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Genetic polymorphism and the risk of diabetic foot: a bibliometric analysis from 2011-2021

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ABSTRACT

Diabetic foot ulcer (DFU) has been associated with genetic and environmental factors, which could potentially have a role in DFU development. Single nucleotide polymorphisms (SNPs) in genes linked to DFU, including inflammation. Bibliometric studies on the SNP on genes affecting DFU still have not been evaluated. This study aims to depict bibliographically and understand the topic trend of genetic polymorphism and the risk of DFU publications. A bibliometric methodology was applied in this study. The data were extracted through the Scopus database from 2011 to 2021. VOS viewer was used to classify and summarize Scopus articles. The 35 articles were evaluated. India topped the list of countries with the most publications, and Tehran University of Medical Sciences was the primary institution. Singh K and his team were the first contributing authors with 44 citations. Keywords analysis indicated that the research hotspots were DFU, type 2 diabetes mellitus (T2DM), diabetic foot ulcers, polymorphisms, hypoxia, vascular endothelial growth factor (VEGF), diabetic foot, diabetes mellitus, and oxidative stress. This study summarizes the current state, trends in genetic polymorphism and risk with DFU research. It may provide researchers with insight into the genetic polymorphism and risk associated with DFU research, as well as useful information for identifying possible collaborators and partner institutions.

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1. INTRODUCTION

Global epidemiological research has revealed a pandemic increase in the prevalence of diabetes, particularly in Asian countries [1]. International Diabetes Federation has reported that in Indonesia, patients with Diabetes Mellitus (DM) will be nearly 20 million people in 2021, and it is estimated will increase to twice in 2045 [2]. Diabetic foot ulcer (DFU) is a severe concern to people with type 2 diabetes mellitus (T2DM) since it frequently results in persistent nonhealing ulcers. DFU is considered the most common and serious microvascular complication of T2DM. They are associated with the development of neuropathic pain, the pricking of the foot, and the gradual onset of numbness toward the area of infection, eventually leading to neuro ischemic ulcers [3], [4]. It has been reported that diabetic subjects show prolonged inflammatory and proliferative phases of wound healing [5], [6].

The previous meta-analysis mentioned that the prevalence of DFU reached 6.3%, with a higher proportion in males to females (4.5% vs 3.5%). The prevalence of DFU in North America, Oceania, Asia, Europe, Africa were 13.0%, 3.0%, 5.5%, 5.1% and 7.2%, respectively. Furthermore, the prevalence of DFU in Australia, Belgium, Canada and the USA were 1.5%, 16.6%, 14.8% and 13.0%, respectively [7]. The DFU is still problematic and requires interdisciplinary therapy. The high expense of treating DFU is one of the country's burdens [8]. DFU is a complex disease involving both genetic and environmental variables, and genetic factors may play a significant role in developing DFU [9].

Single nucleotide polymorphisms (SNPs) in genes that associated with DFU, including inflammation, serve as valuable candidates for DFU therapy. Some of the SNPs, had significant association with DFU, such as: Interleukin (*IL*) rs1800795, tumor necrosis factor (*TNF*)-α rs1800629, rs361525 and stromal cell derived factor (*SDF*)-1 rs1801157. SNPs of C-reactive protein (CRP), including rs11265260, rs1800947, rs2794520, rs1130864, and rs3093059, are related with the risk of developing DFU [9]–[11]. The Vascular Endothelial Growth Factors (*VEGF*) polymorphism rs699947 and the nuclear factor erythroid two related factor 2 (*Nrf2*) polymorphism rs182428269 were linked to the pathophysiology of T2DM and DFU [12], [13]. T2DM patients had decreased NAD-dependent deacetylase sirtuin-1 (SIRT1) and oxidative stress. SIRT1 SNPs have been linked to the development of neural or vascular diseases [14], [15]. Monocyte chemoattractant protein-1 (*MCP-1*) is a pro-inflammatory cytokine that plays an important part in the inflammatory process, and the *MCP-1* polymorphism rs1024611 was significantly correlated with increased DFU susceptibility [16]. SNPs in the vitamin D receptor (VDR) are implicated in the etiology of many inflammatory diseases [17]–[19]. Soroush *et al.* investigated the role of VDR rs2228570 in the development of DFU in an Iranian population. The results demonstrated that the frequency of genotypes TT and TC was considerably higher in patients with DFU than in patients without DFU [20]. In addition, the Matrix metalloproteinases-9 (MMP-9) gene promoter SNP -1562C>T was associated with T2DM and DFU. Increased MMP-9 production from a T allele with a high level of expression may promote matrix degradation [21]. These DFU SNPs can assist identify high-risk patients who need better therapy [22]. Furthermore, recent studies have highlighted the significance of analyzing genetic variants and the risk of diabetic foot [23], [24].

