Sociedad Española de Nefrología

nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Review

Urinary epidermal growth factor in kidney disease: A systematic review

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ARTICLE INFO

Article history:
Received 25 April 2022
Accepted 6 October 2022

Keywords:
Urinary epidermal growth factor
Chronic kidney disease
Nephropathy
Acute kidney injury

ABSTRACT

Urinary epidermal growth factor (uEGF) is primarily produced by the kidney, and alterations of it have been associated with several kidney diseases. The aim of this review was to describe uEGF levels in presence or progression of kidney diseases. We conducted a systematic review of observational studies with uEGF determination, patients with acute kidney injury, chronic kidney disease, primary or secondary nephropathy, or renal cancer were included. Studies were searched in Medline, Google Scholar, Science Direct, and EBSCO up to August 2, 2021. Participants and measurements characteristics from which uEGF were determined as the specificity, sensitivity, and the area under the ROC curve, whenever available, were gathered. 53 studies were included, the most frequent kidney diseases studied were acute kidney injury, chronic kidney disease, and diabetic nephropathy. In most studies, uEGF levels were lower in cases than in controls. Studies showed that uEGF levels can predict presence or progression of acute kidney injury, chronic kidney disease, and nephropathy. Heterogeneity in the reported uEGF values can be attributed to the different techniques, sampling, and ways of reporting uEGF values.

Although uEGF values are lower in patients with almost all kidney diseases and their progression, uEGF evaluation methods should be standardised to be used as a biomarker in clinical practice.

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https://doi.org/10.1016/j.nefro.2022.10.003

Factor de crecimiento epidérmico urinario en la enfermedad renal: una revisión sistemática

Palabras clave:
Factor de crecimiento epidérmico urinario
Enfermedad renal crónica
Nefropatía
Lesión renal aguda

RESUMEN

El factor de crecimiento epidérmico urinario (uEGF) es producido principalmente por el riñón, y sus alteraciones se han asociado con varias enfermedades renales. El objetivo de esta revisión fue describir los niveles de uEGF en presencia o progresión de enfermedades renales. Realizamos una revisión sistemática de estudios observacionales con determinación de uEGF en la que se incluyeron pacientes con insuficiencia renal aguda, enfermedad renal crónica, nefropatía primaria o secundaria, o cáncer renal. Se realizaron búsquedas de estudios en Medline, Google Scholar, Science Direct y EBSCO hasta el 2 de agosto de 2021. Se extrajeron las características de los participantes y de las mediciones del uEGF, así como la especificidad, la sensibilidad y el área bajo la curva ROC, siempre que estuvieran disponibles. Se incluyeron 53 estudios, y las enfermedades renales más frecuentes estudiadas fueron la insuficiencia renal aguda, la enfermedad renal crónica y la nefropatía diabética.

En la mayoría de los estudios los niveles de uEGF fueron más bajos en los casos que en los controles. Los estudios demostraron que los niveles de uEGF pueden predecir la presencia o la progresión de la lesión renal aguda, la enfermedad renal crónica y la nefropatía. La heterogeneidad en los valores de uEGF informados se puede atribuir a las diferentes técnicas, muestreo y formas de informar los valores de uEGF.

Aunque los valores de uEGF son más bajos en pacientes con casi todas las enfermedades renales y su progresión, los métodos de evaluación de uEGF deben estandarizarse para ser utilizados como biomarcadores en la práctica clínica.

Key concepts

- uEGF levels vary with age and there are no cut-off points for normal values.
- uEGF levels are decreased in kidney diseases.
- uEGF does not appear to be useful for the differential diagnosis of renal diseases.

Introduction

Epidermal growth factor (EGF), formed from pro-pre-EGF and pre-EGF, is a polypeptide of 53 amino acids of 6.2 kDa with multiple biological functions such as cell proliferation, transformation, and migration.[1] Synthesised in various tissues including the kidney, EGF exerts its actions through the EGF receptor.

The EGF has been identified in various species including humans, and its renal production is present in both apical and basal membranes of the epithelial cells of the proximal tubules, the loop of Henle, and the distal tubules[2]; and the function exerted by EGF in the kidney is associated with electrolyte homeostasis and proliferation and repair of cell damage also. Kidney diseases that cause acute kidney injury (AKI) and/or chronic kidney disease (CKD) are currently one of the main causes of morbidity and mortality worldwide.[3]

Epidermal Growth Factor has been identified in different situations as a biomarker of kidney function: the alteration of EGF urine levels (generally its decline) has been associated with the presence of nephropathy, AKI, and CKD, or progression towards these states, as well as the presence of kidney cancer, in a population at risk. With new techniques to measure EGF including in urine, the evidence regarding its capacity as a biomarker has been increasing, the alteration in EGF levels usually precedes the alterations in creatinine and blood urea nitrogen levels, albumin-to-creatinine ratio or uresis, which could represent a therapeutic window for kidney disease; yet despite this, there is no consensus on its use in daily clinical practice, mainly due to a lack of specific cut-off points for each scenario. The objective of this systematic review was to describe the urinary EGF (uEGF) levels for the presence or progression of kidney diseases (primary or secondary nephropathy, AKI, CKD, and/or renal cancer).

