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Jadawji, C., Crasto, W., Gillies, C. et al. (4 more authors) (2019) Prevalence and progression of diabetic nephropathy in South Asian, white European and African Caribbean people with type 2 diabetes: A systematic review and meta-analysis. Diabetes, Obesity and Metabolism, 21 (3). pp. 658-673. ISSN 1462-8902

https://doi.org/10.1111/dom.13569

Prevalence and progression of diabetic nephropathy in South Asians, White Europeans and Afro-Caribbeans with Type 2 diabetes; a systematic review and meta-analysis

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Abstract

Introduction: Diabetic nephropathy remains the most common cause of renal disease in patients diagnosed with type 2 diabetes.

Aims: We conducted a systematic review and meta-analysis of published observational evidence to assess the difference in the prevalence and progression of diabetic nephropathy, and the development of end-stage renal failure in three ethnicities with type 2 diabetes.

Methods: Relevant studies were identified in a literature search of MEDLINE, EMBASE, and reference lists of relevant studies to May 2018. We decided *a priori* that there were no differences in the prevalence and progression of diabetic nephropathy, and the development of end-stage renal failure in the three ethnicities with type 2 diabetes. Pooled relative risks of microalbuminuria by ethnicity were estimated by fitting three random effects meta-analyses models. A narrative synthesis of the nephropathy progression in the studies was done. The review was registered on PROSPERO (registration number CRD42018107350).

Results:

Thirty-two studies with data on 153,827 unique participants were eligible. The pooled prevalence ratio of microalbuminuria in South Asian compared to White Europeans was 1.14 (95% CI: 0.99, 1.32 p=0.065). For African Caribbeans vs South Asians the pooled prevalence ration was 1.08 (95% CI: 0.93, 1.24), p=0.327. Results surrounding renal decline were inconsistent with preponderance towards a high rate of disease progression in South Asians compared to White Caucasians. The estimated pooled incident rate ratio for end stage renal disease was significantly higher in African Caribbeans vs White Europeans 2.75 (95% CI: 2.01, 3.48 p<0.001)

Conclusion: This review did not find a significant link between ethnicity (South Asians, White Europeans and Afro-Caribbeans) and the prevalence of microalbuminuria. However, the incident rate ratio of end stage renal disease in African Caribbeans compared to White Europeans was significantly higher. Further research is needed to explore the potential non-albuminuric pathways of progression to end stage renal failure.

Introduction

Diabetes is a substantial public health problem and the most common cause of end stage renal disease globally. The relative contribution of type 2 diabetes (T2DM) to the increasing burden of end stage kidney disease has been well established (1) (2). With the rising epidemic of T2DM, obesity and an ageing population, it is anticipated that the burden of renal disease on health systems will increase further.

A migrant is defined as someone who has either changed their usual country of residence or settled in another country such as the US, Europe or Australia or is a descendant of the former (3). Globally migration is increasing, with the number of international migrants reaching 258 million in 2017 (4). 79.6 million originated from Asia. Many of these migrants were of South Asian origin with 17 million originating from India alone. 24.7 million of the migrants were of African origin, making Africa the fourth largest contributor in 2017 (4).

The 2011 UK Census demonstrated an increase in the ethnic minority population. South Asian and Afro-Caribbean migrants comprise about 8% and 3% of the total population in the UK, respectively. Together these ethnicities make up more than half of the UK's non-European population (5).

It is well established that South Asian and Afro-Caribbean adults develop T2DM at a much younger age compared to their White counterparts and exhibit a marked predisposition to cardiovascular disease and end-stage renal failure (6) (7). In the UK, a higher incidence of central obesity and vascular disease has been reported in migrant South Asians when compared to White Europeans despite lower levels of cardiovascular risk factors (7) (8). It is likely that higher levels of insulin resistance drive the higher rates of vascular disease and diabetes in this population (9).

A number of studies indicate that the risk for the development and progression of diabetic nephropathy varies among different populations (8) (10) (11). The incidence of end stage kidney disease due to both T1DM and T2DM is higher among South Asians compared to White Europeans (12), (13). However, the literature on diabetic nephropathy in ethnic groups is sparse and varied and it is not clear whether progression or higher levels of urine albumin excretion influence similar rates of e-GFR decline among different ethnic populations despite similar competing risks and therefore may impact rates of prevalence of end stage renal failure.

