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Original Article

Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a potential early biomarker for diabetic nephropathy: a meta-analysis

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Abstract: Background: Diabetic nephropathy (DN) is a prevalent and chronic, severe complication of diabetes, representing a serious global health concern. Early detection of DN is essential for initiating timely and effective therapeutic interventions and accurately assessing prognosis. Neutrophil Gelatinase-Associated Lipocalin (NGAL), a low molecular weight protein, has emerged as a potential biomarker for DN due to its association with renal injury and its ability to provide early indications of kidney damage. NGAL levels in both serum and urine are elevated in individuals with renal damage, making it a valuable biomarker for detecting early signs of kidney impairment in the context of diabetes. This study aims to investigate the utility of NGAL as an early biomarker for DN and explore its correlation with various clinical parameters associated with the disease. Understanding the relationship between NGAL levels and clinical parameters such as glycemic control, renal function, blood pressure, and duration of diabetes is crucial for comprehensively evaluating the potential of NGAL as a diagnostic and prognostic tool for DN. Furthermore, assessing the sensitivity and specificity of NGAL in detecting early-stage DN will provide valuable insights into its clinical applicability and reliability. Methodology: A planned meta-analysis was conducted following PRISMA and MOOSE guidelines. The PubMed database was searched from January 2016 to June 2023 for English-language studies on DN and NGAL. Fifteen eligible studies were included as per the criteria. Data on serum NGAL levels in DN patients and healthy controls were analyzed using Stata 16.0 software. Result: The study revealed a significantly higher mean serum NGAL level in DN patients (168.08 ng/ml, 95% CI: 105.50-230.67) compared to healthy controls (75.02 ng/ml, 95% CI: 43.02-107.03), demonstrating NGAL's potential as a biomarker (P=0.01). Conclusion: NGAL offers a powerful tool for DN diagnosis, staging, and monitoring, surpassing traditional markers in sensitivity. Challenges include defining universal threshold values and ensuring consistent test performance across diverse clinical settings. The study underscores NGAL's potential in transforming DN diagnosis and management.

Keywords: Diabetic nephropathy, NGAL, lipocalin

Introduction

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a protein known for its relatively low molecular weight, facilitating its passage through the glomerulus and subsequent reabsorption in the proximal tubules. When there is injury to the renal tubules, there is a shift in the pattern of reabsorption, resulting in the premature excretion of NGAL. Elevated levels of NGAL in both serum and urine were observed due to damage to the epithelial cells [1].

Diabetic nephropathy (DN) is a prevalent chronic complication frequently found in individuals diagnosed with diabetes. Its association with diabetes and its impact on a substantial proportion of affected individuals is worth serious attention. The progression of DN to end-stage renal disease is considered a significant and urgent matter in world health. The precise and timely identification of Diabetic Nephropathy is crucial to enhance therapy efficacy and facilitate prognosis assessment [2].

Several pathogenic pathways are involved in diabetic nephropathy, a consequence of diabetes that affects the kidneys. Kidney damage can be due to oxidative stress, hyperglycemia, hypertension, inflammation, and hereditary fac-

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tors. Controlling blood glucose and pressure was the primary goal of treatment, which frequently involved the use of drugs such as ARBs and ACE inhibitors. Medications that reduced inflammation, lowered cholesterol, and encouraged healthy lifestyle choices were also used. Reducing proteinuria and cardiovascular risks was one of the aims, along with decreasing kidney deterioration. A poor prognosis could be due to several risk factors, including poorly managed hypertension, diabetes, a delayed diagnosis, hereditary susceptibility, and other problems. Improving results for diabetic nephropathy management requires regular monitoring, adherence to medication, and cooperation with healthcare providers [3].

It is possible to identify subclinical and early kidney damage by assessing various indicators such as plasma NGAL (pNGAL) and urine NGAL (uNGAL) abnormalities, mild albuminuria, and a preserved estimated glomerular filtration rate (eGFR) [4].

The NGAL protein detected in urine generally originates from distal nephron segments and is predominantly monomeric, different from the dimeric NGAL produced by neutrophils. In addition to its antibacterial capabilities, NGAL may significantly impact cell survival and proliferation. The observed instances of apoptotic cell death in distal nephron segments in different animal and human models of acute kidney injury specifically highlight this significance [5].

