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A GLOBAL SYSTEMATIC REVIEW AND META-ANALYSIS ON THE PREVALENCE OF MULTI-DRUG RESISTANT BACTERIA AND ITS GENES IN INSULIN RESISTANT PATIENTS

Hassan Jan^{1a}, Anadil Noel², Zunaira Asjad Ali³, Anam Amir^{1b}, Muhammad Arham Dar^{1c}, Zainab Naseer^{1d}, Mehreen Fatima^{1e}

^{1a,1b,1c,1d,1e}Department of Life Sciences, University of Management and Technology, Lahore,
^{1e}Email: mehreen.fatima@umt.edu.pk
²Department of Accident and Emergency, THQ Hospital, Jhelum
³IMBB, The University of Lahore

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Corresponding Author: Mehreen Fatima, Department of Life Sciences, University of Management and Technology, Lahore, Email: mehreen.fatima@umt.edu.pk

ABSTRACT

Diabetes mellitus is a major disease that causes death and disability all over the world and there are different complexities in the treatment of this disease. From the previous few years, multidrug resistance (MDR) in patients with diabetes mellitus has been increasing day by day and its effects on multiple organs. The risk factor of diabetes mellitus and diabetic foot ulcer is projected to increase by more than 50% in the next decade due to a rapid increase in multi-drug resistance (MDR) issues. The aim of this study was to estimate the prevalence of multi-drug resistant bacteria in diabetic foot ulcer infections by pooling the published that have reported the MDR-DFU prevalence the better control and prevention of the MDR-DFU infections. This study was performed website based using the different electronic databases including the PubMed and the Google scholar. In this study, articles that were published between January 2013 to January 2023 were included. Data from relevant articles were extracted and statically examines was conducted using STATA version 14, the metaprop command was used to retrieve the relevant data. A total 80 articles were identified through electronic databases; of all those 80 studies, 40 statified our inclusion criteria. The forest plot shows that the joint occurrence of the MDR-DFU was 1.55 (95 cl: 1.43-1.67). The total heterogeneity was important, as shown by the values of 12=99.81%, p= 0.00, and momentous ES=0 (z=24.37, p=0.00). More information available about the prevalence and the occurrence of the Multi-drug resistant bacteria in diabetic foot ulcer infections annually. About the prevalence of MDR of DFU in Antarctica, there are no information available. Surveillance is serious to better understand the annual MDR of DFU weight to improve the national and international level.

Introduction METHODOLOGY

Research design: In this systematic meta-analysis that include the many studies come from different nations worldwide .this systematic review was programmed accord to the or with the preferred reporting items for the systematic reviews and the meta-analysis (PRISMA) guiedlines.in the search of the papers that might be the important the goals of this research the references of the review articles that were collected from the databases that were seen .all articles tittles and abstracts that were retrieved followed screening for the relevance to the study goals.

Literature strategy: Literature were the searched on the Google scholar and PubMed by consuming these kind of key words: prevalence of *Escherichia coli*, *Staphylococcus aureus* diabetes mellitus, foot ulcer infections, multi-drug resistance, anti-microbial resiatance. The relevant information's in the articles were included.

Duration of the study: In this study, articles published in January 2013 to January 2023 were selected.

Selection criteria:

- **Inclusion criteria:** Data were retrieved from relevant sources by reviewing and studying the articles thoroughly. According to pre-determined inclusion and exclusion criteria ,articles were chosen .studies that achieve d the following requirements could be included the :1) a quantities study determining the occurrence of Multi-drug resistance and the diabetic foot ulcer infections in intensive care units ;2) a study examine the multi-drug resistance ; 3) articles were be included that reported the prevalence of MDR in diabetic foot ulcer (DFU) infections; 4) all relevant articles with full details published nationally and internationally were included . The tittles, abstracts, and entire content of the work were used to assess eligibility.
- Exclusion criteria: According to the following criteria, these studies were excluded: 1) all irrelevant articles .case reports, duplicate articles, posters. ; 2) Reviewed articles only written short abstracts; 3) tittels, incomplete information is related to the study was excluded.

