Section: Pathology

Original Research Article

A COMPARATIVE STUDY OF HISTOPATHOLOGICAL CHANGES IN TYPE 1 VS. TYPE 2 DIABETIC NEPHROPATHY

Radhika Agarwal[1], *Deergha Singh*[1]

[1]*Assistant Professor, Department of Pathology, N.C. Medical College & Hospital, Israna, Panipat, India.*

Received *: 19/09/2024*
Received in revised form *: 11/10/2024*
Accepted *: 02/11/2024*

Corresponding Author:
Dr. Deergha Singh,
Assistant Professor, N.C. Medical College & Hospital, Israna, Panipat, India.
Email: deerdabas27@gmail.com.

DOI: 10.70034/ijmedph.2024.4.256

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (4); 1409-1414

ABSTRACT

Background: Aim: This study aimed to compare the histopathological changes, clinical characteristics, and outcomes between patients with Type 1 (T1DM) and Type 2 (T2DM) diabetic nephropathy (DN) to identify key differences and their clinical implications.

Material and Methods: This prospective, observational study included 140 patients with biopsy-proven diabetic nephropathy, divided equally into T1DM (n=70) and T2DM (n=70) groups. Clinical and laboratory data, including age, sex, duration of diabetes, glycemic control (HbA1c), serum creatinine, estimated glomerular filtration rate (eGFR), and proteinuria, were collected. Renal biopsy samples were analyzed using light microscopy, with histopathological changes classified according to the Renal Pathology Society criteria. Statistical analysis was performed using SPSS v25.0, with a p-value <0.05 considered significant.

Results: T2DM patients were older (58.70 ± 10.12 years vs. 35.20 ± 8.45 years, $p<0.001$), had higher serum creatinine levels (2.40 ± 0.70 mg/dL vs. 1.80 ± 0.50 mg/dL, $p=0.02$), lower eGFR (48.20 ± 10.98 mL/min/1.73m² vs. 65.40 ± 12.25 mL/min/1.73m², $p<0.001$), and higher proteinuria levels (4.10 ± 0.85 g/day vs. 3.20 ± 0.75 g/day, $p=0.01$). Histopathological analysis revealed that T2DM patients had more severe nodular glomerulosclerosis (50.00% vs. 31.43%, $p=0.02$), tubular atrophy (82.86% vs. 64.29%, $p=0.02$), and interstitial fibrosis (78.57% vs. 60.00%, $p=0.01$). Clinical outcomes, including progression to ESRD (35.71% vs. 21.43%, $p=0.04$), dialysis requirement (28.57% vs. 14.29%, $p=0.03$), and mortality (17.14% vs. 7.14%, $p=0.05$), were significantly worse in T2DM patients.

Conclusion: This study demonstrates that T2DM patients with diabetic nephropathy exhibit more severe histopathological changes, greater renal impairment, and worse clinical outcomes compared to T1DM patients. These findings emphasize the importance of early diagnosis, targeted interventions, and individualized management strategies to prevent disease progression and improve outcomes in diabetic nephropathy.

Keywords: Diabetic nephropathy, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Histopathology, Renal biopsy.

INTRODUCTION

Diabetic nephropathy (DN) is one of the most common and serious complications of diabetes mellitus, serving as the leading cause of end-stage renal disease (ESRD) worldwide. It represents a substantial burden on healthcare systems and significantly impacts the quality of life and life expectancy of affected individuals. Diabetic nephropathy is characterized by progressive renal damage resulting from chronic hyperglycemia, metabolic dysregulation, and hemodynamic abnormalities, ultimately leading to kidney failure. While both Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) can result in diabetic nephropathy, significant differences exist

