Familial Mediterranean fever research activity in the Arab world: the need for regional and international collaborations

Elise Assouad,1 Said El Hage,2,4 Steven Safi,2 Antonio El Kareh,2 Elie Mokled2 and Pascale Salameh1,4,5

1Faculty of Medicine, Lebanese American University, Byblos, Lebanon. 2Faculty of Medical Sciences, Lebanese University, Hadath, Lebanon. 3Neuroscience Research Center, Faculty of Medical Sciences, Hadath, Lebanon. 4INSPECT-LB, Institut National de Santé Publique, Épidémiologie Clinique et Toxicologie, Beirut, Lebanon. 5Faculty of Pharmacy, Lebanese University, Hadath, Lebanon. (Correspondence to: Steven Safi: s.safi@st.ul.edu.lb).

Abstract

Background: Familial Mediterranean fever (FMF) is an autoinflammatory, multisystem disease affecting the populations of the Mediterranean basin.

Aims: The aim of this study was to assess the research input of Arab countries on FMF between 2004 and 2019.

Methods: The Medline database (PubMed) was accessed for FMF-related publications. The number of publications was normalized to average: population size, GDP and number of physicians for every country. VOSViewer was used to create a co-occurrence bibliographic map.

Results: Between 2004 and 2019, 69 articles relating to FMF were published in the Arab world, accounting for 0.03% of the total number of publications originating in Arab countries, and 3.60% of all articles relating to FMF worldwide. After normalizing to average population size, GDP and number of physicians, Lebanon ranked first with 4.44, 0.64 and 1.99 publications per million persons respectively. Moderate positive correlations were found between number of publications and average population size (r = 0.385) and average number of physicians (r = 0.513). Half of the articles were published in journals ranked Q1 and Q2. An abundance of keywords relating to genetics hint at a main focus on the genetic aspect of the disease.

Conclusion: The low number of publications could be a result of the absence of research funding and the political and military instability in the Arab world. Given that many articles were published in high quality journals, Arab countries should focus on providing a clinical aspect to their studies and working on regional and international collaborations.

Keywords: familial Mediterranean fever, genetics, bibliometric analysis, health economics, Arab world

Citation: Assouad E; El Hage S; Safi S; El Kareh A; Mokled E; Salameh P. Familial Mediterranean fever research activity in the Arab world: the need for regional and international collaborations. East Mediterr Health J. 2021;27(10):984–992. https://doi.org/10.26719/emhj.21.036

Received: 18/09/20; accepted: 01/03/21

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Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory multisystem disease, inherited in an autosomal recessive pattern. The genetic mutation of the disease is located on the short arm of chromosome 16, on the MEFV gene. The MEFV gene encodes pyrin, a protein generally expressed in myeloid cells, which regulates IL-1 beta processing and apoptosis. A mutation in the pyrin protein seemingly results in uncontrolled inflammation (1).

The condition is characterized by episodes of fever and serositis and recurrent peritonitis, arthritis, pleuritis or erysipelas-like skin disease. Amyloidosis, which could lead to chronic renal failure, is the most devastating complication (2,3). There are 2 phenotypes of FMF: FMF type 1 is characterized by all the symptoms cited above, and can eventually result in amyloidosis, while FMF type 2 is identified by amyloidosis as the initial clinical manifestation in an otherwise asymptomatic person (4). Colchicine has been the treatment of choice for this disease since 1972 (5).