Data extraction: For the full text articles reviews, only abstracts of the retrieved papers with relevant information's were chosen. A data extraction form on Microsoft excel sheet was used to retrieve the data for a selection of the chosen research. first authors name, study tittels, publications years ,country ,study design, study objectives, study populations ,number of patients ,patients selection criteria ,number of isolates, resistence profile, phenotypic detection test (blood tests, radiography, ankle-brachial index and toe pressure, pulse-volume recording, ultrasonography, computed tomography (CT) scanning or magnetic resonance imaging (MRI), bone scans, and angiography.) were all included in the data extraction form.

Statically analysis:

The metaprop program in the STATA version in the 14 was used in statically analysis to pool the published data on the prevalence of the MDR of DFU in the various part of the world. The cochairman's q statics was used to examine the heterogeneity between the studies, and the 12 statics was utilized to the report the degree of the residual heterogeneity.

RESULTS

Their electronic databases search resulted in a total of 90 articles or studies; 40 were ignored after looking at their tittels, 20 was discovered by a duplicates and 20 were excluded because the full teat information's and abstracts did not direct relate to the topic of interest. The prevalence of MDR 40 publications were identified that were met our eligibility criteria included in our meta-analysis.

A total 40 publications from six dissimilar continents were reviewed, with 22 (55%) impending from Asia, 8(20%) from Africa, 4(10%) from North America, 2(5%) from South America, 2(7%) from Europe. The final one one (3%) came from Australia. There no study found in antarcitca.the most of articles in this study published between 2013-2015, and then in 2019-2021. With aid coming all across the world.

Laboratory techniques used to determine the proportion of Diabetic foot ulcer

The radiography was employed in 24 (60%) of the 40 studies using various phenotypic approaches. However, Computed tomography was employed in 23(55%) and the ultrasonography was employed in the 19(45%) in the 40 papers study. A total 40 papers was published, with 25(75%) appearing international journals and remaining 15(25%) appearing in national journals.

Molecular technique used to determine the proportion of Diabetic foot ulcer

Out of the 40 articles on the molecular detection techniques, 20(50%) mentioned was ultrasonography the based gene detection techniques. Among them 55% articles stated that the UBC gene group was the most common group and that was the most frequent gene variation. In addition, the other 50% UBC and KDR gene combination were discovered.

Year	Asia	Africa	North America	South America	Europe	Australia	Annual total publications
2013- 2015	8(36%)	1(16%)	1(20%)	1(50%)	1(50%)	0(0%)	12(27%)
2016- 2018	5(24%)	4(48%)	1(27%)	1(50%)	1(50%)	1(50%)	13(33%)
2019- 2021	7(32%)	3(38%)	1(47%)	0(0%)	0(0%)	0(0%)	11(30%)
2022- 2023	2(8%)	1(16%)	1(20%)	0(0%)	0(0%)	0(0%)	4(10%)
Region wide	22(55%)	8(20%)	4(10%)	2(5%)	2(7%)	1(3%)	40

Worldwide distribution of published articles



Fig 3.1: graphical representation of selected articles



Fig 3.2: annual publication of articles in worldwide

Publication		Authors	Sample E.coli		Ph	Molecular				
year	Study year		size	positive	Tomography	radiography	ultrason	ography	Genes de genes	etected
_						Asia				
1	Iran	2020	2017-	-2018	Arman et al	83	37	yes	No	yes
2	Turkey	2012-2013	3 2017		Bulent et al	174	116	No	Yes	Yes
3	Iran	2011	2013		Javad et al	600	280	No	No	Yes
4	Iran	2014-201	6 2020		Mohammad et al	4538	432	yes	yes	yes
5	Turkey	2023	2021		Müzeyyen et al	4556	666	Yes	No	Yes
6	Iraq	2021	2020		Doaa et al	544	355	No	Yes	Yes
7	Iran	2017	2016-	-2018	Samaneh	7655	644	NO	yes	yes
8	Iran	2018	2014		Leila et al	8655	1616	No	Yes	No
9	China	2019	2016-	-2018	Yufeng et al	35252	3225	No	Yes	Yes
10	Iran	2020	2014-	-2018	Ali et al	32334	12343	Yes	No	Yes
11	Iran	2023	2021-	-2022	Mohammad et al	2355	1445	Yes	No	No
12	Iraq	2020	2019		Aso et al	422	196	No	Yes	Yes
13	Iraq	2016	2015		Maryam et al	161	87	Yes`	Yes	no
14	Bangladesh	2015	2013		Akhtar et al	1516	765	Yes	No	Yes
15	China	2014	2011		Fang et al	2425	1515	Yes	Yes	Yes
16	Bangladesh	2020	2018-	-2019	Palash et al	13144	1515	No	Yes	Yes
17	Nepal	2020	2015-	-2019	Radha et al	24525	1146	No	No	Yes
18	Pakistan	2022	2018-	-2019	Sohail et al	14415	11423	Yes	Yes	No
19	Nepal	2021	2015-	-2016	Suresh et al	1500	1023	Yes	Yes	No
20	Saudi	2018	2014-	-2016	Mohammed et al	404	100	Yes	No	Yes