Bibliometric research is an effective strategy for analyzing qualitative and quantitative data from publications on a specific topic. The approach is frequently employed in the medical industry and aids in identifying innovative and emerging research fields. Bibliometric studies have been published about diabetic foot but not on genetic polymorphism [25], [26]. Polymorphism connections give a foundation and insights for primary care in symptomatic patients, and they help reduce the time it takes to discover diabetic foot. Therefore, studies on genetic polymorphism and the risk of diabetic foot must identify worldwide patterns and prospects. This study is the first to use VOS viewer to analyze articles relating to genetic polymorphisms (SNPs) affecting DFU. This study aims to provide a 10-year (2011-2021) continuous analysis of the evolution of the scientific literature on genetic variation and the risk of diabetic foot. This work will assist researchers in determining future research directions and promote further significant research.

2. RESEARCH METHOD

A bibliometric analysis was implemented using the SciVerse Scopus database. A single database is typically used in bibliometric analysis to conduct subsequent quantitative research. Herein, we systematically performed online retrieval from the Scopus database on Dec 10, 2021 (https://www.scopus.com/home.uri). We used the Medical Subject Heading (MeSH) terms "diabetic" and "foot" and "ulcer" and "genetic" and "polymorphism" to conduct an accurate and expedient search of the articles. In this study, the document type was set to "article", the language was set to "English", and the research period was from 2011 to 2021. We collected the following basic information for each article: the authors' names, the title, the abstract, the institution's name, the nation or region's name, the journal name, keywords, and references.

A list of the articles that meet the following criteria was included: i) The period is between 2011 and 2021; ii) there are articles in the Scopus database; iii) original research articles on DFU gene polymorphism; iv) articles providing basic information. The following document was excluded: i) meeting abstracts, proceedings, revised papers, and reprinted publications; ii) unpublished documents containing insufficient information for further analysis.

The original data download from Scopus database was first imported into a comma-separated value (CSV) file. The downloaded data were analyzed based on the Scopus database literature analysis report and export information function. We used Software VOS viewer (version 1.6.6) to analyze and visualize the co-occurrence of keywords, the co-citation of references, publication outputs, construct knowledge and network visualizations [27]. VOS viewer is a free java-based software program designed by van Eck and Waltman11 (Leiden University) to construct and visualize bibliometric networks. When two words appear next in the bibliometric networks, they may be linked. The more often it happens, the closer that relationship is. In addition, by examining the clusters within bibliometric networks, it is possible to determine the semantic

relationship between various study topics. The VOS viewer software is freely available online [28]. The bibliometric network is based on distance, and each network is made up of many nodes that are mapped in a two-dimensional (2D) space based on similarities.

3. RESULTS AND DISCUSSION

Overall, Scopus database has generated 43 publications of DFU genetic polymorphism, all of which were extracted and filtered following the appropriate standards. Publications with missing records such as missing citing references or publication years, or publications with anonymous authors/references were removed from the search results. A total of 35 publications have been included in the further analysis.

3.1. Countries and number of publications

Globally, the prevalence of diabetic foot ulcers is approximately 6.3 %, and males are more likely to develop them than females [29]. Figure 1 shows the country and number of publications year from 2011 to 2021. India has the most publications related to the associated SNPs with DFU in T2DM patients. There were 12 documents have published and focus on genes associated with DFU. According to by International Diabetes Federation (IDF), India was the leading contributor to regional diabetes mortality, with an estimated 1 million fatalities due to diabetes and its comorbidities [30]. India has been termed the "diabetic capital of the world" due to the widespread Westernisation of its citizens, who range in age from adolescents to the elderly and from all socioeconomic backgrounds. In India, diabetic patients reached 62 million and 25% were DFU patients. Around 50% were infected, and 20% needed amputation during hospitalization. Patients with DFU history had a 40% higher 10-year death rate [31].