The objective of this systematic review and meta-analysis was to examine and analyze published evidence on the prevalence of albuminuria, rates of disease progression and end stage renal disease outcomes in White European compared to South Asian and Afro-

Caribbean adults with nephropathy due to T2DM. We decided *a priori* that there were no differences in the prevalence and progression of diabetic nephropathy, and the development of end-stage renal failure in various ethnicities with type 2 diabetes.

Methods

Search strategy

Medline (1950 to week 1 May 2018), Embase (1980 to week 1 May 2018), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Renal Group trial register were searched using a broad search strategy to identify all potentially relevant publications for this review. Population search terms, including Medical Subject Heading (MeSH) 'Asian Continental registry group', 'Asians', Indians', 'Pakistanis', 'Bangladeshis', 'Afro-Caribbeans' and 'ethnic minority population' were combined with MeSH terms that covered T2DM, diabetes mellitus, nephropathy, renal disease, end-stage renal disease (ESRD) and albuminuria. Free text terms were also used to optimise search sensitivity. Reference lists were checked to identify any further articles. Studies were not limited to the English language, however none of the relevant studies required translation to the English language.

Study selection

Only studies comparing the ethnicities; White Europeans, South Asians and Afro-Caribbeans, in whichever combination, in adult T2DM patients with diabetic nephropathy were included. Where studies compared ethnicities other than the ones included in our selection criteria, data for South Asians, White Europeans and African Caribbeans was extracted separately. We excluded "American Asians" or "Asians" unless clearly defined, since they may comprise of Arab/ Chinese/ Hmong/ Lebanese/ Turkish/ Bangladeshi/ Filipino/ Indian/ Korean/ Pakistani/ Taiwanese populations and therefore could not be categorized as South Asians or people originating from the Indian subcontinent. We used the term "African Caribbeans" to mean people of African descent wherever they are living in world.

Additionally, those studies that did not differentiate between T1DM and T2DM were only included if the estimated T2DM sample was ≥ 80% of the total sample. Since the review was aimed at identifying three key aspects of diabetic nephropathy, we grouped selected studies under "prevalence", "progression" and "outcomes studies".

Prevalence is defined as the number of cases existing at a given time in a given population usually expressed as a percentage (14). Since the definition of “Diabetic nephropathy” encompasses those with “incipient nephropathy”, defined as the presence of microalbuminuria and those with “overt nephropathy”, defined as those with macroalbuminuria or overt proteinuria (15), we included all studies that measured either one or both of these outcomes in terms of prevalence of disease. Microalbuminuria and proteinuria were measured using different definitions across the majority of studies. In this review, microalbuminuria was defined as an albumin creatinine ratio (ACR) of >2 mg/mmol and proteinuria as >30 mg/mmol. Prevalence studies carried out in a representative population and examining at least 50 participants or more were included in the review.

Progression studies included all studies that examined the progression/remission of albuminuria or estimated glomerular filtration rate (eGFR) decline. Studies where progression was based on CKD stages (1-5) as defined by the National Kidney Foundation Disease Outcome Quality Initiative working group guidelines on the classification of chronic kidney disease were included. Studies reporting the doubling of serum creatinine, or changes in creatinine clearance over time were also included in this review.

Outcome studies included any studies related to the development of End-Stage Renal Disease (ESRD), when the kidneys permanently fail to work as a result of diabetic nephropathy in patients with T2DM. The review was registered on PROSPERO CRD42018107350.

Methods of the review

The titles and abstracts of all articles identified by the broad literature search were assessed independently by two reviewers (CJ and SS). Studies that did not meet inclusion criteria were discarded. Full texts of selected articles were retrieved and assessed to determine if they met the inclusion criteria. A consensus was reached in case of any inconsistency with involvement of a third (KK). Those studies which met the inclusion criteria were included in the review and data was extracted independently using a standard data extraction form.