Methods

Study design

The rationale, objective and search strategy of this systematic review were registered in the International Prospective Registers of Systematic Reviews (PROSPERO) under the registration number CRD42021271501.

A systematic review of observational studies with uEGF determination was performed. Studies were searched in Medline, Google Scholar, Science Direct, and EBSCO up to August

2, 2021. Inclusion criteria: the presence of kidney disease, presence of urinary cancer, presence of kidney disease risk factors; in cross-sectional, case-control, or cohort studies, with uEGF determined by enzyme immunoassay (ELISA or EIA) or multiplex magnetic bead-based assay; language, and with availability of the full text. Exclusion criteria: reviews, clinical trials, pre-clinical studies, letters to the editor, or conference posters were excluded. Studies that did not report uEGF levels as means or medians were also excluded (for example, studies that showed data by tertile only).

Setting & study populations

The search strategy structure adopted was based on a PICO-style approach: Problem: human kidney disease; Intervention or prognostic factor: uEGF; Comparison: healthy or without kidney disease risk factors participants; Outcome: presence, absence, or progression of kidney disease.

We consider kidney disease as any primary or secondary nephropathy, ureteropelvic dysfunction or hydronephrosis, renal cancer, AKI, or CKD. Different clinical settings included ICU, hospitalised, or outpatient milieu.

Search strategy & sources

The electronic search strategy for Medline was carried out with the following terms:

((((((((((EGF [Title/Abstract]) OR EPIDERMAL GROWTH FACTOR [Title/Abstract]) OR EPITHELIAL GROWTH FACTOR [Title/Abstract])) OR EPIDERMAL GROWTH FACTOR [mesh])))) OR (EGF [MeSH Major Topic]) AND (((((KIDNEY [Title]) OR NEPHROPATHY [Title/Abstract]) OR RENAL [Title])) OR ((((NEPHROPATHY [MeSH Major Topic]) AND RENAL DISEASE [MeSH Major Topic]) AND KIDNEY DISEASE [MeSH Major Topic])))))) NOT REVIEW[Publication Type] AND (humans[Filter])) NOT (cells[Title]), and the search strategy for other databases is presented in the supplementary material. Reference lists, similar articles or those cited by another article of identified articles, as well as other review studies, were also reviewed manually to identify additional articles. The MOOSE and PRISMA guidelines for reporting systematic reviews were followed[4,5] and quality assessment was performed to assess potential risk of bias for each included study according to the NIH/NHLBI Quality Assessment Tools[6]; depending on the methodological design as cross sectional/cohort, or cases and controls, the respective NIH/NHLBI Quality Assessment Tool was applied; and, the methodological design as indicated by the authors was considered, whereas if it was not specified, or was only mentioned as a prospective study, the methodological design corresponding to the methodology described in the study was identified. The quality of the studies was classified as good, fair, or poor (see supplementary material).

Study selection process

All reviewers are researchers or students from the health area. One person extracted the data, and another person checked the extracted data. Disagreement was discussed and consensus was reached using a third opinion. Two reviewers independently assessed potential risk of bias and were blinded to each other. Disagreement was discussed and a consensus reached using a third opinion. Studies in languages other than English or Spanish were translated using an online Google translator.

Data extraction

Studies were grouped according to the authors' declaration as CKD, AKI, or a specific nephropathy, the latter could present different degrees of renal function. An Excel datasheet was used for data extraction. The variables extracted included: age, sex, sample size, settings, biological material in which uEGF was measured (spot or 24-h urine), uEGF measurement technique, sample storage, uEGF values, and its units of measurement. Also, specificity, sensitivity, area under the ROC curve (AUC), and hazard ratio (HR) with 95% confidence interval (CI) were extracted whenever they were available.

Results

Study characteristics

The initial results of the bibliographic search identified 936 articles, from which 342 were eliminated because they were duplicates, 494 were excluded based on title or abstract review or not retrieved and 19 for using radioimmuno-assay. The main reason for excluding articles after reading the full text was that they did not evaluate uEGF levels. After reading the full articles, 53 studies were ultimately included.[7–59] The flowchart for the selection process was according to PRISMA guidelines, and Fig. 1 shows a flowchart of the study's selection process. The characteristics of studies included are presented in Supplementary Tables 1–4.

