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Review article

Global status of intestinal parasitic infections among diabetic patients: a systematic review and meta-analysis

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ABSTRACT. Intestinal parasitic infections (IPIs) have been identified as a disease agent responsible for infections in immunocompromised patients such as diabetics. We searched six electronic databases and reviewed 38 related studies using the following keywords alone or in combination: "intestinal parasites", "diabetes", "immunocompromised", "prevalence", and "human". The pooled prevalence of IPIs in diabetic patients was 24.4% worldwide. These patients with IPIs are advised to go to health centers and perform the relevant checkups with the advent of the first symptoms of the disease, such as diarrhea and abdominal pain. Moreover, early diagnosis and treatment of IPIs in diabetic patients are highly recommended to maintain quality of life.

Keywords: intestinal parasitic infections, diabetes, prevalence

Introduction

Intestinal parasitic infections (IPIs) are a significant health issue worldwide, especially in Africa and developing countries [1]. Approximately one-fourth of the world's population, particularly disadvantaged communities, are susceptible to IPIs [2]. The prevalence of these infections differs according to community health, education level, and environmental and geographical issues. Intestinal parasites, such as hookworms, can cause varying degrees of diarrhea, weakness, abdominal pain, and even anemia [3].

According to the World Health Organization, approximately 3.5 billion people worldwide are at risk of these infections, of whom 450 million are symptomatic [4]. In addition, it is estimated that over 200,000 people die each year due to complications of intestinal parasites [5].

Diabetes is a chronic hyperglycemia disease classified as noncommunicable [6]. In type 1 diabetes, the affected person lacks insulin, while people with type 2 diabetes cannot use their insulin properly; the reason can be insufficient insulin production and cell resistance to the insulin. Most people with diabetes (about 90%) have type 2 diabetes, and another 10% suffer from type 1 diabetes, which affects young people [7, 8]. In 2019, about 463 million people worldwide were diagnosed with diabetes [9].

IPIs have been considered an important clinical factor responsible for infections in immuno-compromised (diabetes mellitus, malignancy, steroid use, and human immunodeficiency virus (HIV) infection) patients [10,11]. People with diabetes are at a higher risk of infection with opportunistic intestinal parasites and have problems with the adaptive immune response. As a result, they are affected by pathogens [12]. Opportunistic pathogens often cause chronic infections in diabetic

individuals [13]. Many studies have been published on the relationship between diabetes and intestinal parasites. However, so far, no comprehensive and systematic study has examined the findings of these studies, including the general prevalence of parasites in diabetic individuals according to various factors such as age, gender, place of residence, etc. Therefore, this study was conducted to investigate the prevalence of IPI among diabetic patients and its related factors in the world.

Methods

Design and protocol registration

This study used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The study protocol details are available on the International Prospective Register of Systematic Reviews website with the Central Registration Depository of CRD42022297715 [15].

Search strategy

First, two researchers (MT and MHN) independently searched the scientific databases, including ScienceDirect, PubMed, Scopus, ProQuest, Web of Science, and Google Scholar, to find the English paper exploring the prevalence of IPIs in diabetic patients published up to November 21, 2021. They used the following keywords alone or in combination: "intestinal parasites", "diabetes", "immunocompromised", "prevalence" and "human".

Inclusion and exclusion criteria

Two researchers evaluated the abstracts and full texts separately using a pre-designed form. If there were disagreements, a third author would resolve them through negotiation and decide about the studies' inclusion or exclusion. After deleting the duplicates, we evaluated the articles based on 2 inclusion and 5 exclusion criteria. Inclusion criteria included (1) cross-sectional articles concerning the prevalence of the intestinal parasite in diabetes and (2) articles with results published only on humans. On the other hand, the exclusion criteria comprised (1) review articles, case reports, dissertations, and letters, (2) studies with uncertain information, (3) articles not accessible in English, (4) studies conducted on animals, and (5) the abstract of conference papers.

Data extraction

Microsoft Excel software was used to record the required information in statistical analysis. For each study, the extracted information included the name of the first author, the publication year, country, continent, location, sample size, frequency and species of intestinal parasites, and age and gender of the diabetic patients.

Quality assessment

We used the Newcastle-Ottawa Scale (low quality: ≤4.5, moderate quality: 4.6–6.75, and high quality: 6.76–9) to evaluate the quality of cross-sectional studies and included the articles with acceptable quality (≤4.5 for cross-sectional studies) in the meta-analysis [16].

