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Plasma Levels of Growth Differentiation Factor 15 and Adverse Kidney Outcomes

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Objectives : Growth differentiation factor-15 (GDF-15), a stress-responsive cytokine, is implicated in adverse outcomes of cardiovascular disease, diabetes, and malignancies, highlighting its potential as a prognostic marker. However, its association with chronic kidney disease (CKD) development and its underlying mechanisms remain unclear. We aimed to investigate the association between baseline plasma GDF-15 levels and incident CKD, explore potential mechanisms using proteomics, and assess their causal relationship with kidney function using Mendelian randomization (MR).
Methods : We analyzed 31,965 UK Biobank participants without pre-existing CKD. The primary outcome was incident CKD, defined by diagnostic codes or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (eGFR-based CKD). Proteomics-based mediation and protein-protein interaction analyses were performed to identify potential mediators linking GDF-15 to CKD. Additionally, bidirectional two-sample MR analyses were conducted using genome-wide association study summary statistics to evaluate the causal relationship between GDF-15 and eGFR.
Results : In multivariable cause-specific analyses, higher GDF-15 levels were significantly associated with an increased risk of CKD (adjusted HR: Q2, 1.05 [0.87-1.26]; Q3, 1.21 [1.01-1.45]; Q4, 1.87 [1.56-2.26] vs. Q1; P-for-trend <0.001). Similar results were observed with eGFR-based CKD outcome (adjusted HR: Q2: 1.99 [1.22-3.24]; Q3: 2.82 [1.76-4.50]; Q4: 4.70 [2.95-7.48] vs. Q1; P-for-trend <0.001). Proteomics-based mediation analysis identified proteins associated with TNF receptor superfamily signaling, extracellular matrix organization, and immune cell chemotaxis as mediators. MR analysis demonstrated a significant causal association between genetically predicted higher GDF-15 levels and higher eGFR (IVW coefficient: 0.003; 95% CI: 0.001-0.004; P = 0.004). Conversely, higher genetically predicted eGFR was associated with lower GDF-15 levels (IVW coefficient: -1.238; 95% CI: -1.591 to -0.886; P < 0.001).
Conclusions : This study provides evidence supporting the role of GDF-15 as a prognostic biomarker for CKD, suggesting its causal protective effect on kidney function. Further studies are required to explore the mechanistic pathways and therapeutic implications of GDF-15 in kidney disease.

table1.jpg

Table. Incidence Rates and Hazard Ratios for Kidney Outcomes according to GDF15 categories