Quality assessment

Supplementary Table 5 shows the evaluation of the quality of the selected articles. The most frequently found risks of bias were the lack of justification of the sample size power description or variance and effect estimates provided, the lack of a specified and defined study population, and the lack of measurement and analysis of key potential confounding variables. None of the studies reported whether there was blinding to the exposure status of participants of outcome assessors. From the included studies in this review, 30 (56.6%) were identified as "good" quality, 22 (41.5%) were classified as "intermediate", and 1 (1.8%) were classified as "poor" quality.

Overall summary of uEGF in different types of kidney disease

Several studies reported more than one type of kidney disease: the most frequently studied diseases were AKI (20.7%), CKD (18.8%), diabetic nephropathy (9.4%), and reflux or obstructed nephropathy (NPT) (7.5%); while other kidney diseases were: glomerulonephritis, IgA NPT, post-transplantation renal tumour, polycystic kidney disease (PKD), congenital anomalies, lupus nephritis, carcinoma of the bladder, renal amyloidosis, Henoch-Schönlein purpura nephritis, renal

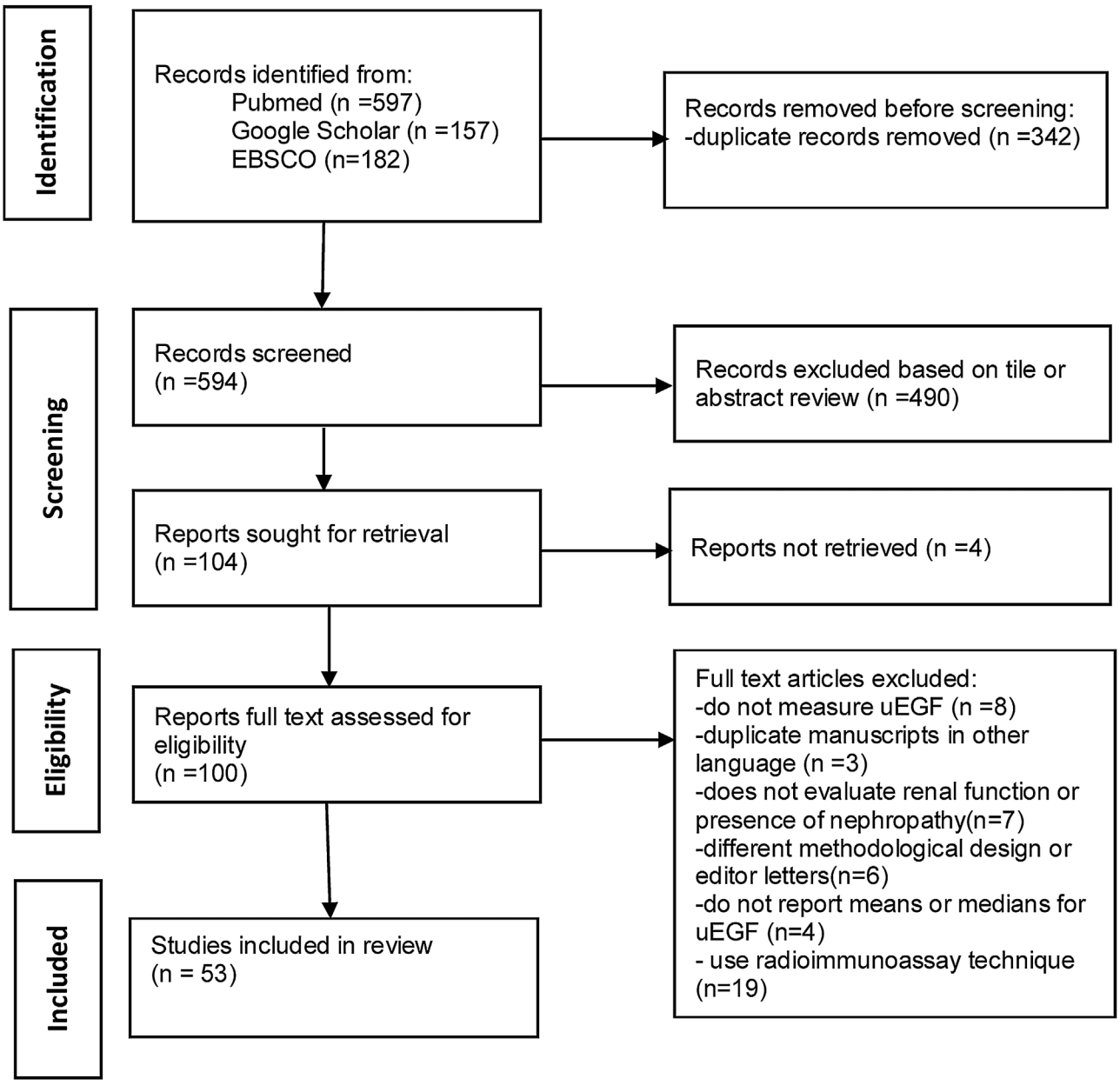

Fig. 1 – Flowchart of the study selection process.

pelvic or calyceal stone, Alport syndrome, Wilms tumour, human immunodeficiency virus (HIV) NPT, and unspecified origin NPT.

The methodological design reported by the authors or identified by the reviewers were, according to inclusion criteria, 34 studies with cohort design, 15 cross-sectional, and 4 with case-control design. The uEGF assays used in the studies were Enzyme Immunoassay/Enzyme-Linked Immunosorbent Assay (ELISA), and multiplex assay. The oldest studies were those using radioimmunoassay (RIA); most of them with a low-quality assessment, so they were not included in the review, while the most recent studies used both ELISA and multiplex assay (a type of immunoassay to simultaneously measure multiple analytes in a single sample). Regarding the units reported for uEGF levels, 39 studies reported uEGF adjusted to urinary creatinine, 9 studies reported uEGF in weight units over volume units (ej, pg/mL), 3 studies presented the levels in weight units over 24 h (ej. pg/24-h), one study reported as a rate (mg/mL/min), and one study did not specify units.

Urinary EGF findings in studies of nephropathy or CKD

The uEGF levels were analysed in 39 studies in both primary and secondary kidney diseases as well as in CKD; they can be seen in Table 1. According to the age of the patients studied, 13 studies were performed on children and adolescents, and 26 on adults and older adults, one of them did not mention the age of the participants.[7] Among the studies that reported Cr-adjusted uEGF values, the lowest values in patients with kidney disease were found in adult patients by