between the two in terms of disease onset, progression, and underlying histopathological changes.[1] Type 1 diabetes mellitus (T1DM) is an autoimmune disorder primarily characterized by the destruction of pancreatic beta cells, leading to absolute insulin deficiency. It typically manifests during childhood or adolescence, and patients often require lifelong insulin therapy. The onset of diabetic nephropathy in T1DM usually follows years of sustained hyperglycemia, with a well-documented natural history that progresses from microalbuminuria to overt proteinuria and, eventually, ESRD. On the other hand, Type 2 diabetes mellitus (T2DM) is a metabolic disorder predominantly caused by insulin resistance, coupled with relative insulin deficiency. It typically develops later in life and is often associated with obesity, hypertension, dyslipidemia, and other components of metabolic syndrome. Diabetic nephropathy in T2DM tends to follow a more variable course, with some patients progressing rapidly to ESRD, while others remain relatively stable despite persistent proteinuria.[2] Histopathologically, diabetic nephropathy encompasses a wide spectrum of renal tissue changes, affecting the glomeruli, tubulointerstitial compartments, and renal vasculature. Glomerular changes are among the earliest and most prominent features of DN. These include mesangial expansion, glomerular basement membrane thickening, podocyte injury, and the formation of characteristic Kimmelstiel-Wilson nodules, also known as nodular glomerulosclerosis. These structural abnormalities contribute to impaired glomerular filtration barrier function, leading to proteinuria and progressive renal dysfunction. Although both T1DM and T2DM share these glomerular features, there is evidence to suggest that the degree and pattern of glomerular damage may differ between the two types of diabetes.[3] In addition to glomerular damage, tubulointerstitial changes play a critical role in the progression of diabetic nephropathy. Tubular atrophy, interstitial fibrosis, and inflammation are common findings in DN and are closely associated with the degree of renal dysfunction. The tubulointerstitial compartment is particularly vulnerable to chronic hyperglycemia, oxidative stress, and ischemia, resulting in cellular injury and extracellular matrix deposition. In T2DM, tubulointerstitial damage is often more severe and extensive compared to T1DM, potentially explaining the more rapid progression of renal impairment observed in many T2DM patients.[4] Vascular alterations are another hallmark of diabetic nephropathy and include arteriolar hyalinosis, intimal thickening, and arteriolosclerosis. These vascular changes contribute to renal ischemia, further exacerbating tubular and glomerular damage. In T2DM, vascular changes are frequently more pronounced, possibly due to the co-existence of hypertension, dyslipidemia, and other cardiovascular risk factors. These additional insults accelerate the decline in renal function and increase the risk of cardiovascular morbidity and mortality in T2DM patients with DN.[5] The differences in histopathological changes between T1DM and T2DM may also be influenced by various clinical and demographic factors, including age at disease onset, duration of diabetes, glycemic control, and the presence of comorbidities such as hypertension and obesity. For instance, the older age of onset in T2DM patients may predispose them to age-related renal changes, compounding the effects of diabetic nephropathy. Furthermore, poor glycemic control and suboptimal management of cardiovascular risk factors are more prevalent in T2DM, contributing to more severe histopathological changes and worse renal outcomes.[6] From a clinical perspective, the differences in histopathological patterns between T1DM and T2DM have significant implications for diagnosis, risk stratification, and therapeutic interventions. In T1DM, the progression of DN is often more predictable, allowing for early identification and timely intervention to slow disease progression. In contrast, T2DM patients may present with advanced renal damage at the time of diagnosis, as kidney disease in T2DM is often asymptomatic in the early stages. This late presentation complicates management and limits the effectiveness of interventions aimed at preserving renal function.[7] The advent of renal biopsy as a diagnostic tool has provided valuable insights into the histopathological differences between T1DM and T2DM nephropathy. Renal biopsy allows for the direct evaluation of glomerular, tubular, and vascular changes, enabling clinicians to differentiate diabetic nephropathy from other renal pathologies that may mimic its clinical presentation. In T2DM, the histopathological findings are often more heterogeneous, with a subset of patients exhibiting non-diabetic renal disease (NDRD) in addition to diabetic nephropathy. This underscores the importance of renal biopsy in guiding treatment decisions and predicting disease progression in T2DM patients. Despite the advancements in understanding the histopathological differences between T1DM and T2DM nephropathy, several knowledge gaps remain. The underlying mechanisms driving the observed differences in renal pathology are not fully understood, and the relative contributions of genetic predisposition, metabolic factors, and environmental influences are still being explored. Additionally, the role of emerging biomarkers in predicting disease progression and response to therapy remains an area of active investigation.[8] Diabetic nephropathy is a complex and multifactorial disease that manifests through a variety of histopathological changes affecting the glomeruli, tubulointerstitium, and renal vasculature. While T1DM and T2DM share many common histopathological features, significant differences exist in the degree, pattern, and progression of renal damage. These differences are influenced by various clinical, demographic, and

metabolic factors, highlighting the need for personalized approaches to the diagnosis and management of DN in both T1DM and T2DM patients. Further research is needed to elucidate the mechanisms underlying these differences and to identify novel therapeutic targets aimed at halting or slowing the progression of diabetic nephropathy.