Quality scoring of selected studies

We created a quality scoring system ranging from 0 to 6 points based on parameters identified by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (16). We used four pre-defined domains namely: selection criteria, measurement of exposure, objective diagnostic procedure and controlling for confounders to assess the

quality of the studies. Six points on the MOOSE reflects the highest study quality. (APPENDIX 1)

Statistical analysis

Pooled relative risks of microalbuminuria by ethnicity were estimated by fitting three random effects meta-analyses models. Heterogeneity between studies was assessed using the I-squared statistics (17). For incidence of ESRD by ethnicity, data from studies was combined in a random effects meta-analysis model. Incidence was reported using incidence rate ratios (IRRs). In some studies the standard error of the IRR was calculated using published formula (18) (19) (20). Studies reporting hazard ratios, which can be assumed to estimations of the IRR, were also included in this review. As the impact of both age and duration of diabetes on the incidence of microalbuminuria may differ by ethnicity, we conducted meta-regression analyses to adjust for both these factors. This was done by extracting data on mean age and duration by ethnicity and calculating the difference in means between ethnic groups for each study. By fitting this difference in means in a meta-regression model, the reported intercept will be the estimated rate ratio for ethnicity when the difference in mean age or duration is zero.

For all meta-analyses models fitted, funnel plots and Egger's tests were carried out to assess for publication bias. Since there was substantial heterogeneity due to large differences in clinical or methodological nature between the studies in terms of the reporting of the progression of diabetes nephropathy, we decided *a priori* not to pool the data on nephropathy progression from the studies in a meta-analysis. Instead, we did a narrative synthesis of the nephropathy progression in the studies. STATA release 15 (Stata Corp, College Station, Texas, USA) was used for all statistical analyses.

Results

The search yielded a total of 2329 articles. 54 articles were retrieved for more detailed evaluation of the full text (Figure 1.1). APPENDIX 1 shows a flow diagram of the search strategy. Applying our inclusion criteria, 22 studies were excluded. 32 studies were identified as being suitable for this review, with the studies collectively reviewing 153,827 patients. The studies identified 84,718 White European participants, 24, 298 South Asian and 19,961 African Caribbean participants.

Among the 32 studies, 18 were conducted in the UK, 3 in Netherlands, 3 in Australia, 7 in the USA and 1 study in Brazil.

Study Quality

Quality scores for 32 studies included in this review are shown in Table 1.2. Overall, the quality of studies was high (median 5, IQR 4-6), with thirteen studies achieving the highest score.

Prevalence of diabetes nephropathy

Data were extracted from 20 studies on prevalence of microalbuminuria in patients with T2DM by ethnic group (Table 1.1). The study by McGill et al. (21) was excluded from the meta-analysis as data was presented as odds of having microalbuminuria rather than the number/percentage of participants affected. The pooled prevalence rate ratio of microalbuminuria in South Asian compared to white European patients with type 2 diabetes was 1.14 (95% CI: 0.99, 1.32 p=0.07) (Fig 2.1). Similarly, for African Caribbeans vs White Europeans the pooled prevalence rate ratio was 1.06 (95% CI: 0.93, 1.20), p=0.35, and for African Caribbeans vs South Asians the pooled prevalence rate ratio was 1.08 (95% CI: 0.93, 1.24), p=0.33 (Fig 2.2). The I-squared value from the three random effects meta-analysis, indicated the amount of variation in the effect sizes attributable to study heterogeneity was moderate to high at 98.70%, 53.00% and 50.10% respectively. After adjusting for differences in mean age and duration of diabetes between ethnic groups in a meta-regression analyses, there was still no statistically significant differences in in the prevalence of microalbuminuria (Table 3 in supplementary material). The estimated prevalence rate ratios in South Asian vs White European was 1.15 (0.99, 1.32) p=0.570, African Caribbeans vs White European was 0.97 (95% CI: 0.63, 1.46) p=0.826, and South Asian vs African Caribbean was 0.95 (0.85, 1.06), p=0.524.