Table 1 – uEGF levels[a] in studies reporting nephropathy (NPT) or chronic kidney disease (CKD).

Author	uEGF controls	uEGF cases	Units	Kidney disease	uEGF outcome
Adults					
Gesualdo, 1995[7]	7242.6[b] ±1530.3	2145 ± 762.7	pg/mg Cr	PKD with CKD	A reduction may be a prognostic marker of renal dysfunction
	9183.7 ± 1049	10,335.5 ± 1273.6		PKD without CKD	
Jørgensen, 1995[8]	2 (1.4–3.4)	1.8 (0.6–2.3)	pmol/h/mL/min	Transplants donors	Lower in cases than controls (pre-operatively donors)
		1.2 (0.5–3.3)		Transplants recipients	
Ranieri, 1996[9]	12.96 ± 11.15	20.05 ± 2.64	ng/mg Cr	IgA NPT grade 1–2	Progressive decreases according to the degree of NPT.
		7.6 ± 1.7		IgA NPT grade 3–4	
		3.14 ± 0.71		IgA NPT grade 5	
Torffvit, 1998[10]		0.47 (0.05–2.51)	nmol/24 h	Glomerular NPT	Lower in cases than normal controls.
		0.13 (0.03–1.08)		Tubular NPT	
Torres, 2008[11]	–	18.35 (8.03–44.5)	ng/mg Cr	IgA NPT	A reduction may be a prognostic marker of renal dysfunction
Stangou, 2009[12]	0.15 ± 0.08	0.05 ± 0.05	pg/mg Cr	IgA NPT	A reduction may be a prognostic marker of renal dysfunction
Stangou, 2012[13]	0.14 ± 0.07	0.15 ± 0.3	pg/mg Cr	Pauci-immune FSNGN	A reduction may be a prognostic marker of histological damage and response to treatment
Harskamp, 2015[14]	32,939 (26,049–63,420)	11,345 (345–26,367)	ng/24 h	Autosomal dominant PKD	Lower in cases than normal controls.
Ju, 2015[15]	–	2.5 ± 1.1	Log_2 ng/mg	CKD stages I–IV	Independent risk predictor of CKD progression
		3 ± 1.3		Primary proteinuric glomerular disease	Progressive decrease according to the degree of NPT
		3.5 ± 1		IgA NPT	
Betz, 2016[16]	10.17 (5.06–16.46)	6.42 (3.29–12.969)	μg/mmol Cr	Diabetic NPT	A reduction may be a prognostic marker of renal dysfunction
Worawichawong, 2016[17]	11.7 (7.5–18.8)	4.4 (2.4–7.6)	ng/mg Cr	Primary GN	Lower in cases than normal controls, associated with tubular atrophy and interstitial fibrosis
Segarra-Medrano, 2017[18]	21.3 (14.5–26)	12.6 (6.3–18)	ng/mg Cr	IgA NPT T1 Oxford criteria	A reduction may be a prognostic marker of interstitial fibrosis
		3.2 (1.7–4.89	ng/mg Cr	IgA NPT T2 Oxford criteria	
Chanrat, 2018[19]	120.6 (58.3–192.4)	59. (150.0–87.2)	ng/mg Cr	Not remission in primary GN	A reduction may be a prognostic marker of renal dysfunction and complete remission
Dincer, 2018[20]	3.66 (1.84–5.60)	2.74 (1.12–6.21)	ng/mg Cr	CKD	Lower in cases than normal controls.
Nowak, 2018[21]	13.1 (8.7–18.6)	10.5 (8.1–15.0)	ng/mg Cr	Diabetic NPT	A reduction may be a prognostic marker of renal dysfunction
Satirapoj, 2018[22]	42.8 (23.4–65.1)	19.5 (11.1–36.3)	ng/mg Cr	Rapid loss function diabetic NPT	Lower in rapid renal progression group than non-rapid renal progression group

