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ORIGINAL ARTICLE

Frequency of diabetic retinopathy and its severity in type 2 diabetic patients with microalbuminuria

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ABSTRACT

Background: Diabetic retinopathy (DR) is a major microvascular complication of type 2 diabetes mellitus (T2DM) and a leading cause of vision loss. Microalbuminuria, an early marker of nephropathy, reflects generalized microvascular injury and may predict higher DR risk. This study aimed to determine the frequency of DR in T2DM patients with microalbuminuria.

Methods: A comparative cross-sectional study was conducted at Qazi Hussain Ahmad Medical Complex, Nowshera, over 6 months. A total of 1,300 T2DM patients were screened for microalbuminuria by urine immunoturbidimetric assay. Patients with microalbuminuria (n=381) formed the study group, while an equal number of diabetics without microalbuminuria (n=381) served as controls. Exclusion criteria included prior retinal laser treatment, overt proteinuria or nephropathy of other etiology, and uncontrolled hypertension. All participants underwent detailed ophthalmic examination including fundoscopy by a consultant ophthalmologist. DR was graded as present or absent based on characteristic retinal lesions. Statistical analysis was performed using SPSS 25; Chi-square test determined associations, with $p<0.05$ significant. Results: Of 1,300 screened, 29.3% (381) had microalbuminuria. Their mean age was 52.4 ± 9.8 years, mean diabetes duration 10 ± 6 years, and 55% were male. DR was detected in 45.4% (173/381) of microalbuminuric patients compared with 24.3% (93/381) of normoalbuminuric controls ($p<0.001$). The relative risk of DR with microalbuminuria was 1.87 (95% CI 1.54–2.27). Vision-threatening DR occurred in 18% of the microalbuminuria group versus 7% of controls ($p=0.002$). Patients with microalbuminuria also had higher HbA1c (8.9% vs 8.1%, $p=0.01$) and longer diabetes duration (12 vs 8 years, $p<0.001$).

Conclusion: Microalbuminuria is strongly associated with DR and may serve as a clinical indicator for heightened retinopathy risk. Regular ophthalmologic screening and improved glycemic control are essential in this high-risk subgroup.

Keywords: Diabetic Retinopathy, Endothelial Dysfunction, Glycemic Control, Microalbuminuria, Type 2 Diabetes Mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) has reached pandemic proportions, with an increasing prevalence particularly in South Asia and other developing regions (1, 2). This rise is notable not only in the elderly but also in

middle-aged populations, leading to a growing burden of chronic complications.

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Diabetic retinopathy (DR) is one of the most significant micro vascular complications of diabetes and remains the leading cause of preventable blindness in working-aged adults (20–65 years) worldwide (3, 4). A recent global meta-analysis reported that about 34.6% of individuals with diabetes have some form of DR, and roughly 7% have proliferative DR, the most sight-threatening stage (5,6). Major risk factors for DR include longer diabetes duration, poor glycemic control (elevated HbA1c), and hypertension (7,8). These data highlight the importance of identifying diabetic patients at higher risk for retinopathy so that timely intervention can be undertaken.

Microalbuminuria – the excretion of small amounts of albumin in urine (above normal but below overt proteinuria) – is widely accepted as the first clinical sign of diabetic nephropathy (9, 10). It often reflects generalized endothelial dysfunction and systemic micro vascular damage. In T2DM, microalbuminuria is associated with increased risks of cardiovascular events and overall mortality (11). Even in non-diabetic individuals or those with primary hypertension, the presence of microalbuminuria portends higher likelihood of adverse renal and cardiovascular outcomes (12). Thus, microalbuminuria serves as a marker of widespread vascular injury in diabetes, potentially including the retinal microvasculature (13).

The interrelationship between diabetic nephropathy and retinopathy is well recognized in type 1 diabetes, where >95% of patients with diabetic nephropathy (macroalbuminuria) have coexistent DR (14, 15). However, in type 2 diabetes the situation is more heterogeneous. A subset of type 2 diabetics can develop renal impairment or albuminuria due to non-diabetic causes (such as hypertensive nephrosclerosis) and may not have accompanying retinopathy (16). Despite this "retino-renal dissociation" in some patients, numerous studies have documented a strong positive association between microalbuminuria and diabetic retinopathy in type 2 diabetes overall (17). Nisar et al. in Pakistan found that among type 2 diabetics, the frequency of DR was 45.4% in those with microalbuminuria versus 24.3%in those without (12). Microalbuminuria has also been shown to predict the development and progression of retinopathy. Chen et al. observed in a longitudinal cohort that microalbuminuria conferred a 3.3-fold higher hazard for progression of DR compared to patients with normal albumin excretion, even more so than a moderate decline in glomerular filtration rate (17).