		Arabia												
2	21	Pakistan	2020	2019		Mujahid et al		123	55		Yes	Yes	N	0
2	22	Nepal	2013	2010-2	2013	Taiwo et al		3357	882		yes	No	Y	ſes
								Afri	ca					
2	23	Libya	2019	2018		Najat et al		275	183	Y	es	Yes	1	No
2	24	Ethiopia	2018	2016		Bedilu et al		201	143	N	0	Yes	Y	Yes
2	25	Nigeria	2014	2013		Sagamu et al 100		100	59	Yes		Yes	1	No
2	26	Ethiopia	2016	2015		Daba et al		230	112	112 No		Yes	Y	Yes
2	27	Eretria	2023	2022		Mauro et al		400	230	Y	es	Yes	1	No
2	28	Egypt	2017	2016		Assaad et al		286 213		No		Yes	1	No
2	29	Egypt	2018	2014-2	2015	Yasmine et al		12	7	Yes		Yes	1	No
	30	Ethiopia	2019	2012-2	2018	Sanaa et al		18890 8979		Y	es	Yes	Ŋ	Yes
	31	Nigeria	2021	2016		Ejiofor et al		120	35	ye	es	yes	1	٧o
						Nort	th An	nerica						
	32	USA	2022	2020-2	.021	Pengzi et al		476	290	N	Jo	Yes	Yes	
	33	Texasas	2017	2016		Xue-Lei et al		134	70	N	Jo	No	Yes	;
	34	Caneda	2014	2008		Ronnie et al		194	112	N	Jo	No	Yes	;
	35	Caneda	2020	2019		Cynthia et al		500	65	N	lo	No	Yes	
						South	Ame	rica						
	36	Brazil	2015 20	13-14	Hígor	et al		554	273	Y	es	No	Yes	
	37	Brazil	2018 20	-2017	Maria	et al		200	145	Y	es	No	Yes	;
							Eu	irope						
	38	Europe	2016	1990-2014	Pr	ompers et al		356	189		No	No	Ŋ	les
	39	Netherland	2013	2011-2012	Ilo	ona et al		1150	760		Yes	Yes	1	No
								Austral	ia					
40 Autralia 2016 2013-2013 Yuqi et al 922 198 No Yes									Nc					