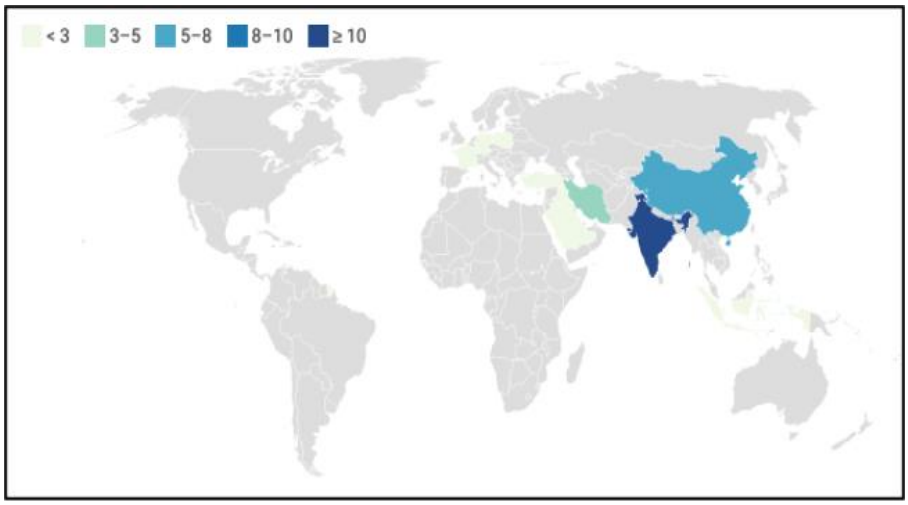

Figure 1. Publications of genetic polymorphism and the risk of DFU by country between 2011–2021

China is the second country with the highest number of publications regarding SNPs of genes associated with DFU. DFU is the most common cause of chronic cutaneous wounds in China. It is related to an increase in the disability rate and death and is the most common reason for hospitalization. The mortality rate among individuals suffering from ulceration reached 14.4% [32]. Furthermore, Iran, Turkey, Germany, Iraq, Poland, Saudi Arabia, France, and Indonesia published several studies on gene polymorphisms associated with DFU. Between 2011 and 2021, the genetic polymorphism and the risk of DFU articles was analyzed. With seven publications in the 2018 was the most productive year, followed by 2015 and 2017 with six and five articles, respectively (Figure 2). In 2018, India, China, Iran, and Turkey were the countries with the most publications. The majority of publications this year investigated the association of polymorphisms in cytokines and chemokine genes with DFU, including TNF, stromal cell-derived factor 1, Interleukin-6 (IL-6), and Monocyte chemoattractant protein-1 (MCP-1) and VEGF [9], [12], [22].

The number of publications relating to the DFU gene polymorphism decreased in the following year, 2019, with four articles reported in 2020 and two papers in 2021. Many genes associated with risk factors for diabetes to progress to DFU and genes connected with the inflammatory phase of DFU have been investigated

in studies on gene polymorphisms associated with DFU. There are numerous cytokine and chemokine genes that play a role in the healing process of DFU, particularly during the inflammatory phase of DFU.

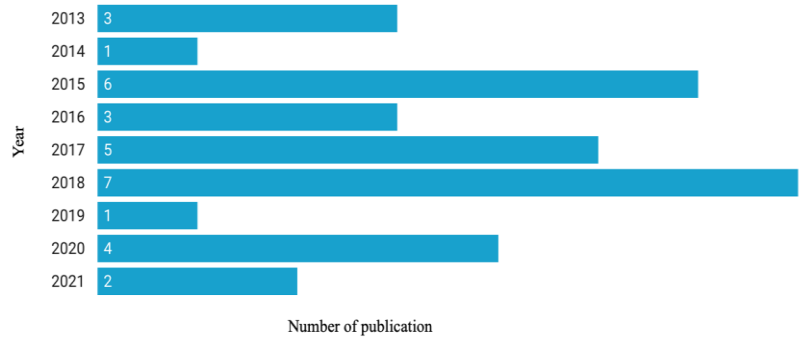

Figure 2. Publications of genetic polymorphism and the risk of DFU by year between 2011–2021