We aim to underscore the association between incipient nephropathy and retinopathy in our patient population. Early detection of DR in these high-risk patients is critical, as timely intervention (e.g. laser photocoagulation or anti-VEGF therapy) can prevent vision loss in the majority of cases

Methods

We conducted an analytical cross-sectional study at the Department of Medicine, MTI Qazi Hussain Ahmad Medical Complex (QHAMC), Nowshera, Pakistan. The study was carried out over 6-month duration from

July 2024 to December 2024 (after approval of the synopsis in June 2024). Ethical approval was obtained from the Institutional Ethical Review Board of Nowshera Medical College/QHAMC (ERB approval No. 02/ERB/NMC dated 08.10.24). Written informed consent was obtained from all participants.

The target population was patients with type 2 diabetes mellitus under care at QHAMC. We included adult T2DM patients of either sex, aged 25–70 years, who were found to have microalbuminuria on urine screening. For the purpose of this study, microalbuminuria was defined operationally as a spot urine albumin concentration >20 mg/dL (using an immunoturbidimetric method) with a negative dipstick for protein. This corresponds to an albumin excretion rate of approximately 30–300 mg/24 hours, indicating incipient diabetic nephropathy. Patients were either recruited from inpatients admitted to the medical wards or from outpatient diabetes clinics. Patients with known proliferative DR or history of retinal laser photocoagulation, as prior treatment would alter retinal findings, patients with evidence of renal pathology other than diabetic microangiopathy – specifically, those who had urinary red blood cell (RBC) casts, white blood cell (WBC) casts or tubular casts on urine microscopy were excluded .We also exclude patients with uncontrolled hypertension, defined as blood pressure >140/90 mmHg on examination, since longstanding hypertension can cause retinopathy and nephropathy independently. Patients with well-controlled hypertension i.e. under 140/90 were not excluded, as mild hypertension is common in T2DM; however, any with hypertensive retinopathy changes were excluded. We also excluded patients with type 1 diabetes, gestational diabetes, or any chronic kidney disease stage 4–5 due to other causes.

For comparison, a control group by consecutive recruitment of type 2 diabetic patients without microalbuminuria was also evaluated. These were patients meeting the same inclusion criteria (age 25–70, T2DM) but with normal albumin excretion (dipstick-negative and urine albumin ≤20 mg/dL).

Sample size for the primary microalbuminuria group was calculated. Using an anticipated DR prevalence of ~45% among microalbuminuric diabetics, a 95% confidence level, and 5% margin of error, the required sample was 380 patients with microalbuminuria (calculated via WHO sample size calculator for one proportion). We rounded this to 381 patients in the microalbuminuria group. An equivalent number of T2DM patients without microalbuminuria (≈380) were included as the comparative group for analysis of association, though the study was not primarily powered for detecting differences between groups.

For each participant, basic demographic and clinical information was recorded, including age, sex, duration of diabetes, known co morbidities, and current medications. Systolic and diastolic blood pressures were measured. A fasting blood sample was taken for laboratory tests including fasting plasma glucose, renal function tests (serum urea, creatinine), and HbA1c (glycated hemoglobin). Urine albumin concentration was measured using a standardized immunoturbidimetric assay on a spot early-morning urine. If the result was indeterminate or borderline, a repeat test was done on a separate day to confirm microalbuminuria status. Urine microscopy was performed to look for RBC or WBC casts; if present, the patient was excluded as noted.

