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Content

CHAPTER I

Effect Of Omega-3 Fatty Acıds On Some Types Of Cancer

Elif Ebru ALKAN[1]

Cancer

Cancer is a disease characterized by the uncontrolled proliferation of cells due to genetic or environmental factors causing DNA damage and mutations. It is one of the most common diseases with the highest mortality rates globally, posing serious health challenges and being difficult to treat (Rouzbahani et al., 2018). Approximately 5-10% of cancer cases are attributed to hereditary genetic changes, while 90-95% result from environmental factors causing gene mutations (Rouzbahani et al., 2018). Cancer comprises over a hundred types, all characterized by uncontrolled cell proliferation due to genetic alterations (WHO, 2017). The rate of malnutrition in cancer patients ranges from 40-80%, depending on the tumor type, stage, and anti-cancer treatment. Malnutrition leads

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to increased morbidity, decreased quality of life, reduced treatment efficacy, and higher healthcare costs. It has been shown that approximately 30% of all cancers in Western countries are influenced by dietary factors. The intake of vitamins, grains, fibers, fruits, vegetables, meats, fats, alcohol, and sugars can affect the progression and prevention of cancer (Senatorov et al., 2018). Conventional therapies (such as gene therapy, chemotherapy, and radiotherapy) are often insufficient in cancer treatment, and appropriate diet and dietary supplements have been found to improve quality of life and positively impact the treatment process. Therefore, research is conducted to determine whether dietary nutrients and supplements, especially those containing antioxidants, can selectively target cancer cells without harming healthy cells. Various clinical, in vivo, and in vitro studies have been conducted on certain nutrients, compounds, and essential vitamins and oils to investigate their effects on different cancer types (Günay, N. 2018).

Omega-3 and Its Effects on Varıous Diseases

α-Linolenic acid is a polyunsaturated fatty acid and an essential fatty acid. ALA is an Omega-3 fatty acid that can convert into eicosanoids and prostaglandins, playing a role in critical cellular processes such as DNA synthesis and cell proliferation. The primary Omega-3 fatty acids include α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Among these, DHA supports normal brain development, as well as the development of the eyes and nervous system, while EPA and DHA together contribute to cardiovascular health. Various studies have shown that α-linolenic acid, an Omega-3 fatty acid source, can regulate and reduce the proliferation of prostate, breast, and bladder cancer cells.

A study on HT 29, HCT116, and MCA38 cell lines found that Omega-3 fatty acids inhibited cell proliferation, adhesion, and invasion (Chamberland JP, 2014; Manson et al., 2012). The antioxidant effects of Omega-3 fatty acids have also been demonstrated in various experimental studies (Zararsız et al., 2006; Kuş et al., 2008; Stone, 1997).

In recent years, in vivo (directly studying the role of diseases in humans) and in vitro (mimicking cellular environments) studies have investigated the effects of essential fatty acids on cardiovascular diseases and cancers (such as breast, pancreatic, colon, and prostate cancer). Essential fatty acids can affect cells directly or indirectly. Due to their structural and physical properties, essential fatty acids can alter membrane fluidity and influence membrane-mediated processes by becoming components of cell membrane phospholipids. Essential fatty acids help maintain triglyceride levels, prevent HDL cholesterol decline, reduce insulin resistance aiding in the control of Type 2 diabetes, prevent hypertension, support the immune system, and reduce the risk of coronary artery disease. Another study on rats found that Omega-3 fatty acids prevented oxidative tissue damage in the testes caused by formaldehyde toxicity, increased SOD and GSH-Px enzyme activities, and reduced MDA levels compared to those not receiving Omega-3, as determined biochemically (Kuş et al., 2008). Another study found that Omega-3 fatty acids prevented oxidative damage in the renal tissue, strengthened the antioxidant defense system, and provided a protective effect on renal tissue in rats, with increased SOD and GSH-Px activities and decreased MDA levels compared to the control group (Gülcen et al., 2012). Studies have shown that Omega-3 fatty acids possess antihypertensive effects. These fatty

acids inhibit the activities of Δ6 desaturase, cyclooxygenase, and lipoxygenase enzymes in platelets, preventing the synthesis of arachidonic acid from linoleic acid, which is used in the synthesis of vasoconstrictive and thrombin-forming thromboxanes (TXA 2, PGE 2, and PGI 2). Instead, EPA, a precursor to vasodilatory and anti-aggregation compounds (TXA 3, PGE 3, and PGI 3), is used, thereby lowering blood pressure (Boudreu et al., 1991). While the activities increase, MDA levels decrease (Gülcen et al., 2012).

Omega-3 Fatty Acids and Cancer

Various studies have shown that α-linolenic acid (ALA), an Omega-3 fatty acid source, regulates and reduces the proliferation of prostate, breast, and bladder cancer cells. A study on HT 29, HCT116, and MCA38 cell lines found that Omega-3 fatty acids inhibited cell proliferation, adhesion, and invasion (Chamberland JP, 2014; Manson et al., 2012). In one study, a diet rich in ALA was applied to mice, and it was observed to reduce growth and proliferation in MCF-7 tumors (Mason-Ennis et al., 2016). In vitro studies on several breast cancer cell lines have shown that ALA did not convert to EPA and DHA, exhibiting independent effects and reducing in vitro breast cancer cell proliferation (Mason-Ennis et al., 2016; Wiggins et al., 2015; Bardon et al., 1996; Grammatikos et al., 1994). Another study found that ALA had no effect (Horia et al., 2005). Various studies have shown that ALA, an Omega-3 fatty acid source, regulates and reduces the proliferation of prostate, breast, and bladder cancer cells. A study on HT 29, HCT116, and MCA38 cell lines found that Omega-3 fatty acids inhibited cell proliferation, adhesion, and invasion (Chamberland, 2014). In vivo and in vitro studies have shown that α-linolenic acid metabolites,

eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are effective in cancer treatment when used with anticancer drugs. Omega-3 supplements have been found to be effective in improving the recovery of oncology patients. Ten controlled clinical studies involving the administration of DHA and/or EPA during chemotherapy and/or radiotherapy have shown that Omega-3 fatty acid supplements are beneficial in maintaining body composition in different patients during chemotherapy and/or radiotherapy. However, significant results such as reducing tumor size and extending patient survival have not been achieved. Fish oil, a source of Omega-3, has cytotoxic effects on cancer cells due to its antioxidative effects, inhibiting cell growth and viability (Silva et al., 2015). A study on rats with a diet rich in fish oil and Western fats found that the effects on colon cancer and normal tissues were determined by prostaglandin E2 (PGE2) concentrations. The use of fish oils was found to be effective in cancer prevention by reducing inflammation. Dietary fish oils have the potential to prevent colon cancer, and Omega-3 fatty acids are effective in the formation of prostaglandins and other eicosanoids. PGE2 is a key pro-inflammatory mediator that plays a significant role in the initiation and progression of colon cancer (Djuric et al., 2017).