Table 1 (*Continued*)

Author	uEGF controls	uEGF cases	Units	Kidney disease	uEGF outcome
Wu, 2018[23]	4.34 ± 0.76	2.04 ± 1.41	Log_2 ng/mg	Active patients with AAV	Progressive decrease according to the degree of NPT,
		2.63 ± 1.31		Remission patients with AAV	A reduction may be a prognostic marker of resistance to treatment and renal dysfunction
Wu, 2020[24]	3.08 ± 1.12	2.94 ± 0.98	Log_2 ng/mg	Diabetic NPT	Lower in diabetic with NPT than diabetic without NPT controls.
Yang, 2020[25]	7.6 (6.0–10.1)	3.8 (2.9–5.1)	μg/g Cr	IgA NPT GFR < 60 mL/min/1.73 m^2	Lower in the <60 mL/min/1.73 m^2 and associated with progression
Zheng, 2020[26]	8.2 (6.5–10.2)	8.3 (6–12.6)	ng/mg Cr	Idiopathic membranous NPT	No statistically significant difference between cases vs controls
Ascher, 2021[27]	14.7 (9.4–20.7)	9.2 (5.9, 13.4)	ng/mL[b]	Incident CKD/baseline women with HIV	A reduction may be a prognostic marker of incident CKD
	13.7 (9.2–20.6)	9.2 (5.2, 12.0)		Incident CKD/follow up	
Hefny, 2021[28]	50.7 ± 0.9	30.2 ± 16.7	ne	Lupus nephritis	Lower in cases than normal controls.
Heidari, 2021[29]	1717.2 ± 482.2	1146.8 ± 585.3	pg/mg Cr	Kidney allograft rejection	A reduction may be a prognostic marker of antibody mediated rejection
		1671.5 ± 695.6		Stable kidney allograft function	
Mejía-Vilet, 2021[30]	16.8 (16.0–17.9)	10.9 (6.7–15.4)	ng/mg Cr	Active lupus nephritis first flare	Urine EGF levels correlate with histologic kidney damage.
		5.3 (2.6–9.3)		Second flare	A reduction may be a prognostic marker of renal dysfunction
		3.5 (1.4–8.6)		Third flare	
		1.8 (1.1–2.8)		Fourth flare	
		19.9 (16.6–25.7)		Inactive/mildly active SLE no previous nephritis	
		8.9 (6.0–17.8)		Previous nephritis	
		18.2 (10.8–27.5)		Systemically active SLE	
Pediatrics					
Konda, 1997[31]	36.5 (22.7–58.6[a])	23.8 (10.5–54)	μg/g Cr	Reflux NPT normal function	Lower in cases than normal controls.
		18.5 (9.5–36.2)		Reflux NPT unilateral low function	
		3 (1.1–8.4)		Reflux NPT total low function	
Tsau, 1999[32]	15.2 ± 6.5	6.9 ± 3	ng/mg Cr	CKD	Lower in cases than normal controls.
		13.6 ± 5.1		NPT with normal renal function	
Chiou, 2004[33]	681.8 ± 113.7	800.2 ± 118.3	pg × 10^2/mg Cr	Obstructed vs unobstructed kidney	Correlated with preservation of postoperative renal function
	937.41 ± 124.98	577.07 ± 154.43		Preserved vs poorly preserved function	