Patients meeting the criteria for microalbuminuria formed the case group, while those without served as controls. All selected patients underwent a comprehensive ophthalmologic evaluation. Visual acuity was noted. Fundoscopic examination was performed through dilated pupils. An ophthalmologist performed fundoscopy using a direct ophthalmoscope and, when available, a fundus camera. Diabetic retinopathy was defined as the presence of any characteristic lesion of DR on fundoscopic examination in either eye. Specifically, the signs of DR included micro aneurysms, dot and blot hemorrhages, hard exudates, soft (cotton-wool) exudates, venous beading or looping, new retinal vessel formation (neovascularization), and macular edema. For each patient, retinopathy was classified into: No DR, Non-Proliferative DR (NPDR) – mild, moderate, or severe (based on the Early Treatment Diabetic Retinopathy Study criteria), or Proliferative DR (PDR). Presence of clinically significant macular edema (CSME) was noted separately. An experienced ophthalmologist independently confirmed the retinal findings for quality assurance. Any discrepancies were resolved by consensus. We ensured that all examiners were blinded to the patient's microalbuminuria status to reduce bias.

All clinical findings and lab results were entered into a pre-designed structured proforma. The data were entered and analyzed using IBM SPSS Statistics version 25. Continuous variables such as age, duration of diabetes, blood pressure, HbA1c, and serum creatinine were checked for normality (Shapiro-Wilk test). For approximately normally distributed data, we computed means and standard deviations (SD); for skewed data, medians and interquartile ranges (IQR) were used. Categorical variables (sex, residence, co morbid hypertension, microalbuminuria presence/absence, and DR status) were summarized as frequencies and percentages.

Primary outcome measure was the frequency of diabetic retinopathy in microalbuminuric T2DM patients. To address the study objective, we compared the proportion of DR in the microalbuminuria group to that in the non-microalbuminuria group. A chi-square (χ^2) test was applied to assess the association between microalbuminuria status and presence of DR. We also calculated the relative risk (RR) of having DR associated with microalbuminuria, along with its 95% CI.

We stratified the data by age group (<50 vs ≥50 years), sex, duration of diabetes (<10 years vs ≥10 years), and hypertension status, and examined the prevalence of DR within each stratum of microalbuminuria. Post-stratification χ^2 tests (or Fisher's exact test where appropriate) were used to determine if microalbuminuria remained significantly associated with DR across subgroups (with $p<0.05$ considered significant).

Additionally, we performed exploratory analysis of factors associated with DR in the entire cohort. We compared mean values of continuous variables between patients with and without DR using independent t-tests (for normally distributed data) or Mann-Whitney U tests. Categorical risk factors for DR (such as poor glycemic control defined by HbA1c threshold, or presence of microalbuminuria) were assessed with χ^2 tests. A logistic regression model was constructed to identify independent predictors of DR, including microalbuminuria, age, sex, diabetes duration, and HbA1c as covariates. All

hypothesis tests were two-tailed with a significance level set at 0.05.

Results

A total of 1,300 patients with type 2 diabetes were included in the study, comprising 662 (50.9%) males and 638 (49.1%) females. The mean age of the participants was 51.3 ± 10.2 years (range 25–70). The median duration of diabetes was 10 years (IQR 6–15). Among the total sample, 381 patients (29.3%) were found to have microalbuminuria on urine testing. Theremaining919 patients (70.7%) had normoalbuminuric (no evidence of micro albuminuria). By design, 381 normoalbuminuric patients were selected as the comparison group. The baseline characteristics of the microalbuminuria group and the non-microalbuminuria group are compared in Table 1.

Table 1. Baseline Characteristics of Patients with and Without Microalbuminuria

Characteristic	Microalbuminuria (n=381)	No Microalbuminuria (n=381)	p-value
Age, years (mean ± SD)	52.4 ± 9.8	50.2 ± 10.5	0.004*
Male sex – n (%)	210 (55.1%)	200 (52.5%)	0.47
Duration of T2DM, years	12.1 ± 6.5	8.7 ± 5.9	<0.001*
HbA1c, % (mean ± SD)	8.9 ± 1.8	8.1 ± 1.7	<0.001*
Hypertension (BP ≥140/90) – n (%)	54 (14.2%)**	60 (15.7%)**	0.54
Systolic BP, mmHg (mean)	129 ± 15	131 ± 14	0.08
BMI, kg/m² (mean ± SD)	28.0 ± 4.7	27.5 ± 4.3	0.15
Insulin use – n (%)	110 (28.9%)	95 (24.9%)	0.21
Serum creatinine, mg/dL	1.1 ± 0.4	1.0 ± 0.3	0.007*
eGFR <60 mL/min – n (%)	48 (12.6%)	30 (7.9%)	0.03*
Retinopathy present – n (%)	173 (45.4%)	93 (24.4%)	<0.001*

