epidemiology. Autoimmun Rev [Internet]. 2018;17(11):1090–1096. Available from: https://doi.org/10.1016/j.autrev.2018.05.008

44. Jakše B, Jakše B, Pajek M, Pajek J. Uric acid and plant-based nutrition. Nutrients. 2019;11(8):1–15.

45. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: A systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr. 2017;57(17):3640–3649.

46. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: The CARDIA study. Ann Epidemiol. 1998;8(4):250–261.

47. Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: The Multiple Risk Factor Intervention Trial. Rheumatology. 2010;49(12):2391–2399.

48. Stamostergiou J, Theodoridis X, Ganochoriti V, Bogdanos D, Sakkas L. The role of the Mediterranean diet in hyperuricemia and gout. Mediterr J Rheumatol. 2018;29(1):21–25.

Annex

Patient interview

1. What do you know about your pathology?

   I know that gout is an inflammatory disease, linked with a high blood levels of uric acid. I think that my body eliminates less uric acid than a normal person, this increases the uric acid blood levels and then crystals of this substance are formed in the joints. Once the crystals are formed an attack of gout appears and it is extremely painful.

2. How old were you when you got diagnosed?

   I was 44 years old

3. Which were the symptoms you felt?

   I am a bizarre case, because if normally the gout starts in a toe or in a knee, I noticed in the external part of my left foot. It was an uncomfortable and painful feeling, that didn't even allow me to walk, so I thought I had broken a bone. When I arrived to the doctor they didn't think on gout for the first moment, because they thought it was a trauma problem and it wasn't till the rheumatologist suspect of gout, and ordered a blood analysis that they found out.

4. **What is normally the period between one flare and the next?**

   There is no period exactly between flares, for example right now I did not experience one for the last 6 months, but when I was diagnosed the first time, I got an attack every 2 months, more or less. I will say that is random but sometimes if I do an abuse of feasting for 3 days, is more likely an attack will appear.

5. **How long does a flare last?**

   Right now, because I take medication, the acute part of a flare, which is when I can barely move, only lasts for 24h, and then 3 more days till the symptoms totally disappear. However, the first times I was not being treated the acute part lasts for at least 2 days and it took a week to feel totally recovered.

6. **Can you notice if a flare is about to occur 24h before?**

Yes. Normally the feeling comes when I'm going to sleep, it feels warm and a little bit itchy around a joint area, is not uncomfortable at all, but in general when this appears I normally got a flare next morning, but its good because it helps me reacting to the attack before it even occurs.

7. **Which treatment are you on? Do you know the mechanism of action of the drugs?**

My treatment consists only in two medications for the flare, colchicine and naproxen, for the gout treatment. Then I also take a drug for help regulating the hypertension called enalapril.

8. **Is the treatment effective?**

Is not effective on reducing the pain, because every time I have an attack the feeling that I got is exactly the same. Although, is really helpful on reducing the time a flare lasts, as I said before, the treatment reduces the time an attack will last.

9. **Are there any foods that if you eat will bring on a flare?**

I know there are some foods that helps an attack happen, like red meat or peas, but in general I can eat some of that in moderation and nothing happens to me. However, as I also commented before, when I do an excess in feasting like Christmas celebrations, when I eat a lot of heavy and sugary foods and I also drink a lot of alcohol, is more likely for me to have an attack the days after.

10. **What was your diet before getting diagnosed? Have you changed something since then?**

My diet before getting diagnoses is more or less the same I have right now. However, is it true that I have delete some foods or drinks, not only because of gout, also for the high levels of sugar. I try to moderate my alcohol intake and drink more wine than beer, also I have deleted the sweetened drinks like coke or sprite 6 months ago. However, if one day I want to eat something I do, I don't deprive myself of nothing. I tried to reduce my red meat intake, because before I used to eat at least one piece every day. And the most important think is managing properly the food hours. Before I got diagnosed and the 5 years after I

was quite chaotic in my eating hours, I used to skip breakfast and don't eat anything during the morning till lunch, and it was the period when I have experienced more attacks. Right now, I try to have at least 5 meals a day, 3 important ones and 2 small ones between the other 3.

11. **Is there any food you cannot take because of the medication?**

I know alcohol is not recommended but that's it.