3.2. Authors' country, authors and author's affiliation of publications

Figure 3 shows the description of the authors' country, the authors, and the author's affiliation of genetic polymorphism and the risk of DFU publications by country between 2011–2021. Many authors from India, Iran and Turkey contributed to their affiliation with the universities. The India published most papers, followed by Iran and Turkey. India has the highest number of citation (205 times), followed by Iran (95 times) and Turkey (11 times). The first contributing author to genetic polymorphism and the risk of DFU research was Singh K. He co-authored 40 publications and had H-index of 15. He was followed by Viswanathan V (322 publications, H-index 46), and NK Agrawal (50 publications, H-index 13). The most productive organization on genetic polymorphism and the risk of DFU research is the Tehran University of Medical sciences with 25 publications, followed by Banaras Hindu University, Medical University of Warsaw, Cangzhou Central Hospital and Ege University Medical School, with 19, 12, 10 and 10 publications, respectively.

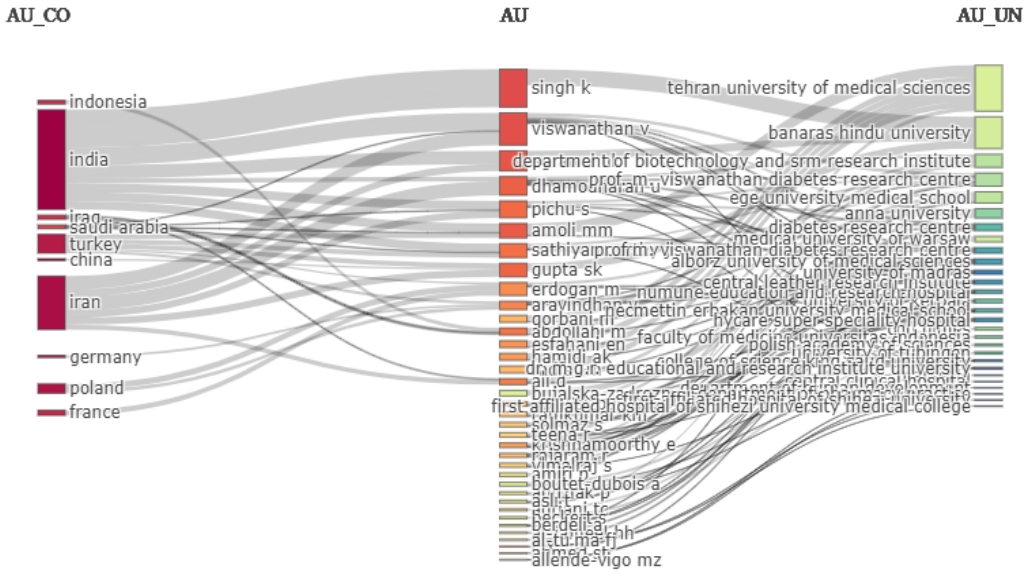

Figure 3. Publications of genetic polymorphism and the risk of DFU by the author country, author and organization between 2011–2021 (AU_CO: Author_Country, AU: Author, AU_UN: Author_University)

3.3. Journals of publications

In this analysis we highlighted that top three most productive journals consecutively published the genetic polymorphism and the risk of DFU in patients with DM. Top three of these journals were international journal of biological macromolecules (IF (2021) 6.953), international journal of lower extremity wounds

(IF (2021) 2.104), and Medicine (United State) (IF (2021) 1.889) as shown in Figure 4. The journals are showing that its scope encompasses genomic variants as risk factors for developing DFU in patients with DM.

