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RESEARCH ARTICLE

Serum Levels of Growth Differentiation Factor 15 as a Biomarker for Chronic Kidney Disease in Patients with Type 2 Diabetes Mellitus

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ABSTRACT:

Background: Growth Differentiation Factor 15 (GDF-15) has been identified as a biomarker of cellular stress conditions and has demonstrated functional implications in kidney disease, metabolic disorders, and diabetes. However, the relationship between GDF-15 and the coexistence of type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) remains unclear. This study aims to investigate the association between GDF-15 levels and the presence of CKD in patients with T2DM, then analyze the cut off value. **Method:** A cross-sectional study was conducted, enrolling a total of 60 patients. T2DM patients were categorized into two groups based on the presence or absence of CKD. Serum GDF-15 levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit. **Results:** The study population (n=60) predominantly consisted of male individuals with an average age of 53 years. The receiver operating characteristic (ROC) curve analysis yielded an area under the curve (AUC) of 0.846 (95% CI = 0.748 – 0.945) with a statistically significant p-value of < 0.001. The optimal cut-off value for serum GDF-15 to detect the presence of CKD was determined as 362.80 pg/mL, with corresponding sensitivity and specificity values of 77% and 79%, respectively. Furthermore, a significant association between GDF-15 levels and both T2DM without CKD and T2DM with CKD was observed ($p < 0.001$). **Conclusion:** There is a significant association observed between serum GDF-15 levels in patients with type 2 diabetes mellitus (DM) and the presence of CKD. The cut of value GDF-15 to detect the presence of CKD was determined as 362.80 pg/mL with sensitivity and specificity values of 77% and 79%, this is can be considered as a potential biomarker for the detection of CKD in individuals with T2DM.

KEYWORDS: GDF 15, CKD, DM, T2DM.

INTRODUCTION:

The transforming growth factor-β superfamily encompasses growth differentiation factor 15 (GDF-15), an anti-inflammatory cytokine.[1]

Aside from its role as a responsive factor to cellular stress, GDF-15 has been implicated in kidney disease, metabolic disorders,[2] and diabetes.[3] Elevated levels of GDF-15 in patients with type 2 diabetes mellitus (T2DM) have been associated with an increased risk of impaired kidney function.[4] Chung et al. (2021) conducted a study that demonstrated an inverse relationship between GDF-15 levels and estimated glomerular filtration rate (eGFR),[5] indicating a higher GDF-15 level was associated with reduced kidney

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function. Furthermore, elevated GDF-15 levels have been linked to microvascular complications, specifically the development of chronic kidney disease (CKD) in patients with diabetes mellitus (DM).[6] Another study revealed elevated GDF-15 levels in patients with T2DM, suggesting GDF-15's potential as a biomarker for identifying individuals at risk for prediabetes.[1] Ruszala et al. (2020) found that GDF-15 served as a predictor for the development of DM.[7] Despite the available evidence in DM and CKD patient populations, research on GDF-15 in Indonesia remains limited. Therefore, further investigation into GDF-15 is warranted as data on GDF-15 in relation to diabetes and kidney disease in Indonesia are scarce.[8]

Diabetes mellitus (DM) is a metabolic disorder with a rising prevalence worldwide. According to the International Diabetes Federation (IDF) in 2019, DM accounted for 4.2 million deaths.[9-12] Type 2 diabetes constitutes the majority of diabetes cases globally, with over 90% of incidence.[13-16] CKD significantly contributes to the risk of end-stage renal disease in individuals with diabetes[17] and is increasingly prevalent, leading to elevated mortality rates[18] and imposing a substantial economic burden on healthcare systems.[19]

CKD is characterized by a decline in kidney function resulting in decreased glomerular filtration rate (GFR).[20-23] Hemodynamic changes within renal tissue and impaired cellular function contribute to the reduced GFR, leading to elevated blood levels of GDF-15[5]. Consequently, GDF-15 levels increase as a marker of cellular stress response,[3] inflammation,[24] and the presence of kidney and metabolic diseases.[2]

Understanding the differentiation of GDF-15 levels and their association with CKD incidence in patients with DM, particularly within the Indonesian population, remains unclear. Therefore, further research is necessary to investigate the role of GDF-15 as a potential biomarker and its relationship with CKD in patients with DM.

MATERIAL AND METHODS:

Research Methods:

This study employed a cross-sectional design and was conducted at Universitas Airlangga Hospital between September 2022 and January 2023. The research protocol received ethical clearance from the institutional ethics committee of Universitas Airlangga Hospital, with approval number 082/KEP/2022. All data analyzed in this study were obtained from medical records, ensuring anonymity and confidentiality of the subjects involved.