Familial Mediterranean fever affects the populations located on the Mediterranean basin. It is virtually limited to Armenians, Turks, Arabs and non-Ashkenazi Jews (2). However, some cases have been described in European countries, including Italy, France, Spain, Portugal and Greece (6). Turkey is presumed the country with the highest number of FMF patients worldwide, with a prevalence ranging from 1:400 to 1:1000. With a population of around 70 million, Turkey is predicted to have more than 100 000 patients with FMF (7,8). Armenia has a prevalence of approximately 1:500, and with a population of 3 million, the overall number of patients is presumed at 6000. Furthermore, 1 in 5 healthy individuals in Armenia are heterozygous carriers of one of the several mutations that can affect the MEFV gene (8,9). Countries in the Middle East such as Lebanon and Jordan have considerable numbers of FMF patients, but the exact numbers are unknown. A report on the frequencies of MEFV mutations in these 2 populations revealed the severity of 1 specific mutation (M694V) and 3 novel mutations in the Lebanese group only (10). In the Syrian Arab Republic, the frequency of carriers is approximately 1:57, and the M694V mutation is the most common in FMF patients but not in healthy carriers. The severity of the disease and the development of amyloidosis is
presumably associated with this specific mutation (11). Additionally, FMF is the leading cause of periodic fever in the Maghreb, affecting Algerians, Moroccans and Tunisians. The frequency of carriers among the Arab Maghrebian population is, however, significantly inferior to the Turkish, Armenian, and non-Ashkenazi Jewish populations, being estimated at only 1% (12).

The aim of this study is to assess the research input of Arab countries on FMF since this disease characteristically affects this region. In addition, this study focuses on evaluating the collaborations between regional organizations as well as the abandoned research areas in this field, which could warrant further appraisal.

Methods

Analysis

A bibliometric analysis analyses quantitatively the number of publications in a certain area of research, collaboration between authors and number of citations to assess research output (13).

Database and search strategy

The Medline database was accessed for FMF-related publications. Publications from this database are indexed on PubMed, the largest biomedical archive (14). PubMed uses MeSH (medical subheadings) terms: each article is given certain MeSH terms depending on the subject or area of study. The search strategy used for FMF included the “Familial Mediterranean Fever” MeSH term, which also included publications with other FMF synonyms such as “Benign Paroxysmal Peritonitis”, “Familial Mediterranean Fever, Autosomal Recessive”, “Familial Paroxysmal Polyserositis”, “Mediterranean Fever, Familial”, “Periodic Disease”, “Periodic Disease, Wolff’s”, “Periodic Peritonitis”, “Polyserositis, Familial Paroxysmal”, “Polyserositis, Recurrent”, “Recurrent Polyserositis”, “Wolff Periodic Disease” and “Wolff’s Periodic Disease”. In addition to this MeSH term, the author’s affiliation was used in the search strategy to determine the country of publication.

All 22 Arab countries were included in the search strategy: Algeria, Bahrain, Comoros, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates and Yemen. The time frame of the study was fixed between 2004 and 2019 to highlight the latest advances and publications in the last 16 years. In fact, research output before 2004 was low and sparse and did not deserve inclusion in the search strategy.

An example of the search strategy used to obtain the number of publications in Qatar, using Boolean operator “AND” is: “Familial Mediterranean Fever” [MeSH Terms] AND “2004” [Date – Publication] : “2019” [Date – Publication] AND “Qatar” Affiliation. In the case of Lebanon, all cities in the United States of America named Lebanon were removed, and in the case of Palestine, West Bank and Gaza Strip were used in the author’s affiliation. Additionally, countries with a high prevalence of FMF such as Turkey and Israel, and those with a higher publication input such as the United States of America were included in this study as control groups (15).

Socioeconomic assessment of publications

Comparison of the number of publications between countries cannot be assessed without proper normalization of the results. For instance, countries with a higher population and gross domestic product (GDP) are expected to have a higher research output. Therefore, the average GDP (2004–2018) and average population (2004–2019) were calculated for each of the countries cited earlier (16,17). An additional index was used in this study: the number of physicians in the population. Mean number of physicians per 1000 population were retrieved from the World Data Bank between 2004 and 2018 (18). The ratio was multiplied by the average population during this period. Thus, we obtained the number of physicians in each country. Effectively, the rationale for using this index was founded on the idea that an increase in the physician workforce in a certain area would lead to a greater biomedical research output.

Subsequently, this allowed us to normalize our findings by dividing the number of publications for each Arab country by its own average GDP, population size and number of physicians. Linear regression was executed using SPSS (2013) to assess the relationship \( R^2 \) between the above 3 socioeconomic factors and the number of publications.

