Rheumatoid Arthritis Perspectives Across Three Libyan Cities, Voices of Patients and Physicians; A Two-Group Survey Study

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ABSTRACT

Arthritis in general can be classified into non-inflammatory types (e.g., osteoarthritis) and infectious (e.g., *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and *Lyme disease*). Rheumatoid arthritis (RA) is a systemic autoimmune disorder, which is characterized by chronic inflammation, affecting various body organs. In this study, a two-group survey study regarding to RA medication treatment and disease management has been done. The double survey includes perspectives from patients and physicians, from three Libyan cities (Zilten, Al-khoms and Massallatah). In this work, one hundred patients and fifty treating physicians are answering the two-group survey, they are almost equally from mentioned cities.

The obtained results indicate that the majority of patients respond well to their treatment. Despite the side effects remain a concern, the effectiveness of medications used, about the one third of treated patients, the treatments were very effective, around two third of treatments patients were effective, and only just < 9% they feel their treatment is not effective. The majority of physicians have moderate experience are well-versed in treating RA patients. The RA predominantly affect individuals aged 30 to 60 years, Prednisolone and Methotrexate are the most commonly prescribed medications, with supplementary medications also playing a significant role in RA treatment. Physicians reported that irregular adherence to long-term treatments. It is not clear 100% that there is a clear presence of protocol or national guidelines for treatment of RA patients in Libya to the date. Furthermore, various other issues such as patients distrbution, most used drugs, supplementary and vitamines, diet, lifestyle changes, etc have been discussed in detail, in this manuscript. In addition, we can recommend that there is a need for continuous monitoring, patient education, and the development of more effective treatments for treatment of RA disease.

 KEYWORDS: Rheumatoid arthritis, RA, RA treatment, RA management, Libyan RA treatment protocol.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder. RA is characterized by chronic inflammation, affecting the joints and possibly other damaged organs such as gastrointestinal tract, lungs, kidneys, the heart, eyes, skin, and nervous system. Arthritis in general can be classified into non-inflammatory types (such as osteoarthritis) and infections (such as *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and *Lyme disease*); inflammatory types resulting from crystal deposits (such as pseudogout) or autoimmune processes. In addition, systemic lupus erythematosus (SLE), scleroderma, Sjögren's syndrome, psoriatic arthritis, spondylitis, and polymyositis are considered as autoimmune rheumatic diseases. The latter cases are required carefully differential diagnosis because of the overlapping symptoms [1].

Due to more than one factor contributes to the RA development so, it is considered as a complex, multifactorial disease. Several factors such as genetic factors, environmental factor (e.g., smoking), and random or unexpected factors which occur without a clear or predictable cause are playing an important role in developing the RA. The genetic factors alone account for approximately 50% of the risk factors developing RA. RA can be divided into two main types based on the presence or absence of antibodies. The first type in which RA is seropositive where one or both the rheumatoid factor (RF) and anti-cytoplasmic proteinase antibodies (ACPA) are present, whereas, the second type occurs when both are absent, in the latter case the RA is named as seronegative [1].

The important signs that serve as guidelines for diagnosis of RA include: (i) Joint stiffness that lasts at least an hour in the morning before improving, (ii) Soft tissue swelling around three or more joints, (iii) Swelling in specific joints, such as the middle finger joints or wrist, (iv) Symmetric arthritis (appearing on both sides of the body in the same pattern), (v) Nodules, which are small, hard lumps under the skin, usually appearing on the elbows or hands, (vi) A positive blood test for rheumatoid factor, Lastly, (vii) Radiographic evidence of joint erosion or

osteoporosis around joints which are more especially in the hand and the wrist [2]. Interestingly, genetic factors play an important role in the development of RA [3].

Approximately, two-thirds of RA patients are women. Therefore, many epidemiological studies are focusing on the factors related to female gender as risk factors for RA. So, the relationship between female gender and the risk of developing RA is not simple; it is rather complex [3].