Data synthesis and statistical analysis

The present study used StatsDirect software (version 2.8) and the random-effects model. First, we examined the heterogeneity among the studies using Cochran's Q and I^2 statistics test; $I^2 \geq 50\%$ was considered heterogeneous [17]. Then, we used a forest plot to estimate the prevalence of intestinal parasites in diabetic patients. Finally, we conducted subgroup analyses to determine the heterogeneity source. In a subgroup, analysis was estimated based on year, gender, country, continent, type of intestinal parasites, location, and sample size. Publication bias was estimated graphically and statistically using Egger and Begg's tests [18]. The significance level was considered P-value≤0.05.

Results

According to Figure 1 and Table 1, we found 1600 articles in six databases based on the initial search parameters. After deleting the duplicates, those unavailable due to non-English language, and the animal reports, 38 articles were eligible for entry. These articles were the basis of this study.

The mean score obtained for Newcastle-Ottawa Scale was 6.23, indicating the moderate quality of the studies. As Figure 2 illustrates, the random-effects model estimated the prevalence of IPI in diabetics at 24.4%. (95%CI, 18.1–31.3%) worldwide.

According to Figure 3, the results of the Egger test show a significant substantial publication bias for this study (Egger bias=7.09, P<0.001).

The analysis of the studies in this review estimated the combined prevalence of *Giardia lamblia*, *Entamoeba histolytica/dispar*, *Cryptosporidium* spp., *Blastocystis* spp., and *Entamoeba coli*

Table 1. Baseline characteristics of included studies

No.	First author	Year	Country	No. Sample	No. IPI	% Pos	Method	Parasite species (frequency)	Ref
1	Abaza S.	1995	Egypt	100	8	8	Microscopy	*Giardia lamblia* (6), *Entamoeba histolytica/dispar* (1), *Cryptosporidium* (1)	[19]
2	Lysy J.	1999	Israel	861	26	3.01	Microscopy	*G. lamblia* (10), *E. histolytica/dispar* (16)	[20]
3	Hunter P.	2002	United Kingdom	128	3	2.34	Microscopy	*Cryptosporidium* (3)	[21]
4	Akhlaghy L.	2005	Iran	250	39	15.6	Microscopy	*G. lamblia* (14), *Blastocystis* (2), *Cryptosporidium* (6), *Entamoeba coli* (9), *Ascaris* (2)	[22]
5	Baqai R.	2005	Pakistan	20	3	15	Microscopy	*Cryptosporidium* (3)	[23]
6	Mendonca S.	2006	Brazil	78	21	26.92	Microscopy/ ELISA	*Strongyloides stercoralis* (21)	[24]
7	Baiomy A.	2010	Egypt	30	2	6.66	Microscopy	*G. lamblia* (1), *Cryptosporidium* (1)	[25]
8	Hakim G.	2011	Turkey	200	30	15	ELISA	*G. lamblia* (30)	[26]
9	Akinbo F.	2013	Nigeria	150	28	18.66	Microscopy	*G. lamblia* (8), *E. histolytica/dispar* (5), *Blastocystis* (4), *Cryptosporidium* (4), hookworm (3), *Ascaris* (4)	[27]
10	Sabah A.	2015	Egypt	29	16	55.17	Microscopy	*G. lamblia* (1), *E. histolytica/dispar* (12), *Ascaris* (1) *Schistosoma mansoni* (1), *Enterobius vermicularis* (1)	[28]
11	Elnadi N.	2015	Egypt	100	25	25	Microscopy	*G. lamblia* (9), *E. histolytica/dispar* (3), *Cryptosporidium* (3), *E. coli* (5), *Hymenolepis nana* (3), *Microsporidia* (2)	[29]
12	Wiria A.	2015	Indonesia	646	424	65.63	Microscopy/PCR	Hookworm (242), *Ascaris* (93), *Trichuris trichiura* (85), *S. stercoralis* (4)	[30]
13	Bafghi A.	2015	Iran	250	61	24.4	Microscopy	*G. lamblia* (19), *Blastocystis* (16), *Cryptosporidium* (6), *E. coli* (12), *Ascaris* (2), *H. nana* (2), *Iodamoeba buetschlii* (2), *E. nana* (1), *Trichomonas hominis* (1)	[31]
14	Cabral A.	2015	Brazil	167	8	4.79	Microscopy	*S. stercoralis* (8)	[32]
15	Bora B.	2016	India	22	3	13.63	Microscopy	*E. histolytica/dispar* (2), *Trichuris* (1)	[33]
16	Boris Tangi F.	2016	Cameroon	150	15	10	Microscopy	*E. histolytica/dispar* (10), *Blastocystis* (2), *Cryptosporidium* (1), hookworm (1), *Ascaris* (1)	[34]