Visualization of bibliographic networks

In order to assess collaborations between Arab country organizations and authors as well as MeSH and author keywords, data were imported to VOSViewer, a software program that builds bibliographic networks. Collaborations of authors and organizations were evaluated by the program. In addition, co-occurrence of keywords was analysed, resulting in a bibliographic map of the most relevant keywords. Colours in the map define clusters of keywords and lines define the strength of relationships between the keywords. Such maps highlight the primary focus on specific topics and fields of science.

Assessment of quality

Quality assessment can be evaluated by several factors: journal impact factor, journal h-index and journal quartiles. We chose to consider the journal quartiles (Q1, Q2, Q3, Q4) as a quality index, especially since they show the ranking of a journal worldwide (19). Hence, top quartile journals (Q1) are usually of higher quality and have an international audience. Other metrics such as the impact factor do not impart the ranking of a journal and numbers can be variably interpreted.
Results

From 2004 to 2019, 69 articles relating to FMF originated from Arab countries, i.e. in only 0.03% of the total publications in the Arab world, and 3.60% of all FMF-related articles worldwide. Among the Arab countries, Lebanon (with 25 publications) and Egypt (with 18 publications) were the only 2 with a double digit FMF-related article count, accounting for more than half of the total number (62.32%). Conversely, 11 Arab countries failed to publish any articles focusing on FMF in the 16-year period under study. The Syrian Arab Republic and Lebanon had the highest percentage of FMF-related articles to total publications between 2004 and 2019, with 0.35% and 0.12% respectively. This lack of FMF-related articles in the Arab world is further demonstrated when compared to non-Arab countries such as Israel, Turkey and the United States of America, which completely outscored the Arab world and published 162, 699 and 109 FMF-related documents respectively between 2004 and 2019 (Table 1).

The average population size, average GDP, and mean number of physicians in Arab countries are shown in Table 2. The number of publications was normalized according to these variables in order to remove any bias when comparing between different countries. In fact, after normalization, Lebanon still proved to be the most efficient country in terms of number of publications, with 4.44 per million population, while Qatar came in second with a total of 1.02 publications per million persons. These relatively small countries proved to be the most productive in terms of publications per million persons when compared to larger publishers such as Egypt, Saudi Arabia and Tunisia (20). In fact, Tunisia and Saudi Arabia had the 2 lowest non-null numbers of publications per million persons, with values of 0.09 and 0.14 respectively.

Average GDP is a widely used variable to assess and compare national economies. The economic performance of the countries had to be taken into consideration as most research work requires funding (21). By normalizing

### Table 1 Distribution of publications on familial Mediterranean fever (FMF) for the Arab countries and selected non-Arab countries (2004–2019)

| Country                  | Total no. of publications | Publications on FMF |
|-------------------------|---------------------------|----------------------|
|                         | No. | % of total |
| Algeria                 | 4 345 | 1 | 0.02 |
| Bahrain                 | 1 582 | – | – |
| Comoros                 | 42  | – | – |
| Djibouti                | 101 | – | – |
| Egypt                   | 57 976 | 18 | 0.03 |
| Iraq                    | 4 885 | – | – |
| Jordan                  | 11 841 | 6 | 0.05 |
| Kuwait                  | 6 071 | 1 | 0.02 |
| Lebanon                 | 20 283 | 25 | 0.12 |
| Libya                   | 1 047 | – | – |
| Mauritania              | 120 | – | – |
| Morocco                 | 8 085 | 5 | 0.06 |
| Oman                    | 5 201 | – | – |
| Palestine\(^b\)          | 1 126 | – | – |
| Qatar                   | 9 168 | 2 | 0.02 |
| Saudi Arabia            | 56 357 | 4 | 0.01 |
| Somalia                 | 111 | – | – |
| Sudan                   | 3 295 | – | – |
| Syrian Arab Republic    | 1 438 | 5 | 0.35 |
| Tunisia                 | 15 505 | 1 | 0.01 |
| United Arab Emirates    | 8 176 | 1 | 0.01 |
| Yemen                   | 1 271 | – | – |
| Total (Arab countries)  | 218 026 | 69 | 0.03 |
| Israel                  | 218 753 | 162 | 0.07 |
| Turkey                  | 237 490 | 699 | 0.29 |
| United States of America| 4 732 225 | 109 | <0.001 |

\(^a\)Percentage of the total number of publications for each country in the study period.

