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Comparison of Vitamin B12 Values and Kidney Function Tests in Patients Diagnosed with FMF and Gout under Colchicine Treatment

Kolşisin Tedavisi Altında FMF ve Gut Tanısı Alan Hastalarda B12 Vitamin Değerleri ile Böbrek Fonksiyon Testlerinin Karşılaştırılması

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ABSTRACT

FMF (Familial Mediterranean Fever); It is an inherited disease manifested by recurrent periodic increasing fever and abdominal pain, chest and joint pains. It is a process that causes an autoinflammatory syndrome, usually manifested by recurrent attacks of fever and aseptic polyserositis. The cause of FMF is mutations in the MEFV gene, which encodes the purine protein.

Gout is a joint disease caused by the accumulation of monosodium urate (MSU) crystals in or around the joints. Disorders of purine metabolism, decreased excretion of uric acid (UA) or hyperuricemia (HUA) caused by increased UA production in the body are directly related to gout.

Colchicine is an alkaloid obtained from the seeds of the *Colchicum autumnale* L plant, which is used in the treatment of rheumatic diseases such as FMF and GUT. It is an antimitotic agent that binds to the intracellular tubulin protein and inhibits the polymerization of new microtubules. It shows its effect through microtubules. Colchicine treatment in FMF patients prevents the development of amyloidosis and attacks. Thus, in addition to preventing acute attacks, it also slows down the formation of amyloidosis, which is the most important side effect of the disease.

In this review, studies on the subject were examined and vitamin B12 and kidney function tests were compared in FMF or GUT patients receiving colchicine treatment.

Keywords: *FMF, GOUT, Colchicine, BUN*

ÖZET

FMF (Ailesel Akdeniz Ateşi); Tekrarlayan periyodik artan ateş ve karın ağrısı, göğüs ve eklem ağrıları ile kendini gösteren kalıtsal bir hastalıktır. Genellikle tekrarlayan ateş ve aseptik poliserozit atakları ile kendini gösteren bir otoinflamatuar sendroma neden olan bir süreçtir. FMF'nin nedeni ise pürin proteinini kodlayan MEFV genindeki mutasyonlardır.

Gut, monosodyum ürat (MSU) kristallerinin eklemlerin içinde veya çevresinde birikmesi ile oluşan bir eklem hastalığıdır. Pürin metabolizması bozuklukları, ürik asit (UA) atılımının azalması veya vücutta artmış UA üretiminin neden olduğu hiperürisemi (HUA), gut doğrudan ilişkilidir.

Kolşisin, FMF ve GUT gibi romatizmal hastalıkların tedavisinde kullanılan *Colchicum autumnale* L bitkisinin tohumlarından elde edilen bir alkaloiddir. Hücre içi tübülin proteinine bağlanan ve yeni mikrotübüllerin polimerizasyonunu engelleyen bir antimitotik ajandır. Etkisini mikrotübüller aracılığıyla gösterir. FMF hastalarında kolşisin tedavisi amiloidoz ve atakların gelişmesini engeller. Böylece akut atakları önlemenin yanı sıra hastalığın en önemli yan etkisi olan amiloidoz oluşumunu da yavaşlatır.

Bu derlemede konu ile ilgili yapılan çalışmalar incelenerek kolşisin tedavisi alan FMF veya GUT hastalarında B12 vitamini ve böbrek fonksiyon testleri karşılaştırılmıştır**.**

