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Microalbumin and Diabetes Mellitus Type 2(T2DM): A Mendelian Randomization Study

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Microalbumin; Diabetes mellitus type 2; Mendelian Randomization

Abbreviations:

T2DM: Diabetes mellitus type 2; MR: Mendelian randomization; SNPs: single nucleotide polymorphisms; IVW: inverse variance weighted; WHO: World Health Organization; IR: insulin resistance; CKD: chronic renal disease; GWAS: genome-wide association studies; MAF: minor allele frequency; LD: linkage disequilibrium

1. Abstract

1.1. Background: The observational link between microalbumin and type 2 diabetes (T2DM) is well established. However, it is uncertain if the link is causative.

1.2. Methods: The current study performed Mendelian randomization (MR) on publicly accessible genome-wide association study (GWAS) summary data in order to investigate the causal linkages between microalbumin and T2DM. A single set of MR analyses was performed. As instrumental variables, a dataset of single nucleotide polymorphisms (SNPs) with significance value smaller than the genome-wide criteria (5*10-8) was employed.

1.3. Results: The results suggested that microalbumin had a causal influence on T2DM risk based on the 0.05 threshold. Microalbumin was shown to be positively linked with the risk of T2DM using the inverse variance weighted (IVW) technique (OR = 1.346, 95% CI, 1.062-1.706, P = 0.014). The weighted median MR estimations revealed that microalbumin was positively associated with the incidence of T2DM (OR = 1.356, 95% CI, 1.038-1.771, P = 0.0254).

1.4. Conclusions: The data showed that microalbumin may increase the incidence of T2DM dependent on the genome-wide statistical significance level. This study supports the notion that microalbumin has a negative causal influence on T2DM risk.

2. Background

The World Health Organization (WHO) describes diabetes mellitus as a long-term metabolic illness marked by high blood glucose levels that. As time goes by, it will also affect the heart, blood vessels, eyes, kidneys, and nerves. Over 90% of patients of diabetes are T2DM, which is defined by tissue insulin resistance (IR) and inadequate compensatory insulin secretory response [1, 2]. The key causes of the T2DM pandemic, which has increased the frequency and prevalence of T2DM, include the global rise in obesity, unhealthy lifestyles, high-calorie meals, and population aging [3, 4]. To deal with T2DM, early identification and diagnosis are essential.

Microalbuminuria, identified as the excretion of 20–200 mg/L of albumin in the urine [5], is a precursor to chronic renal disease (CKD). What's more, it has been associated with a higher risk of cardiovascular disease, overall mortality, and metabolic diseases, such as type 2 diabetes mellitus (T2DM) [6-9]. Urinary microalbumin concentrations have been linked to metabolic diseases; epidemiologic research shows that the prevalence of microalbuminuria is considerably greater in those with T2DM [10, 11]. To some extent, there were conflicting correlations among microalbuminuria and several T2DM components [12-15]. However, it is unclear if there is a causal connection between microalbumin and T2DM.

A technique called Mendelian randomization (MR)[16] incorporates summary information from genome-wide association studies (GWAS), minimizing the impact of confounding variables. MR is a popular technique for determining if exposure and complex outcomes have any causal connections. To infer causation, the selection of instrumental factors includes genetic variants that are closely related to exposure [17]. If the exposure is causal, the findings will be impacted in line with the instrumental parameters that influence the exposure. The current investigation used MR to determine whether there is a link between microalbumin and the risk of T2DM.

3. Materials and Methods

3.1. Sources of Data

SNPs associated to microalbumin were chosen as instrumental factors in a GWAS (https://gwas.mrcieu.ac.uk/) with 108706 sample size (GWAS ID: ukb-d-30500 irnt). We also use summary data from 122 GWAS for 80,154 people with T2DM and 853,816 controls (effective sample size, 492,191) from five ancestry groups. Data is from a previous study [18].

The above quality check procedures were utilized to select appropriate indicator variables, ensuring the accuracy and validity of the findings on the causal link between microalbumin and T2DM risk. As instrumental factors, a collection of SNPs fewer than the genome-wide statistical significance criterion (5 × 10-8) was used. Second, for variations of interest, the minor allele frequency (MAF) criterion was 0.01. Third, the absence of linkage disequilibrium (LD) among the selected explanatory variable is a crucial MR approach's guiding principles, because significant LD might lead to biased conclusions. The clumping technique (R 2 < 0.001 and clumping distance = 10,000kb) was used in the current investigation to analyze the degree of LD between the added SNPs. Fourth, confirming that the impacts of SNPs in exposure match to the similar genotype as the impacts on outcome is an essential part in MR. The explanatory variables wouldn't contain palindromic SNPs, according to the concept. Fifth, where SNPs linked with exposure were missing from GWAS results, the surrogate SNPs with r 2 > 0.8 substantially related with the variants of interest were chosen.