Table 1 (*Continued*)

Author	uEGF controls	uEGF cases	Units	Kidney disease	uEGF outcome
Li, 2012[34]	50 (35–81)	38 (20–57)	ng/mg Cr	Hydronephrosis	A reduction may be a prognostic marker of need of surgery
Madsen, 2013[35]	4 (1.2–60.2)	7.4 (1.2–13.8)	ng/mg Cr[b]	Ureteropelvic junction obstruction	Higher in cases than normal controls
Pastore, 2017[36]	790 ± 190	681 ± 277	pg/mL	Vesico-ureteral reflux	Lower in cases than normal controls.
Ledeganck, 2018[37]	67.4 (17.9–218.8)	7.0 ± 1.1	ng/mL	Transplanted/ Calcineurin inhibitor	Correlated with renal function
		11.5 ± 2.4		CKD	
		35.4 ± 6		Nephrotic syndrome/Calcineurin inhibitor	
		47.7 ± 6.6		Nephrotic syndrome	
Li, 2018[38]	54.17 ± 22.84	10.59 ± 6.863	ng/mg Cr	Progressors Alport syndrome	Lower in cases than normal controls.
	30.87 ± 9.37	27.83 ± 12.67		Non-progressors Alport syndrome	A reduction may be a prognostic marker of renal disfunction
	22.06 ± 5.78				
Azukaitis, 2019[39]	–	3.46 (1.92–6.47)	ng/mg Cr	CKD	A reduction may be a prognostic marker of progression in children with CKD.
Bartoli, 2019[40]	515 ± 168	754 ± 4335	pg/mL	Hypoplastic	Lower in cases than normal controls.
		628 ± 252		Agenesic	
		794 ± 243		Multicystic	
		408 ± 201		Nephrectomy	
Gipson, 2019[41]	71.4 (40.0–91.3[a])	39.9 (27.3–55.69)	ng/mg Cr	Minimal change disease GN	A reduction may be a prognostic marker of renal dysfunction
		24.9 (11.4–41.29		Focal segmental glomerulosclerosis	
Srivastava, 2020[42]	18,637 (15,298–25,622)	20,098 (13 238–30 263)	pg/mgCr	Solitary functioning kidney	No statistically significant difference between cases vs controls
Ledeganck, 2021[43]	46 (23.1–121)	32.8 (6.2–96.3)	ng/mg Cr	Diabetic NPT	Lower in cases than normal controls.

[a] uEGF levels are presented as mean ± standard deviation or median (interquartile range).
[b] Use multiplexing technique. To convert nmol/mmol Cr to ng/mg Cr, multiply by 52.694. AAV = antineutrophil cytoplasmic antibody-associated vasculitis, FSNGN = pauci-immune focal segmental necrotising glomerulonephritis, GFR = estimated glomerular filtration rate, GN = glomerulonephritis, PKD = polycystic kidney disease, SLE = systemic lupus erythematosus.

Stangou et al., in IgA NPT and in pauci-immune focal segmental necrotising glomerulonephritis[12,13]; however, the controls of these patients presented with the lowest levels of uEGF reported where, in both cases, values equal to or less than 0.00014 ng/mg Cr were reported; while the highest values in patients with kidney disease were 80 ng/mg Cr in paediatric patients with obstructive nephropathy,[33] and the highest values for controls were 120.6 ng/mg Cr in adults.[19]

Urinary EGF findings in AKI studies

Table 2 shows the studies that analysed and reported uEGF levels in children or adults patients with AKI. Values reported in these cases were from 1.7 ng/mg Cr in adults[45] to 18.8 ng/mg Cr in children hospitalised in the ICU.[47] In the 4 studies regarding AKI, all of them reported lower levels of uEGF in cases versus healthy or exposed controls.

Urinary EGF findings in studies of renal or bladder cancer

Malignant neoplasms of the kidney or bladder were evaluated only in one of the included studies[48] where paediatric Wilms tumour survivors with eGFR < 90 mL/min/1.73 m^2, uEGF levels were lower.

Urinary EGF findings in studies of neonates

The uEGF was evaluated in 9 studies carried out in neonates, in all of them reported the diagnostic accuracy analysis values and 6 also showed the specific values of uEGF (see Table 3); of which, the lowest values were those reported in neonates of term with, and without, AKI by Askenazie et al.[52]; yet when adjusting the values with urinary Cr levels, the values reported in neonates with AKI and with ureteropelvic obstruction were similar.