Main causes of RA are summarized as following: (a) Smoking; since large studies have been conducted on women smokers, the Iowa Women's Health Study (IWHS) reported that the risk of RA was 18% which means one in six new RA cases can be due to smoking and can be prevented if smoking is eliminated. (b) Alcohol; since the relationship between alcohol consumption and the risk of developing RA shows that the moderate alcohol consumption may have a protective effect against RA. (c) Dietary factors; nutritional factors play an important role in the initiation and development of inflammatory processes in the body, including chronic diseases such as RA. (d) Socio-economic status; the social class and socio-economic position are collectively called socio-economic status (SES). The term SES has prominent impacts on many medical conditions, as it knows in our communities, the SES is associated with higher psychiatric diseases, depression and higher mortality rates [4]. In addition to the above-mentioned factors, the development and progression of RA have been associated with many other factors with minor or major effects. Miscellaneous factors include high birth weight, oral contraceptives, breast feeding, sex hormonal factors, infectious agents (including bacteria, viruses, mycoplasma), complex gene-environment interactions, age and gender and other pollutants may play a role in the risk factor for RA. Interestingly, coffee is considered as an important factor of the food factors affecting upon RA patients. Since, there is a study on Scandinavian-type boiled coffee found that an association between consumption of the coffee and increased levels of rheumatoid factor (RF) in the blood. That is even in the absence of clinical symptoms of the disease itself (i.e., without the presence of actual arthritis). This may indicate that a role for boiled coffee in stimulating certain pre-disease immune responses. In contrast, a recent cohort study of

women revealed that there is no significant association between consumption of coffee, decaffeinated coffee, or total coffee and risk of developing RA [5]. In addition, patients with RA face elevated cardiovascular risks that begin early stages of RA disease and may persist despite treatment if not comprehensively managed [6]. Depression also considered as an important factor in the RA patients, in addition to the common former symptoms there is some other symptoms such as depression and irritability, anemia, and flu like symptoms (e.g., feeling generally ill, feeling hot and sweating) [7]. the symptoms of RA could be summarized as (a) Joint pain, stiffness, swelling affecting multiple joints. (b) Symmetrical symptoms affecting both sides of the body. (c) Morning stiffness lasting longer than 30 minutes. (d) Additional symptoms like fatigue, fever, and malaise [8, 9].

The RA could be diagnosed by the following means: 1. Morning stiffness in and around joints that persists for at least an hour before reaching maximum improvement. 2. Soft tissue swelling (arthritis) in three or more joint areas. 3. Joint swelling in the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, or wrist joints. 4. Symmetric swelling in the affected joint. 5. Subcutaneous rheumatoid nodules. 6. Serum rheumatoid factor (RF). 7. Radiographic evidence of bone erosion and/or decreased bone density around the joints of the hand or wrist, as seen on radiographs [10].

Pharmacological therapies of RA: The key factor for improving the chances of successful RA disease control is the early diagnosis of RA along with early initiation of treatment. Traditional treatment strategies include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, and corticosteroids. The treatment approach primarily aims to relieve pain and inflammation, limit loss of joint function, and prevent complications and structural joint deterioration [11]. Pharmacological treatments for RA patients can be classified into three main approaches:

The first approach involves symptom management using NSAIDs, in addition to mild analgesics, to reduce the inflammatory response and alleviate the clinical symptoms associated with the RA. Although these treatments are effective in controlling clinical manifestations, they have no significant impact on RA progression or the underlying pathological mechanisms. The second approach relies on the use of low-dose corticosteroids, often administered orally, to reduce inflammation and relieve pain. Various studies indicate that these low doses may contribute, to some extent, to slowing the progression of bone erosions which related to RA symptoms. While, the third therapeutic approach is the use of disease-modifying antirheumatic drugs (DMARDs), also known as slow-acting antirheumatic agents. This class includes compounds such as gold salts, D-penicillamine, and sulfasalazine [11]. Biological agents are the newest class of therapeutic options is represented by biological response modifiers, which are used in the treatment of RA, which include the followings: (a) TNF-α Inhibitors, (b) Interleukin 1inhibitors, (c) Co-stimulation Blockers; Abatacept is considered to be the first agent classified within a novel class of biological drugs aimed at suppressing inflammation, (d) Anti-B-cell Agents, (e) Janus-activated kinase (JAK) inhibitors; Although, the mitogen-activated protein kinase (MAPK) pathway has been implicated in the pathogenesis of RA, clinical trials targeting this pathway have not yielded promising therapeutic outcomes [12].