Progression of diabetes nephropathy

Five studies reported the progression of diabetic nephropathy (Table 2). Three studies measured progression of disease in South Asians, White Europeans and Afro Caribbeans (22) (23) (24) whereas two only compared progression in South Asians and White Europeans (25) (26). Three out of the five studies recorded annual eGFR decline (22) (23). The remaining two studies assessed progression of renal disease by recording serial serum creatinine measurements (26), assessing time taken for serum creatinine to double (24) and lastly measuring creatinine clearance over a set period of time (25). In summary, in three of

the studies, differences were noted in the progression of renal deterioration among the three ethnic groups, thus confirming the alternative hypothesis. Two studies showed no differences in the progression of renal deterioration. Assessing the annual decline in eGFR, one study found a non-significant decline in Afro-Caribbean's of -2.12 ml/min/1.73m^2 compared to White European's (-1.93 ml/min/1.73m^2) and South Asians (-1.85 ml/min/1.73m^2) (22). The second study reported a significant difference in all three groups with White Europeans demonstrating an annual decline of -0.64 (95% CI -0.68, -0.60), South Asians of -0.77 (-0.81, -0.74) and Afro-Caribbeans of -0.55 (95% CI -0.61, -0.48) (23). Similarly, Chandie-Shaw et al (25) assessed eGFR decline but over a 5-year period. They found a decline of 32 ml/min in South Asians and 22 ml/min in White Europeans (p=0.049). Of the remaining two studies, one study found a mean estimated rise in creatinine (ß) of 5.36 (95% CI, 2.21-8.52) vs 2.22 (95% CI, 1.31-3.14) in White Europeans and 3.14 (95% CI, 0.82-5.46) in Afro-Caribbean's, p<0.05 (24). Finally, Koppiker et al, (26) compared the interaction between creatinine-ethnicity using serum creatinine as a time dependent variable. Results from extended Cox modelling found a risk ratio (95% CI) of 1.00 (0.99, 1.02) between South Asians and White Europeans. A meta-analysis was not performed since measurement of disease progression differed across the studies.

End-Stage Renal Disease

Ten studies reported the incidence of ESRD in the three ethnicities relevant to this review. However, three of the studies where data were extracted were not included in the study; Chandie Shaw et al (27) and Gerchman et al (28) reported odds of having eGFR rather than incidence rates, and Omer Ali (22) reported different clinical outcomes relating to decline in kidney function.

The estimated pooled IRR for ESRD was significantly higher in African Caribbeans vs White Europeans 2.75 (95% CI: 2.01, 3.48 p<0.001) (Fig 3.1). The pooled IRR for South Asians vs Western Europeans (Fig 3.2) was 0.88 (95% CI: -0.18, 1.94), p=0.104, from three studies. Between study heterogeneity was again high, with I-squared values of 86.9% and 76.6% for the two meta-analyses.

All Egger's tests for publication bias were non-significant, and an examination of the funnel plots raised no concerns for the presence of publication bias. The number of studies included in the meta-analyses models were fairly small, and heterogeneity was high.

Discussion

This systematic review and meta-analysis of published prevalence studies showed no significant differences in the prevalence of microalbuminuria in South Asians and Afro-Caribbeans compared to White Europeans with T2DM. Of the 5 studies identified for this review for various markers of renal impairment progression, when comparing the rates of deterioration between south Asians and white Caucasians, the results were inconsistent with preponderance towards a high rate of disease progression in south Asians compared to white Caucasians. This is consistent with previous literature (23) (27) (24). Similarly, an inconsistent pattern of renal disease progression rates was found in studies that compared blacks with white Caucasians, but two (22) (24) out of the three studies identified showed a higher rate in blacks compared to white Caucasians. These results are in keeping with studies assessing the progression of renal disease in non-diabetics. In the observational analysis of combined data from the Third National Health and Nutrition Examination Survey and the US Renal Data System, which includes patients without diabetes, even though the prevalence of CKD was similar among African Americans and among persons of white race/ethnicity, the estimated progression rates among those with CKD were 5-fold higher among African Americans (29). It is acknowledged that some of the differences found in this systematic review for prevalence of microalbuminuria between ethnic groups, may be due to differences in age and duration of diabetes by ethnicity. This was explored through meta-regression analyses, although the analyses that could be carried out were limited as not all studies reported the relevant data. Meta-regression analyses lack power, as only study level data is available. To really understand the complexity of these relationships individual patient data is needed.