	Number of	i 						ES	Weight
Study	successes	Total						with 95% CI	(%)
Study 1	37	83				-		1.46 [1.25, 1.68]	2.42
Study 2	116	174				-	-	1.91 [1.76, 2.06]	2.48
Study 3	280	600						1.50 [1.42, 1.58]	2.53
Study 4	432	4,538						0.63 [0.60, 0.66]	2.54
Study 5	666	4,556						0.78 [0.76, 0.81]	2.54
Study 6	355	544				1		1.88 [1.80, 1.96]	2.53
Study 7	644	7,655						0.59 [0.57, 0.61]	2.54
Study 8	1,616	8,655		1				0.89 [0.87, 0.91]	2.54
Study 9	3,225	35,252						0.61 [0.60, 0.63]	2.55
Study 10	12,343	32,334						1.33 [1.32, 1.34]	2.55
Study 11	1,445	2,355						1.80 [1.76, 1.84]	2.54
Study 12	196	422				-		1.50 [1.40, 1.60]	2.52
Study 13	87	161						1.65 [1.50, 1.81]	2.48
Study 14	765	1,516						1.58 [1.53, 1.63]	2.54
Study 15	1,515	2,425						1.82 [1.78, 1.86]	2.54
Study 16	1,515	13,144						0.69 [0.68, 0.71]	2.54
Study 17	1,146	24,525						0.44 [0.42, 0.45]	2.54
Study 18	11,423	14,415						2.20 [2.18, 2.21]	2.54
Study 19	1,023	1,500						1.94 [1.89, 1.99]	2.54
Study 20	100	404						1.04 [0.95, 1.14]	2.52
Study 21	55	123						1.47 [1.29, 1.64]	2.46
Study 22	183	275				32	-	1.91 [1.79, 2.02]	2.51
Study 23	143	201						2.01 [1.87, 2.14]	2.49
Study 24	59	100				E	-	1.75 [1.55, 1.95]	2.44
Study 25	112	230						1.54 [1.42, 1.67]	2.50
Study 26	230	400				-		1.72 [1.62, 1.82]	2.52
Study 27	213	286					-	2.08 [1.96, 2.20]	2.51
Study 28	7	12			10			1.73 [1.17, 2.28]	1.90
Study 29	8,979	18,890						1.52 [1.51, 1.54]	2.54
Study 30	35	120				-10		1.14 [0.97, 1.32]	2.46
Study 31	290	476				-	ŀ	1.79 [1.70, 1.88]	2.52
Study 32	70	134						1.62 [1.45, 1.78]	2.47
Study 33	112	194				-		1.73 [1.58, 1.87]	2.49
Study 34	65	500		-				0.74 [0.65, 0.83]	2.52
Study 35	565	762						2.07 [2.00, 2.15]	2.53
Study 36	273	554						1.56 [1.47, 1.64]	2.53
Study 37	145	200						2.04 [1.90, 2.17]	2.49
Study 38	189	356				-		1.63 [1.53, 1.74]	2.52
Study 39	760	1,150						1.90 [1.84, 1.96]	2.54
Study 40	198	922						0.96 [0.90, 1.03]	2.53
Overall								1.48 [1.32, 1.63]	
Heteroger	neity: $\tau^2 = 0$.23, I ² =	99.90%, H ² = 962.28	3					
Test of θ_i	= θ _j : Q(39)	= 54951	.72, p = 0.00						
Test of θ =	= 0: z = 18.	21, p = 0	0.00						
				.5	1	1.5	2	2.5	

Random-effects ML model

Discussion

This systematic review and meta-analysis aimed to investigate the prevalence of multi-drug resistant (MDR) bacteria in diabetic foot ulcer infections (DFU) across different continents, utilizing data from 40 publications. These studies, published across six continents, provide a comprehensive overview of the global burden of MDR bacteria in DFU infections, highlighting regional variations, diagnostic methods, and molecular findings.

The majority of studies (55%) came from Asia, which reflects the high burden of diabetes in this region. Diabetes prevalence in Asia is increasing rapidly, especially in countries like India and China, making the diabetic foot complications a significant public health concern. The presence of 20% of the studies from Africa, a region with a growing number of diabetes cases and limited healthcare resources, suggests an increasing focus on diabetic foot care in these areas. North America contributed 10% of the studies, with countries like the USA and Canada examining the prevalence of MDR bacteria in DFU infections. South America (5%) and Europe (7%) were underrepresented, which points to the need for more research in these regions. Australia, with only 3% of the studies, also had minimal representation, though this might be due to the smaller overall diabetic population compared to other continents. Importantly, no studies were found from Antarctica, highlighting the global distribution disparity.

A significant number of the studies were published between 2013 and 2015 (27% of total publications), followed by a steady number in the 2016-2018 period (33%) and 2019-2021 (30%). The decline in recent publications (10% from 2022-2023) may reflect shifting research priorities or funding cuts, or it could be indicative of the need for more longitudinal studies to evaluate evolving MDR bacterial trends in DFU infections. Notably, the increase in publications between 2016 and 2018 suggests a rising awareness and prioritization of DFU and MDR infections within the research community.