In general, the combination of methotrexate with sulfasalazine and hydroxychloroquine, so called 'triple therapy', has greater efficacy than monotherapy in both early RA and non-responders, but higher toxicity. Combining methotrexate with biologic DMARDs has also demonstrated superior outcomes compared to methotrexate monotherapy in those with an inadequate response [13].

Non pharmacological therapies of RA. Physical therapy [14], Therapeutic Rest [15], Naturopathy [16], Massage and Yoga Therapy [16, 17], Acupuncture Therapy [18], Food [19], Antioxidants [20]; (a) Vitamins E and C, (b) Selenium, (c) Zinc, (d) Copper, (e) Essential Fatty Acids [21], Surgery; Surgery in RA includes synovectomy, tenosynovectomy, tendon realignment, reconstructive surgery or arthroplasty, and arthrodesis [22]. Finally, we should take always in our consideration that the plants play an important role in the treatment of RA patients [23].

METHODOLOGY

In order to enhance understanding, optimize treatment outcomes, and improve the quality of life

for RA patients, this constricted ultimate goals of this work.

1 .To determine the prevalence of rheumatism in some Libyan cities.

2 .To identify the most age group affected by this disease.

3 .To identify the most important medications available locally used to treat rheumatism.

4 .To identify the most important side effects of RA and the extent to which they can be overcome.

5. To determine whether there is a general protocol or not followed by physicians in treating RA.

The descriptive-analytical method was used to evaluate "Evaluation of Rheumatoid Arthritis medications used by RA Patients from Alkhoms, Massallatah, and Zeltin Cities." This method aims help to compare, interpret, and assess in order to reach meaningful conclusions that enhance understanding of the RA and its medications.

First: Study Sample: This study relied on personal interview sampling to collect information and data. During this phase, personal interviews were conducted with a sample of patients and doctors. The researchers distributed 100 questionnaires forms to a simple random sample of patients and 50 questionnaires forms to a sample of treating doctors. These were collected after being filled out and completed by the study participants. The data obtained were interpreted and discussed below.

Second: Personal Interview Model

The interview questions were designed to cover all aspects mentioned early in the study aims for evaluating rheumatism drugs for rheumatoid patients in some Libyan cities. These questions were developed from both theoretical sources and interviews with a number of patients and treating doctors. The questionnaires consisted of two main parts:

Part One: Concerns the patients use of RA drugs in some Libyan cities, including 14 items.

Part Two: Concerns the treating doctor's perspective on the use of RA drugs in some Libyan cities, also containing 12 items. Applying the above method to compare, interpret, and assess of obtained data and summarized and discussed in the following section.
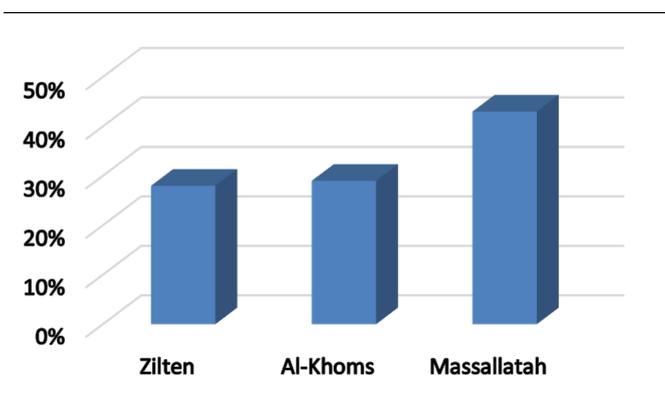
RESULTS and DISCUSSION:

The most susceptible age group of the RA disease of the three cities together is localized between 40 to 60 years, as we summarized that in the Table 1.

Table 1. The most susceptible age group for RA.