Discussion and Conclusion

Today, it is accepted that the diet is very important in the prevention and treatment of diseases. Nutrition is particularly crucial in cancer, which ranks second as the most common cause of death worldwide. Therefore, the effect of dietary nutrients and supplements on cancer cells is being investigated in terms of their nutrient and antioxidant content. A multitude of scientific research

investigating the impact of omega-3 fatty acids on human health has revealed that these fatty acids possess substantial positive effects in preventing and treating various diseases, including cardiovascular conditions, hypertension, Alzheimer's, depression, rheumatoid disorders, asthma, immune system disorders, and osteoporosis. Another omega-3 fatty acid, α-linolenic acid, and its derivatives, such as the anti-inflammatory eicosanoids (TXA 3, PGE 3, PGI 3), EPA, and DHA, have been found to have significant positive effects in preventing and treating diseases such as prostate, breast, lung, and intestinal cancers, cardiovascular diseases, hypertension, rheumatoid arthritis, osteoporosis, diabetes, asthma, Alzheimer's, depression, and schizophrenia. They also have important positive effects on strengthening the immune system, early cognitive development, and high birth weight (Çelebi, 2017; Ceylan et al., 1999; Leskanich and Noble, 1997). Omega-3 fatty acids have been found to be potentially beneficial for cancer treatment, with antitumor, anti-inflammatory, anti-proliferative, pro-apoptotic, anti-invasion, anti-metastatic, and epigenetic regulation properties, suggesting that they can modify tumor cell response through multiple mechanisms (Silva et al., 2015). In conclusion, numerous studies in the literature demonstrate the preventive and therapeutic effects of omega-3 fatty acids on many diseases, and although there are fewer studies on cancer, the results are promising.

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CHAPTER II

Psorıasıs and Its Treatment

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Cemal BİLAÇ[3]
F. Sırrı ÇAM[4]

1. Introduction

Psoriasis with inflammatory skin disease significantly reduced the quality of life of patients and is associated with many comorbidity (Armstrong & Read, 2020). This disease, which affects 125 million people around the world, is a chronic immune -mediated disease characterized by the development of scaly, itchy, hardened, erythematous and often painful skin plaques (Korman, 2020).

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The pathogenesis of psoriasis is complex and cannot be fully illuminated. The extreme activations of the immune system elements are effective in the pathogenesis of the disease, and in the first steps of pathogenesis, natural lethal T cells, keratinocytes, macrophages, plasmasitoid dendritic cells and various cell types were found to be responsible (Lin, Ambikairajah, & Holmes, 2002).

With a better understanding of psoriasis pathogenesis, many new therapeutic targets have been identified (Jiang, Chen, Yu, & Shi, 2023). However, since the disease is associated with many comorbid conditions, no single treatment option is suitable for all patients (Korman, 2020). Therefore, these comorbid disease conditions may affect treatment options (Kaushik & Lebwohl, 2019). Biological therapies that affect proinflammatory cytokines in disease pathogenesis not only improve skin symptoms but also alter systemic inflammation. Thus, comorbidity may also affect outcomes (Girolomoni vd., 2015; Suárez-Fariñas vd., 2012).

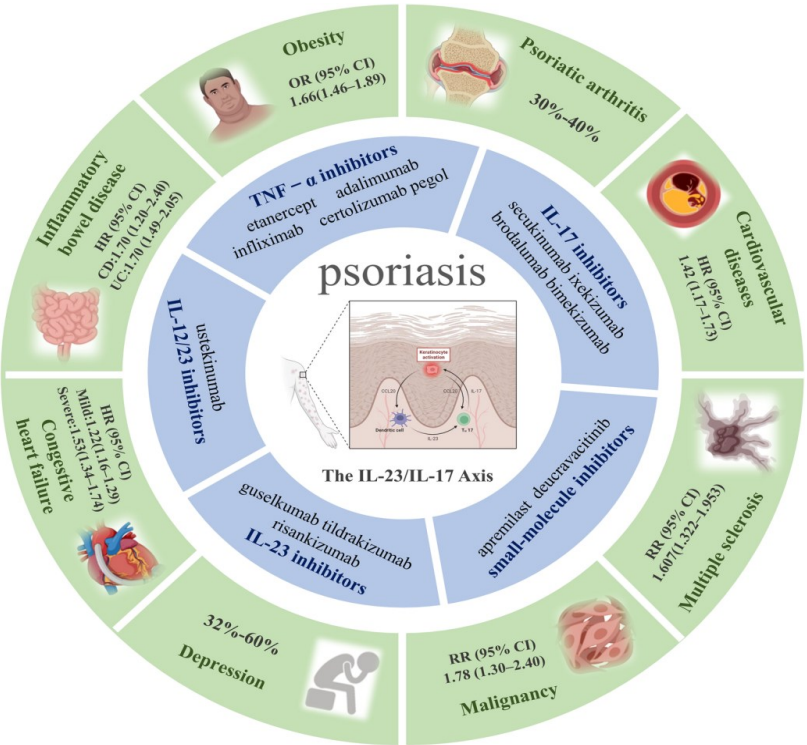

Figure 1. Comorbidities and Systemic Treatment Options in Psoriasis (Jiang vd., 2023).

There are currently several treatments that help with the disease. Current treatments only improve patients' quality of life and relieve their symptoms (Mrowietz vd., 2011). Appropriate treatment varies according to the patient's age, the type of pathology, comorbidity, the affected body part, and the patient's general health. In recent years, new drugs have been discovered as a result of new findings related to the disease.

2. Treatments for Mild Psoriasis

Individuals with psoriasis whose body surface area is less than 5% affected are known as the patient group diagnosed with mild

psoriasis. General treatments usually begin with the evaluation of psoriatic arthritis (Singh vd., 2019). Individuals with mild psoriasis are often controlled with topical therapy (Boehncke, Boehncke, & Schön, 2010). Topical treatments are usually used as the first choice to treat patients with mild psoriasis and in cases where daily functions are not severely affected by the disease (Singh vd., 2019).

Treatments for mild to severe psoriasis include topical vitamin D analogs, topical corticosteroids, topical keratolytics, targeted phototherapy, and calcineurin inhibitors (C vd., 2015; Griffiths vd., 2015).

2.1. Topical Vitamin D Analogs

Topical vitamin D analogs bind to vitamin D receptors on T cells and keratinocytes to inhibit keratinocyte proliferation and increase keratinocyte differentiation. They are free to use in patients with renal failure (Armstrong & Read, 2020).