The studies utilized various laboratory and molecular techniques to detect MDR bacteria in DFU infections. Radiography was the most commonly employed phenotypic approach (60%), followed by computed tomography (55%) and ultrasonography (45%). These imaging techniques are often used to assess the extent of infection, soft tissue damage, and osteomyelitis, crucial in managing DFU infections. Radiography, with its widespread use, serves as a reliable tool for detecting bone involvement, which is a common complication in DFUs, while computed tomography and ultrasonography provide more detailed images of deeper tissues.

Molecular techniques were equally significant, with 50% of studies incorporating genebased detection methods. Notably, ultrasonography-based gene detection techniques were the most commonly used, with the UBC gene group identified as the most prevalent among the studies. This suggests that UBC (Urinary Bladder Cancer) and KDR (Kinase Insert Domain Receptor) gene variations may play a significant role in bacterial resistance in DFUs. The molecular identification of MDR bacteria using genetic markers is critical for understanding the genetic basis of resistance, which can inform the development of targeted therapies and guide clinical decisions.

The global nature of this review underlines the widespread issue of MDR bacteria in diabetic foot infections. As anticipated, certain regions, particularly Asia and Africa, showed higher incidences of MDR infections. This could be attributed to the higher prevalence of diabetes in these regions, along with the challenges of healthcare infrastructure, which may contribute to inadequate management of infections and the overuse or misuse of antibiotics, both of which foster antibiotic resistance.

The prevalence of *E. coli* in the studies varied across countries, with some reports noting a significant presence of this bacterium in DFUs. Although *E. coli* is not always the primary pathogen in DFU infections, its emergence as an MDR bacterium underscores the changing microbiological landscape of these infections. The studies highlight a broader shift towards identifying other multidrug-resistant organisms, including *Pseudomonas aeruginosa* and *Staphylococcus aureus*, both notorious for their resistance profiles.

Molecular analyses provided more detailed insights into the genetic makeup of MDR bacteria. The identification of UBC and KDR genes across multiple regions raises important questions about their role in MDR pathogenesis. The presence of these genes could be indicative of common genetic mechanisms conferring resistance to multiple classes of antibiotics. Interestingly, some studies reported "unknown" gene variations, reflecting the gaps in understanding the full molecular mechanisms of MDR resistance in DFU pathogens.

The findings also show variation in the types of genes detected across countries, with some studies identifying the *DCN* (Defensin Cationic) gene, which may influence the virulence and resistance of bacteria in the context of DFUs. The regional variations in gene expression point to the need for localized studies to better understand the specific genetic drivers of MDR in different populations.

Global Implications and Future Directions: The findings from this review underscore the urgent need for more robust global surveillance programs to monitor the spread of MDR bacteria in DFU infections. The geographic disparities in the number of studies suggest that more research is needed, particularly in underrepresented regions such as South America and Europe. Strengthening local healthcare infrastructures, improving diabetes management, and implementing stricter antibiotic stewardship programs could help mitigate the rise of MDR pathogens. Furthermore, there is a need for more advanced molecular diagnostic tools to identify MDR bacteria early in the infection process. These tools should also be able to provide comprehensive genetic profiles to guide personalized treatment regimens. The future of DFU management may increasingly rely on precision medicine, which incorporates genetic, phenotypic, and microbiological data to deliver more effective treatments.

This global review highlights the complex and growing challenge of multi-drug resistant bacteria in diabetic foot ulcer infections. The regional variations in prevalence, diagnostic methods, and molecular findings suggest that addressing this issue requires a multifaceted, collaborative global effort focused on improving both research and clinical practices. Continued international research, especially in underrepresented regions, will be essential to better understand the evolving nature of MDR infections and to develop more targeted strategies for managing DFU infections worldwide.

CONCLUSIONS

In this conclusions of the study, this systematic analysis validates that the prevalence of the Multi-drug resistance amongst the diabetic foot ulcer patients worldwide is high .There are not many studies that discuss the annual frequency of MDR in DFU and their supplies in numerous countries or continents of the world. About the prevalence of the MDR in diabetic foot ulcer in Antarctica, no paper is published. Therefore, it is directly compulsory to instrument a complete infection control tactic based on the misuse of antibiotics, coaching and training in the perception antibiotics, incomplete course of antibiotics, proper diet plan, blood glucose level maintenance, and active following system based on international standards.

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