Patient Enrollment:

The patients included in this study met the eligibility criteria of confirmed type 2 diabetes mellitus based on medical records and age ≥ 18 years and provided informed consent. Exclusions encompassed patients with tumors or receiving immunosuppressive drugs. The patients were categorized into CKD and Non-CKD groups based on renal function, determined by the doctor's diagnosis and medical record data. The CKD group encompassed stages G2-G5 or dialysis requirement, while the non-CKD group had eGFR ≥ 90 ml/minute/1.73 m^2. Serum samples were stored at -40°C until transportation, and GDF-15 measurement using ELISA was conducted at the Laboratory of the Institute of Tropical Diseases, Universitas Airlangga.

Data Collection:

Relevant characteristics of the participants, including age, gender, smoking history, duration of diabetes mellitus (DM), hypertension status, and body mass index (BMI), were systematically collected through a comprehensive review of medical record data and structured interviews conducted by trained personnel.

Materials:

Blood serum samples were utilized in this study for the measurement of Growth Differentiation Factor 15 (GDF-15). To quantify GDF-15 levels, a commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kit (Elabscience) was employed, following the manufacturer's instructions precisely.

Statistical Analysis:

The demographic characteristics of the study participants were presented using descriptive statistics, summarized in the form of a table. Prior to analysis, the normality of the data was assessed using the Shapiro-Wilk test ($p > 0.05$). Additionally, the homogeneity of variances was examined using Levene's test ($p > 0.05$). For normally distributed data, an independent sample t-test was employed. In cases where the data deviated from normality, the Mann-Whitney U test was utilized. To determine the optimal cut-off value and assess sensitivity and specificity, receiver operating characteristic (ROC) curve analysis was performed. For categorical data, the chi-square test was employed to evaluate relationships. Statistical significance was established at a p-value ≤ 0.05. All statistical analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) software, version 26.0.

RESULTS:

The demographic characteristics of the study population, consisting of 60 individuals, are presented in Table 1. The average age of the patients was determined to be 53.43±9.21 years. Among the study participants, 34 individuals (56.7%) were identified as female, while 26 individuals (43.3%) were identified as male.

Table 1: Characteristics of the Study Population

	Total	Group		p-value
		DM non-CKD	DM-CKD	
n	60	29	31	
Age [e]	53.43±9.21	51.34± 9.42	55.38 ± 8.69	0.089[c]
Gender, n(%)				
Male	34 (56.7)	17 (50.0)	17 (50.0)	0.972[b]
Female	26 (43.3)	12 (46.2)	14 (53.8)	
Smoking	11 (18.3)	7 (23.3)	4 (13.3)	0.429[b]
DM duration				0.232[b]
< 5 years	24 (40)	13 (54.2)	11 (45.8)	
5-10 years	23 (38.3)	8 (34.8)	15 (65.2)	
> 10 years	13 (21.7)	8 (61.5)	5 (38.5)	
BMI[c]	24.26 ± 2.49	24.13 ± 2.55	24.38 ± 2.46	0.693[c]
Hypertension, n(%)	26 (43.3)	11 (42.3)	15 (57.7)	0.578[b]
eGFR	80 (3-170)	101 (90-170)	38 (3-86)	0.000[a*]
Creatinine	0.99 (0.19-14.35)	0.79 (0.19-0.95)	1.7(0.81-14.35)	0.000[a*]

[d] Median (min-max), [e] Mean ± SD, [a] Mann Whitney, [b] Chi-Square, [c] Independent T- test, *significant p < 0.05

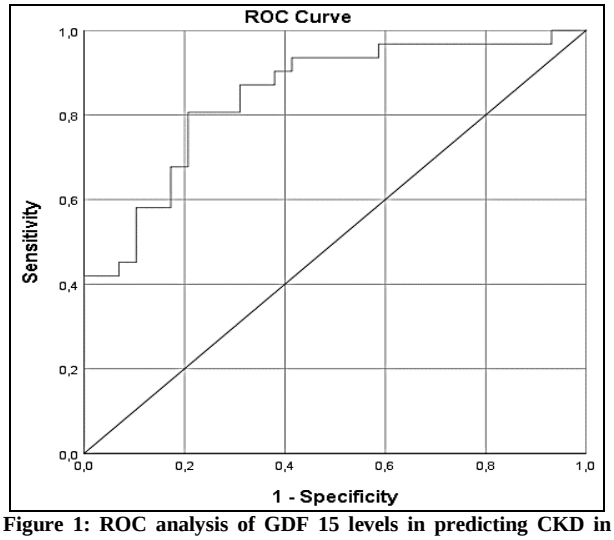

Figure 1: ROC analysis of GDF 15 levels in predicting CKD in individuals with diabetes

AUC = 0.846 (p = <0.001); (95% CI: 0.748–0.945); identification of cut-off = 362.80 pg/mL; Sensitivity = 77% dan specificity = 79% (Figure 1). ROC = receiver operating characteristic; AUC = area under the curve; CI = Confidence Interval.

In the DM non-CKD group, the maximum recorded GDF-15 value was 544.95 pg/mL, whereas in the CKD group, it reached 1896.76 pg/mL. Conversely, the minimum values were observed as 61.68 pg/mL and 118.15 pg/mL, respectively. The obtained p-value of <0.001 (Table 2) indicates a significant association between GDF-15 levels and the differentiation of DM non-CKD and DM-CKD groups.