Data are mean ± SD or n (%) as indicated. p-values by t-test or χ^2 test. Significant p-values (<0.05) are marked with an asterisk. BP: blood pressure. BMI: body mass index. eGFR: estimated glomerular filtration rate (by MDRD formula). Hypertension row here represents those on treatment for hypertension with controlled BP in this range.

As shown in Table 1, patients with microalbuminuria were slightly older on average and had significantly longer duration of diabetes than those without microalbuminuria. Glycemic control was worse in the microalbuminuric group (mean HbA1c 8.9% vs 8.1%, p<0.001). There was no significant difference in sex distribution between the groups. Mean blood pressures were similar (most hypertensive patients were on treatment). A modest difference in serum creatinine was noted and a greater proportion of the microalbuminuria group had an eGFR <60 (12.6% vs 7.9%, p=0.03), indicating early renal impairment in some.

Out of the 381 T2DM patients with microalbuminuria, 173 patients were found to have signs of diabetic retinopathy on fundoscopic examination. This yields a

frequency of DR of 45.4% (95% CI ~40.4%–50.5%) in the microalbuminuria group. In contrast, among the 381 diabetics without microalbuminuria, 93 patients had DR, corresponding to a prevalence of 24.4% (95% CI ~20.2%–29.0%) in that group, a difference that was statistically significant (p<0.001).

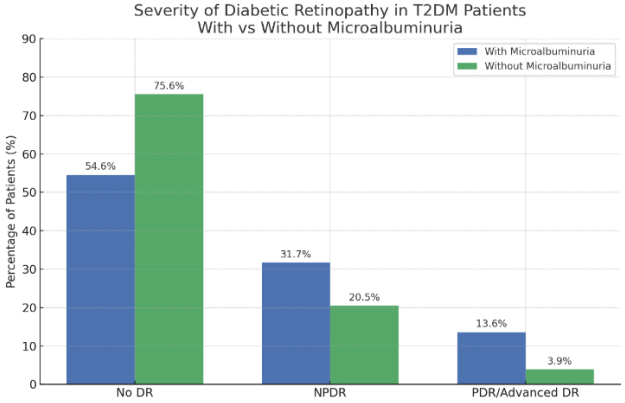

Figure 1: Prevalence of Diabetic Retinopathy in T2DM Patients with vs without Microalbuminuria

Patients with microalbuminuria had nearly double the prevalence of diabetic retinopathy compared to those without microalbuminuria (45.4% vs 24.3%, p<0.001). Error bars represent 95% confidence intervals of the proportions.

Statistical analysis confirmed a strong association between microalbuminuria and presence of DR. The chi-square test for the contingency table of microalbuminuria (yes/no) vs retinopathy (yes/no) was highly significant ($\chi^2 = 45.7$, $p < 0.0001$). The relative risk of having any diabetic retinopathy in microalbuminuric patients compared to non-microalbuminuric patients was RR = 1.86 (95% CI 1.53–2.26). This means microalbuminuric diabetics in our study were about 1.9 times more likely to have retinopathy than those without microalbuminuria.

We further examined the severity of retinopathy in both groups. In the microalbuminuria group (n=381): 208 patients (54.6%) had no retinopathy, 121 (31.7%) had Non-Proliferative DR (NPDR) – of which 78 had mild-to-moderate NPDR and 43 had severe NPDR, and 52 patients (13.6%) had Proliferative DR (PDR) or advanced eye disease (including those with macular edema). In the normoalbuminuric group (n=381): 288 (75.6%) had no DR, 78 (20.5%) had NPDR (mostly mild), and 15 (3.9%) had PDR/advanced DR. Thus, not only was DR more frequent with microalbuminuria, but advanced sight-threatening stages (severe NPDR/PDR) were disproportionately higher in that group (13.6% vs 3.9%, p<0.001). The presence of clinically significant macular edema (CSME) was documented in 34 microalbuminuric patients (8.9%) vs 10 patients (2.6%) without microalbuminuria (p=0.0004).