With regards to ESRF, there was a significant difference in the IRR between African Caribbeans vs White Europeans. In the African American Study of Kidney Disease and Hypertension (AASK) (30) (31) (32), which did not meet the inclusion criteria of this review, a beneficial effect of RAAS inhibition was noted which is likely to be along the proteinuria axis, as this has been confirmed in other landmark trials (33) (34). Despite these benefits, other studies have shown that African Americans who are treated with RAAS therapy continue to progress during the long term follow ups (35). This progression to ESRF could be occurring across other non-albuminuric pathways that yet remain to be established (36). Other reasons including genetic predisposition (particularly with recent discovery of apolipoprotein L1) (37)**,** obesity, low socioeconomic status, high-risk health behaviours (such as poor diet),

and limited access to healthcare could also account for the continuous progression. In our analysis, despite the finding of equivalence in prevalence of albuminuria between the African Caribbeans and White Europeans, the IRR of ESRF was 2.75, suggesting an alternative pathway to ESRF in addition to the albuminuric pathway, probably more predominant in the African Caribbean race.

Whatever the reasons for this disparity, standardized interventions and improved health care delivery in these high-risk individuals is required to reduce the variations in renal outcomes in these populations. In a recent post-hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial looking at the longitudinal change in eGFR, time to development of microalbuminuria, macroalbuminuria, incident CKD, and kidney failure or serum creatinine > 3.3 mg/dL (38), it was noted that even though the mean values of systolic blood pressure, hemoglobin A1c microalbuminura, macroalbuminira and serum creatinine levels were higher in blacks at baseline, both blacks and whites achieved similar rapid improvement of both clinical parameters, which were maintained during study follow-up. This suggests that optimization of the delivery of diabetes care prior to the development of CKD may lead to similar short-term kidney outcomes, irrespective of race.

Strengths and Limitations of the review

The strengths of this systematic review are the use of a broad search strategy performed on multiple databases and the involvement of two independent reviewers for the study selection and the data extraction phases. Limitations in the studies include estimating the prevalence of microalbuminuria and proteinuria using albumin creatinine ratio (ACR) that was reported on the basis of a single random urine sample or an early morning sample. The use of a single ACR value may underestimate microalbuminuria in those with a higher muscle mass, including males and could be affected by variations in diet or physical exercise (39). The presence of selection bias is another limiting factor which can have a considerable impact on prevalence estimates of the different stages of diabetic nephropathy. Different methods for ascertainment of outcomes were also used in the studies, making this a limiting factor during comparisons.

The number of studies in this review was limited because seven of the 22 excluded studies was due to lack of differentiation between the types of diabetes as a cause of underlying diabetic nephropathy. This is an important differentiating feature which has been ignored in these studies. Generally, it is estimated that 20-30% of people with T1DM develop proteinuria, and a large number progress to renal failure (40). Fewer patients with T2DM progress to ESRD but despite this they account for a large majority of patients on renal units.

This is largely due to the higher prevalence of T2DM compared to T1DM. Racial differences have also been observed between T1DM and T2DM patients with nephropathy (12).

Conclusion

This systematic review and meta-analysis of published prevalence studies showed that the pooled estimates of microalbuminuria, were numerically higher in South Asians compared to White Europeans, however these results were not statistically significant. This review was able to identify few studies relating to progression of diabetic nephropathy between South Asians and White Europeans. Our results were inconsistent with South Asians and African Caribbeans demonstrating a faster progression than White Europeans in some of the studies, however due to considerable heterogeneity between these studies, no definite conclusion can be drawn on whether disease progression is significantly different in these individuals. This review found a significantly higher IRR of ESRF in African Caribbeans compared to White Europeans. These results have highlighted the need for more research on the potential non-albuminuric pathways of progression to ESRF with a focus on ethnic origin to explore if a correlation between the two exists. This systematic review has also revealed the sparsity in studies looking at the progression of diabetic nephropathy in patients with T2DM. This has highlighted the need for more research studies to determine if ethnic disparities do exist in disease progression and outcomes of T2DM nephropathy which can guide early, targeted interventions and improved health care delivery in these high-risk individuals.

Funding

DK, CG, MJD, KK and SS acknowledge the support from National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM) and the NIHR Leicester, Biomedical Research Centre.

Duality of Interest

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme.

SS has acted as consultant, advisory board member and speaker for Novo Nordisk, Amgen, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, NAPP and Novartis. He has received research grants Jansen.

MJD has acted as consultant, advisory board member, and speaker for Novo Nordisk, Sanofi, Eli Lilly and Company, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. MJD has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi, and Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

CG, DK WC and CJ have no conflicts of interest

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