\(^b\)West Bank and Gaza.

### Table 2 Distribution of average population, gross domestic product (GDP) and mean number of physicians in the Arab countries (2004–2019)

| Country                  | Average population | Average GDP (billion US$) | Mean no. physicians (thousand) |
|-------------------------|--------------------|---------------------------|-------------------------------|
| Algeria                 | 37 359 438         | 160.65                    | 54.59                         |
| Bahrain                 | 1 249 091          | 27.05                     | 1.22                          |
| Comoros                 | 718 660            | 0.94                      | 0.15                          |
| Djibouti                | 866 421            | 1.59                      | 0.18                          |
| Egypt                   | 86 266 141         | 215.90                    | 140.63                        |
| Iraq                    | 32 084 985         | 151.16                    | 23.84                         |
| Jordan                  | 7 885 521          | 28.09                     | 17.43                         |
| Kuwait                  | 3 234 030          | 125.03                    | 6.90                          |
| Lebanon                 | 5 626 327          | 38.89                     | 12.57                         |
| Libya                   | 6 245 227          | 52.76                     | 11.58                         |
| Mauritania              | 3 683 546          | 4.23                      | 0.54                          |
| Morocco                 | 33 134 913         | 91.13                     | 22.06                         |
| Oman                    | 3 538 838          | 59.49                     | 6.78                          |
| Palestine\(^b\)          | 4 205 124          | 9.64                      | –                             |
| Qatar                   | 1 962 132          | 122.42                    | 4.73                          |
| Saudi Arabia            | 28 763 301         | 569.45                    | 64.17                         |
| Somalia                 | 12 636 382         | 4.22\(^c\)                | 0.36                          |
| Sudan                   | 36 084 250         | 63.26                     | 10.90                         |
| Syrian Arab Republic    | 19 046 416         | 31.92\(^c\)               | 25.83                         |
| Tunisia                 | 10 812 039         | 41.23                     | 12.96                         |
| United Arab Emirates    | 7 980 982          | 312.86                    | 14.34                         |
| Yemen                   | 24 224 626         | 28.89                     | 9.10                          |

\(^a\)West Bank and Gaza.

\(^b\)Somalia data only available from 2013 to 2018.

\(^c\)Syrian Arab Republic data only available from 2004 to 2007.
the number of publications to the average GDP, we obtained the number of publications per billion US$ for each country. Lebanon and Jordan surpassed other larger and wealthier countries, with values of 0.51 and 0.21 respectively. Saudi Arabia and Kuwait were the last 2 countries with non-null publication numbers per billion US$, with a value of 0.01 each.

Finally, Lebanon again managed to come first in terms of number of publications per 1000 physicians, with an average of 1.99, followed by Qatar with 0.42. Saudi Arabia had the lowest number of publications per 1000 physicians with an average of only 0.06 in the 16-year period (Table 3).

Linear regression indicated a rather moderate, positive correlation between number of publications and average population size \( r = 0.385 \), as well as between number of publications and average number of physicians \( r = 0.513 \). However, a weak positive correlation was also found between number of publications and average GDP in the Arab countries \( r = 0.116 \).

When FMF-related publications were categorized according to journal rankings, it was found that the majority were published in Q3 ranked journals (43.94%), and the least published in Q4 journals (6.06%); however, 50.00% were published journals ranked in Q1 (15.15%) and Q2 (34.85%).

According to the bibliographic map of the co-occurring MeSH keywords (Figure 1), most articles contained keywords such as “familial Mediterranean fever”, “mutation”, “humans”, “cytoskeletal proteins”, “pyrin”, and “genotypes”, suggesting a main focus on the genetic and cellular aspect of FMF. Three main “clusters” (colours) classify the keywords into groups in which they seem to be present together.