Anahtar kelimeler: *FMF, GUT, Kolşisin, BUN*

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INTRODUCTION

FMF (Familial Mediterranean Fever) is an autosomal recessive hereditary disease that lives in the Mediterranean region and especially affects ethnic origins (Padeh and Berkun, 2007). It is the MEFV (Mediterranean Fever-MEFV) gene mutation that causes the disease (Dönder et al., 2012). The MEFV gene, which is responsible for FMF disease, is localized to the area on the short arm of chromosome 16. It encodes the protein known as pyrin or marenocrin (Aksentijevich et al., 1997). Pyrin protein is noted to play a role in the activity of neutrophils in the inflammation zone at the time of FMF attacks and by inhibiting inflammation (Güran et al., 2003). Pyrin is a regulatory protein with restricted tissue description, especially in neutrophils, which suppresses neutrophil activation (Şahan and Cengiz, 2005). In priority attacks, sterile peritonitis, pleuritis, and arthritis are observed, to a lesser extent pericardium, skin (erysipelas-like erythema; ELE) and tunica vaginalis may also be affected. In 90% of patients, the first attack is seen before the age of 20 (Ben-Chetrit and Levy, 1998). Characteristics of FMF disease are accompanied by inflammation of the synovial and serosal membranes and recurrent febrile attacks. Although the duration of the attack usually varies between 2-4 days, longer and shorter seizure patterns may be seen. Infection or tension is thought to be important because the triggers are often not understood. Attacks often appear suddenly without giving any symptoms and then disappear for no reason (Soylemezoglu et al., 2010). When the Turkish community is compared with other affected societies, it is understood that the severity of renal failure caused by amyloidosis increases (Kasapçopur and Arisoy, 2006). FMF; is a disease accompanied by fever, characterized by painful, non-infectious bouts of inflammation of the serous membranes and, gradually, the development of Amyloidosis (Üstebay et al., 2015). In response to progressive inflammation with FMF, the development of amyloidosis is observed due to the accumulation of a protein called serum amyloid A in the organs made in the liver (Cowan et al., 2013). Among the supportive criteria, the family history of FMF comes first. The vital and clinical side effect of FMF is amyloidosis (Köse, 2012). Secondary amyloidosis that occurs in FMF is in the AA form. In response to inflammation developed by FMF, AA progresses to amyloidosis due to the collection of a protein called amyloid A in the liver. The precursor protein of AA-shaped amyloidosis is serum amyloid A, one of the acute phase reactants. Although amyloid accumulates in many organs, it is a renal deformation that often causes morbidity and mortality (Keskin, 2018).

GOUT (Drop disease) hyperuricemia is a hereditary disease that continues with recurrent attacks of acute arthritis, in which monosodium urate crystals are increased in the joints and purine metabolism is impaired (Tetik et al., 2012). GOUT disease is manifested by the inflammatory picture formed by the settlement and accumulation of urate crystals from supersaturated extracellular fluids into tissues (Demir et al., 2007). GOUT hyperuricemia is a disease in which monosodium urate crystals are collected in the joints that progress with recurrent episodes of acute arthritis. There are four stages in the development of GOUT arthritis (İliçin et al., 2003). The first stage is asymptomatic hyperuricemia. At this stage, only the serum urate level is increased, and the symptoms of arthritis are not yet manifested in trophies or urate nephrolithiasis. The tendency to acute gouty arthritis is observed with an increase in serum urate concentration. Average blood uric acid levels vary between groups (Gibson et al., 1984). The second stage is acute GOUT arthritis. The first attack of the stage is mostly seen between the ages of 40-60 in male patients and 60 years in the female patient (Marinello et al., 1985). An attack before the age of 25 is most often associated with a specific enzyme defect leading to the unusual synthesis of purine, unconventional renal disease, or the use of cyclosporine if any. GOUT arthritis is generally seen as recurrent attacks characterized by very strong, painful articular and periarticular inflammation, erythema, and bloating of the skin (Tetik et al., 2012). The strength of the attack reaches its peak within 12-24 hours, and the full spread of attacks develops between a few days and a few weeks, even in people who refuse treatment. Acute attack pain interrupts sleep, makes it difficult to walk, and prevents work and leisure activities. Especially the first few attacks are severe. A visual analog template (VAS) numbered 0-100 has been developed to indicate the strength of pain in patients (Silman and Hochberg, 2001). The first attacks can begin monoarthricularly in 85-90% of cases and occur mostly on the big toe, respectively, on the toe, ankles, heels, knees, wrists, fingers and elbows are other commonly affected joints (Wortmann, 2002). It acts more on peripheral and end joints than on middle joints. Involvement is expected in tendons, tenosinoveum, and bursa structures along with joints (Nakayama et al., 1984). Olecranon and prepatellar are additional common ones among those we consider bursitis (Recht et al., 1994). Urate storage and successive GOUT select previously ruined tissues. GOUT arthritis is evident in Heberden nodules in older women (Lally et al., 1989). In 1/3 of the cases, 2 or 3 joints may be affected in the first attack. Wrist and elbow involvement was found to be related to the disease process (Hadler et al., 1974). The third stage is the intercritical stage of gouty arthritis. This stage is the most noiseless time of GOUT arthritis attacks (Liang et al., 2015). Although some patients do not have a second attack of arthritis, most patients may have a new attack in the range of 6 months to 2 years. It is difficult to diagnose gouty arthritis in hyperuricemic patients with a history of monoarticular attacks in the interim period. If urate crystals can be observed during aspiration of an asymptomatic joint (the