Age Group	Frequency	(%)
1 to less than 20	7	7%
20 to less than 40	20	20%
40 to less than 60	50	50%
60 to less than 80	21	21%
80 to less than 100	2	2%
Total	100	100%

In order to know which city of the three cities those considered in this study has the high range of RA patient, Massallatah city shows the most where the RA patients localized, compared with other to cities Al-khomss and Zilten, 43%, 29% and 28%; respectively. as seen in the Figure 1. This could be manifested with the low number of the sample taken in this study (just 100 patients).

Figure 1. shows the city where the patients resides.

To know the duration of diagnosis for all patients under the study were diagnosed as RAic patients in a period more than five years, with a percent of 39% as seen in the Table 2. This is little bit strange why RA takes all this time to be diagnosed in Libya (at least in these three cities under the study). Whereas, those diagnosed in less than one year were with 35%, while in between are accounted only 26%.

Table 2. The duration of diagnosis of RA.

Duration of Diagnosis	Frequency	Percentage (%)
Less than 1 year	35	35 %
1 to 5 years	26	26 %
More than 5 years	39	39 %
Total	100	100 %

We in this work interestingly asked about what is the most used RA medications in these Libyan cities, the answers were as follows: (a) the most used one is prednisolone with 40 %; (b) while the second one is methotrexate with 28 %, whereas, (c) the third one is cortisone with 12 %, most other drugs were with a very little precent with just 2% (as seen the Table 3).

Table 3. The most used medications for RA patients.

Medication	Frequency	Percentage (%)
Methotrexate	14	28%
Prednisolone	20	40%
Ibuprofen	1	2%
Cortisone	6	12%
Penicillin	1	2%
NSAID	1	2%
NSAID + Prednisolone	1	2%
NSAID + Methotrexate	1	2%
Steroid	1	2%
Pain Relievers	4	8%
Total	50	100%

Various other criteria were taken in our considerations and summarized herein. Around 87% of all patients in the study respond well to treatment, and the rest (13%) do not respond well to the given treatment. More than half of the asked patients change their treatment periodically, they were representing 58% of the study sample, conversely, 42% do not change their treatment. In the same line about 82% of the study sample were compliant about their treatment, While, 18% were not compliant with the given treatment. Effectiveness of

drugs used also were taken in our considerations, the data were shown in the Figure 2. 58% of the sample said somewhat just effective, about 30% of the sample feel it is very effective, whereas, 9% feel it is not effective, and only 3% are unsure about the effectiveness of their treatment.
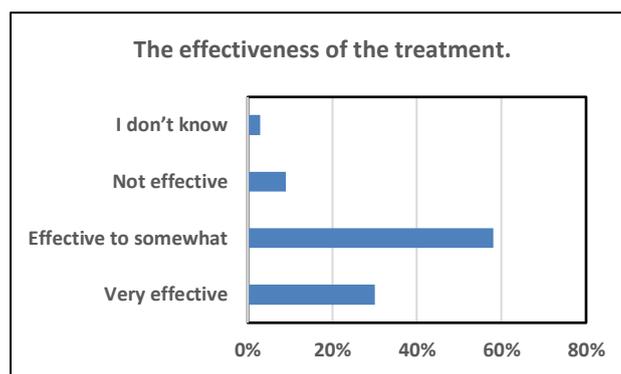

Figure 2. The effectiveness of the treatment.

From the obtained data, it is clear to us that 54% of patients did not notice any side effects from the given treatment, while, the rest 46% noticed side effects. In the same line, around 47% of the study patients reported that their daily lives were not affected by the side effects of the treatment. Whereas, 33% experienced slight effects, and about 20% experienced significant effects. This study shows that about 54% of patients changed their diet after being diagnosed with RA, instead, the others 46% did not. Additionally, and interestingly, we found that the majority of patients who answered "Yes" in the changing their diet, 43% of them noticing an improvement after changing their diet. Meanwhile, only 11% did not notice any improvement after changing their diet.