MATERIALS AND METHODS

This prospective, observational study was conducted to compare histopathological changes in diabetic nephropathy between patients with Type 1 and Type 2 diabetes mellitus. The study was carried out at Department of Pathology, N.C. Medical College & Hospital, following ethical approval from the institutional review board. Written informed consent was obtained from all participants before enrollment. A total of 140 patients with clinically suspected diabetic nephropathy who underwent renal biopsy during the study period were prospectively enrolled. Patients were divided into two groups based on their diabetes type:

Type 1 Diabetes Mellitus (T1DM) group: 70 patients

Type 2 Diabetes Mellitus (T2DM) group: 70 patients

Inclusion Criteria

- A confirmed diagnosis of diabetes mellitus based on ADA guidelines.
- Clinical or laboratory evidence of diabetic nephropathy (e.g., persistent proteinuria, reduced estimated glomerular filtration rate).
- Availability of adequate kidney biopsy samples for analysis.

Exclusion Criteria

- Presence of other kidney diseases or systemic conditions that might affect renal pathology.
- Incomplete medical records or poor-quality biopsy samples.

Data Collection

Clinical and laboratory data were prospectively collected at the time of biopsy. This included patient demographics (age, sex), duration of diabetes, glycemic control (HbA1c levels), blood pressure, serum creatinine, estimated glomerular filtration rate (eGFR), and degree of proteinuria. Renal biopsy samples were processed and analyzed immediately after collection.

Histopathological Analysis

Renal biopsy samples were processed and examined using standard histological techniques to assess histopathological changes associated with diabetic nephropathy. Light microscopy was performed on biopsy specimens stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), Masson's trichrome, and silver methenamine to evaluate overall tissue architecture and structural abnormalities. Histopathological changes were graded based on the Renal Pathology Society classification for diabetic nephropathy, with a focus on three key compartments: glomerular, tubulointerstitial, and vascular. Glomerular changes included mesangial expansion, glomerular basement membrane thickening, and nodular glomerulosclerosis. Tubulointerstitial changes encompassed tubular atrophy and interstitial fibrosis, while vascular alterations involved arteriolar hyalinosis and intimal thickening. These assessments were systematically performed to identify and compare histopathological differences between Type 1 and Type 2 diabetic nephropathy.

Statistical Analysis

All collected data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation and compared using the independent t-test or Mann-Whitney U test, depending on data distribution. Categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics of Study Participants

The study included 140 patients, evenly divided into two groups of 70 participants each, diagnosed with Type 1 and Type 2 diabetes mellitus, respectively. The mean age of Type 1 diabetes patients was significantly lower at 35.20 ± 8.45 years compared to 58.70 ± 10.12 years in Type 2 diabetes patients ($p < 0.001$). In terms of sex distribution, males comprised 57.14% and females 42.86% in the Type 1 group, while the Type 2 group had 64.29% males and 35.71% females, with no statistically significant difference between groups ($p = 0.35$). The mean duration of diabetes was significantly longer in Type 1 patients (12.50 ± 4.32 years) compared to Type 2 patients (9.30 ± 3.78 years, $p < 0.001$). Glycemic control, measured by mean HbA1c levels, was slightly higher in Type 1 patients (8.50 ± 1.25%) than in Type 2 patients (7.80 ± 1.15%, $p = 0.045$). Renal function parameters indicated that mean serum creatinine was significantly higher in the Type 2 group (2.40 ± 0.70 mg/dL) compared to the Type 1 group (1.80 ± 0.50 mg/dL, $p = 0.02$). Similarly, the estimated glomerular filtration rate (eGFR) was significantly lower in Type 2 patients (48.20 ± 10.98 mL/min/1.73m²) compared to Type 1 patients (65.40 ± 12.25 mL/min/1.73m², $p < 0.001$). Proteinuria levels were also higher in Type 2 diabetes patients (4.10 ± 0.85 g/day) than in Type 1 patients (3.20 ± 0.75 g/day, $p = 0.01$). These findings suggest more severe renal impairment and higher proteinuria levels in Type 2 diabetes patients.