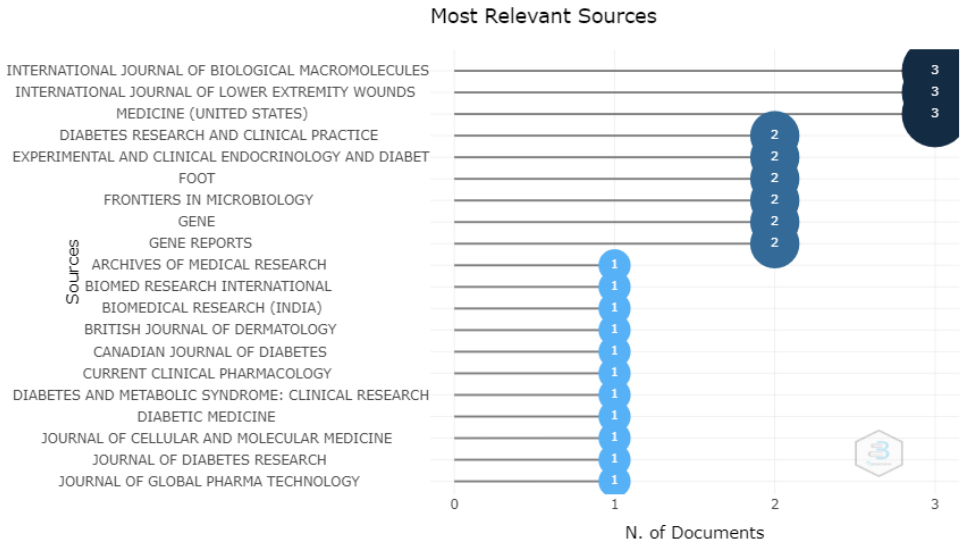

Figure 4. Journals of genetic polymorphism and the risk of DFU publications between 2011–2021

3.4. The top ten of publications

The 10 most productive publications are shown in Table 1. To provide a better overview, several other bibliometric indicators including author name, year, digital object identifier (DOI) number, the number of citations and the total citations per year are also considered. The most article citated was published by of Singh *et al.* and Miranda-Massari *et al.* [33], [34]. Singh *et al.* reported an association between the *Toll-Like Receptor 4* (*TLR4*) rs4986790, rs4986791, rs11536858, rs1927911, and rs1927914 to an increased risk of DFU in T2DM. TLR4 is required for immunity, tissue repair, and regeneration. TLR4 SNPs and haplotypes may increase the risk of impaired wound healing in T2DM patients and can be used to assess DFU risk in T2DM patients [33]. Furthermore, Miranda-Massari *et al.* studied the polymorphic *Methylene-tetrahydrofolate reductase* (*MTHFR*) genes, in the risk of developing *diabetic peripheral neuropathy* (DPN) and how metabolic correction can reduce these risks [34]. Khodaeian *et al.* had a total citation (TC) score per year that was 5,571 higher than other authors, this paper examines the association between genetic variants and diabetes and its complications in studies with Iranian populations [35].

Table 1. The top ten of genetic polymorphism and the risk of DFU Publications with the most citation frequency

Author	Years	PMID	Total citations	TC per year	Normalized TC
[33]	2013	23936790	44	4,889	1.6098
[34]	2011	22082324	44	4	1.1733
[35]	2015	26587547	39	5,571	2
[10]	2015	25839939	32	4,571	1.641
[36]	2011	21596454	31	2,818	0,8267
[21]	2013	24043671	27	3	0.9878
[37]	2015	26113285	23	3,286	1.1795
[38]	2014	24861096	21	2,625	1
[39]	2015	26579581	19	2,714	0.9744
[40]	2016	27374075	18	3	1.5882

Abbreviations TC = Total citations; PMID = PubMed identifier

3.5. Trending keywords of publications

The 28 most often occurring author keywords in the genetic polymorphism and the risk of DFU publications are depicted in Figure 5. The size of words indicates the frequency of occurrence. The keyword "DFU" is central to the graph, followed by T2DM, diabetic foot ulcers, polymorphisms, hypoxia, VEGF, diabetic footdiabetes mellitus, and oxidative stress.

