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Genetic Factors in Renal Failure and Diabetes Mellitus in the Black Population: A Systematic Review and Meta-Analysis

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Review Article

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ABSTRACT

Several risk factors for renal failure and diabetes mellitus have been identified, including genetic factors. The objective of this study was to analyse the influence of genetic risk factors on the development of renal failure and diabetes mellitus in the black population. This is a systematic review and meta-analysis prepared in accordance with the recommendations of the PRISMA protocol. The search was conducted during April 2018, using the following MeSH terms: "African Continental Ancestry Group", "Genetics", "and Diabetes mellitus "and" Renal insufficiency". After eligibility criteria were applied, a total of 31 studies were included in the review. According to the meta-analysis, genetic factors have a high effect size for the development of renal failure and diabetes mellitus with $p<0.05$. The results support the existence of susceptibility in the black population to the development of renal failure and diabetes mellitus.

INTRODUCTION

Health profile analysis conducted with black populations has raised evidences of a higher susceptibility of this population to a specific group of diseases. Among these diseases are chronic diseases such as diabetes mellitus and renal disease, especially renal failure [1,2]. Several factors can lead to the development of renal failure and diabetes mellitus, and some factors are also related to the development of complications. Genetic factors may be related to the development of such diseases, especially when it comes to specific populations, such as the black population [3,4]. The analysis of the various factors that are part of this process is extremely important, but the determination of specific genetic factors in black populations is essential, as it provides better health guidance [1,2].

Although several genetic factors have been identified that increase susceptibility to chronic diseases, they have not yet been analysed in a combined way, in the recent studies, to determine concrete evidence on how these factors influence the development of renal failure and diabetes mellitus [5-7].

Thus, it is questioned whether genetic factors influence the development of renal failure and diabetes mellitus in the black population. This study was designed to analyse the influence of genetic risk factors in the development of renal failure and diabetes mellitus in the black population, thus contributing to a greater understanding of the subject. A systematic review and meta-analysis was conducted to enable the integration of various research findings on the theme, as well as to show which gaps remain in the knowledge about this relationship.

The study purpose is unprecedented considering that there is no systematic review and meta-analysis examining both aspects in one study, especially about genetics factors.

LITERATURE REVIEW

A systematic review and meta-analysis were performed to analyse the relationship between of genetic factors and the development of renal failure and diabetes mellitus. Two databases were comprehensively searched - MEDLINE and SCOPUS, through PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and the Capes Portal of Journals (http://www.periodicos.capes.gov.br/).

The systematic review and meta-analysis were conducted following the methodological recommendations of the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

The PRISMA protocol is composed of 27 items that are related to the construction of the manuscript with greater writing criteria and data analysis.

The searches were performed during April 2018 using the following MeSH terms:

1) "African continental ancestry group",
2) "Genetics",
3) "Diabetes mellitus",
4) "Renal insufficiency".

The descriptors were combined with the Boolean terms "AND" and "OR" as follows: "1 AND (3 OR 4) AND 2". The following search filters were set: in SCOPUS: "2016-2018", "Journal (Source type)", and "Article (document type)"; and, in PUBMED/MEDLINE: "Last Five Years (period)", "2016-2018", and "free full text".

The following eligibility criteria were imposed:

1) Clinical studies;
2) Manuscripts in any language;
3) Studies published from 2016 to 2018;
4) Studies with theoretical or practical interfaces on the subject;
5) Original articles available in full.

The following exclusion criteria were applied:

1) Narrative/traditional reviews of literature, systematic or integrative reviews;
2) Editorials, prefaces, brief communications and letters to the editor;
3) Reports;
4) Gray literature;
5) Full text not available online at the Capes Portal of Journals;
6) Studies that have not included black participants;
7) Studies that have not addressed the theme of interest.

Two reviewers independently assessed the studies for inclusion in the review. The reviewers were students of the master's degree course in Nursing. The PICO strategy was used to guide the research, in which P refers to the population (black people), I to the intervention/factor of interest (genetic factors), C to the comparison (general population), and O to the outcome (risk for renal failure and diabetes).

The following research question was formulated: Are genetic factors associated with increased susceptibility to renal failure and diabetes mellitus in the black population? **Figure 1** shows the flow diagram of information derived from the systematic review.

The statistical package “R-studio” was used for the quantitative analysis and the Downs and Black Checklist was used to rate study quality and bias 7. The Downs and Black Checklist has 27 items, and when an item was rated with a score below 20 points, the study was excluded from the review.