2.2. Topical Corticosteroids

Topical corticosteroids, which are the main treatment for most patients with mild psoriasis, have anti-inflammatory, antiproliferative and vasoconstrictive effects. In general, patients with mild and localized psoriasis respond when used at appropriate doses. The effectiveness of topical corticosteroids varies. If the lesions are thick, super-potent topical corticosteroids are preferred, while low-potency topical corticosteroids are preferred for sensitive areas such as the groin, axilla, sub-breast and facial areas (Armstrong & Read, 2020).

2.3. Topical Keratolytics

Topical keratolytic agents include tazarotene and salicylic acid. Topical tazarotene inhibits the proliferation of keratinocytes and helps break down the thick scales on the plaque. Salicylic acid is a keratolytic agent that is not suitable for use in children and can reduce scaling (Armstrong & Read, 2020).

2.4. Targeted Phototherapy

Phototherapy, also known as light therapy, uses specific wavelengths of light to treat individuals with psoriasis. Phototherapy provides specific wavelengths and minimizes the emission of wavelengths responsible for carcinogenesis. Targeted phototherapy is used to treat localized psoriasis patients, while full body surrounding phototherapy is used to treat more widespread psoriasis patients. Targeted phototherapy is UV-B excimer light therapy with a wavelength of 308 nm. Individuals with psoriasis are subjected to phototherapy twice a week, and UV-B excimer light therapy has a very low carcinogenic potential. The main side effects are burning and swelling (Armstrong & Read, 2020).

2.5. Calcineurin Inhibitors

Topical calcineurin inhibitors inhibit IFN-γ and IL-2 cytokines, preventing T cell activation. Calcineurin inhibitors include pimecrolimus and tacrolimus. Long-term use of these inhibitors is often used to treat psoriasis without adverse effects on skin atrophy (Gribetz vd., 2004).

3. Treatments for Medium and High Severity Psoriasis

Moderate psoriasis is defined as covering 5% to 10% of the body surface area, while severe psoriasis is typically defined as

covering a surface area of more than 10%. Phototherapy and systemic treatments are the treatment for patients with moderate and severe psoriasis (Boehncke vd., 2010).

3.1. Systemic Treatments

Systemic treatments used to treat individuals with moderate to severe psoriasis are divided into two categories: biologics and small molecule inhibitors. Systemic medications can also be used for localized disease involving specific areas such as the palms, soles, genitals, and scalp, or for patients who do not respond to topical treatments (Armstrong vd., 2020).

3.1.1. Biological Drugs

Biological drugs, which are quite effective in psoriasis, are generally well tolerated. Biological drugs, which are more effective than treatments with small molecule inhibitors, have limited side effects (Sawyer vd., 2019). Since the applications of biological drugs administered by subcutaneous injection are expensive, new treatment options are needed. For this purpose, small molecule drugs that are being tested clinically are being studied. Biologicals used in the treatment of psoriasis are among the most important therapeutic developments in dermatology (Armstrong & Read, 2020). There are four classes of biologic drugs approved by the U.S. Food and Drug Administration (FDA) to treat psoriasis (Mahil vd., 2020). These are TNF-α inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors. All biological drugs except infliximab are administered subcutaneously. There is no increase in the malignancy and infection rates of patients treated using biological drugs (Armstrong & Read, 2020).

3.1.1.1. TNF-α Inhibitors

The effectiveness of TNF-α inhibitors, the oldest group of biologicals used in treatment, can also vary. Those with this group of inhibitors are adalimumab, etanercept, infliximab and certolizumab. These biologicals inhibit the proinflammatory cytokine TNF-α and reduce inflammation (Syed vd., 2021). According to the meta-analysis results, infliximab has the highest efficacy for psoriasis among TNF-α inhibitors. This is followed by adalimumab and certolizumab, followed by etanercept (Armstrong vd., 2020). TNF-α inhibitors are more frequently administered subcutaneously than IL-17 inhibitors and IL-23 inhibitors. If the approved dose is not effective and the patient chooses to continue treatment with a TNF-α inhibitor, the general approach is to first increase the dosing frequency of the TNF-α inhibitor in question (Kimball vd., 2015; Menter vd., 2017). Malignancy rates were not increased in psoriasis patients treated with these inhibitors (Kalb vd., 2015).

3.1.1.2. IL-17 Inhibitors

Another biologic drug, IL-17 inhibitors, is a class of biologics that target the IL-17 receptor or ligand. FDA-approved IL-17 inhibitors include brodalumab, ixekizumab, and secukinumab. These biologics inhibit the proinflammatory cytokine IL-17 and reduce inflammation (Armstrong & Read, 2020). Brodalumab inhibits IL-17α; while ixekizumab and secukinumab inhibit the IL-17A ligand. Bimekizumab, which is not currently approved, inhibits both IL-17A and IL-17F ligands and significant results are obtained in treatment. Comparative studies show that bimekizumab, which has high efficacy, has higher efficacy than other IL-17 inhibitors. In

addition, it has been determined by data analysis studies that neutralizing both IL-17A and IL-17F may be more effective than targeting IL-17A alone (Freitas, Blauvelt, & Torres, 2021). There was no increase in malignancy or infection rates in patients with psoriasis treated with these inhibitors. These inhibitors are also approved for the treatment of psoriatic arthritis.

3.1.1.3. IL-12/23 Inhibitors

The only biologic currently approved to inhibit IL-12/23 is ustekinumab. This biologic works by binding to the p40 protein subunit used by both IL-12 and IL-23. Ustekinumab disrupts IL-12 and IL-23 mediated signaling, thereby reducing inflammation (Armstrong & Read, 2020). The effect of ustekinumab, which is administered every 3 months by taking into account body weight, is primarily mediated through the inhibition of IL-23.

3.1.1.4. IL-23 Inhibitors

IL-23 inhibitors inhibit the p19 subunit of IL-23, which reduces the activities of the Th17 pathway (Armstrong & Read, 2020). IL-23 plays a role in the protection of Th17 cells and has an effect on mucosal immunity (Haberman vd., 2020). Approved IL-23 inhibitors include guselkumab, risankizumab, and tildrakizumab. Mirkikizumab, which has not yet been approved, also binds to the p19 subunit of IL-23 (Brownstone vd., 2021). Risankizumab is also approved for the treatment of psoriatic arthritis. Psoriasis patients treated with these inhibitors did not have increased rates of malignancy or infection (Armstrong & Read, 2020).

3.1.2. Small Molecule Inhibitors

Results from studies of small molecule inhibitors and biologic agents provide important information. Small molecule

inhibitors such as oral phosphodiesterase 4 inhibitor (apremilast) and tyrosine kinase 2 inhibitor (deucravacitinib) have been approved (Hu, Chen, Gong, & Shi, 2018). Apremilast may cause weight loss as a side effect.