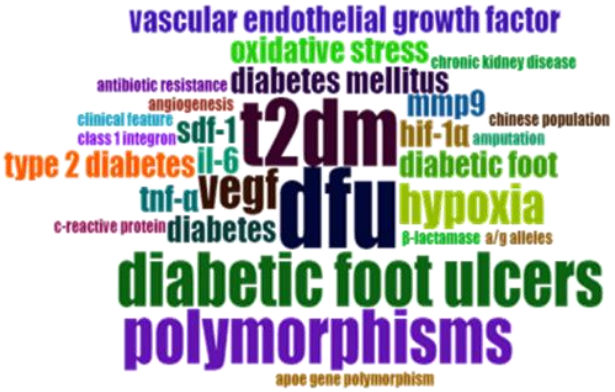

Figure 5. Keyword analysis among the articles in genetic polymorphism and the risk of DFU by year between 2011–2021

SNPs in genes related to DFU, such as inflammation, make them promising candidates for DFU therapy. The keyword analysis data shows several target genes polymorphisms, including *VEGF)* [12], [36], [41]–[43], *Stromal cell-derived factor-1 (SDF1)* [10], *IL-6* [44], *TNF-* [45], *Apolipoprotein E (APOE)* [46], *MMP9* [38], and *hypoxia inducible factor-1 alpha* (*HIF-1* [37]. The VEGF produces collagen and promotes angiogenesis by removing the matrix, allowing endothelial cells to migrate and sprout [39], [47]. VEGF regulates transforming growth factor- and platelet-derived growth factor in patients with DFU during wound healing [48]. Modulating VEGF expression has been proposed as an effective technique for diabetic complications treatment. *VEGF -2578*A* polymorphism is associated with the development of DFU, and a lower frequency of the A allele in patients with DFU confers a protective effect that might result from increased angiogenesis in patients carrying this allele [36], [49]. SNPs in inflammatory genes are promising candidates for DFU because the proinflammatory cytokines IL-6, TNF-, and SDF-1 have been shown to coordinate the three phases of wound healing and appear to influence a variety of DFU risk factors, including glycemic control, serum lipid profile, kidney function [44], [50]. Mehmet *et al*. reported that ApoE gene polymorphism is a risk factor for diabetes, but it is not an independent risk factor for diabetic foot. It is possible that the lack of a relationship between ApoE gene polymorphism and Type 2 diabetic foot ulcers is related to ethnic differences [46]. MMPs degrade extracellular matrix and rebuild connective tissue. Functional SNP -1562C>T in the MMP-9 gene promoter decreases nuclear protein binding and increases transcriptional activity. The polymorphism -1562 C>T in the promoter region of the MMP9 gene is associated with pathogenesis and progression of wound healing impairment in patients with T2DM [51].

HIF-1 gene polymorphism has been linked to a variety of diseases, including angiogenesis and neovascularization. Decreased HIF-1 gene expression in foot ulcer patients suggests its possible role in pathogenesis [37]. Furthermore, identifying SNPs on genes has contributed to DFU would help identify high-risk individuals who need better treatment care.

3.6. Strengths and limitations

This is the first bibliometric analysis to identify trends in genetic polymorphism and the risk of DFU research. It can help us determine the overall status of historical and contemporary genetic polymorphism and the risk of DFU papers and their patterns over time. The bibliometric analysis spanned more than a decade of genetic polymorphism and the risk of DFU research. In addition, it could be used as a guide for scholars in the future by identifying the expected upcoming trends. Our bibliometric study has some limitations. The Scopus database is the major source of input data for VOS reader, rather than several search engines (Pubmed, Ovid, WosCC, and Google Scholar). The raw data collected was linked to a specific timestamp. As a result, the conclusion may evolve over time, and the study needs to be updated.

4. CONCLUSION

The bibliometric analysis in this paper demonstrated that the polymorphism gene has been associated with DFU and published papers in the past ten years. India leads to genetic polymorphism and the risk of diabetic foot related publications. Singh K and the team (Department of Molecular & Human Genetics, Banaras Hindu University, India) were the first contributing authors with 44 citations and the leading institute was Tehran University of Medical Sciences. International Journal of Biological Macromolecules, International Journal of Lower Extremity Wounds, and Medicine (United States) are the three most productive journals in the genetic polymorphism and the risk of diabetic foot field. DFU, T2DM, polymorphisms, hypoxia, VEGF,

diabetic foot, and oxidative stress could be the genetic polymorphism and the risk of diabetic foot trending investigation hotspots.

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