Table 1. Baseline characteristics of included studies

No.	First author	Year	Country	No. Sample	No. IPI	% Pos	Method	Parasite species (frequency)	Ref
17	Siddiqua T.	2017	Bangladesh	697	234	33.57	Microscopy/ ELISA	*G. lamblia* (127), *E. histolytica/dispar* (107)	[35]
18	McGuire E.	2018	United Kingdom	114	46	40.35	ELISA	*S. stercoralis* (46)	[36]
19	Alemu G.	2018	Southern Ethiopia	244	29	11.88	Microscopy	*G. lamblia* (6), *Cryptosporidium* (8), hookworm (4), *Ascaris* (8), *Trichuris* (1), *Taenia* (2)	[13]
20	Ali O.	2018	Iraq	347	62	17.8	Microscopy	*G. lamblia* (16), *E. histolytica/dispar* (12), *Blastocystis* (22), *Cryptosporidium* (8), *S. stercoralis*(1), *H. nana* (3)	[37]
21	Machado E.	2018	Brazil	156	102	65.3	Microscopy	*G. lamblia* (39), *E. histolytica/dispar* (23), hookworm (4), *Ascaris* (19), *S. mansoni* (1), *S. stercorali s* (4), *H. nana* (5), *Taenia* (6), *E. vermicularis* (1)	[38]
22	Htun N.	2018	Switzerland	329	33	10.0	Microscopy	hookworm (14), *S. stercoralis* (6), *Taenia* (13)	[39]
23	El Drawany Z.	2019	Egypt	185	50	27.0	Microscopy	*G. lamblia* (8), *E. histolytica/dispar* (5), *Blastocystis* (10), *Cryptosporidium* (16), *Ascaris* (2), *Trichuris* (2), *S. stercoralis*(3), *H. nana* (4)	[40]
24	Rady H.	2019	Egypt	190	86	45.2	Microscopy	*G. lamblia* (28), *E. histolytica/dispar* (13), *Blastocystis* (16), *Cryptosporidium* (17), *Ascaris* (6), *H. nana* (6)	[41]
25	Poorkhosravani Z.	2019	Iran	254	32	12.5	Microscopy	*G. lamblia* (3), *Blastocystis* (23), *E. coli* (5), *S. stercoralis* (1)	[42]
26	Ambachew S.	2020	Ethiopia	234	45	19.2	Microscopy	*G. lamblia* (2), *E. histolytica/dispar* (9), hookworm (9), *Ascaris* (15), *S. mansoni* (7), *E. vermicularis* (3)	[43]
27	Chandi D.	2020	India	110	15	13.6	Microscopy	*G. lamblia* (1), *E. histolytica/dispar* (7), *Cryptosporidium* (5), *Ascaris* (2)	[44]
28	Abdullahi I.	2020	Nigeria	160	16	10	Microscopy/ ELISA	*Cryptosporidium* (16)	[45]
29	Popruk N.	2020	Thailand	130	16	12.3	PCR	*Blastocystis* (16)	[46]

Table 1. Baseline characteristics of included studies

No.	First author	Year	Country	No. Sample	No. IPI	% Pos	Method	Parasite species (frequency)	Ref
30	Barca A.	2020	Mexico	37	28	75.6	PCR	*G. lamblia* (7), *E. histolytica/dispar* (1), *Blastocystis* (6), *Cryptosporidium* (13), *Cyclospora* (1)	[47]
31	Ibrahim SH.	2020	Egypt	100	87	87	Microscopy	*Blastocystis* (87)	[48]
32	Kamki Y.	2021	India	10	4	40	Microscopy	hookworm (1), *Ascaris* (2), *Trichuris* (1)	[49]
33	Waly W.	2021	Egypt	100	44	44	Microscopy	*G. lamblia* (6), *E. histolytica/dispar* (4), *Blastocystis* (14), *Cryptosporidium* (9), *H. nana* (6), Microsporidia (5)	[50]
34	Sisu A.	2021	Ghana	152	19	12.5	Microscopy	*G. lamblia* (9), *E. histolytica/dispar* (2), *Cryptosporidium* (3), *E. coli* (3), hookworm (1), *Ascaris* (1)	[51]
35	Sabaa T.	2021	Iraq	500	60	12	Microscopy	*G. lamblia* (35), *E. histolytica/dispar* (25)	[52]
36	De Melo G.	2021	Brazil	99	37	37.3	PCR	*Blastocystis* (37)	[53]
37	Almugadam B.	2021	China	150	31	20.6	Microscopy	*E. histolytica/dispar* (7), *Cryptosporidium* (13), *S. mansoni* (5), *H. nana* (6)	[54]
38	Al-Mousavi A.	2021	Iraq	372	137	36.8	Microscopy	*G. lamblia* (49), *E. histolytica/dispar* (47), *Blastocystis* (13), *Cryptosporidium* (9), *Ascaris* (19)	[12]