Table 2 – uEGF levels[a] in studies reporting acute kidney injury (AKI).

Author	uEGF controls	uEGF cases	Units	Specific kidney disease	Settings	uEGF outcome
Adults						
Di Paolo, 1993[44]	12.96 ± 1.15	6.28 ± 1.52 3.09 ± 0.68 5.23 ± 0.92	ng/mg Cr	Stable graft function Acute rejection Acute tubular damage	ns	Lower than normal controls
Kwon, 2010[45]	9549.81 (5758.75–20,271.5)	1705.58 (814.57–2924.97)	pg/mg Cr[b]	Ischaemic	Hospitalized	Lower than normal controls, a reduction may be a prognostic marker of recovery and mortality
Singal, 2018[46]	4253 (2517–6983)	2254 (1350–4651)	pg/mg Cr[b]	No	Cirrhosis patients listed for liver transplantation	Lower than no AKI controls
Paediatrics						
Wai, 2013[47]	56,324 (26,342–142,460)	18,889 (729–58,889)	pg/mg Cr	No	ICU/septic shock or requiring ECMO	Lower than no AKI controls

[a] uEGF levels are presented as mean ± standard deviation or median (interquartile range).
[b] Use multiplexing technique. ECMO = extracorporeal membrane oxygenation, ICU = intensive care unit, ns: not specified.

Table 3 – uEGF levels[a] in studies in neonates.

Author	uEGF controls	uEGF cases	Units	AKI	Specific kidney disease	Settings	uEGF outcome
Askenazi, 2012[49]	17.4 (12.7–23.8)	6.7 (4.0–11.3)	pg/mL[b]	Yes	No	ICU/term	Infants with AKI had lower uEGF levels
Mohammadjafari, 2014[51]	20.06 (19.73–28.11)	16.86 (11.76–23)	ng/mg Cr	No	Ureteropelvic junction obstruction	Outpatient	No significant differences between case and controls
Askenazi, 2016[52]	790 (496–1200)	468 (363–872)	pg/mL[b]	Yes	No	ICU/preterm	Lower than no AKI controls
Hanna, 2016[53]	0.016	0.006	μg/mL[b]	Yes	No	ICU/preterm	uEGF was a predictor of renal injury
Sweetman, 2016[54]	3871.6 (1978.9–6776.3)	585.7 (363.4–1836.7)	pg/mL[b]	Yes	No	ICU/perinatal asphyxia	Lower than normal and no AKI controls
Ahn, 2020[57]	6193.2 (1793.3–11,033.1) 24.9 (23.4–29.6)	16.3 (13.9–22.0)	ng/mg Cr[b]	Yes	No	Healthy controls ICU/preterm	Lower than no AKI controls

[a] uEGF levels are presented as mean ± standard deviation or median (interquartile range).
[b] Use multiplexing technique. AKI = acute kidney injury, ICU = intensive care unit.

In all cases, uEGF values were lower in cases with kidney disease versus healthy controls or those without kidney disease.

Studies with diagnostic accuracy in analysis of urinary EGF

Of the studies included, only 7 in adults, 1 in children and 6 in neonates reported a cut-off value: 13 of them showed the AUC of the respective cut-off value, and 11 reported sensitivity and specificity (see Table 4). In adults, the lowest cut-off values in ng/mg Cr or ng/mL were observed in CKD and in antibody-mediated kidney allograft rejection,[23,29] while the highest values were described in primary glomerulonephritis.[19] The highest AUC values were observed with cut-off values of 10.8 ng/mg Cr to identify primary glomerulonephritis, and 5.3 ng/mg Cr for lupus nephritis: these cut-off values also presented the highest sensitivities.[17,30]

In neonates, the lowest cut-off value (1.75 pg/mL) was observed in patients with AKI treated with hypothermia for hypoxic ischaemic encephalopathy,[56] and when the uEGF was

Table 4 – Studies with diagnostic accuracy analysis of uEGF.