3.2. The MR Presumptions

The MR technique needs to conform to three crucial presumptions in order to lessen the impact of bias on the outcomes. To begin with, explanatory variables that change exposure and outcome have no effect on explanatory factors. Second, the variations of interest should be strongly related with exposure in the study. The F value is frequently used to assess how strongly explanatory variables and exposure relate to one another. F = R 2(n-k-1)/k(1-R 2) is the formula for the F statistic. N is the sample size, k is the amount of explanatory variable, and R 2 is the treatment variance represented by the chosen SNPs. The relationship between explanatory variable and exposure is poor when F value is lower than 10. Third, there is no vertical pleiotropy impact among explanatory variables and outcomes because instrumental factors only affect outcomes through exposure.

3.3. MR Predictions

For the research at hand, elevated methods such as inverse variance weighted (IVW), MR-Egger, weighted median, and weighted mode were utilized to determine if microalbumin had a causal influence on T2DM risk. To create an overall estimate of the influence of microalbumin on T2DM risk, IVW simply converts the outcome impacts of explanatory variable on exposure effects to a weighted regression, with the intercept set to zero [19]. In the absence of vertical pleiotropy, IVW could produce estimates that are free from confounding factors.666 Outlying genetic factors may have a considerable impact on MR-Egger, resulting in incorrect estimations. The MR-Egger method can still produce accurate estimates even if all of the selected explanatory factors are wrong. The weighted median could produce precise predictions of the causality relationship even if up to 50% of the study's data came from false explanatory factors. Because it enhances the accuracy of the findings, compared to the MR-Egger technique, the weighted median approach has a number of important benefits. When the majority of explanatory variables have identical causal estimates, Despite the fact that other explanatory variables don't really match the MR method's conditions for interpretation, the weighted mode approach remains viable [20].

To determine if the contained SNPs had any vertical pleiotropic impacts, the MR-Egger regression was performed. A technique called MR-Egger regression uses pleiotropy detection and correction to evaluate the causal influence of MR analysis [21] and to establish if directed vertical pleiotropy is the cause of the results [22]. Due to the reduced reliability and confidence interval of MR-Egger regression, Mendelian randomization pleiotropy residual sum was used to identify any outliers that would reflect potential pleiotropic bias and rectify vertical pleiotropy. In addition, in order to assess the degree of heterogeneity from among selected SNPs, Cochran's Q statistic was used. R program was used for statistical analysis (R version 4.0.2, TwoSampleMR package).

4. Results

When T2DM was used as the result, microalbumin was found to be causally related to T2DM, as demonstrated in Table 1 and Figures 1 and 2. Microalbumin (odds ratio (OR) = 1.346, 95% confidence interval (CI), 1.062-1.706, P = 0.014) was shown to be positively linked with the risk of T2DM in IVW analysis (Table 1). The weighted median MR estimations revealed that microalbumin (OR = 1.356, 95% CI, 1.038-1.771, P = 0.0254) was a risk factor for T2DM (Table 1). The comprehensive statistical findings of the microalbumin were reported in Supplementary Table 1. To test for vertical pleiotropy between explanatory variable and result, MR-Egger regression was utilized. and the findings revealed that no

indication of vertical pleiotropy was found (P = 0.736). Furthermore, Statistics from Cochrane Q showed no discernible heterogeneity (P = 0.703), and there was no mild explanatory variable bias, according to the F values of the SNPs, which were all more than 10 (Table 2). Table 2 contains extensive information on the instrumental factors. Thus, the MR estimations discovered that microalbumin was positively associated to the probability of T2DM.

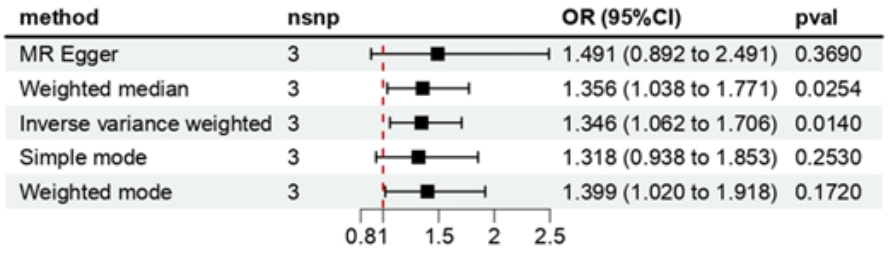

Figure 1: MR results of causal links between microalbumin and T2DM.