3.1.2.1. Phosphodiesterase 4 (PDE4) Inhibitors

Phosphodiesterase (PDE) is involved in the degradation of adenosine monophosphate (AMP) and PDE is divided into 8 families (Schafer vd., 2010). PDE4, expressed by keratinocytes, is the most prevalent in immune cells (Houslay, Schafer, & Zhang, 2005). Phosphodiesterase inhibitors prevent T cell secretion. Inhibition of PDE4 increases AMP concentration and reduces the production of proinflammatory cytokines. The therapeutic drug Apremilast is from the PDE4 inhibitor group and significantly reduces proliferation and epidermal thickness. It also reduces the expression of TNF-α, human leukocyte antigen-DR and intercellular adhesion molecule-1 in lesional skin (Claveau vd., 2004).

3.1.2.2. Protein Kinase C (PKC) Inhibitors

The protein kinase C (PKC) family is grouped within the protein G-related protein class, which plays a role in various signal transduction cascades, the immune signaling cascade, and the adaptive immune system (Ortiz-Ibáñez, Alsina, & Muñoz-Santos, 2013). This family of proteins is expressed in cells that regulate immune processes (Matz vd., 2011).

3.1.2.3. Mitogen-Activated Protein Kinase (MAPK) Inhibitors

Mitogen-activated protein kinase (MAPK) is of great importance in cell proliferation, differentiation and inflammation (Dubois Declercq & Pouliot, 2013). The p38 protein is a potential molecular target for therapy because of its role in the expression and

biosynthesis of many inflammatory cytokines (Ortiz-Ibáñez vd., 2013). p38-MAPK is overexpressed in psoriasis lesions (Johansen vd., 2010).

3.1.2.4. Janus Kinase (JAK) Inhibitors

Janus kinases (JAKs), a family of cell signaling molecules, are involved in the binding of many cytokine receptors to signaling carriers (Borie, Si, Morris, Reitz, & Changelian, 2003). While JAK 1 and 2 play a role in IFN signaling, JAK 3 plays a role in the signal transduction of IL-2, IL-6, IL-7, IL-15 and IL-21 (Pesu vd., 2005). INCB28050 inhibits JAK 1 and JAK 2, while ASP015K inhibits JAK 3. Drugs such as VX-509 and R348 are also being investigated as JAK 3 inhibitors. Tofacitinib (CP-690550), which has completed clinical trials, is also designed to inhibit JAK 1 and JAK 3 (Ortiz-Ibáñez vd., 2013).

3.2. Phototherapy

The use of phototherapy has decreased due to the use of biological drugs in patients with moderate and severe psoriasis. These types of phototherapy include narrow-band UV-B, broad-band UV-B and psoralen and UV-A (PUVA). Narrow-band UV-B is more effective and is preferred.

3.2.1. UV-B

UV-B phototherapy, consisting of a broad band at 290-320 nm wavelength and a narrow band at 311 nm wavelength, is used for the treatment of plaque psoriasis. UV-B causes keratinocyte apoptosis by reducing DNA synthesis and the production of proinflammatory cytokines by T cells is reduced. The frequency of application is initially 3 times a week, and after 2-3 months it is

reduced to 2 times a week. It can be further reduced according to the patient's response. Narrow-band UV-B is more commonly used because it is more effective compared to broad-band UV-B. Its side effects are erythema, photocarcinogenesis, itching and swelling. The effectiveness of narrow-band UV-B can be increased and the carcinogenic risk can be reduced with the combination of systemic retinoids (Armstrong vd., 2020).

3.2.2. Psoralen and Ultraviolet A (PUVA)

In PUVA treatment, which includes the use of psoralens, psoralens intercalate into DNA and suppress DNA synthesis. Oral methoxsalen photochemotherapy (PUVA) is used as an effective tool. The frequency of application is initially 2 to 3 times a week by oral PUVA and then decreases. Although oral PUVA treatment has a superior effectiveness compared to UV-B, there is a risk of skin cancer development in long-term use and therefore it is not preferred (Stern & PUVA Follow-Up Study, 2012). Other side effects include hypertrichosis, gastrointestinal discomfort, burning and itching.

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CHAPTER III

Psorıasıs and Its Comorbıdıtıes

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1. Introduction

Psoriasis is a common inflammatory disease associated with conditions such as psoriatic arthritis, type II diabetes, atherosclerosis, hypertension, hyperinsulinemia, dyslipidemia, osteoporosis, metabolic syndrome, gastrointestinal diseases, psoriatic pustular, kidney disease, malignancy, obesity, depression,

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and cardiovascular comorbidities (Griffiths & Barker, 2007; Mehta vd., 2010; Nijsten & Wakkee, 2009; Ouchi, Parker, Lugus, & Walsh, 2011; Takeshita vd., 2017a). Although these disorders appear to be different, they have underlying pathological pathways that overlap. Comorbidities that accompany psoriasis are often seen in severe disease (Christophers, 2007). Chronic inflammatory entity of psoriasis contributes to the development of cardiovascular comorbidities (Gottlieb & Dann, 2009). Therefore, it is very important to determine biomarkers that can predict the risk of comorbidity formation (Rietzschel & De Buyzere, 2012).

2. Psoriasis and Psoriatic Arthritis

Although psoriasis is a chronic disease, the severity of the disease can be reduced with appropriate treatment methods. Patients with psoriasis should also be screened for psoriatic arthritis because this disease can cause permanent joint damage. Therefore, diagnosis and treatment are essential to prevent joint disea**se** (Goulabchand vd., 2014).

3. Psoriasis and Cancer

Psoriasis can be associated with cancer, especially lymphoma. People who have cancer and also have psoriasis have a 41% higher risk of dying from cancer (Takeshita vd., 2017a). Cancer risks are higher among individuals with severe psoriasis. Among the types of lymphoma associated, T-cell lymphoma has been identified as the strongest (Chiesa Fuxench, Shin, Ogdie Beatty, & Gelfand, 2016). TNF inhibitors may increase the risk of melanoma and non-melanoma skin cancer. Therefore, skin cancer screening should be performed in patients with psoriasis receiving treatment. There is a concern about the risk of malignancy among patients receiving

phototherapy or immunosuppressive therapy. It is observed that there is an increase in the risk of squamous cell carcinoma in patients receiving phototherapy with Psoralen and Ultraviolet A (PUVA) (Stern & Lunder, 1998). Melanoma risk with oral PUVA is controversial. Increased skin cancer risk with topical PUVA and narrow-band UV-B phototherapy types has not been proven (Hearn, Kerr, Rahim, Ferguson, & Dawe, 2008).