incidence varies between 12.5% and 90%), it may be useful in diagnosing gouty arthritis (Erdem et al., 2007). The fourth stage is chronic tophilate GOUT arthritis. If the treatment of recurrent acute GOUT arthritis and hyperuricemia is not started at this stage and the underlying factors (excessive alcohol use, obesity, diuretic treatment, etc.) cannot be eliminated, chronic tophilate GOUT arthritis occurs. The formation of tophi is proportional to the level and duration of hyperuricemia (Nakayama et al., 1984). Traceable tophies occur in approximately 1/3 of patients with chronic GOUT arthritis (Karatay, 2015). As urate accumulation increases, uric acid crystals continue to appear in cartilage, synovial membranes, tendons, soft tissues, and other places (Tetik et al., 2012). The presence of tophies is important for diagnosis. Purines are nitrogenous compounds that break down into uric acid in the body (Akcan, 2016).

Colchicine; GOUT is used to treat Familial Mediterranean Fever (FMF) and Behçet's disease (Emre et al., 2011). It is a fat-soluble alkaloid that is immediately absorbed from the gastrointestinal tract (Wallace and Ertel, 1973). The main mechanism of interaction is that it inhibits microtubule polymerization (Üstebay et al., 2015). Each molecule binds the tubule molecule by molecule and prevents the relationship between the polymers, and microtubule elongation is stalled, mitotic needles disperse, and cell division is disrupted. It inhibits multiple cellular signaling pathways by distributing the cytoskeleton. Many effects of cytokines and chemokines are altered in this way (Hazen, 1979). Colchicine exerts its obvious effect from changes in leukocytes, adhesion, mobility, and cytokine production (Gemici, 2010). Colchicine is absorbed from the jejunum and ileum, but the amount absorbed may vary between patients. After a certain period after taking colchicine 1 mg (single dose), the peak plasma concentration is monitored within a minimum of 30-90 minutes. Colchicine is metabolized in the intestine by cytochrome and transported by P-glycoprotein. The absorbed colchicine is metabolized by CYP3A4 in the intestine and liver. With P-glycoprotein, it is removed from the liver by 16-50% with the help of the biliary tract. The absorption of colchicine is restricted due to the blood-brain barrier p-glycoprotein (Rochdi et al., 1994). Colchicine is excreted in the urine by glomerular filtration and tubular secretion halves (Zemer et al., 1974). As a result, colchicine is absorbed immediately, but it remains for a long time in certain tissues (Hunter and Klaassen, 1975). Colchicine is a powerful and reliable drug used in the long-term treatment of FMF. For the first time in 1972, the use of daily oral colchicine treatment was envisaged in the supervision of FMF attacks. Treatment of colchicine in addition to alleviating the intensity and severity of FMF attacks is protective against the occurrence of amyloidosis (Hazen, 1979).