In few words about the part one of this study: It aimed to assess the evaluation of the RA drugs for patients in three of the Libyan cities 'Zilten, Alkhoms and Massallatah'. The obtained results indicate that: (i) The majority of patients respond well to their treatment, with a significant proportion experiencing moderate to high effectiveness. (ii) Despite this, side effects remain a concern, the effectiveness of medications used about the one third of treatments patients were very effective, around two third treatments patients were effective, just < 9% they feel their treatment is not effective. (iii) There is a need for continuous monitoring, patient education, and the development of more effective treatments for RA. The second part of this study is a questionnaire which aimed in order to assess the perspectives of physicians about RA disease in general. Specially, for their challenges they face while prescribing such RA treatment. It contains a variety of questions, including their

experiences with treating patients, the medications they prescribe, and how they evaluate the progress of the treatment and the medications effectiveness. The most experience of physicians in treating the RA patients range from 5 to 10 years, whereas, around quarter of the experience of the treating doctors less than five years, while others more than 10 years of experience. According to physicians answers the most affected age group by RA disease is between 30 to 60 years, this is in the line with the patients answers. Then followed by the age group 60-90 years with 18%, and the young age group (<30 years) accounted only 14%. Interestingly, for further studies, some physicians believe that the older women are more susceptible to the RA disease compared to that of men. The most important question asked for treating doctors is; What is the most commonly used medication for RA? That's in order to see the most used and effective drug(s) for treating RA disease in Libya (at least the three cities in this work). The Figure 3 summarized the most used drugs according to physicians.
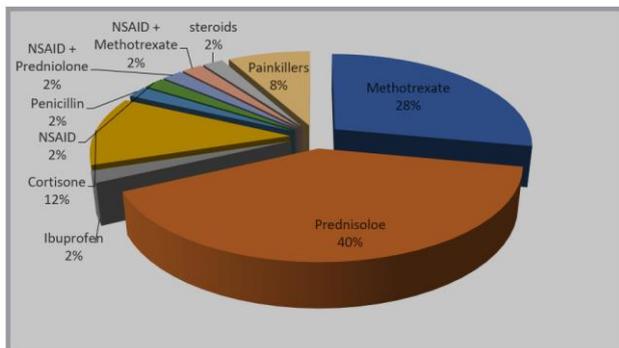

Figure 3. The most commonly used medication for RA

The obtained data represents the distribution of medications prescribed by 50 physicians. The data provides insight into the most commonly used treatments and the diversity of medication strategies in the prescribed in Libya. The most common prescribed medication is prednisone and reported with 40% of the physicians sample. Interestingly, this suggests that corticosteroid treatment is a

mainstay in managing the condition being addressed likely a chronic inflammatory or autoimmune disease. Then the Methotrexate drug, a disease-modifying antirheumatic drug (DMARD), follows with a prescribed range of 28%. This is indicating

that its importance in long-term disease control. Cortisone, a steroid drug, is prescribed with 12%, reinforcing the reliance on corticosteroids in the treatment protocols. From other side the less prescribed common medications or combinations are prescribed in a very low percentage with around 2% only. These include: a common NSAID; Ibuprofen, NSAID, and combination therapies such as NSAID + Prednisolone and NSAID + Methotrexate, in addition to steroid and other painkillers.

Furthermore, the data from this questionnaire show that it is clear that most treating physicians (74%) prescribe supplementary medications for RA patients. Some of these medications include stomach protectants with supplements and vitamins, folic acid, calcium tablets, and others. However, 26% of physicians believe that no need to supplementary medications for RA patients.

54% of physicians do not consider any warnings related to taking RA medications with food or drinks, while 46% warn patients about this. Whereas, the obtained data represented that 70% of treating physicians change the medication prescribed for RA patients once the patient does not respond, while 30% change the medication once the complications such as allergies, stomach problems, or fear of the disease spreading occurs, once we asked physicians about what is the most important factors considered for prescribing treatment; their answers were summarized in the Table 4.

Table 4. the most important factors considered for prescribing RA treatment

Attribute	Frequency	Percentage (%)
Effectiveness of the medication	33	66 %
Side effects and effectiveness	9	18 %
Cost of treatment	4	8 %
Side effects and cost	3	6 %
Other factors	1	2 %
Total	50	100 %

It is clear from the data available in the Table 6 that the majority of physicians (66%) consider the effectiveness of the medication as the most important factor when prescribing treatment. 18%

of them consider both the side effects and effectiveness of the medication, whereas, 8% consider the cost of treatment, and the rest 6% of the physicians consider both side effects and cost.