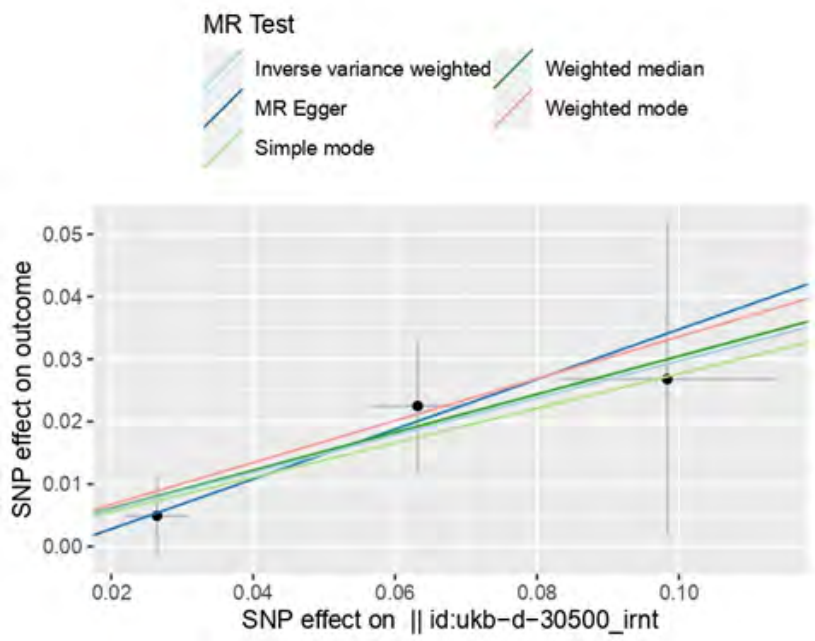

Figure 2: MR results of causal links between microalbumin and T2DM.

Table 1: MR results of causal links between microalbumin and T2DM.

method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
MR Egger	3	0.39932	0.261846	0.369489	-0.1139	0.912538	1.490811	0.89235	2.490635
Weighted median	3	0.304668	0.1363	0.025399	0.03752	0.571815	1.356174	1.038233	1.77148
Inverse variance weighted	3	0.297119	0.120968	0.014042	0.060022	0.534216	1.345975	1.06186	1.70611
Simple mode	3	0.276472	0.173746	0.252538	-0.06407	0.617013	1.31847	0.93794	1.853384
Weighted mode	3	0.335793	0.161095	0.172482	0.020047	0.651538	1.399049	1.02025	1.91849

Table 2: SNPs used as instrumental variables from microalbumin and T2DM GWASs.

SNP	chr	pos	effect_ allele	other_ allele	beta. exposure	beta. outcome	se.exposure	se. outcome	pval. exposure	pval. outcome	eaf. exposure	R2	Fvalue
rs116867125	10	17033504	A	G	0.098354	0.0268	0.015188	0.0251	9.48E-11	0.2862	0.020059	0.00038	41.32461
rs6665323	1	47953054	C	T	0.026458	0.0049	0.00441	0.0066	1.98E-09	0.4576	0.622863	0.000329	35.73879
rs74942409	10	16928301	C	T	0.063186	0.0225	0.006658	0.0104	2.34E-21	0.02996	0.114877	0.000812	88.1885

5. Discussion

The MR method was used in this study to investigate the causal relationship between T2DM and microalbumin using GWAS summary-level data. The primary analyses discovered evidence that genetically predicted T2DM was linked to microalbumin levels. It also suggested that microalbumin was related to the risk of T2DM.

Because of the increased proportion of microvascular complications associated with diabetes, such as diabetic nephropathy, the amount of diabetics with end-stage renal disease (ESRD) will rise sharply [23]. As a result, diabetes, particularly type 2 diabetes, is increasingly becoming the primary cause for patients to begin renal replacement treatment [24, 25].On average, 20-40% of diabetic people will have renal impairment [26]. Microalbuminuria is frequently the initial symptom of renal dysfunction, indicating the presence of overt nephropathy [27]. As a result, urine albumin measurement is frequently employed as a sensitive diagnostic and predictor of ESRD in diabetic patients [28]. Microalbuminuria and other risk factors linked with this illness must be monitored in order to avoid or postpone overt nephropathy [29]. The gold standard is microalbuminuria measurement in a 24-hour urine collection [30]. Furthermore, even within the normal range, the urinary microalbumin-to-urine creatinine ratio (UACR) is a significant predictor of diabetic nephropathy and an important risk factor for cardiovascular disease, and it shows endothelial dysfunction in DM [31, 32].