IPI: Intestinal Parasitic Infection, No: Number, Pos: Positive, Ref: References

to be 4.75% (95%CI, 2.19–8.22%), 3.93% (95%CI, 1.67–7.1%), 2.67% (95%CI, 1.37–4.38%), 2.1% (0.09–3.8), and 0.04% (95%CI, 0.02–0.08%), respectively. However, Table 2 reports the following information based on the type of helminth among diabetic patients: *Ascaris* 1.59% (95%CI, 0.05–3.28%), hookworm 1.17% (95%CI, 0.003–3.9%), *Trichuris* 0.05% (95%CI, 0.006–1.5%), *Strongyloides stercoralis* 0.04% (0.001–0.09%), *Hymenolepis nana* 0.04% (95%CI, 0.002–0.08%), and *Taenia* 0.02% (95%CI, 0.01–0.05%).

Analysis of 20 studies in terms of subgroups with gender data demonstrates no significant relationship between gender and IPI prevalence. In other words, it showed a 24% prevalence of IPIs in women (95%CI, 15–34%) and 25% in men (95%CI, 17–33%). In addition, the subgroup analysis on nine studies with age data reports that the IPI prevalence in diabetic patients older than 45 (31%, 95%CI, 19–45%) is higher than in those younger than 45 (26%, 95%CI, 12–42%).

On the other hand, analysis of the subgroups based on location (9 studies), year (38 studies), and continent (38 studies) data demonstrates no significant relationship between these variables and the IPI prevalence. Data analysis showed a prevalence of 29% IPI in cities (95%CI, 15–45%) and 38% in rural areas (95%CI, 23–55%). Moreover, the IPI prevalence was 10.2% (95%CI, 4.6–17.8%) before 2010, while it was 28% (95%CI, 21–35%) between 2011 and 2021. According to Table 2, data analysis based on continental divisions