4. Psoriasis and Depression

It has been reported that individuals with psoriasis have an increased risk of suicide, depression and anxiety (Dommasch vd., 2015). Psoriasis patients using apremilast and acitretin should be closely monitored as they are affected by warnings of depression and mood changes.

5. Psoriasis and Infection

Immunosuppressive treatments used in the treatment of psoriasis are a matter of debate. Before starting this treatment, patients should be screened for hepatitis B, hepatitis C and HIV. According to the results of the study, the risk of infection is seen to increase in patients (Takeshita vd., 2017b). Live vaccines should be avoided in patients who are on immunosuppressive therapy and who have received treatment for at least 1 month (Wine-Lee, Keller, Wilck, Gluckman, & Van Voorhees, 2013). The most common type of infection in patients is respiratory tract infections, and therefore influenza and pneumonia vaccines may be important (Wakkee, de Vries, van den Haak, & Nijsten, 2011). A study found that the risk of herpes zoster may increase in psoriasis patients receiving combination therapy with methotrexate and biologics (Shalom vd., 2015).

5.1. Psoriasis and Chronic Kidney Disease

Patients with severe psoriasis should be monitored for kidney health and caution should be exercised in the use of nephrotoxic drugs such as cyclosporine. According to data showing that the risk of kidney disease and chronic kidney disease is increased in patients with moderate and severe psoriasis, the risks and benefits of treatment with nephrotoxic drugs such as cyclosporine should also be considered (Chi vd., 2015).

6. Psoriasis and Gastrointestinal Disease

Adalimumab, infliximab, ixekizumab, secukinumab and ustekinumab are used in patients with both psoriasis and Crohn's disease. Acitretin and methotrexate should be used with caution in patients with psoriasis and liver disease. TNF inhibitors should be avoided in patients with moderate to severe psoriasis and also alcoholic hepatitis (Takeshita vd., 2017b).

6.1. Psoriasis and Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease is more common in individuals with psoriasis than in those without. Adalimumab and infliximab are approved for both psoriasis and inflammatory bowel disease. More recently, ustekinumab has been approved for the treatment of Crohn's disease. Therefore, these biologics are the preferred treatments for both psoriasis and IBD.

6.2. Psoriasis and Liver Disease

The prevalence of non-alcoholic liver disease is high in individuals with psoriasis. Therefore, hepatotoxic drugs such as methotrexate and acitretin should be used with caution in individuals with both diseases. Non-invasive tests used to determine hepatic

fibrosis, such as cross-sectional imaging, ultrasound-based elastography, magnetic resonance elastography, and acoustic radiation force impulse imaging, have been suggested as promising methods (Maybury, Samarasekera, Douiri, Barker, & Smith, 2014). In individuals with moderate and severe psoriasis, treatment with TNF inhibitors, especially etanercept, is a contraindication for alcoholic hepatitis. According to the results of a study, when etanercept, one of the TNF inhibitors used in the treatment of alcoholic hepatitis, was compared with another study group, placebo, serious infection rates and mortality were determined in the TNF inhibitor group (Boetticher vd., 2008). Therefore, treatment with TNF inhibitors, especially etanercept, should be avoided in patients with moderate to severe psoriasis and alcoholic hepatitis (Takeshita vd., 2017b).

Psoriasis and Cardiometabolic Disease (CV)

Although psoriasis patients have a higher risk of cardiovascular disease and mortality, patients are inadequately screened for CV risk and are treated inadequately (Kimball vd., 2012). According to a study, people with psoriasis and hypertension are more likely to have uncontrolled hypertension than patients without psoriasis (Takeshita vd., 2015).

Psoriasis and Cardiovascular Disease

It is very important to reduce the risk of disease by screening psoriasis patients for CV risk factors. It is not known whether successful treatment of psoriasis can reduce the risk of CV. The results of the study showed that TNF inhibitors and methotrexate can reduce the risk of CV in psoriasis patients (Ahlehoff vd., 2013). C-reactive protein, also one of the most reliable biomarkers, is a

validated marker of cardiovascular disease (Ridker & Morrow, 2003; Rietzschel & De Buyzere, 2012).

6.3. Psoriasis and Insulin Resistance/Type 2 Diabetes

The prevalence of insulin resistance/type 2 diabetes is high in individuals with psoriasis and its mechanisms are still not fully understood. A study found a significant relationship between levels of resistin, a cytokine that increases in insulin resistance and psoriasis severity (Boehncke vd., 2007). Another study found that psoriasis carries a risk of developing insulin resistance (Kaye, Li, & Jick, 2008). Impaired glucose tolerance is seen before type 2 diabetes and therefore insulin resistance is high in psoriasis patients (Lillioja vd., 1988; Ucak, Ekmekci, Basat, Koslu, & Altuntas, 2006). The relationship between psoriasis and type 2 diabetes is quite strong. A relationship has been found between increased type 2 diabetes and serum glucose levels in patients with psoriasis (Sommer, Jenisch, Suchan, Christophers, & Weichenthal, 2006). The results of the study showed that psoriasis carries a risk of diabetes and is correlated with disease severity (Cohen vd., 2008). In addition, study results have shown that women with psoriasis are more likely to have diabetes than men (Henseler & Christophers, 1995). Although the relationship between type 2 diabetes and psoriasis is supported by literature, the confounding factor of obesity should be taken into account. Therefore, the relationship between type 2 diabetes and psoriasis needs to be investigated further.

6.4. Psoriasis and Dyslipidemia

Due to the side effect of acitretin and cyclosporine used in individuals with psoriasis, hyperlipidemia, caution should be exercised in the use of these drugs in psoriasis patients with

dyslipidemia. These drugs should be used with caution and close lipid monitoring is required due to dyslipidemia, which is common in patients with psoriasis (Rosmarin, Lebwohl, Elewski, & Gottlieb, 2010).

6.5. Psoriasis and Hypertension

Psoriasis patients with hypertension are likely to have more severe hypertension. Therefore, standard blood pressure screening should be performed on psoriasis patients and monitoring is very important (Siu, 2015; Takeshita vd., 2015). Hypertension is known as a side effect of cyclosporine used in individuals with psoriasis, and caution should be exercised in the use of cyclosporine in psoriasis patients who also have hypertension (Rosmarin vd., 2010).