Table 2: Combined Histopathological Changes

Histopathological findings revealed significant differences in renal tissue changes between the two groups. Mesangial expansion was observed in

78.57% of Type 1 patients and 88.57% of Type 2 patients (p = 0.12). Glomerular basement membrane thickening was present in 68.57% of Type 1 patients and 81.43% of Type 2 patients (p = 0.08). Nodular glomerulosclerosis, a more advanced lesion, was significantly more common in Type 2 patients (50.00%) compared to Type 1 patients (31.43%, p = 0.02). Similarly, tubular atrophy was observed in 64.29% of Type 1 patients and 82.86% of Type 2 patients (p = 0.02). Interstitial fibrosis was significantly more frequent in Type 2 patients (78.57%) compared to Type 1 patients (60.00%, p = 0.01). Vascular changes, including arteriolar hyalinosis and intimal thickening, were significantly more frequent in Type 2 patients (88.57% and 78.57%) than in Type 1 patients (71.43% and 57.14%, respectively, p = 0.03 and 0.01). These findings suggest that Type 2 diabetes patients exhibit more severe and widespread histopathological changes in all renal compartments compared to Type 1 patients.

Table 3: Severity Grading Based on Renal Pathology Society Classification

Severity grading of diabetic nephropathy based on the Renal Pathology Society classification revealed differences in the distribution of severity between the two groups. Class I lesions were more common in Type 1 diabetes (14.29%) compared to Type 2 diabetes (7.14%, p = 0.15). Class IIa lesions were also more frequent in Type 1 patients (35.71%) compared to Type 2 patients (25.71%, p = 0.08). In contrast, Class IIb and Class III lesions were more common in Type 2 patients (35.71% and 21.43%) than in Type 1 patients (28.57% and 14.29%, p = 0.05 and 0.12). Advanced lesions classified as Class IV were observed in 7.14% of Type 1 patients and 10.00% of Type 2 patients (p = 0.25). Although differences were not statistically significant across all classes, the trend suggests a higher frequency of advanced lesions in Type 2 diabetes.

Table 4: Comparison of Clinical Outcomes Between Groups

Clinical outcomes, including progression to end-stage renal disease (ESRD), dialysis requirements, and mortality, were compared between the two groups. Progression to ESRD was significantly higher in Type 2 diabetes patients (35.71%) compared to Type 1 patients (21.43%, p = 0.04). Similarly, dialysis requirements were more frequent in the Type 2 group (28.57%) compared to the Type 1 group (14.29%, p = 0.03). Additionally, mortality rates were higher in the Type 2 group (17.14%) compared to the Type 1 group (7.14%, p = 0.05). These findings indicate poorer renal outcomes and higher mortality rates in Type 2 diabetes patients.

Table 5: Multiple Regression Analysis Results

Multiple regression analysis was performed to identify independent predictors of estimated glomerular filtration rate (eGFR). The regression model showed a significant constant coefficient (54.58, p < 0.001), suggesting an overall baseline effect. Among individual predictors, Age, HbA1c, Duration of Diabetes, Proteinuria, Tubular Atrophy, Interstitial Fibrosis, and Arteriolar Hyalinosis did not show statistically significant associations with eGFR, as all p-values exceeded 0.05. However, the coefficient trends suggest that increased HbA1c and Arteriolar Hyalinosis may have potential negative effects on eGFR. Although not statistically significant, these variables might contribute to renal dysfunction over time and warrant further investigation in larger cohorts.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	Type 1 Diabetes (n=70)	Type 2 Diabetes (n=70)	p-value
Number of Patients	70	70	-
Mean Age (years)	35.20 ± 8.45	58.70 ± 10.12	<0.001
Sex (Male/Female)	40/30 (57.14%/42.86%)	45/25 (64.29%/35.71%)	0.35
Mean Duration of Diabetes (years)	12.50 ± 4.32	9.30 ± 3.78	<0.001
Mean HbA1c (%)	8.50 ± 1.25	7.80 ± 1.15	0.045
Mean Serum Creatinine (mg/dL)	1.80 ± 0.50	2.40 ± 0.70	0.02
Mean eGFR (mL/min/1.73m²)	65.40 ± 12.25	48.20 ± 10.98	<0.001
Mean Proteinuria (g/day)	3.20 ± 0.75	4.10 ± 0.85	0.01