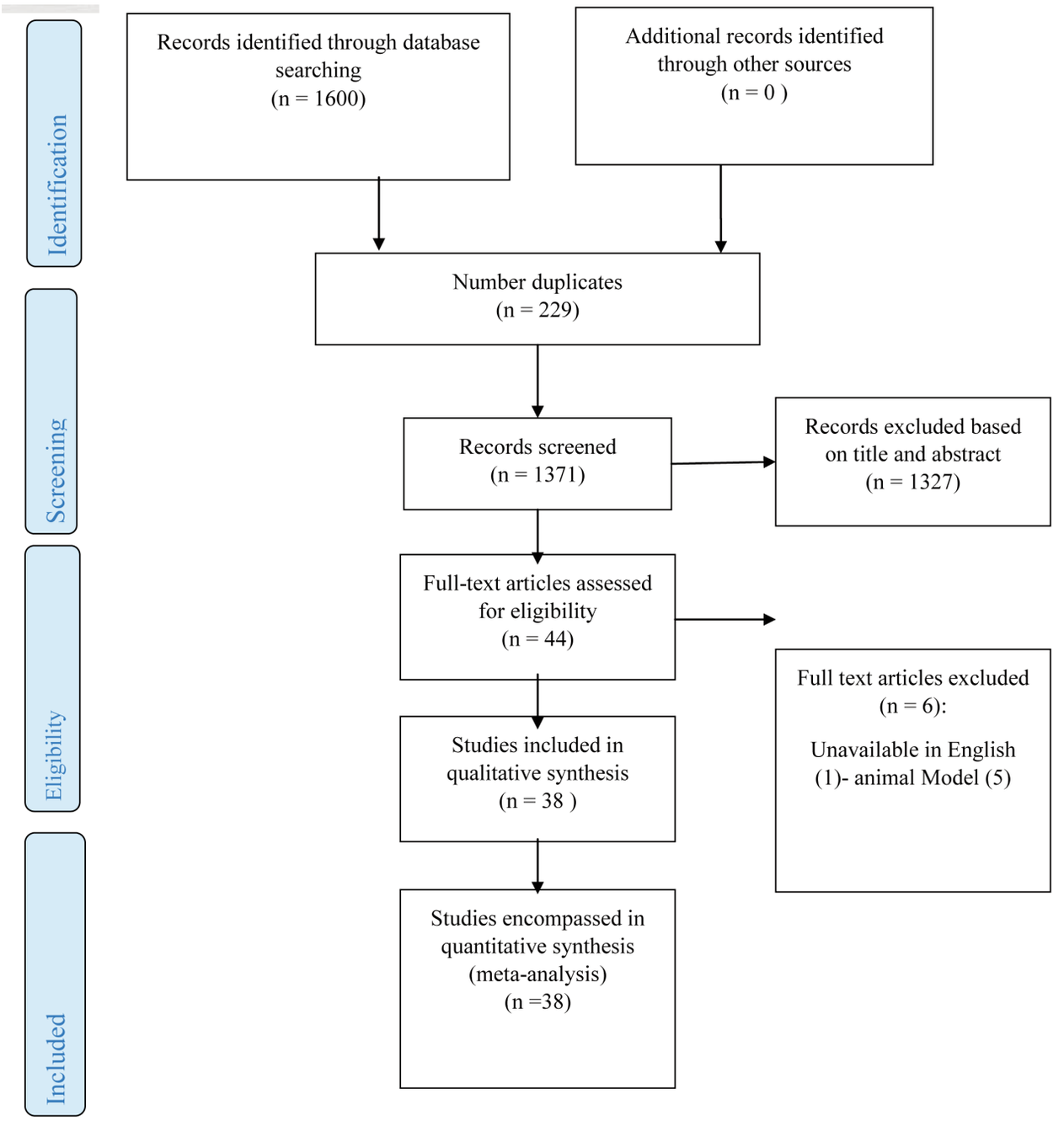

Figure 1. Flow diagram describing the study design process

(38 studies) reveals that IPI prevalence among diabetic patients is 30% (95%CI, 6–63%) in America, 26.7% (95%CI, 17.3–37.3%) in Africa, 22% (95%CI, 13–34%) in Asia, and 16.5% (95%CI, 2.1–40.6%) in Europe.

Discussion

IPIs are a major health issue, especially in some parts of the world. These infections, transmitted through oral-faecal contamination, water, and contaminated surfaces, indicate people's low quality of life, especially in these communities [55]. Moreover, these infections are one of the factors reducing the standard of living and leading to mortality in patients with immune system defects, such as diabetes, which need to be taken seriously]56[.

This is the first meta-analysis that evaluates IPIs in a population of diabetic patients worldwide. The overall prevalence is 24.4%, with the highest and lowest prevalence in America and Europe,