Table 2: Association GDF 15 with DM non-CKD and DM-CKD

	Median (minimum-maxsimum) (pg/mL)	**P-value**
DM-Non CKD	231.35 (61.68 – 544.95)	<0.001*
DM-CKD	514.92 (118.15 – 1896.76)	

DISCUSSION:

The present study demonstrates a significant difference in GDF-15 levels between the DM non-CKD and DM-CKD groups (p < 0.001), indicating that the DM-CKD group exhibits significantly higher GDF-15 levels compared to the DM non-CKD group. These findings corroborate previous research, which also reported elevated GDF-15 levels in diabetic kidney disease patients compared to diabetic patients without kidney disease.[25]

Elevated levels of GDF-15 have also been observed in patients with type 2 diabetes mellitus, suggesting its potential as a biomarker for identifying individuals with prediabetes.[1] The expression of GDF-15 increases with disease progression, and it is associated with factors such as age, BMI, insulin resistance, and the development of type 2 diabetes. GDF-15 is released by various cell types, including macrophages, cardiomyocytes, and adipocytes, particularly under stressful conditions.[26]

The average GDF-15 value was found to be higher in the CKD group, with a median value of 231.35 pg/mL in the non-CKD DM group and an average of 514.92 pg/mL in the DM-CKD group. Increased GDF-15 levels are associated with chronic inflammation, oxidative stress, and tissue injury, which may reflect kidney disorders.[27] Moreover, the upregulation of GDF-15 expression in the early stages of kidney injury is believed to serve a protective role against tissue damage and, consequently, serves as a predictor of tissue injury[28]. Further investigations are warranted to elucidate the precise underlying mechanisms.

Additionally, it has been noted that GDF-15 levels are lower in type 2 diabetes patients with normal kidney function and without heart disease, while they are higher in patients with decreased kidney function. Furthermore, elevated GDF-15 levels have been identified as a risk

marker for renal endpoints.[4] Elevated levels of GDF-15 in the bloodstream, as observed in previous research, have been found to be associated with factors such as age, muscle performance, and heightened inflammation. Notably, a previous study demonstrated that plasma levels of GDF-15 tend to increase with age and exhibit an inverse correlation with an active lifestyle. Specifically, among individuals of different age groups, circulating GDF-15 was notably higher in sedentary patients, while significantly lower levels were observed in physically active individuals, such as cyclists.[29]

The increased in GDF 15 is also influenced by several conditions, including smoking, increasing age, diabetes mellitus, low eGFR, anemia[30], and sepsis[31]. The GDF value of 15 increases in smokers and ex-smokers, with a higher average value shown in former smokers[30], diabetic retinopathy[5], endometriosisis severity[32],cancer, heart disease, as well as chronic liver disease[33].

The current study reveals significantly elevated GDF-15 levels in DM-CKD patients compared to DM non-CKD patients. CKD, as one of the microvascular complications in diabetes mellitus, triggers the interaction of mediators produced by endothelial cells, resulting in endothelial dysfunction and imbalanced intracellular mechanisms.[34,35] It is worth mentioning that GDF-15 is predominantly secreted by endothelial cells, and elevated serum levels of GDF-15 are indicative of endothelial and microvascular damage.[36]

GDF-15, also known as Macrophage Inhibiting Cytokine 1 (MIC-1), belongs to the Transforming Growth Factor (TGF-β) superfamily. Although the exact function of GDF-15 remains to be fully understood, it plays a crucial role in regulating cell growth, apoptosis, and inflammatory activation. GDF-15 exhibits both anti-inflammatory and pro-inflammatory signaling properties in various cardiovascular complications.[26,37]

The cut-off analysis was conducted to determine the optimal threshold for the identification of chronic kidney disease (CKD), while the sensitivity and specificity measures were employed to assess the potential of GDF-15 as a biomarker. Based on the analysis outcomes, the determined cut-off value for predicting CKD was 362.80 pg/mL, accompanied by a sensitivity of 77% and a specificity of 79%. These sensitivity and specificity values align with those reported in a prior study that investigated GDF-15 in CKD and non-CKD cohorts, demonstrating a sensitivity of 76.5% and a specificity of 76.0%.[27]

One limitation of this study is the existence of several other factors that may influence the decrease of GDF-15 levels in DM-CKD and the increase in GDF-15 levels in DM non-CKD. These factors were not included in the exclusion criteria, which may have impacted the observed results.

CONCLUSION:

There is a significant association observed between serum GDF-15 levels in patients with DM and the presence of CKD. Specifically, GDF-15 levels were found to be elevated in patients with CKD complication. The cut of value GDF-15 to detect the presence of CKD was determined as 362.80 pg/mL with sensitivity and specificity values of 77% and 79%. These findings suggest that GDF-15 holds potential as a biomarker for the detection of CKD in patients with DM.

CONFLICT OF INTEREST:

All the authors declare no conflict of interest.

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