In the Arab world, many researchers from various organizations made their interest in FMF clear by either authoring or co-authoring publications related to the issue. However, out of 284 authors, only 5 showed significant co-authorship, with a minimum threshold of 5 documents per author. In addition, researchers from different organizations co-authored a maximum of 2 documents in only 4 out of 104 organizations and 3 of these originated from a single country, Lebanon (Table 4).

An increase in the number of publications related to FMF was seen during 2013–2015, but this increasing trend diminished in the following years, with the Arab world displaying less interest in FMF-related publications until the end of our study period (Table 5).

### Discussion

The countries of the Arab world published 189 medical articles per million persons between 2007 and 2016. Qatar, Tunisia, Lebanon, and Kuwait were the only Arab countries to exceed the world average in term of papers per million people (22). For FMF in particular, half of the Arab countries did not publish any articles during 2004–2019. Lebanon recorded the highest total number of publications on FMF (23) as well as the highest number per million persons (4.44), highest number in relation to GDP (0.64) and highest number per thousand physicians (1.99) over the 16-years of the study. However, the Syrian Arab Republic is the country that recorded the highest percentage of FMF articles out of all its published articles.

Along with other health care providers and researchers, physicians are at the core of the research process. In fact, greater numbers of physicians in a country can be a valuable indicator of this workforce’s contribution in the biomedical scientific community. A novel parameter was introduced in this study: calculating the number of published articles per 1000 physicians (24). This allowed us to evaluate the rate of publications in proportion to the physicians’ workforce, rather than the entire population. This parameter might be able to give a better insight on the publication rate since the number of physicians might vary from country to country differently from population size. This is because the number of physicians is affected by variables such as the country’s financial and political stability and level of education. In this study, a moderate positive correlation was observed between the number of publications and the number of physicians. The average GDP and the population size had weaker correlations with the number of FMF publications. In contrast,
looking at psoriasis-related articles from the Arab world, the strongest correlation was found between number of publications and population size, while for stroke, the strongest correlation was found between number of published articles and average GDP (23,25).

During most years, the total number of publications fluctuated between 4 and 7, reaching a peak of 12 articles in 2015. The calculated annual mean for the number of publications issuing from the 22 countries of the Arab world is 4.31. This means that the annual number of publications per country only amounts to 0.20. In fact, the Arab world released 3.60% of the total FMF related articles worldwide. This number, which is achieved by 22 countries, is much lower than the 36.52% contribution made by Turkey alone to FMF research articles. According to several studies, the Arab world falls behind other regions in many medical research fields, for instance ophthalmology and mental health research, since they only publish about a quarter of the volume of other countries (22,26,27). However, the Arab world’s contribution in some other fields like urology/nephrology is relatively important (28). It is essential to keep in mind that, although the number of publications released in the Arab world is relatively low, they were published in rather high quality journals. Actually, 50.00% of the articles were published in Q1 and Q2 ranked journals.

All of the articles included in this study covered the genetic and immunological aspect of FMF, giving emphasis to the mutated MEFV gene and 64.18% focused on the biochemistry and molecular biology of FMF. In fact, the most common MeSH and author keywords found in the 69 articles of this study were “mutation”, “pyrin”, “cytoskeletal proteins”, “genotype”, “genetic predisposition to disease”, “phenotype”, and “gene frequency”. All of these keywords pertain to genetics and cellular biology. This shows that most of the published articles fall into the biological and biochemical field rather than the clinical one. In fact, there is a lack of clinical follow-up concerning FMF in the Arab region, which is why clinical trials and clinical research should be implemented in this region to tackle the issues of diagnosis, prognosis and treatment, and give a clinical impact to their findings. Other less commonly studied aspects of FMF include amyloidosis, arthritis and

Table 4 Distribution of co-authored documents (> five documents on familial Mediterranean fever) from the Arab world (2004–2019)

| Source | No. co-authored documents |
|--------|---------------------------|
| Organization |  |
| Department of Medical Genetics, National Institute of Health, Rabat, Morocco | 2 |
| Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center, Beirut, Lebanon | 2 |
| Division of Rheumatology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon | 2 |
| Unité de Genétique Médicale, Faculté de Médecine, Université Saint Joseph, Beirut, Lebanon | 2 |
| Author |  |
| Chouery, Eliane | 8 |
| Delague, Valérie | 6 |
| Medlej-Hashim, Myrna | 11 |
| Mégarbané, André | 9 |
| Salem, Nabiha | 5 |
treatment with colchicine; arthritis is a common and significant feature of the disease, renal amyloidosis is one of its most severe complications and colchicine is the primary treatment (29–31).