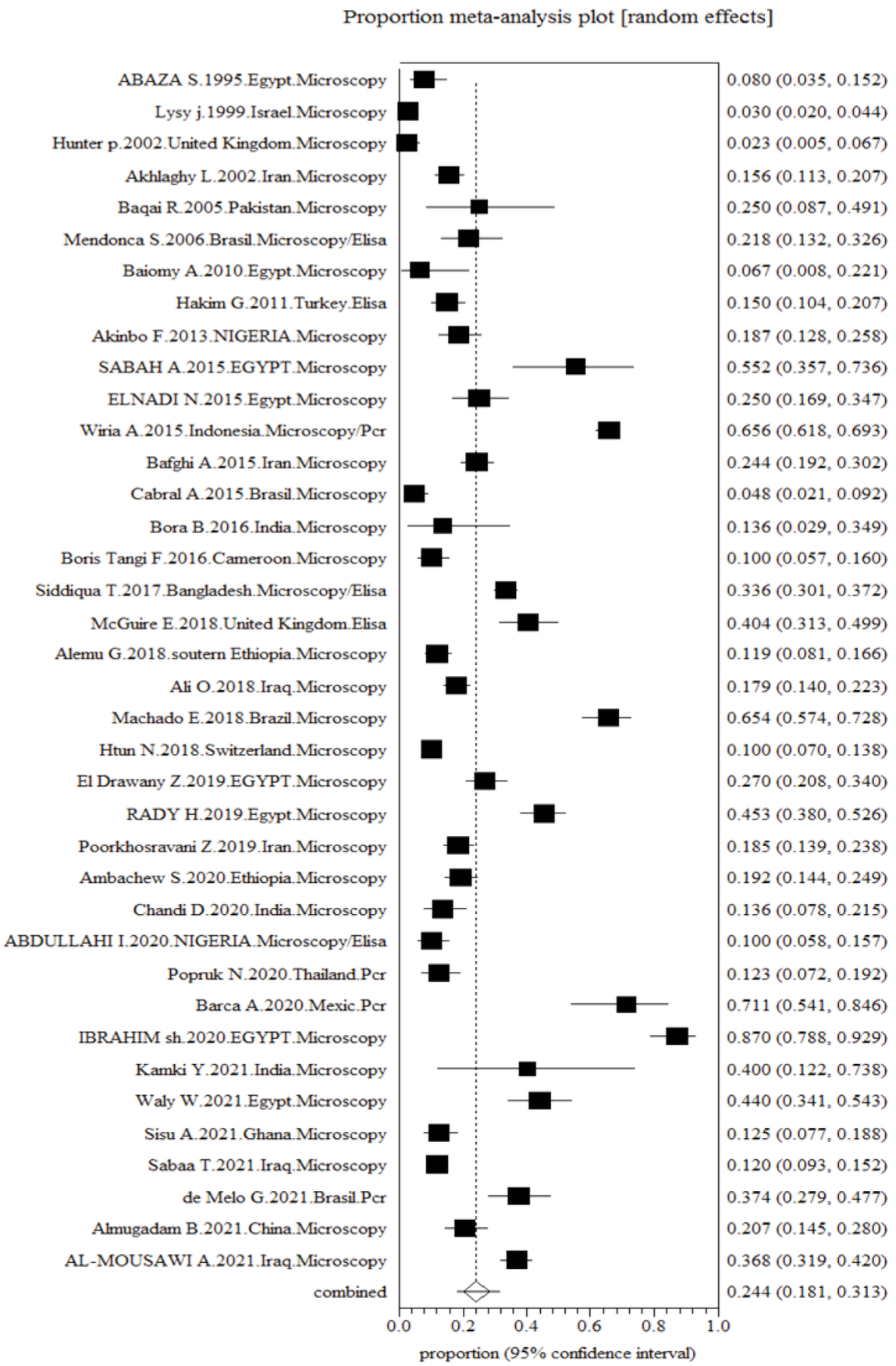

Figure 2. Forest plot of prevalence of IPIs in diabetic patient

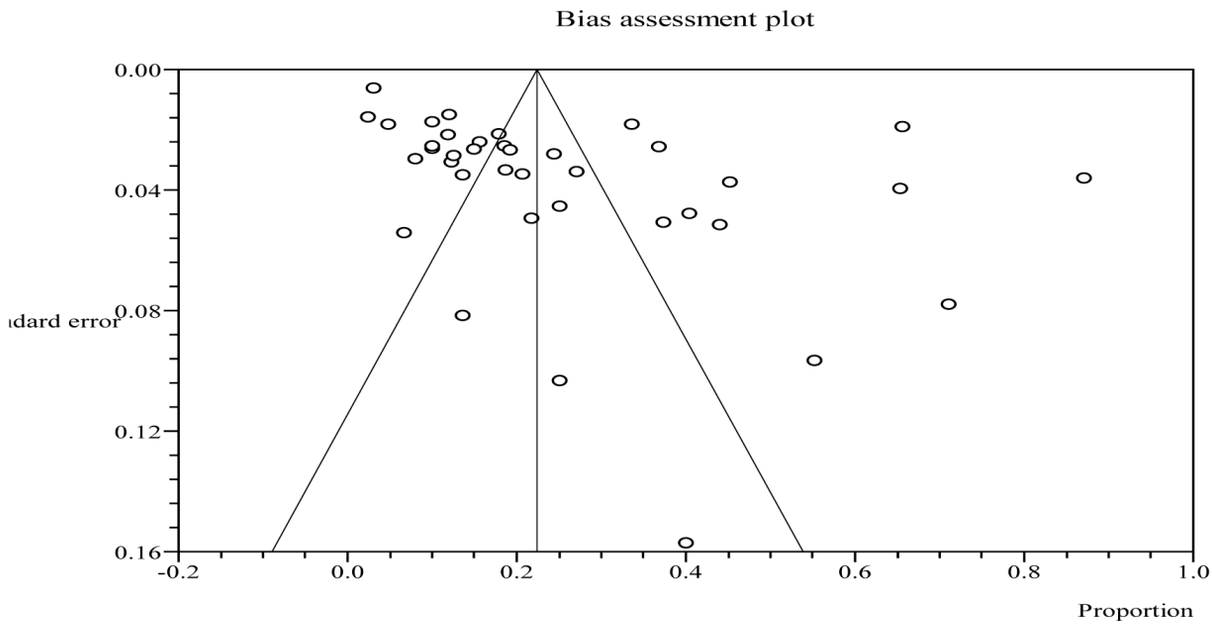

Figure 3. Bias assessment plot based on standard error

respectively. However, the prevalence varies in different countries, mainly due to different routes of contamination, such as food contamination and soil and faecal contamination of the water used for daily needs. In addition, overcrowding, malnutrition, unhealthy behaviors, weather conditions, and lack of garbage collection affect the reported prevalence [57].

The most reported protozoa in this study are *G. lamblia* (4.75%) and *E. histolytica*/*dispar* (3.93%). Studies show that diabetes in diabetics is related to changes in the gut microbiota that reduce the abundance of some butyrate-generating bacteria. Opportunistic protozoa such as *G. lamblia* and *E. histolytica/dispar* are more likely to become pathogenic due to hyperglycemia in these patients and consequent decreased immune system capacity [58].

In this review study, the most reported worms are *Ascaris* (1.59%) and hookworms (1.17%). Most of the patients with diabetes were from rural areas and may have been at risk for these parasites due to poor hygiene habits such as improper use of toilets, water pollution, agricultural work, household chores, and malnutrition]49[.

According to the study findings, IPIs have no statistically significant advantage over each other in diabetic males (25%) compared to diabetic females (24%), revealing that gender is not related to the prevalence of the parasite in diabetic patients [33].

In this study, the prevalence of IPIs in diabetics was 31% in patients <45 years and 26% in those > 45 years. The increased parasite in these patients may be due to the combined effect of aging and diabetes on the immune system, which causes a weak immune system]44[.

In the present study, the prevalence (10.2%) is much lower in the years before 2010 than in 2011 to 2021 (28%), which is mainly due to the use of highly accurate and updated tools such as enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) compared to the past [59].

Furthermore, we found high heterogeneity in the relationship between the prevalence of intestinal parasites and diabetes. The findings show high heterogeneity, possibly due to variations in the genetic capacity of diabetes, such as eating habits, environmental pollution, social and economic status, and types of infections [60].

Analysis of the results indicates that the prevalence of IPIs is 24.4% in diabetic patients worldwide, which is different from other studies, investigating the prevalence of IPIs in high-risk individuals such as HIV+ patients (39.15%) and preschool children (18.5%). The difference between the results of this study and similar studies is probably due to differences in sample size, study population, location, season, identified worm and protozoa, access to healthcare systems, and study methods, which can have a distorting effect on the reported results [61,62].