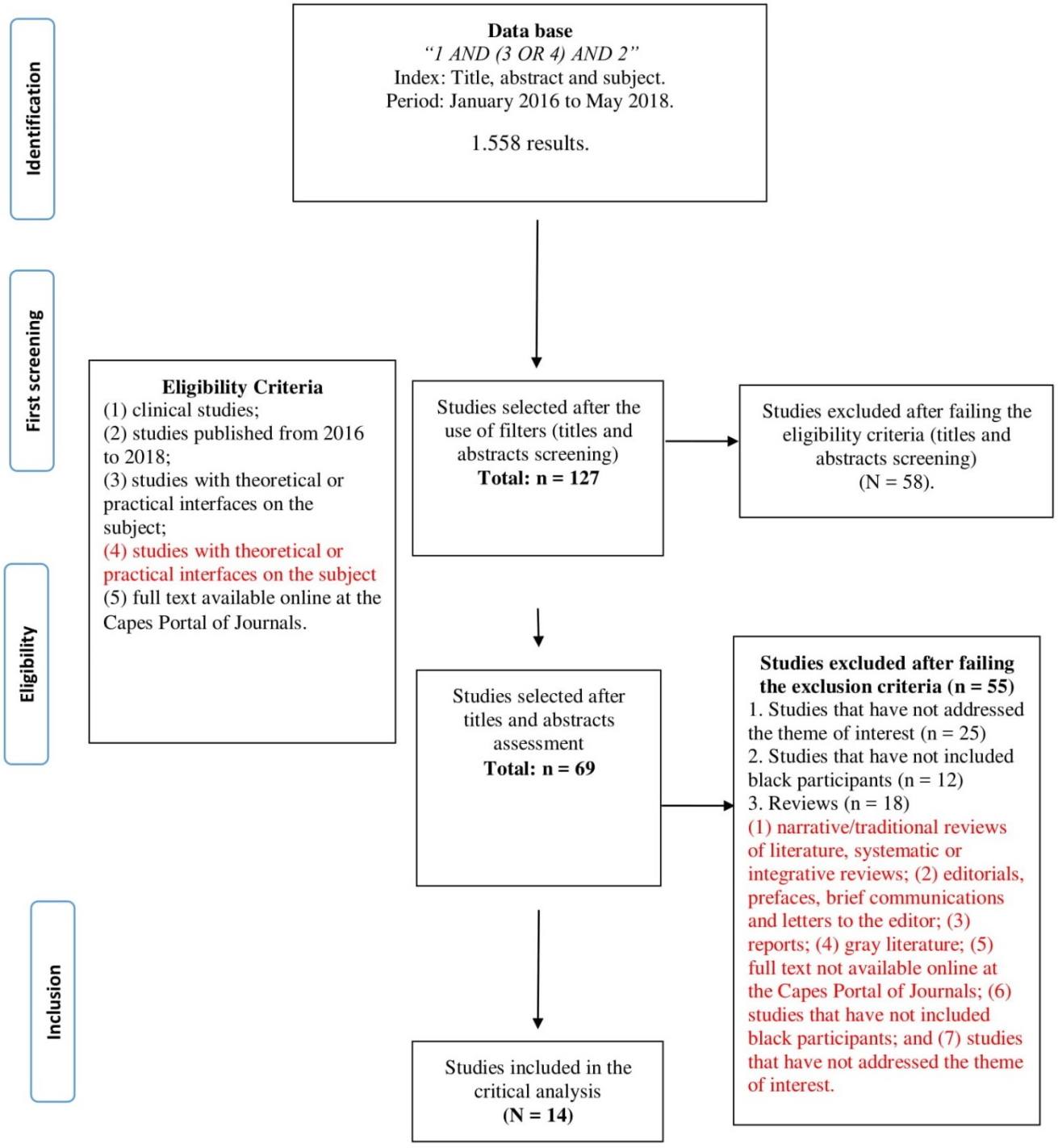

Figure 1. Flow diagram of the literature search and study selection in PubMed and Scopus.

RESULTS

Through the initial search, screening was conducted to filter the results. After reading the articles in full, eligibility criteria were assessed. Fourteen studies remained in the final assessment and had their main information synthetized in Table 1 and Table 2 that contains data about author, year, source, sample size and main findings of the studies. All information was taken from the selected studies.

Table 1. Description of articles about diabetes mellitus included in the systematic review.