	Cohort 1				Univariable		Multivariable [a]	
	Person-years	Events	Incidence rate [b]		HR (95% CI)	P	HR (95% CI)	P
CKD				Con	2.21 (2.10 - 2.32)	<0.001	1.62 (1.49 - 1.76)	<0.001
Q1	108345.8	193 (2.4%)	17.8 (15.5-20.5)	Q1	(Reference)		(Reference)	
Q2	107645.2	287 (3.6%)	26.7 (23.7-29.9)	Q2	1.5 (1.25 - 1.80)	<0.001	1.05 (0.87 - 1.26)	0.640
Q3	106890.3	431 (5.4%)	40.3 (36.7-44.3)	Q3	2.26 (1.91 - 2.68)	<0.001	1.21 (1.01 - 1.45)	0.043
Q4	104013.2	887 (11.1%)	85.3 (79.8-91.1)	Q4	4.78 (4.09 - 5.59)	<0.001	1.87 (1.56 - 2.26)	<0.001
Total	426894.4	1,798 (5.6%)	42.1 (40.2-44.1)		*P* for trend [c]	<0.001	*P* for trend [c]	<0.001
	Sub-Cohort 1				**Univariable**		**Multivariable [a]**	
	Person-years	**Events**	**Incidence rate [b]**		**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
CKD-eGFR				Con	2.74 (2.57 - 2.92)	<0.001	1.88 (1.66 - 2.13)	<0.001
Q1	30337.8	21 (0.5%)	6.9 (4.5-10.6)	Q1	(Reference)		(Reference)	
Q2	30057.2	76 (1.9%)	25.3 (20.2-31.7)	Q2	3.65 (2.25 - 5.92)	<0.001	1.99 (1.22 - 3.24)	0.006
Q3	29742.9	168 (4.3%)	56.5 (48.6-65.7)	Q3	8.16 (5.19 - 12.85)	<0.001	2.82 (1.76 - 4.50)	<0.001
Q4	28519.6	431 (10.9%)	151.1 (137.5-166.1)	Q4	21.88 (14.12 - 33.90)	<0.001	4.7 (2.95 - 7.48)	<0.001
Total	118657.5	696 (4.4%)	58.7 (54.5-63.2)		*P* for trend [c]	<0.001	*P* for trend [c]	<0.001
	Sub-Cohort 1				**Univariable**		**Multivariable [a]**	
	Person-years	**Events**	**Incidence rate [b]**		**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Albuminuria				Con	3.33 (2.97 - 3.74)	<0.001	1.9 (1.48 - 2.43)	<0.001
Q1	30407.8	4 (0.5%)	1.3 (0.5-3.5)	Q1	(Reference)		(Reference)	
Q2	30286.7	10 (1.9%)	3.3 (1.8-6.1)	Q2	2.51 (0.79 - 8.00)	0.120	1.97 (0.61 - 6.38)	0.260
Q3	30316.4	21 (4.3%)	6.9 (4.5-10.6)	Q3	5.27 (1.81 - 15.35)	0.002	2.97 (0.97 - 9.07)	0.056
Q4	29948.1	99 (10.9%)	33.1 (27.1-40.3)	Q4	25.33 (9.32 - 68.81)	<0.001	5.27 (1.75 - 15.87)	0.003
Total	120958.9	134 (4.4%)	11.1 (9.4-13.1)		*P* for trend [c]	<0.001	*P* for trend [c]	0.002

Note: [a] Adjusted for age, sex, ethnicity, BMI, alcohol, smoking, income score, town deprivation index, hypertension, diabetes, CVD, COPD, asthma, liver disease, cancer, statin use, and RASB use, eGFR, uACR, hsCRP, fasting glucose, LDL-cholesterol, HDL-cholesterol, and Triglyceride.
[b] Incidence rate is presented as per 10,000 person-year.

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Table. Bidirectional Two-sample MR analysis between GDF-15 and eGFR

	IVW		Weighted median		MR-Egger	
Exposure/Outcome	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
GDF-15/eGFR						
GDF-15/eGFR [CKDGen+UKB]	0.003 (0.001 to 0.004)	0.004	0.002 (0.000 to 0.004)	0.031	-0.002 (-0.014 to 0.009)	0.664
GDF-15/eGFR [CKDGen]	0.003 (0.0002 to 0.005)	0.021	0.003 (0.0004 to 0.005)	0.035	0.002 (-0.013 to 0.016)	0.813
eGFR/GDF-15						
eGFR [CKDGen+UKB]/GDF-15	-1.238 (-1.591 to -0.886)	<0.001	-1.368 (-1.937 to -0.798)	<0.001	-1.172 (-1.976 to -0.367)	0.004
eGFR [CKDGen]/GDF-15	-1.356 (-1.783 to -0.929)	<0.001	-1.530 (-2.184 to -0.877)	<0.001	-1.416 (-2.474 to -0.359)	0.009

	MR-Egger Pleiotropy test	Cochran's Q Heterogeneity		Global test	F-statistic	I
Exposure/Outcome	P-value	Q	P-value	P-value		
GDF-15/eGFR						
GDF-15/eGFR [CKDGen+UKB]	0.367	3.1	0.542	0.580	200.7	0.0%
GDF-15/eGFR [CKDGen]	0.893	2.4	0.691	0.829	200.7	0.0%
eGFR/GDF-15						
eGFR [CKDGen+UKB]/GDF-15	0.856	574.4	0.110	0.114	74.9	7.0%
eGFR [CKDGen]/GDF-15	0.903	291.6	0.087	0.070	66.2	10.8%

Note: [a] Global test of the MR-PRESSO.
Abbreviation: CI, confidence interval; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor 15; IVW, inverse-variance weighted; MR, Mendelian randomization; OR, odds ratio; UKB, UK Biobank.