From adherence to treatment point of view, the obtained analyzed data in this work show that the 60% of treating physicians believe that patients adhere to long-term treatment irregularly, while 36% believe that patients do not adhere at all, and only 4% of the treating physicians believe that patients adhere well to long-term RA treatment. Physicians from these three cities believed that the preferred pharmaceutical dosage form for most patients (with 90% of the participating of physicians) is tablets, while just 6% prefer other forms like syrup, and only 4% of physicians are preferring injections dosage forms.

Lastly, the physicians were asked about if the age of the patient affect the choice of RA medications. Their answers indicate that more than a half of the sample (58%) believe that age sometimes affects the choice of medications for RA patients, while 22% believe that age does play a role in choosing medications, and 20% do not consider age as a factor.

The physicians believe that RA patients should visit the doctor every 3 months, with 46% of the sample agreeing, while 38% believe visits should be every 6 months, only 12% of physicians recommend monthly visits, and only 4% of physicians suggest annual visits. Finally, and the most interesting question oriented to the physicians were If there a national (Libyan) protocol for treating RA patients. The answers show that the most treating physicians (74%) believe that there is a national protocol for treating RA patients in Libya. 20% of physicians believe that no such protocol exists, and 6% are unsure.

This work provides valuable insights into the prescribed treatment by Libyan physicians for Libyan RA patients in the three western cities (Zilten, Al-khoms and Massallatah). The important obtained data from this work highlight the impotance of mdication effectiveness, patient adherence, and the aim of the national guidelines in shapping treatment approaches. We can summarize

the obtianed results from the second part as follows: (i) Specialization diversity shows that a significant portion of physicians treating RA specialize in orthopedics (with 46%), this indicates that orthopedic specialists are at the forefront of managing these cases. (ii) Experience level of physicians indicate that the majority of physicians have moderate experience (with 50%), having 5-10 years of practice. This suggests that most treating physicians are well-versed in treating RA. (iii) RA predominantly affect individuals aged between 30 to 60 year (with 74% of treating physicians) identifying this group as the most susceptible to affected by RA disease. This emphasizing the importance of early diagnosis and treatment in this age range. (iv) From medication preferences point of view, prednisolone as well as methotrexate are the most commonly prescribed medications for treating the RA, highlighting their central role in the management of RA, with supplementary medications also playing a significant role in treatment those for the most physicians believeing. (v) Regarding to the medications adherence 60% of participants physicians report irregular adherence to long-term treatments. This suggests the need for improved patient education and support. Additionally, doctors are proactive in adjusting medications when patients show no response with 70% of participants physicians. (vi) According to Libyan participating physicians, the primary factor influencing treatment decisions is the effectiveness of the medication (66%). while, the side effects and cost come secondly in their considerations, underlining the importance of effective therapies in managing RA treatments. In order to know if there is a protocol or any national guidelines for RA patients treatment, one question was oreiented to the Libyan physicians in the three cities. The most physicians answers (74%) believe that there is a national protocol for treating RA in Libya, this is indicating that a structural approach to treatment, but there is still little a portion of physicians who are unsure or unaware of these guidelines.

CONCLUSION

The data obtaibed from this study revealed that RA patients in three Libyan cities (Zilten, Alkhoms and Massallatah) predominantly use medications such as prednisolone and methotrexate, with the majority responding well to treatment. In short, compliance with treatment was relatively high, indicating a

good level of patient adherence. Additionally, dietary changes appeared to play a role in symptom management for some RA patients, although not all of them reported improvements. These findings underscore the importance of ongoing monitoring and personalized treatment strategies in managing RA, the further investigation into the impact of lifestyle changes, such as diet and exercise. A significant portion of pysicians treating RA are orthopedic specialists are at the forefront of managing RA cases. The majority of physicians have moderate experience are well-versed in treating RA patients. The RA predominantly affect individuals aged 30 to 60 years, Prednisolone and Methotrexate are the most commonly prescribed medications, with supplementary medications also playing a significant role in RA treatment. Physicians reported that irregular adherence to long-term treatments. It is not clear 100% that there is a clear presence of protocol or national guidelines for treatment of RA patients in Libya to the date.