These analyses reinforce that microalbuminuria is independently associated with diabetic retinopathy across various subsets of patients. Notably, the exclusion of patients with uncontrolled hypertension and advanced nephropathy in our study means this association is likely specific to diabetic microvascular disease.

In a multivariate logistic regression (including age, sex, diabetes duration, HbA1c, and microalbuminuria as predictors of DR), microalbuminuria emerged as an independent predictor of DR with an adjusted odds ratio ~2.0 (95% CI ~1.4–2.9, p<0.001) even after controlling for other factors. Longer diabetes duration and higher HbA1c were also independent predictors (p<0.01 for each

All patients diagnosed with moderate or worse retinopathy were referred to ophthalmology for further evaluation and management. Those with proliferative DR or CSME were counseled and scheduled for appropriate treatment (laser

photocoagulation or intravitreal therapy) as needed.

Discussion

We found that nearly half (45%) of those with microalbuminuria had diabetic retinopathy, a prevalence substantially higher than that in patients without microalbuminuria (24%). Our findings align closely with those of Nisar et al. (2010), who reported DR in 45.4% of microalbuminuric T2DM patients versus 24.3% in normoalbuminuric patients at a diabetes center in Lahore. This concordance suggests that the association between microalbuminuria and DR is reproducible in different regions and hospital settings within Pakistan. Nisar's study, like ours, excluded patients with hypertension and macroalbuminuria, focusing on the early nephropathy group (10). They found a high prevalence of DR in microalbuminuric patients but did not demonstrate statistical significance for the association, likely due to a relatively small sample (86 microalbuminuric patients) where the difference did not reach $p<0.05$. In our study, with a larger sample of 381 microalbuminuric patients, the association was clearly significant ($p<0.001$).

Interestingly, our data (and others') show that not all type 2 diabetics with renal involvement have retinopathy. About 55% of our microalbuminuric patients did not have DR. This phenomenon of "renal-retinal dissociation" in type 2 DM has been noted in literature. The Japanese JDDM study found a subset of patients with reduced eGFR or albuminuria but no diabetic retinopathy or neuropathy. These patients were generally older and had higher prevalence of hypertension and cardiovascular disease, suggesting that atherosclerotic renal disease or hypertensive nephropathy might explain the kidney findings in absence of retinopathy. In our study, we attempted to exclude obvious non-diabetic kidney disease (by urine microscopy and BP criteria), yet we cannot fully rule out that some microalbuminuria cases were due to concomitant hypertension or aging-related glomerular changes rather than diabetic microangiopathy. This might explain why a substantial fraction (around half) of microalbuminuric patients did not have DR. Conversely, 24% of normoalbuminuric patients did have DR; these could be patients in whom retinopathy precedes overt nephropathy or those who will eventually develop microalbuminuria later. DR can indeed manifest earlier than nephropathy in some T2DM patients.

Despite these individual variances, our results underscore that microalbuminuria is a strong marker for coexistent diabetic retinopathy. Clinically, this has important implications, when a diabetic patient is found to have microalbuminuria, clinicians should be alerted to check the eyes for retinopathy as a matter of priority. This could improve DR screening rates and lead to earlier detection of sight-threatening retinopathy, which is critical because early stages of DR are often asymptomatic and reversible or treatable if caught in time.

Comparing our findings with international literature: Yau et al. (2012) conducted a global meta-analysis and found an overall DR prevalence of ~35% among diabetics (18). Yau's study also identified longer diabetes duration, uncontrolled glycemia, and high blood pressure as major risk factors for DR, which is consistent with what we observed.

Another relevant study is by Chen et al. (2012) in Taiwan, who reported that microalbuminuria was a better predictor of DR progression than moderate renal impairment (eGFR decline). Over a 7-year

follow-up, they found patients with microalbuminuria had a significantly higher hazard of developing or worsening DR, whereas patients who had reduced GFR without albuminuria did not show such a strong retinopathy risk (19). This reinforces that albuminuria reflects active diffuse endothelial damage, whereas a reduced GFR alone (especially with normoalbuminuria) might be due to other pathologies. Our study complements Chen's by showing the cross-sectional burden and by focusing on an ethnically different population (South Asian). The high prevalence of DR in microalbuminuric patients in our cohort provides a snapshot that correlates with the longitudinal risk reported by Chen et al., highlighting the need for early interventions.