6.6. Psoriasis and Obesity

Several studies have shown that psoriasis and obesity may be linked. However, there is ongoing debate about whether obesity is a cause or a result of psoriasis (Herron vd., 2005; Naldi vd., 2005). When psoriasis patients were compared with healthy controls, the risk of obesity was increased in patients and was associated with disease severity (Neimann vd., 2006). Excessive TNF-α and other proinflammatory cytokines may influence obesity severity (Park, Park, & Yu, 2005). Herron et al. found that the effect of smoking and obesity on psoriasis is approximately 2-fold in their study (Herron vd., 2005). Adipose tissue is considered an endocrine organ that can secrete hormones, inflammatory cytokines and acute phase proteins in response to various stimuli (Eckel, Grundy, & Zimmet, 2005; Kershaw & Flier, 2004). Leptin, a hormone that increases in obesity, functions as a proinflammatory cytokine. It can stimulate adipose tissue to produce TNF-α, IL-1β, IL-6 cytokines and T lymphocytes

to produce Th1-type cytokines (Gottlieb & Dann, 2009). Therefore, weight loss is thought to improve psoriasis and additional studies are needed to better understand it. At the same time, weight gain can negatively affect the response to systemic and biological treatments(Al-Mutairi & Nour, 2014). Being overweight may also pose a risk of hepatic fibrosis in patients with psoriasis receiving methotrexate therapy (Takeshita vd., 2017b). Overweight psoriasis patients have a higher risk of loss of response to methotrexate than non-obese patients (Herron vd., 2005). This suggests that obese people with psoriasis may be at increased risk for side effects of the drug methotrexate (Takeshita vd., 2017b). In a study on obese subjects, proinflammatory cytokines such as TNF-α, leptin and resistin are secreted (Ouchi vd., 2011). Therefore, resistin and leptin can be investigated to predict atherosclerosis and insulin resistance (Molteni & Reali, 2012). Oxidative stress markers and neutrophils are seen to increase in patients. Therefore, lipid peroxidation and oxidative damage should be taken into consideration in the detection of atherosclerosis (Rashmi, Rao, & Basavaraj, 2009).

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CHAPTER IV

Restoration of nickel-induced damage to rat kidneys to normal with ursolic acid treatment

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Introduction

Nickel (Ni) is used in a wide variety of industrial and consumer applications, with approximately 65% of the nickel produced going into the manufacture of stainless steels and 20% into other alloys specialized for uses such as aerospace and military applications (Genchiet al., 2020).

Ni is an essential element for at least several animal species. These animal studies associate nickel deprivation with depressed

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growth, reduced reproductive rates, and alterations of serum lipids and glucose (Liuet al., 2021).

Ni damages the liver (Adjroud 2013), testes, sperm, and prostate and seminal glands (Doreswamy et al. 2004, Das et al. 2008, Lukac et al. 2014) by inducing oxidative stress. Many studies have been conducted to determine the protective effects of various substances (bromelain, nano selenium, zinc, sesamin, L ascorbic acid and grape seed proanthocyanidin extract) against the harmful effects of nickel sulfate (Sidhu et al. 2006, Das and Buchner 2007, Su et al. 2011, Liu et al. 2013, Cebi Sen et al. 2019, Zhang et al. 2019).

Ursolic acid (UA) is a widespread, natural triterpene compound with many pharmaceutical properties. Triterpenes are composed of six isoprene units from mevalonic acid, most of them with 30 carbon atoms. According to their molecular classification, triterpenes can be divided into acyclic, monocyclic, bicyclic, tricyclic, tetracyclic and pentacyclic triterpenoids (including UA) and miscellaneous compounds (Kashyap et al., 2016:201). UA is a pentacyclic triterpenoid. UA-associated compounds include oleanolic acid, betulinic acid, uvaol and α- and β-amyrin (Hill & Connolly, 2013:1028).

Tetracyclic and pentacyclic triterpenoids are the most studied in the field of bioactive compounds extracted from medicinal plants and natural materials. UA is a pentacyclic triterpene carboxylic acid present as a free acid or as an aglycone part of saponins (Mahatoet al., 1992: 2199).

Indeed, UA has a beneficial role in various diseases, such as cancer, diabetes, and some cardiovascular diseases, in experimental animal models. Moreover, several clinical trials have been reported to test the effects of various formulations of UA on healthy subjects or patients with different cancers (Kim & Moon, 2015:897;Feng & Su 2019:4761).

The aim of this study was to evaluate the possible protective effect of UA against damage induced by Ni administration in rat kidneys.

Materials and Methods

Animals

Twenty four male Sprague-Dawley rats (280–300 g) obtained from the animal facility of the Medical Experimental Application and Research Center, at Atatürk University in Erzurum were used in the present study. Animals were kept maintained at hygienic laboratory conditions in room with temperature 23 ± 2°C and 60 ± 8% humidity with 12-h light:12-h dark cycle. They accessed to food and water ad libitum. The experimental studies were approved by Local Ethical Committee of Atatürk University, Erzurum, Turkey (protocol number:2019-06/01) All animal experiments were conducted in accordance with the U.S. National Institutes of Health (NIH) Guide for the Care and Use of Lab animals.

Drug and Chemicals

UA was purchased from Extrasynthèse (Genay, France). Williams' medium E. supplements for cell culture and other reagents

for the evaluation of enzyme activities were obtained from Sigma (St Louis, MO).

Experiment groups and protocols

To experimental studies, rats were randomly divided into four groups (n = 6 each): (1) Control group (C); (2) nickel chloride (NiCl2) group, (3) ursolic acid (UA) group and (4) NiCl2 plus UA (NiCI2+UA) group. Male Sprague-Dawley rats were administered intraperitoneally with $NiCl_2$ at dose of 10 mg/kg (Tyagi et al. 2012). Rats received UA (50 mg/kg) alone, or in combination (10 mg/kg NiCl2 +50 mg/kg UA). (Yuliang et al., 2015). The hypolipidemic effect of artesunate and ursolic acid in rats. Pak J Pharm Sci. 2015 May;28(3):871-4. PMID: 26004719.).

The kidneys were collected for biochemical and histopathological analyzes 24 hours after NiCl2+UA treatment.

Biochemical examination

Measurement of tissue total antioxidant status and total oxidant status levels

TOS and TAS from each sample supernatant was measured via colorimetric methods by using commercially available kits (Rel Assay Diagnostics, Gaziantep, Turkey). The results of the TAS and TOS in the tissues were expressed as mmol/mg protein, μmol/mg protein, respectively.

Histopathological examination

The kidney tissue samples were individually fixed in 10% neutral-buffered formalin, dehydrated in alcohol, and embedded in paraffin. The paraffin-embedded blocks were serially sectioned (5 μm thick) using a Leica RM2135 microtome (Leica, Berlin,

Germany). Sections were deparaffinized and stained with hematoxylin and eosin (H&E) using a periodic acid–Schiff (PAS) base (Sigma Aldrich, Periodic Acid Schiff Kit) staining kits, respectively.