Author/Reference	Journal	Sample size	Main findings	Downs and Black (bias)
Divers et al. [1]	BMC Genet.	691	The genetic association between single nucleotide polymorphisms (SNPs) on chromosomes 2, 6, 7, 9, 16 and 18 and CAC was detected in black people with type 2 diabetes.	25
Aamboe Klemsdal [2]	Tidsskr Nor Laegefore.	2000	The findings are clinically relevant. Better perception in this field allows optimal treatment adaptation for each patient.	26
Lau et al. [3]	Am J Hum Genet.	111	Sequencing of three cosmopolitan sites provided potential functional variants that coexist accurately with cell-specific chromatin domains and pancreatic islet enhancer.	27
Matsha et al. [4]	J Diabetes Res.	564	The association of global DNA methylation with screen-detected diabetes but not treated diabetes suggests that glucose control agents to some extent may be reversing DNA methylation.	26
Chikowore et al. [5]	Diabetes Res Clin Pract.	256	The genetic risk score of variants derived from Europe and Asia has limited clinical utility in the black South African population. The inclusion of specific variants of the population in the genetic risk scores is fundamental.	25
Yoshiuchi [6]	Acta Diabetol.	50	A high population differentiation between European and African populations at two MC3R childhood obesity and insulin resistance-associated single-nucleotide polymorphisms (rs3746619 and rs3827103) was observed.	24
Haddad et al. [8]	PLoS One.	5228	The PSMD2 gene was significantly associated with type 2 diabetes based on the nine most significant single variants in the +/- 20 kb region surrounding the gene, which includes nearby genes EIF4G1, ECE2 and EIF2B5.	27
Keaton et al. [9]	Pac Symp Biocomput.	6892	In single variant analyses, suggestively significant (Pinteraction < $5\text{Ч}10^{-6}$) interactions were observed at several loci including DGKB (rs978989), CDK18 (rs12126276), CXCL12 (rs7921850), HCN1 (rs6895191), FAM98A (rs1900780), and MGMT (rs568530).	24

Table 2. Description of articles about renal failure included in the systematic review.

Author/Reference	Journal	Sample size	Main findings	Downs and Black (bias)
Hayek et al. [10]	Nat Med.	100	Apolipoprotein L1 (*APOL1*) gene variants G1 or G2 augment $\alpha v \beta 3$ integrin activation and causes proteinuria in mice in a soluble urokinase plasminogen activator receptor (suPAR)-dependent manner. The synergy of circulating factor suPAR and *APOL1* G1 or G2 on $\alpha v \beta 3$ integrin activation is a mechanism for chronic kidney disease.	24
Guan et al. [11]	Hum Genet.	1037	Gene-based associations revealed suggestive significant aggregate effects of coding variants at four genes. The findings suggest that genetic variation in kidney structure-related genes may contribute to type 2 diabetes attributed end-stage kidney disease in the African American population.	25
Gutierrez et al. [12]	Clin J Am Soc Nephrol.	3013	A higher percentage of African ancestry was independently associated with lower 24-hour urinary phosphorus excretion and lower fractional excretion of phosphorus among African Americans with chronic kidney disease.	25
Parsa et al. [13]	J Am Soc Nephrol.	1331	In summary, SNPs in LINC00923, an RNA gene expressed in the kidney, significantly associated with chronic kidney	26

			disease progression in individuals with non-diabetic chronic kidney disease.	
Kramer et al. [14]	J Am Soc Nephrol.	12226	The urine albumin-to-creatinine ratio genome-wide association scan identified associations with the HBB variant among all participants.	27
Peralta et al. [15]	J Am Soc Nephrol.	176	Blacks with two *APOL1* risk alleles had the highest risk for albuminuria and eGFRcys decline in young adulthood, whereas disparities between low-risk blacks and whites were related to differences in traditional risk factors.	24

Each row is represented by a horizontal line and a square. In each line, there is a representation of the lower and upper limit of each individual study. The diamond and the vertical line represent the net effect considering all studies. Both the fixed and the randomized effect were calculated. The fixed effect is used when the studies are homogeneous, and the randomized effect when they are heterogeneous. The results of the randomized effect resulted in 0.62 with a significance of 0.01 which represents an average effect of the genetic factor as a risk marker for the development of diabetes in the black population. A similar analysis was performed for renal failure **(Figures 2 and 3).**

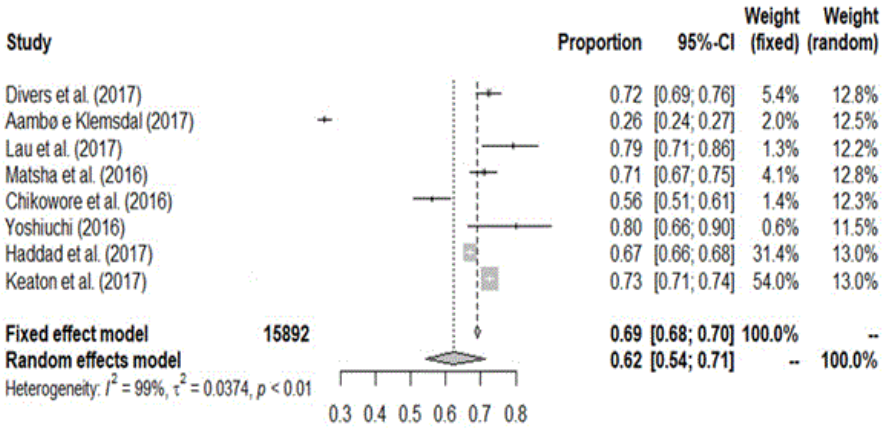

Figure 2. Meta-analysis of genetic risk factors for diabetes in the black population.