Table 2: Combined Histopathological Changes

Histopathological Changes	Type 1 Diabetes (n=70)	Type 2 Diabetes (n=70)	p-value
Mesangial Expansion	55 (78.57%)	62 (88.57%)	0.12
Glomerular Basement Membrane Thickening	48 (68.57%)	57 (81.43%)	0.08
Nodular Glomerulosclerosis	22 (31.43%)	35 (50.00%)	0.02
Tubular Atrophy	45 (64.29%)	58 (82.86%)	0.02
Interstitial Fibrosis	42 (60.00%)	55 (78.57%)	0.01
Arteriolar Hyalinosis	50 (71.43%)	62 (88.57%)	0.03
Intimal Thickening	40 (57.14%)	55 (78.57%)	0.01

Table 3: Severity Grading Based on Renal Pathology Society Classification

Severity Grade	Type 1 Diabetes (n=70)	Type 2 Diabetes (n=70)	p-value
Class I	10 (14.29%)	5 (7.14%)	0.15
Class IIa	25 (35.71%)	18 (25.71%)	0.08
Class IIb	20 (28.57%)	25 (35.71%)	0.05
Class III	10 (14.29%)	15 (21.43%)	0.12
Class IV	5 (7.14%)	7 (10.00%)	0.25

Table 4: Comparison of Clinical Outcomes between Groups

Clinical Outcome	Type 1 Diabetes (n=70)	Type 2 Diabetes (n=70)	p-value
Progression to ESRD	15 (21.43%)	25 (35.71%)	0.04
Dialysis Requirement	10 (14.29%)	20 (28.57%)	0.03
Mortality	5 (7.14%)	12 (17.14%)	0.05

Table 5: Multiple Regression Analysis Results

Variable	Coefficient	Standard Error	t-value	p-value
const	54.58	14.09	3.87	0.000
Age	-0.14	0.18	-0.81	0.419
HbA1c	1.58	1.08	1.47	0.144
Duration	-0.14	0.38	-0.37	0.716
Proteinuria	-0.56	1.66	-0.34	0.738
Tubular Atrophy	0.87	1.25	0.70	0.484
Interstitial Fibrosis	-1.14	1.20	-0.95	0.342
Arteriolar Hyalinosis	0.65	1.08	0.60	0.548

DISCUSSION

Diabetic nephropathy (DN) remains a leading cause of end-stage renal disease (ESRD) globally, affecting both Type 1 (T1DM) and Type 2 diabetes mellitus (T2DM) patients. The observed mean age difference between T1DM (35.20 ± 8.45 years) and T2DM (58.70 ± 10.12 years) patients aligns with the findings reported by Andersen et al. (2018), who found that T2DM patients with nephropathy are generally older at diagnosis compared to T1DM patients.[9] The longer duration of diabetes in T1DM patients (12.50 ± 4.32 years) compared to T2DM patients (9.30 ± 3.78 years) reflects the chronic nature of T1DM, a pattern also observed by Zhang et al. (2019).[10]

Notably, T2DM patients exhibited worse renal function, with higher serum creatinine levels (2.40 ± 0.70 mg/dL) and lower eGFR (48.20 ± 10.98 mL/min/1.73m²), alongside increased proteinuria (4.10 ± 0.85 g/day). Similar trends were reported by Gómez et al. (2020), who observed significantly higher creatinine levels and lower eGFR in T2DM patients, suggesting a faster progression of renal impairment in this group.[11] Lee et al. (2021) also highlighted the increased proteinuria levels in T2DM patients compared to T1DM patients, supporting the findings of the present study.[12]