Genetic and immunological studies are conducted in advanced laboratories and need substantial funding. Nevertheless, Arab countries spend only 0.15% of their GDP on scientific research, which is significantly lower than the world average of 1.4% (32). This could be due to the political instability in the Arab region, where money is spent on military equipment rather than scientific research. In the absence of financial support, safety and peace, development and research are very challenging. Over recent years, the Arab world has faced hunger, economic insecurity, human insecurity, military intervention and occupation (33). It witnessed 15% of the world’s conflicts between 1948 and 2017, experienced 62% of the total terrorist attacks in 2005, and accounted for 55% of the world’s refugees in 2017 (34).

The main limitation of this study was the use of a single database (PubMed) to retrieve the released articles. Additionally, other references and variables such as the funding per article and the type of article could prove to be useful in assessing the research nature and costs per country.

**Conclusion**

Arab societies are among the populations most prone to FMF, however, their research input in this field only reaches 3.60% of the total number of FMF-related articles worldwide; half of the Arab countries published no relevant research throughout the 16 years of the study. The low number of publications could be resultant on the political instability in this region as well as the absence of research funding. Nonetheless, articles were published in rather high quality journals, which shows a certain potential in this region for publishing quality research that could help their own, and other, health care systems. To achieve this goal, Arab countries should not...
only give more importance to and provide funding for research but also guide their work into the more clinical aspects in order to tackle issues like diagnosis, prognosis and treatment. Furthermore, collaboration between Arab researchers from different countries and worldwide experts should be encouraged to generate publications with a greater impact and broader ramifications.

Funding: None.
Competing interests: None declared.

Activités de recherche sur la fièvre méditerranéenne familiale dans le monde arabe : la nécessité des collaborations régionales et internationales

Résumé
Contexte : La fièvre méditerranéenne familiale (FMF) est une maladie auto-inflammatoire multisystémique touchant les populations du bassin méditerranéen.
Objectifs : L'objectif de la présente étude était d'évaluer la contribution des pays arabes à la recherche sur la FMF entre 2004 et 2019.
Méthodes : La base de données Medline (PubMed) a été consultée pour accéder aux publications concernant la FMF. Le nombre de publications a été normalisé à la moyenne pour la taille de la population, du PIB et du nombre de médecins pour chaque pays. VOSViewer a été utilisé pour créer une carte bibliographique de co-occurrence.
Résultats : Entre 2004 et 2019, 69 articles concernant la FMF ont été publiés dans le monde arabe, ce qui représente 0.03 % du nombre total de publications en provenance des pays arabes, et 3.60 % de tous les articles relatifs à la FMF dans le monde. Après normalisation en fonction de la taille moyenne de la population, du PIB et du nombre de médecins, le Liban s’est classé premier avec respectivement 4.44, 0.64 et 1.99 publications pour un million de personnes. Des corrélations positives modérées ont été observées entre le nombre de publications et la taille moyenne de la population (r = 0.385) et le nombre moyen de médecins (r = 0.513). La moitié des articles ont été publiés dans des revues classées Q1 et Q2. Un grand nombre de mots-clés relatifs à la génétique indique que l'accent est mis sur l'aspect génétique de la maladie.
Conclusion : Le faible nombre de publications pourrait être dû à l'absence de financement de la recherche et à l'instabilité politique et militaire dans le monde arabe. Etant donné que de nombreux articles ont été publiés dans des revues de grande qualité, les pays arabes devraient s'attacher à donner un aspect clinique à leurs études et à établir des collaborations régionales et internationales.
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