Statistical analysis

The results were expressed as mean± standard error. The statistical significance between the different groups was determined using one-way analysis of variance (ANOVA) with GraphPad Prism 5.0 statistics software (GraphPad, La Jolla, CA, USA). Tukey's test was carried out for betweengroup comparisons using the Tukey multiple comparison test. Analyses between two groups were carried out using the Mann–Whitney U test. Statistical significance was set at $P<0.05$.

Results

Biochemical observations

TOS and TAS levels

In the rat kidney tissues, the Ni group displayed remarkable elevation in the levels of TOS (Fig. 1). In addition, the UA treated group has revealed significant decrease in level of TOS when compared with Ni toxicity group (Fig. 1). TAS level in Ni toxicity group has shown to be significantly lower when compared with control group (Fig.2). However, TAS level in UA treated group has appeared significantly higher when compared with Ni toxicity group (Fig. 2).

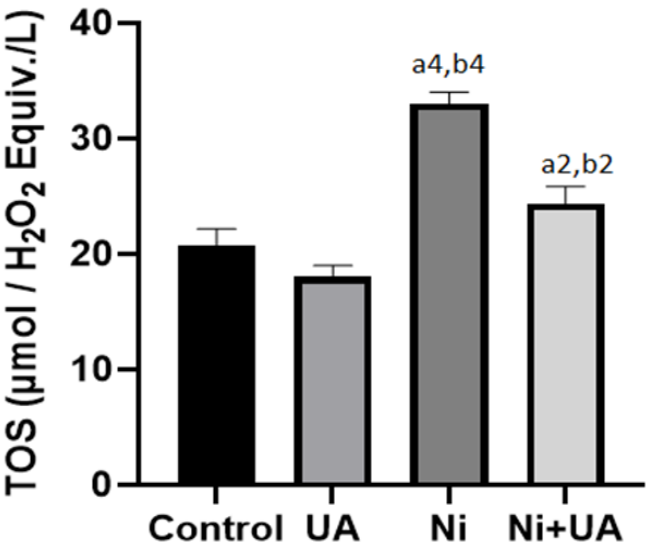

Figure 1. *Data are presented as mean ± SEM (n=5). a denotes significant differences between other studied groups and control (a1:p<0.05, a2:p<0.01, a4<p.0001), b denotes significant differences between other studied groups and RIR group (b2:p<0.01, b4:p<0.0001) by Tukey's multiple range tests.*

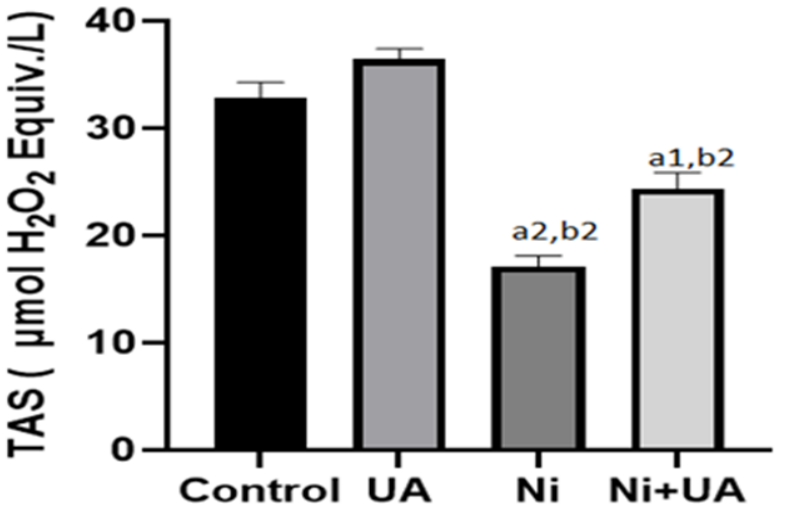

Figure 2. *Data are presented as mean ± SEM (n=5). a denotes significant differences between other studied groups and control (a1:p<0.05, a2:p<0.01, a4<p.0001), b denotes significant differences between other studied groups and RIR group (b2:p<0.01, b4:p<0.0001) by Tukey's multiple range tests.*

Effects of UA and $NiCI_2$ on kidney histology

The histology of the kidney tissue showed no morphological change in the UA-treated group (Figure 3B) compared to the control rats (Figure 3A). Histologic observations showed that glomerular and tubular structures were normal in the control group (Figure 3A). In Ni-treated and Ni+UA-treated groups, showed tubular degeneration and glomerular atrophy (Figures 3C and 3D). Tubular degenerations and edema observed in the kidney tissue of rats in the Ni group (Figure 3C). We examined the PAS granules in the rat kidneys using PAS staining. This staining method is used to detect macromolecules such as glycogen-containing glycans,

proteoglycans, and glycolipids (Spicer et al., 1961). In this study, PAS reactivity labeled the granules more homogeneously in the control (Figure 4A) and UA (Figure 4B) groups than the Ni (Figure 4C) and Ni + UA (Figure 4D) groups. Using PAS stain, we observed that abnormal clusters accumulated in the kidneys. Clusters of granules were observed in the kidneys of the rats in the Ni (Figure 4C) and Ni + UA (Figure 4D) groups.