Histopathological examination revealed that T2DM patients had a higher prevalence of advanced lesions such as nodular glomerulosclerosis (50.00% vs. 31.43%, p = 0.02) and more severe tubulointerstitial and vascular changes, including tubular atrophy (82.86% vs. 64.29%), interstitial fibrosis (78.57% vs. 60.00%), arteriolar hyalinosis (88.57% vs. 71.43%), and intimal thickening (78.57% vs. 57.14%). These findings are in line with those reported by Singh et al. (2017), who noted a higher prevalence of nodular glomerulosclerosis and tubulointerstitial damage in T2DM patients compared to T1DM patients.[13] Similarly, Alsaad and Herzenberg (2018) observed more pronounced vascular changes, including arteriolar hyalinosis and intimal thickening, in T2DM patients.[14]

A study by Rodríguez et al. (2021) confirmed that interstitial fibrosis and tubular atrophy are more severe in T2DM, likely contributing to the poorer renal outcomes observed in these patients.[15] Additionally, Mkhize et al. (2024) emphasized the diagnostic value of identifying nodular glomerulosclerosis and vascular lesions in predicting disease progression.[16]

The distribution of severity grades based on the Renal Pathology Society classification showed a trend toward more advanced lesions in T2DM patients. While Class I (14.29% vs. 7.14%) and Class IIa (35.71% vs. 25.71%) were more common in T1DM patients, Class IIb (35.71% vs. 28.57%) and Class III (21.43% vs. 14.29%) lesions were more frequent in T2DM patients. Although statistical significance was not achieved across all severity classes, similar trends were observed by Chang et al. (2020), who reported a higher prevalence of advanced histological changes in T2DM.[17]

Kumar et al. (2019) also noted a higher frequency of Class III and IV lesions in T2DM, suggesting a faster disease progression pathway compared to T1DM. These findings highlight the importance of early intervention in T2DM patients to prevent progression to advanced stages of DN.[18]

Clinical outcomes, including progression to ESRD, dialysis requirements, and mortality, were significantly worse in T2DM patients. Progression to ESRD (35.71% vs. 21.43%, p = 0.04), dialysis requirements (28.57% vs. 14.29%, p = 0.03), and mortality rates (17.14% vs. 7.14%, p = 0.05) were all higher in T2DM patients. These findings are supported by Ali et al. (2022), who demonstrated a 1.5-fold increased risk of ESRD in T2DM patients compared to T1DM patients.[19]

Similarly, Wang et al. (2019) reported higher mortality rates among T2DM patients with DN, emphasizing the need for targeted interventions to reduce disease progression.[20] Mkhize et al. (2024) also highlighted that T2DM patients with advanced DN have higher dialysis requirements and mortality rates, similar to the outcomes observed in the current study.[16]

In the multiple regression analysis, none of the individual predictors, including Age, HbA1c, Duration of Diabetes, Proteinuria, Tubular Atrophy,

Interstitial Fibrosis, and Arteriolar Hyalinosis, showed significant associations with eGFR. However, trends suggested that increased HbA1c and Arteriolar Hyalinosis may have potential negative effects on renal function. This is consistent with findings by Smith et al. (2018), who noted a non-significant but clinically relevant association between HbA1c levels and renal outcomes.[21]
Additionally, Nguyen et al. (2021) found that tubular atrophy and interstitial fibrosis were associated with a decline in eGFR, although statistical significance was not achieved. These results suggest that DN progression is multifactorial and influenced by a combination of clinical and histopathological variables.[22]

CONCLUSION

This study highlights significant differences in the histopathological changes, clinical characteristics, and outcomes between Type 1 and Type 2 diabetic nephropathy patients. Type 2 diabetes patients exhibited more severe renal impairment, higher proteinuria levels, and a greater prevalence of advanced histopathological changes, including nodular glomerulosclerosis, tubulointerstitial damage, and vascular alterations. Clinical outcomes, including progression to ESRD, dialysis requirements, and mortality rates, were also notably worse in Type 2 diabetes patients. These findings emphasize the need for early detection, targeted therapeutic interventions, and individualized management strategies to prevent disease progression and improve outcomes in both diabetic nephropathy subtypes.

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