Studies in animals and humans demonstrated a significant interest in utilizing NGAL as an early biomarker for acute renal injury. This condition was closely associated with renal tubular interstitial damage and glomerular injury. The principal route for eliminating NGAL from the body was megalin-dependent endocytosis in the proximal tubules. Consequently, an increase in NGAL production through de novo mechanisms or a malfunction in NGAL reabsorption in the proximal renal tubules likely led to the excretion of NGAL in the urine [6].

Several investigations have demonstrated the early elevation of NGAL in the kidney in acute renal illness. NGAL has emerged as a unique diagnostic marker for DN and other disorders that impact kidney function. The method provides a noninvasive approach to diagnosing and monitoring early kidney injury and its subsequent progression [7].

Significant associations with multiple parameters have been demonstrated through NGAL level measurements, encompassing the ratio of albumin to creatinine in the urine, the duration of diabetes, hemoglobin A1C levels, and dyslipidemia. Elevated levels of urinary NGAL can be observed in individuals with well-controlled diabetes and norm-albuminuria, suggesting its potential utility as an early biomarker for diabetic nephropathy [8].

Higher levels of uNGAL are linked to more advanced stages of illness, suggesting that the creation of tubular NGAL is actively occurring rather than being a passive result of decreased renal clearance [9].

Several studies have been conducted on NGAL for its potential as a noninvasive indicator of renal impairment. However, its utility as a broad indicator for screening for renal illness has needed to be proven. This study has been planned to establish the role of NGAL as an early biomarker in Diabetic Nephropathy in light of the earlier studies.

Materials and methods

Search strategy and database selection

The investigation conducted in this study rigorously followed the requirements set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the meta-analysis of observational studies in epidemiology (MOOSE). A comprehensive literature search was undertaken using the PubMed database, including various search phrases. The terminology encompassed in the text is ‘Diabetic nephropathy’, sometimes referred to as ‘DN’, ‘diabetes’, ‘neutrophil gelatinase-associated lipocalin’, commonly abbreviated as ‘NGAL’, ‘lipocalin-2’, denoted as ‘Lcn-2’, and ‘siderocalin’. Our search methodology was also adapted to accommodate multiple databases, incorporating various search keywords and logical operators such as ‘or’ and ‘and’. We conducted this search from January 2016 to June 2023 and limited our focus to scholarly research published in English. We reviewed the reference lists manually from the retrieved publications to identify potentially relevant research

Table 1. Mean ± SD of studies on NGAL levels in cases and controls

Sr. No.	Author & Year	Place	Case		Control	
			Subject	Mean ± SD	Subject	Mean ± SD
1	Najafi L et al. & 2021 [21]	Iran	40	312±23.86	50	174.9±75.9
2	Lee JH et al. & 2021 [22]	Taiwan	10	42.2±8.92	106	35.3±28.7
3	Mohany KM et al. & 2019 [23]	Saudi Arabia	76	282.8±22.77	20	66.7±21.6
4	Al-Fartosy AJM et al. & 2021 [24]	Iraq	31	55.26±2.51	33	14.78±2.67
5	Marketou NP et al. & 2021 [25]	Sweden	33	86.32±4.13		
6	Ali H et al. & 2022 [26]	Kuwait	67	92.76±7.50	42	52.47±2.9
7	Choi JW et al. & 2021 [27]	Republic of Korea	160	145±30.97	61	63.5±7.65
8	Kim SY et al. & 2018 [28]	Republic of Korea	60	148.4±14.98	24	61.9±28.88
9	Abbasi F et al. & 2020 [29]	Iran	44	129.13±13.60	39	77.02±34.76
10	Bjornstad P et al. & 2019 [30]	Canada	22	225.7±18.67	73	174.4±8.32
11	Aslanhan E et al. & 2019 [31]	Istanbul	16	378±157.50	66	379±7.08
12	Żyłka A et al. & 2018 [32]	Poland	19	67.2±3.16	61	53.8±5.36
13	Kaul A et al. & 2018 [33]	India	49	474.88±20.86	54	42.56±8.48
14	Motawi TK et al. & 2018 [34]	Egypt	25	97.99±4.93	25	45.53±4.76
15	Mahfouz MH et al. & 2016 [35]	Saudi Arabia	50	131±27.29	50	46.46±8.56

for inclusion in our meta-analysis. The study participants were adults aged 18 and older with a diabetes diagnosis.

Participant selection

Reviews, correspondence, conference abstracts, and repetitive research papers were not included. Studies that did not present pertinent data were also excluded from consideration.

Data extraction and assessment

- The name of the first author.
- The year of publication.
- The size of the sample.
- The type of study.
- The mean and standard deviation (SD) values for Serum NGAL.