Table 2. Prevalence of IPIs in diabetic patients by variables

Variable		Number of studies	Heterogeneity			Prevalence (95%CI)	Publication bias	
			Cochran's Q	I^2	*P*-value		Egger	*P*-value
Gender	Male	20	310.38	93.9%	*P*<0.001	25(17–33)	-1.36	0.67
	Female		577.19	96.7%	*P*<0.001	24(15–34)	1.72	0.71
Residence	Urban	9	171.02	95.3%	*P*<0.001	29(15–45)	7.34	0.045
	Rural		133.96	94%	*P*<0.001	38(23–55)	3.74	0.43
Age	>45	9	126.55	93.7%	*P*<0.001	31(19–45)	7.67	0.018
	<45		183.97	95.7%	*P*<0.001	26(12–42)	6.86	0.39
Year	≤2010	38	73.54	91.8%	*P*<0.001	10.2(4.6–17.8)	2.76	0.054
	2011-2021		1224.09	97.5%	*P*<0.001	28(21–35)	5.12	0.11
Continent	Asia	38	1023.98	98.6%	*P*<0.001	22(13–34)	7.22	0.062
	Africa		448.62	98.6%	*P*<0.001	26.7(17.3–37.3)	9.02	0.28
	America		170.6	98.2	*P*<0.001	30(6–63)	12.48	0.255
	Europe		66.86	97%	*P*<0.001	16.5(2.1–40.6)	14.1	0.76
Types of intestinal parasites	*Giardia lamblia*	38	926.86	97%	*P*<0.001	4.75(2.19–8.22)	3.54	*P*<0.001
	Hookworm		1513.93	98.2%	*P*<0.001	1.17(0.003–3.9)	2.26	*P*=0.095
	E. histolytica /dispar		902.23	96.9%	*P*<0.001	3.93(1.67–7.1)	3.25	*P*<0.001
	S. mansoni		45.76	38.8%	*P*<0.001	0.02(0.009–0.04)	0.36	*P*=0.028
	Ascaris		563.58	95%	*P*<0.001	1.59(0.05–3.28)	1.89	*P*=0.005
	Blastocystis		482.97	94.2%	*P*<0.001	2.1(0.09–3.8)	2.11	*P*<0.001
	Cryptosporidium		388.82	92.8%	*P*<0.001	2.67(1.37–4.38)	2.22	*P*<0.001
	Entamoeba coli		87.64	68%	*P*<0.001	0.04(0.02–0.08)	0.63	*P*=0.009
	Trichuris		444.09	93.7%	*P*<0.001	0.05(0.006–1.5)	1.03	*P*=0.07
	Strongyloides stercoralis		118.84	76.4%	*P*<0.001	0.04(0.00 1–0.09)	0.7	*P*=0.022
	H. nana		79.64	64.8%	*P*<0.001	0.04(0.002–0.08)	0.68	*P*=0.002
	Taenia		66.31	57.8%	*P*<0.001	0.02(0.01–0.05)	0.41	*P*=0.062

Infection with parasites, especially intestinal parasites, affect the metabolism, absorption, and intestinal ecosystem. There is a complex correlation between parasites and diabetes. The mechanisms of both show that they influence each other. Different studies showed that worm infections or antigens purified from it could reduce glucose and increase insulin sensitivity. Nevertheless, the mechanisms of this process are not entirely elucidated; it may be due to the anti-inflammatory effect of the worms because they can decrease pro-inflammatory cytokines and increase anti-inflammatory cytokines in circulation. Worms also lead to weight loss, improve metabolic outcomes by reducing energy sources, and cause changes in the intestine microbiome, which plays a vital role in blood glucose equilibrium [37,63].

Diabetics are more likely to be infected than healthy people [64–67]. One of the possible reasons is their defective immunity. Lack of factor 4 supplementation and decreased cytokine response after stimulation of humoral immunity in diabetic patients are among the disorders described in these patients. Regarding cellular immunity, most studies indicate reduced function (chemotaxis, phagocytosis, and killing) of polymorphonuclear cells and diabetic monocytes/macrophages]43[. Diabetic patients often do not discuss the issue of diarrhea with their physician and accept it as the typical nature of their disease. As a result, in case of diarrhea and clinical symptoms, the usual bowel follow-up and diagnostic and therapeutic measures should be performed for these patients.

The comprehensive search of six international databases and the review of various diagnostic methods are all significant strengths of the current work. Methods with high specificity (microscopic), methods with high sensitivity (serological), analysis of various variables and subgroups, worldwide distribution of studies, and evidence of diffusion bias were not observed. However, this study has limitations, and the results should be interpreted accordingly. First, the standard method of microscopic reporting is three stool samples, but only one sample was used in the current review articles. Second, different laboratory methods in the final report have led to the prevalence of accurate methods such as PCR compared to higher microscopic methods. Third, most articles did not use the Graham test method, which is the standard method for detecting *E. vermicularis*; this is probably the reason for the low prevalence of this worm. Forth, the standard diagnostic method for some intestinal protozoa is specific staining, which was used in only a few of these articles.

In conclusions, the present study showed that the IPI prevalence in diabetic patients is very important. These patients with intestinal problems are advised to go to health centers and perform the relevant checks with the appearance of the first symptoms of the disease, such as diarrhea and abdominal pain. Further studies can investigate the relationship between the type of parasites and the type of diabetes. Finally, early diagnosis and treatment of IPIs among diabetes patients are highly recommended to maintain quality of life.

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