Colchicine may have a role in preventing the absorption of some vitamins and minerals in continuous use. Characteristically, vitamin B12, which is absorbed from the terminal ileum, is known to make it difficult to absorb it reversibly in the consumption of chronic colchicine (Stopa et al., 1979). Colchicine has been reported to cause damage to the structures of the villi in the ileal mucous cells, reducing the number of villi, thereby disrupting the receptor functions that carry out the absorption of vitamin B12 in the ileum (Wickramasinghe and Ratnayaka, 1996). Serum vitamin B12 absorption disorder becomes evident in patients receiving long-term and coordinated colchicine. Vitamin B12, which cannot be synthesized in the human body, should be taken from animal foods such as meat, milk, and eggs. The most common cause of B12 withdrawal in humans is low food consumption due to socioeconomic status disorder (Erdöl, 2017). Colchicine limits the absorption of vitamin B12 by reducing the receptor level of the B12-intrinsic factor (IF) structure in mucosal cells. This effect is dose-dependent and reversible (Başaran and Uncu, 2018). It has been reported to cause damage to the structure of the villi in the ileal mucosa cell, limiting the number of villi, thus disrupting the receptor functions that provide the absorption of vitamin B12 in the ileum (Wickramasinghe and Ratnayaka, 1996).

FMF and GOUT patients have been observed to show the same symptoms. Both diseases have intense joint pain, swelling, redness, and inflammation. Usually, the leg joints (foot, ankle, knee) are the most affected areas. FMF and GOUT are characterized. Colchicine and anti-inflammatory drugs have a preventive effect on attacks of GOUT and FMF (Çınkıl, 2019). It is used as a preventive treatment, especially in people with normal blood uric acid levels (Dokuzlar et al., 2018). In humans, uric acid is the end product of purine metabolism. The total body uric acid reservoir is 1800 mg. In gout patients, this rate can increase up to 2000-4000 mg (Üstü and Uğurlu, 2012). The main route of excretion of uric acid is the kidneys (Tetik et al., 2012). Colchicine is commonly used in FMF attacks and lowering blood uric acid levels. When used regularly, it reduces attacks and completely corrects them. Thus, as well as preventing acute attacks, it also slows down the formation of amyloidosis, the most important side effect of the disease (Zemer et al., 1974).

Conclusion and Discussion

Familial Mediterranean Fever (FMF); Mediterranean Fever-MEFV (MEFV) is a disease that occurs after a gene mutation and usually affects ethnic groups living in the Mediterranean region (Zemer et al., 1974; Padeh and Berkun, 2007; Dönder et al., 2012). In other literature, FMF; is a disease accompanied by fever, the pain of serous membranes, characterized by bouts of non-infectious inflammation, and, gradually, the formation of Amyloidosis (Üstebay et al., 2015). Amyloidosis occurs due to the accumulation of serum Amyloid A protein produced in the liver in the organs in response to

the inflammation that occurs (Cowan et al., 2013; Keskin, 2018).

The MEFV gene is located on the no-length arm of chromosome 16. This gene encodes a protein identified as pyrin or marenocrin. Pyrin is a regulatory protein with restricted tissue expiration, especially in neutrophils, that suppresses neutrophil activation (Aksentijevich et al., 1997; Güran et al., 2003; Şahan and Cengiz, 2005). In attacks are observed mainly sterile peritonitis, pleuritis, arthritis compared to the pericardium, skin (erysipelas-like erythema; ELE) and tunica vaginalis may also be affected. In 90% of patients, the first attack occurs before the age of 20. Attacks often occur unexpectedly without any symptoms and then disappear for no reason (Ben-Chetrit and Levy, 1998; Soylemezoglu et al., 2010).

According to Tetik et al.; GOUT (Drop disease) is an inherited disease caused by purine metabolism disorder and characterized by recurrent acute arthritis attacks, in which monosodium urate crystals are increased in the joints (Tetik et al., 2012).