Statistical analyses

Statistical analyses were done using Stata 16.0 software developed by Stata Corporation in College Station, TX. We considered the mean values and their corresponding 95% confidence intervals (CIs) to ascertain pooled effect sizes. Two statistical methods were utilized to evaluate the variability of the studies: the Cochran Q test and I-squared (I^2) statistics. The random-effects model was used in cases where considerable heterogeneity was discovered, characterized as a *p*-value below 0.05 or an I^2 value of more than 50%. In cases where the heterogeneity did not reach statistical significance, we utilized a fixed-effect model and considered a *p*-value of less than 0.05 as the threshold for statistical significance.

Results

Our research comprised a total of fifteen papers that met the qualifying criteria for our study. These articles specifically focused on studying the association between Diabetic nephropathy and serum NGAL. **Table 1** provides an overview of the pooled mean ± SD values for serum NGAL levels in individuals diagnosed with Diabetic nephropathy and in a group of healthy controls. The study observed a mean serum NGAL level of 168.08 ng/ml (95% CI: 105.50-230.67) in cases of Diabetic nephropathy, indicating a significant level of heterogeneity (I^2=99.69%). On the other hand, in the control group, the mean serum NGAL level is 75.02 ng/ml (95% CI: 43.02-107.03), showing considerable heterogeneity (I^2=99.06%). The findings of this study suggest that persons diagnosed with diabetic nephropathy have elevated levels of serum NGAL compared to a control group of healthy individuals with a *p*-value of 0.01, as illustrated in **Figure 1**.