A recent study discovered that people with excessive urine microalbumin concentrations had a considerably greater risk of developing T2DM [33]. Furthermore, there were favorable relationships between microalbumin concentrations and various metabolic syndrome components, such as hypertension and hyperglycemia. Urinary microalbumin concentration increases of 10 mg/L were linked to a 10% increase in the incidence of T2DM [33]. Microalbumin levels below the threshold for microalbuminuria might substantially predict the risk of cardiometabolic problems [34]. The NHANES study discovered a connection among microalbuminuria and the possibility of hypertension and hyperglycemia [35]. The risk of developing T2DM was shown to be 1.90 (95% CI = 0.88-4.06) in an 11-year follow-up of 882 people aged 20 to 74, for those with microalbuminuria and 2.51 (95% CI = 1.08-5.87) for those with macroalbuminuria, respectively [36]. Microalbuminuria affects roughly 20-40% of diabetes individuals in various populations [37-39], This might be a precursor to diabetic nephropathy and other diabetes problems. To prevent future difficulties, adequate screening programs and tight control of modifiable risk factors are required. These outcomes matched the findings of the current investigation.

However, the fundamental processes linking urine microalbumin levels to the development of metabolic diseases are not entirely understood. Microalbuminuria is most commonly associated with vascular injury and endothelial dysfunction [40], culminating in type 2 diabetes [41]. On the other hand, the metabolic syndrome Endothelial permeability and intraglomerular capillary pressure may be increased by factors such abdominal obesity, hypertension, or hyperglycemia, which can cause kidney failure and microalbuminuria [42]. Thus, the mechanisms through which microalbumin has a negative impact on T2DM need to be investigated further.

Diabetic nephropathy can be used to investigate the mechanism of microalbumin's negative influence on T2DM. Despite the convoluted pathophysiology of diabetic nephropathy, podocyte damage has been recognized as being critical [43]. Podocyte structural alterations or destruction are linked to kidney injury, culminating in proteinuria and severe renal insufficiency, finally leading to diabetic nephropathy [44]. Furthermore, defective podocytes result in poor selective glomerular filtration and contribute to proteinuria development [45]. Meanwhile, the continuous hyperglycemia-induced formation of reactive oxygen species (ROS) would ultimately harm the antioxidant defense system, triggering oxidative stress (OS) and inflammatory reactions [46].

For many years, a role for inflammation in the development of T2DM has been hypothesized based on the reported associations between higher concentrations of inflammatory biomarkers such as CRP and interleukin-6 (IL-6) and T2DM risk [47]. A large MR research with CHD as the major outcome found that a functional variation causing defective signaling at the IL-6 receptor had a substantial influence on reduced T2DM risk [48]. However, in a comprehensive GWA meta-analysis, the same functional variation was found to be unrelated to T2DM risk [49]. Although the inflammatory theory in T2DM pathogenesis looks feasible, data from magnetic resonance imaging studies has yet to support it. However, bigger trials and investigations into additional inflammatory pathways may provide different results.

The application of the MR technique reduced inverse causality and confounding factors' influence with the findings, which may make them more credible than results from epidemiological studies. To the greatest of our knowledge, this study offers the first MR analysis of this problem. There must be some restrictions mentioned, though. First, we were incapable of identify whether individuals who participated in the GWAS used in the MR investigations coincided. Nonetheless, the F statistic has the potential to reduce the departure from participant overlap [50]. Second, using a rigorous various testing adjustment would have been overly conservative given the biologic validity and the cross statistical technique, potentially omitting possible causal factors for T2DM. As a result, We neglected to take repeated testing into consideration. Third, the findings of the research may not be generalizable to other ethnic groups because the most of GWAS volunteers were of European heritage.

6. Conclusions

In conclusion, our MR investigation reveals that microalbumin has a causal influence on T2DM. It may hold promise for the preven-

tion and treatment of type 2 diabetes.

7. Declarations

7.1. Ethics approval and consent to participate: All included participants gave their oral and written informed consent.

7.2. Author Contributions: Yanhui Wu and Pengqian Duan conceived the presented idea. Hao Lu and Yanhui Wu performed the manuscript writing. Pengqian Duan was involved in acquisition and processing of data. Hao Lu was involved in interpretation of data. Hao Lu and Pengqian Duan have contributed equally to this work and share first authorship.

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7.4. Data Availability Statement: SNPs associated to microalbumin were chosen as instrumental factors in a GWAS (https://gwas.mrcieu.ac.uk/) with 108706 sample size (GWAS ID: ukb-d-30500 irnt). We also use summary data from 122 GWAS for 80,154 people with T2DM and 853,816 controls (492,191) from five ancestry groups. Data is from a previous study.

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