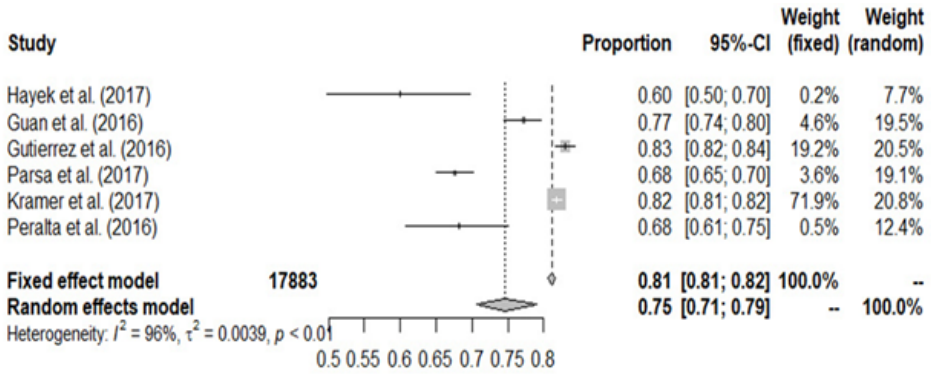

Figure 3. Meta-analysis of genetic risk factors for renal failure in the black population.

The net effect resulted in 0.75 with a p-value of 0.0039. This represents an average effect of genetic influence on the development of renal failure in the black population.

DISCUSSION

The results show that there is an association between genetic factors and increased susceptibility to diabetes mellitus and renal failure in the black population worldwide. Single nucleotide polymorphisms (SNPs) were most strongly associated with the development of diabetes mellitus in the black population [1]. The association between rs1799983 polymorphism and DNA methylation suggests epigenetic mechanisms by which vascular complications of diabetes develop despite adequate metabolic control [4].

SNPs are identified as the first factors to the onset of risk factors for developing type 2 diabetes in blacks [1]. Associated with this, the location of certain points of change in chromatin, especially when it relates to changes in pancreatic islets, was also significantly associated as an important risk factor for type 2 diabetes [3].

In a genomic association study and meta-analysis, it was verified by Langefeld et al. [16] that *APOL1*-environment interactions may be of greater clinical importance in triggering nephropathy in African Americans. In meta-analysis by Matsushita et al. [17], it was found that some markers are present in the development of kidney disease as well as metabolic diseases. In a study by Guan et al. [18], it was found that there is presence of association in five loci, TTC21B, COL4A3, NPHP3-ACAD11, CLDN8 and ARHGAP24. Similar results were found by Ng et al. [19], where in the TCF7L2, KLF14 and HMGA2 loci.

The DNA methylation, which already includes an epigenetic approach, also influences the development of diabetes. Diabetes control agents can influence this methylation process and thereby increase the chances of developing the disease [4,5]. Other specific factors such as MC3R, EIF4G1, ECE2, EIF2B5, DGKB, CDK18, CXCL12 and FAM98A were also identified as significant factors in this overall process [6,8,9].

The main limitations are related to the small number of publications on the subject in the black population, which encourages further analysis of the theme, especially in a clinical manner. In relation to the development of chronic renal disease, there is indication that this factor may be associated with genetic changes that affect the cell cycle, as the G1 and G2 phases, and thus the promoting function of these cells [10]. Risk factors such as age and association with other chronic diseases are also part of the genetics theoretical framework associated with chronic diseases [15-19].

CONCLUSION

In conclusion, it was found that there are important genetic risk factors associated with the development of diseases such as diabetes mellitus and chronic renal disease in black people. This association needs to be further analysed, especially in the black population, since the lack of studies analysing this subject is quite considerable. There is significant evidence of increased susceptibility of black people to diabetes mellitus. These points to the need for strategies of risk screening and guidance on health for this population, since it has been shown that it is genetically susceptible to chronic diseases. Added to other facts, black race increases the genetic risk score for the development of the disease.

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