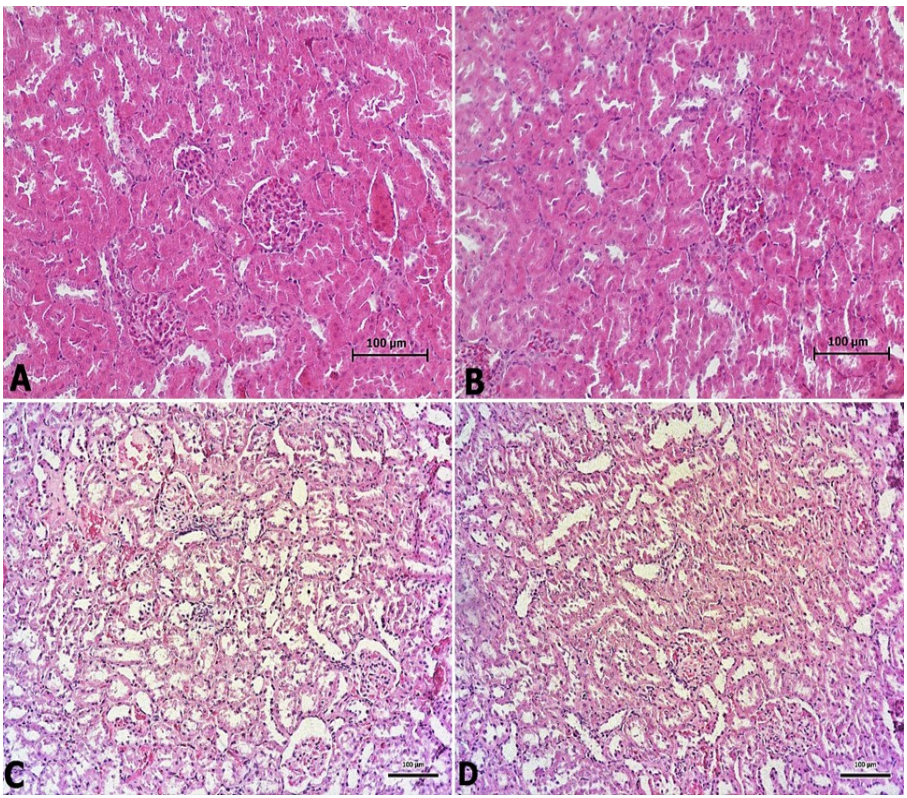

Figure 3. *Histopathology examination of kidney sections. (A) Normal kidney, (B) UA, (C) Ni treated kidney and (D) Ni+UA treated kidney (Magnification 100×). Representative micrographs are shown.*

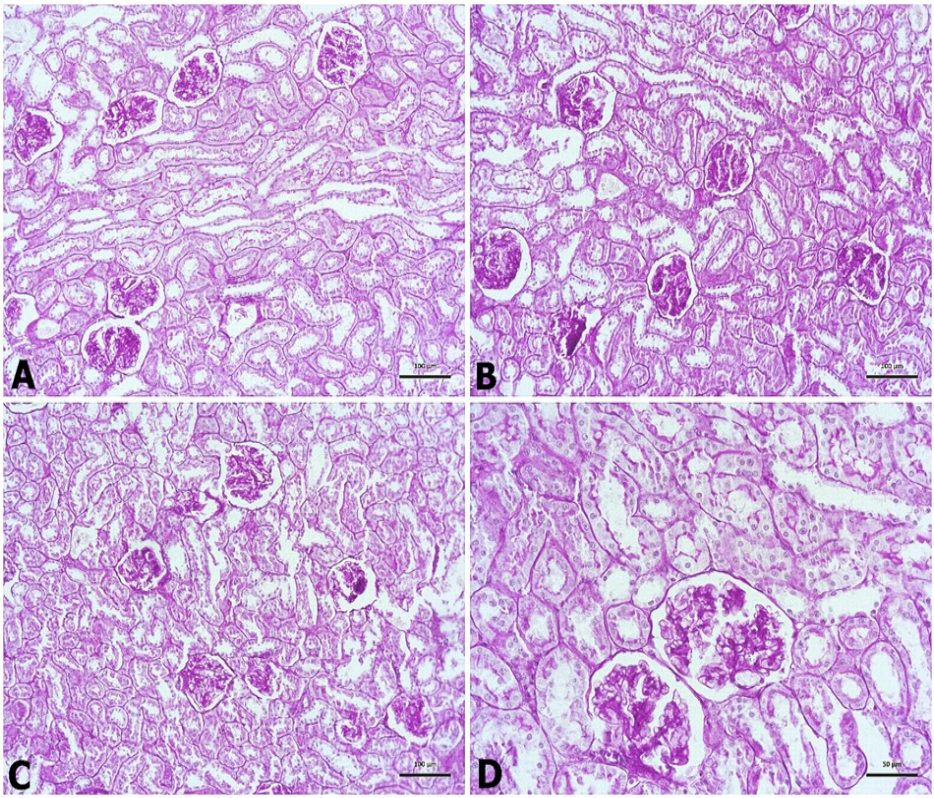

Figure 4. *Effects of UA treatment on kidney tissue. Periodic acid-Schiff (PAS) staining of kidney sections was used to evaluate pathologic changes. A) Normal kidney, (B) UA, (C) Ni treated kidney, (D) Ni+UA (Magnification 100×). Representative micrographs are shown.*

Discussion

In mammals, the kidney is a crucial organ that plays a central role in the secretion of erythropoietin and renin hormones, as well as performing various functions such as fluid homeostasis, excretion of end products, and osmoregulation. The liver and kidney are the main organs where metal elements accumulate (Sedki et al., 2003:201). In

this study, a kidney injury rat model was used to determine the effects of Ni exposure on rat renal damage, and elucidate the mechanisms underlying Ni mediated renal damage and toxicity.

Ni, which is recognized as one of the most toxic environmental and industrial pollutants, is a ubiquitous toxic metal that induces oxidative damage by disturbing pro-oxidant/antioxidant balances in tissue. Ni induced oxidative damage was previously observed in rats treated with this metal. Ni accumulate in the tissues of living organisms causing an increase in the reactive oxygen species (ROS). Cellular antioxidants and acellular systems convert the resulting ROS into non-toxicity structures. If the ROS formed is excessive, the oxidant/antioxidant balance disrupte, and oxidative stress occurs. It is known that nanoparticles cause ROS production by creating changes in cell metabolism, and this is an indicator of oxidative stress caused by metal toxicity in living things. It has been reported that toxic metal exposures can accumulate of defense elements such as macrophages and neutrophils in the body, leading to the activation of cytokines such as interleukin-1 beta (IL-1β) (Gillespie et al. 2010). It is well known that nickel exposure can induce reactive oxygen species generation (Chervona and Costa, 2012).

In this study, we aimed to investigate oxidative stress via the measurements of TAS and TOS which could have been a systematic reflection of oxidative stress in individuals with Ni induced kidney injury. Our data showed significant increased in the levels of TAS and TOS in Ni treated groups kidney tissue. These data show that exposure to Ni rises oxidative stress in the kidneys of rats. However, treatment with UA caused a significant decrease in the levels of TAS

and TOS. The above results demonstrated that Ni-induced increase in TAS, TOS may be one of the main causes of kidney injury.

Histopathology results showed normal nephritic ultrastructure in the control and the UA co-treated groups. Ni treatment caused wide-ranging kidney injury. The glomerular epithelial cells showed nuclear membrane damage, nuclear chromatin condensation, and margination in Ni-induced kidneys. The Ni+UA co-treated group exhibited normal nephritic ultrastructure as like in the control group. Studies have shown that nanoparticles cause kidney tissue damage.

In the kidneys of Ni group rats, only a small increase of PAS positive mesangial matrix was observed indicating the presence of neutral polysaccharides especially in basement membranes (filtration membranes) and brush borders in tubules. Increased amounts of PAS positive mesangial matrix indicate a thickened basement membrane in glomeruli. This is one of the features of glomerular filtration membrane damage and increased permeability for proteins.

Taken together, our results show that nickel contributes to kidney damage and treatment with UA can be alleviated this damage. The results of these studies suggest that UA and its distinct derivatives may become potential therapeutic drugs for treating similar diseases.

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