In the study conducted by İliçin et al. (2003), it was stated that there are four stages in the development of GOUT arthritis. In the literature review, different researches on the attacks of GOUT disease were also found. According to the study conducted by Gibson and colleagues; the first stage is indicated by an asymptomatic increase in the level of uric acid in the blood (Gibson et al., 1984). In another piece of literature, it was reported that the attack of this stage was observed earlier in men and later in women (Marinello et al., 1985). Goldman and Ausiello reported that stage two is acute GOUT arthritis and that GOUT arthritis is generally seen as very strong, painful articular, and recurrent attacks characterized by periarticular inflammation, erythema, and bloating of the skin (Goldman and Ausiello, 2008; Shide et al., 2015). According to Karatay's study; the third stage is the intercritical stage of gouty arthritis. This stage is the quietest period among GOUT arthritis attacks (Karatay, 2015). According to the study conducted by Nayakama and his colleagues; the fourth stage is chronic tophilate GOUT arthritis. If treatment for recurrent acute gouty arthritis and hyperuricemia is not started at this stage and the underlying factors (such as excessive alcohol consumption, obesity, diuretic therapy) are not eliminated, chronic tophilate GOUT arthritis occurs. The formation of tophi is proportional to the stage of hyperuricemia and the time of occurrence (Nakayama et al., 1984). In addition to the study conducted by Nayakama et al., in the Karatay study in 2015, it was reported that visible tophies occurred in approximately 1/3 of patients with chronic GOUT arthritis (Karatay, 2015). In the study conducted by Tetik et al. in 2012, it was reported that uric acid crystals began to appear in cartilage, synovial membrane, tendons, soft tissues, and other areas as urate accumulation increased (Tetik et al., 2012). In 2016, as a result of Akcan's study, it was reported that the presence of tophies is important in terms of diagnosis and purine is one of the nitrogenous compounds that are broken down to uric acid in the body (Akcan, 2016).

Colchicine; It is a fat-soluble alkaloid that is rapidly absorbed from the gastrointestinal tract and is widely used in acute attacks of gouty arthritis and pseudogout, FMF, and Behçet's disease (Wallace and Ertel, 1973; Emre et al., 2011; Başaran and Uncu, 2018). In the study conducted by Yalçınkaya et al., it was reported that the main mechanism of action was that it inhibited microtubule polymerization (Üstebay et al., 2015). In another study, the obvious effects of colchicine were shown on differences in the adhesion, mobility, and cytokine production of leukocytes (Gemici, 2010). After the intake of colchicine in the literature; colchicine is removed by urine by glomerular filtration and tubular secretion. However, colchicine is rapidly absorbed, but it has been observed to reside in certain tissues for a long time (Zemer et al., 1974; Hunter and Klaassen, 1975; Rochdi et al., 1994).

According to the study conducted by Stopa et al., it has been reported that colchicine may cause absorption of some vitamins and minerals when used continuously (Stopa et al., 1979). Similar studies were conducted by Wickramasinghe et al. in different years and colchicine has been reported to cause damage to the structure of villi in ileal mucosa cells, reducing the number of villi and disrupting receptor functions that provide absorption of vitamin B12 in the ileum (Wickramasinghe and Ratnayaka, 1996). In addition to these studies, Başaran and Uncu said; Colchicine may reduce vitamin B12 absorption by limiting the receptor level of the B12-intrinsic factor (IF) complex in mucosal cells, and this effect has been reported to be dose-dependent and reversible (Başaran and Uncu, 2018).

FMF and GOUT patients show similar symptoms such as intense joint pain, swelling, redness, and inflammation. The last product of purine metabolism in humans is uric acid. The total body uric acid reservoir is 1800 mg. In patients with gout, this value increases to 2000-4000 mg. The kidneys are the main route of excretion of uric acid (Üstü and Uğurlu, 2012; Üstebay et al., 2015). Colchicine and anti-inflammatory drugs have a preventive effect on attacks of GOUT and FMF (Çınkıl, 2019).

As a result; Colchicine is a drug that can be used for the treatment of FMF and GOUT diseases. However, one of the biggest side effects is that the blood vitamin B12 level decreases by disrupting the absorption of vitamin B12. The literature examined supports this conclusion. While the drug is used regularly during colchicine treatment, we think that the initiation of vitamin B12 to patients as a supplement can provide a healthier progression of the treatment process.

Ethical Approval

Ethics because research articles included in sampling are taken using databases and search

engines that are open to access no board permission was obtained. The work was carried out in accordance with all the principles contained in the Declaration of Helsinki. Throughout the entire study research and publication, ethics were treated in accordance with the ethics.

Conflict of Interest

There is no conflict of interest in this study.

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