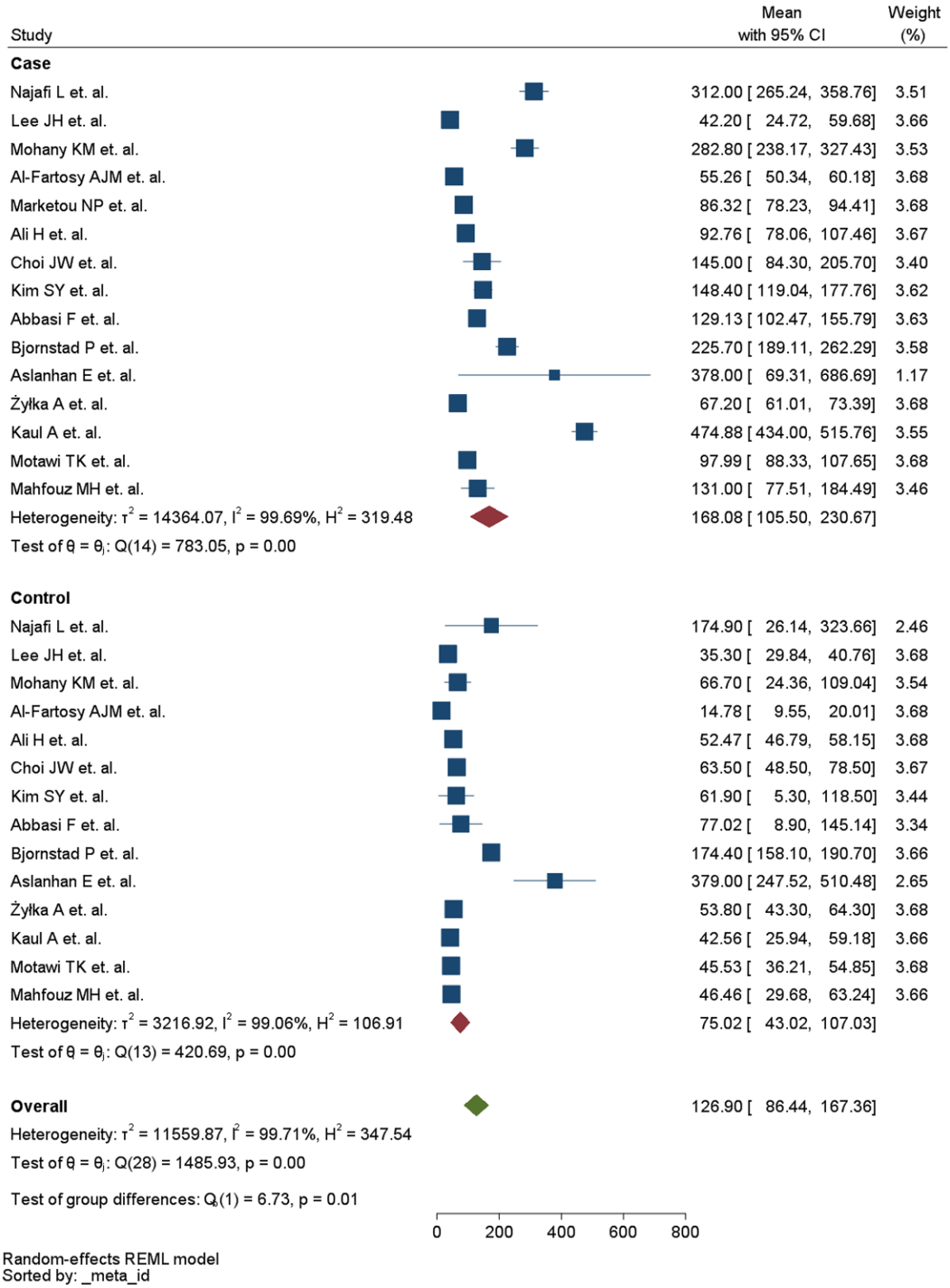

Figure 1. Forest plot for Serum NGAL in diabetic nephropathy cases and control group.

Discussion

Diabetes is a public health concern worldwide and is considered a pandemic. The incidence of type 1 diabetes mellitus (T1DM) is relatively stable due to its involvement of hereditary and genetic factors, whereas the prevalence of type 2 diabetes (T2D) was progressively rising.

Diabetes frequently correlates with enduring consequences, such as diabetic nephropathy, retinopathy, and other complications. Diabetic nephropathy is prevalent in persons diagnosed with type 1 and type 2 diabetes [2]. The identification of diabetic nephropathy can be achieved through conventional laboratory examinations, with specific emphasis on the surveillance of microalbuminuria levels surpassing 300 mg per 24 hours and observing a progressively declining glomerular filtration rate. Since microalbuminuria is a diagnostic sign that typically manifests in the later stages of renal injury, it has become imperative to ascertain an early biomarker for detecting renal impairment [10].

The present diagnostic indicators for diabetic nephropathy, such as microalbuminuria and blood creatinine levels, are plagued by concerns over their reliability. Various factors, such as physical activity, dietary choices, infections, and hydration state, can influence the efficacy of these markers in detecting early kidney impairment. Factors such as age, gender, muscle mass, and overall renal function were found to influence serum creatinine levels, with an increase typically observed only in the later stages of the disease [11].

Regular monitoring of NGAL levels may aid in the timely identification of DN before the onset of clinical manifestations. Integrating NGAL with specific biomarkers can potentially augment diagnostic precision, hence facilitating the discrimination between renal etiologies and alternative clinical diseases [12]. The present study observed that serum NGAL concentrations were significantly higher in DN patients than in healthy controls (P=0.01). Many studies reported similar results that NGAL was a highly sensitive biomarker with lower specificity than DN. So, NGAL could be utilized as a single reliable biomarker for early detection of DN [13-17]. On the other hand, some studies reported results contradicting our study, and they did not observe any significant associations of NGAL with DN [18, 19].

NGAL is a crucial transporter protein pivotal in various physiological processes within the human body. These processes, including inflammation regulation, immune response generation, and maintenance of metabolic homeostasis, were affected by NGAL. NGAL is documented as a potential indicator of initial renal impairment, even in cases where urine microalbumin levels remain undetectable. Hence, a comprehensive elucidation of the intricate role of NGAL in detecting DN and a deeper understanding of its underlying mechanism could contribute to establishing NGAL as a promising early biomarker for DN [20].

Our investigation demonstrates a thorough comprehension of the potential function of NGAL in diagnosing DN. Appreciating both the advantages and drawbacks of NGAL and recognizing conflicting results in other research helps to develop a fair and knowledgeable viewpoint on the application of NGAL as a biomarker for Diabetic Nephropathy. According to the study, more research into the mechanics of NGAL, how it interacts with other biomarkers, and validation studies to prove its dependability in different groups can be conducted in the future.

Conclusion

NGAL is a powerful diagnostic, staging, and monitoring tool for DN and other renal ailments. The marker in question provides heightened sensitivity compared to traditional biomarkers and serves as a crucial component in the timely identification of kidney damage and assessing therapy efficacy. Nevertheless, ongoing obstacles must be addressed to advance in this field. These challenges encompass establishing universally accepted threshold values and assuring consistent test performance in diverse clinical environments.

Disclosure of conflict of interest

None.

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