REFERANCES

1- Radu, Andrei-Flavius, and Simona Gabriela Bungau. "Management of rheumatoid arthritis: an overview." *Cells* 10.11 (2021): 2857.

2- Harris Jr, Edward D. "Rheumatoid arthritis: pathophysiology and implications for therapy." *New England Journal of Medicine* 322.18 (1990): 1277-1289.

3- Deane, Kevin D., et al. "Genetic and environmental risk factors for rheumatoid arthritis." *Best practice & research Clinical rheumatology* 31.1 (2017): 3-18.

4- Jalil, Syed Fazal, et al. "Rheumatoid arthritis: What have we learned about the causing factors?." *Pakistan journal of pharmaceutical sciences* 29.2 (2016).

5- Aho, Kimmo, and Markku Heliövaara. "Risk factors for rheumatoid arthritis." *Annals of medicine* 36, no. 4 (2004): 242-251.

6- Hansildaar, Romy, et al. "Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout." *The Lancet Rheumatology* 3.1 (2021): e58-e70.

7- Margaretten, Mary, et al. "Depression in patients with rheumatoid arthritis: description, causes and mechanisms." *International journal of clinical rheumatology* 6.6 (2011): 617.

8- Gaffo, Angelo, Kenneth G. Saag, and Jeffrey R. Curtis. "Treatment of rheumatoid arthritis." *American journal of health-system pharmacy* 63.24 (2006): 2451-2465.

9- Chauhan, Krati, et al. "Rheumatoid arthritis." *StatPearls* (2023).

10.https://cdn.intechopen.com/pdfs/26088/InTechComple mentary_and_alternative_medicine_in_the_treatment of_rheumatoid_arthritis.pdf

11- Kourkouta, Lambrini, et al. "Drug Treatment in Rheumatoid Arthritis." International Journal of *Engineering and Applied Sciences* 5.3 (2018): 46-49.

12- Abbasi, Mojtaba, et al. "Strategies toward rheumatoid arthritis therapy; the old and the new." *Journal of cellular physiology* 234.7 (2019): 10018-10031.

13- Radu, Andrei-Flavius, and Simona Gabriela Bungau. "Management of rheumatoid arthritis: an overview." *Cells* 10.11 (2021): 2857.

14- Rae Jr, James W., and Leonard F. Bender. "Physical therapy in rheumatoid arthritis." (1957).

15- Akram, Muhammad, et al. "Traditional and modern management strategies for rheumatoid arthritis." *Clinica Chimica Acta* 512 (2021): 142-155.

16- Nair, Rukamani, et al. "Improvement in physical parameters of rheumatoid arthritis patients by naturopathy and Yoga." *Int J Multidiscip Approach Stud* 1 (2014): 132-146.

17- Ganesan, Selvakumar, et al. "Effect of yoga therapy on disease activity, inflammatory markers, and heart rate variability in patients with rheumatoid arthritis." *The Journal of Alternative and Complementary Medicine* 26.6 (2020): 501-507.

18- Lee, M. S., B-C. Shin, and E. Ernst. "Acupuncture for rheumatoid arthritis: a systematic review." *Rheumatology* 47.12 (2008): 1747-1753.

19- Philippou, Elena, and Elena Nikiphorou. "Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis." *Autoimmunity reviews* 17.11 (2018): 1074-1077.

20- Darlington, L. Gail, and Trevor W. Stone. "Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders." *British Journal of Nutrition* 85.3 (2001): 251-269.

21- Stone, Jonathan, et al. "Inadequate calcium, folic acid, vitamin E, zinc, and selenium intake in rheumatoid arthritis patients: results of a dietary survey." Seminars in arthritis and rheumatism. Vol. 27. No. 3. WB Saunders, 1997.

22- Da Silva, Eleonora, et al. "Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment." *Arthritis Care & Research: Official Journal of the American College of Rheumatology* 49.2 (2003): 216-220.

23- Kaur, Amandeep, Parminder Nain, and Jaspreet Nain. "Herbal plants used in treatment of rheumatoid arthritis: a review." *Int J Pharm Pharm Sci* 4.4 (2012): 44-57.