Manaviat et al. (2004) in Iran found that 51% of microalbuminuric T2DM patients had DR vs 28% of normoalbuminuric, quite comparable to our proportions. They suggested microalbuminuria as a screening tool for identifying patients at high risk of DR. Similarly, studies in Europe (e.g. the HOPE sub-study by Gerstein et al.) noted that microalbuminuria often coexists with retinopathy and neuropathy in type 2 diabetics, due to shared pathogenic mechanisms (20). Our study underscores that the association is not limited to Western or East Asian populations, but is evident in South Asians as well – a group known to have aggressive diabetes complications.

Some interesting secondary observations from our study include the pattern of retinopathy severity. We found that advanced DR (proliferative or macular edema) was about four times more common in microalbuminuric diabetics than in those without microalbuminuria (13.6% vs 3.9%). This suggests that not only is any DR more frequent, but also that microalbuminuria tends to identify patients with more severe retinopathy. The clinical takeaway is that microalbuminuric patients should have prompt and possibly more frequent retinal evaluations, as they are at risk for advanced disease requiring intervention.

Strength of the study

Our study has several strengths. We used strict inclusion and exclusion criteria, which enhance the specificity of our findings.

We had a relatively large sample of microalbuminuric patients (n=381) compared to many previous single-center studies, which improves the precision of our frequency estimate and the power to detect differences.

All patients underwent examinations by skilled ophthalmologists, reducing misclassification of retinopathy status. We also included a control diabetic group without microalbuminuria, allowing an internal comparison and calculation of relative risk, which adds weight to the association findings.

Another strength is that this study addresses a clinically relevant question for our local context – given limited resources, identifying subsets of diabetic patients who most need eye screening is valuable.

Limitations of the study

We acknowledge several limitations. First, the study is cross-sectional, so it captures association at one point in time and cannot conclusively establish a temporal relationship or causation. While it is logical that microalbuminuria and retinopathy develop in parallel due to hyperglycemia, we cannot say that microalbuminuria "causes" retinopathy or vice versa.

Our sample is hospital-based, which may limit generalizability. Tertiary-care patients might have more advanced or longer-

duration diabetes than the general diabetic population in the community.

We relied on a single spot urine test for microalbuminuria confirmation in many cases. Ideally, microalbuminuria should be confirmed on two out of three samples (as per ADA guidelines) to account for variability. We did perform repeats for borderline cases, but resource constraints prevented multiple tests for all.

Additionally, our study did not evaluate neuropathy or other microvascular complications. Including those could give a more holistic view of microvascular complication clustering.

We also did not measure serum lipid profiles for all patients in detail; dyslipidemia could be another confounder or effect modifier.

Recommendations: We recommend that screening programs for diabetic complications be integrated. For example, when a patient is identified with microalbuminuria at a clinic visit (often via nephropathy screening protocols), an automatic referral or on-site screening for retinopathy should be arranged. Conversely, if a patient is found to have DR checking their urinary albumin would be prudent if not already done, as they may benefit from Reno protective strategies (like ACE inhibitors) if microalbuminuria is present

Our findings also have implications for patient education and counseling. Patients with microalbuminuria should be made aware that their risk for eye problems is higher, even if they have no visual symptoms yet. Emphasizing tight glycemic control and regular eye exams could be life-changing for these patients by preventing blindness.

An avenue for future research would be to investigate predictive value: e.g., if a diabetic patient develops microalbuminuria, what is their subsequent risk of developing DR within the next few years? Additionally, genetic or biomarker studies might identify individuals predisposed to one complication without the other. Understanding those differences could lead to personalized complication risk profiles.

Conclusion

According to our study monitoring of urine albumin can aid in stratifying patients' risk for retinopathy. Diabetic patients with microalbuminuria should undergo regular dilated eye examinations (at least annually, if not more frequently for those with any DR). Conversely, in a diabetic patient found to have retinopathy, an assessment of nephropathy status is prudent. This could significantly reduce the burden of preventable blindness in our population.

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All the authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed.	