Author	Cut-off value	Sensitivity[a]	Specificity[a]	HR	95%IC HR	AUC	95% IC AUC	Outcome	Kidney disease or settings
Adults									
Torres, 2008[11]	nr	nr	nr	0.95	0.92–0.98	0.83	0.76–0.89	Doubling sCr and/or ESKD	IgA NPT
Ju, 2015[15]	nr	nr	nr	0.33	0.21–0.51	0.89	0.84–0.95	CKD progression	CKD stages I-IV
	nr	nr	nr	0.33	0.21–0.52	0.82	0.73–0.91		Primary proteinuric glomerular disease
	nr	nr	nr	0.57	0.46–0.70	0.71	0.64–0.77		IgA NPT
Betz, 2016[16]	nr	nr	nr	0.45	0.3–0.69	0.78	0.74–0.82	Incident GFR < 60 mL/min per 1.73 m^2 and rapid decline of renal function	Type 2 diabetes
Worawichawong, 2016[17]	10.8 ng/mg Cr	0.94	0.55	0.77	0.64–0.92	0.83	0.71–0.95	Moderate to severe interstitial fibrosis and tubular atrophy	Primary glomerulonephritis
Segarra-Medrano, 2017[18]	nr	nr	nr	0.59	0.36–0.96	0.87	nr	Fibrosis interstitial T1 and T2 Oxford grade	IgA NPT
Chanrat, 2018[19]	75 ng/mg Cr	0.71	0.66	2.28	1.08–4.84	0.72	0.60–0.84	Complete remission	Primary glomerulonephritis
Satirapoj, 2018[22]	29.9 ng/mg Cr	0.703	0.69	0.98	0.97–0.99	0.68	0.57–0.80	Rapid GFR decline	Type 2 diabetic patients with NPT
Wu, 2018[23]	0.46 log^2 uEGF/Cr	0.63	0.63	0.88	0.80–0.97	0.66	nr	ESKD or 30% reduction of GFR.	Antineutrophil cytoplasmic antibody-associated vasculitis
Yepes-Calderón, 2019[58]	nr	nr	nr	0.68	0.59–0.78	0.81	nr	Risk of graft failure	Renal Transplant Recipients
Wu, 2020[24]	nr	nr	nr	0.66	0.53–0.82			ESKD or a 30% reduction in GFR.	Type 2 diabetic patients with NPT
						0.96	0.95–0.96	Discrimination of diabetic NPT	Type 2 diabetes
Yang, 2020[25]	4.7 μg/g Cr	nr	nr	3.9[a]	2.4–6.7[a]	nr	nr	NPT progression	IgA NPT
Zheng, 2020[26]	nr	nr	nr	0.502	0.16–2.81	nr	nr	Massive proteinuria	Idiopathic membranous NPT
	nr	nr	nr	2.476	0.94–3.35	nr	nr	GFR decreased	
	nr	nr	nr	0.748	0.41–2.18	nr	nr	Interstitial fibrosis and renal tubular atrophy	
Norvik, 2020[59]	nr	nr	nr	1.17	0.89–1.53	nr	nr	per 1 μg/mmol lower uEGF GFR decline > 3.0 mL/min/ 1.73 m^2/year	Subjects without diabetes or established CKD (Norway cohort)
				1.32	1.13–1.54				Subjects without diabetes or established CKD (Netherlands cohort)

Table 4 (*Continued*)

Author	Cut-off value	Sensitivity[a]	Specificity[a]	HR	95%IC HR	AUC	95% IC AUC	Outcome	Kidney disease or settings
Ascher, 2021[27]	nr[c]	nr	nr	0.61[b]	0.50–0.75	nr	nr	Incident CKD	Women living with HIV
Heidari, 2021[29]	1199.9 pg/mL	0.77	0.68	nr	nr	0.74	nr	Early diagnosing of rejection	Antibody mediated kidney allograft rejection
Mejía-Vilet, 2021[30]	5.3 ng/mg	0.81	0.77	0.88[b]	0.77–0.99	0.82	nr	Progress to ESKD	Lupus nephritis
Paediatrics									
Li, 2012[34]	43 ng/mg Cr	0.667	0.75	nr	nr	0.69	0.47–0.91	Surgery in the first 6 months of life	High-grade hydronephrosis
Azukaitis, 2019[39]	nr	nr	nr	0.76	0.69–0.84	nr	nr	Incident CKD	Children with several kidney diseases
Gipson, 2019[41]	nr	nr	nr	2[#]	1.1–2.9	nr	nr	Incident CKD	Children with Nephrotic Syndrome,
Neonates									
Askenazi, 2012[49]	nr[c]	nr	nr	nr	nr	0.81	nr	AKI	Newborns
Hoffman, 2013[50]	45,000 pg/mg Cr	0.73	0.82	nr	nr	0.77	nr	AKI	Critically ill neonates
	3179 pg/mL	0.64	0.84	nr	nr	0.73	nr		
Mohammadjafari, 2014[51]	300.485 ng/L	0.6	0.53	nr	nr	0.56	nr	Needed surgery	Ureteropelvic junction obstruction
	16.8554 ng/mg Cr	0.71	0.77	nr	nr	0.72	nr		
Askenazi, 2016[52]	590 pg/mL[c]	nr	nr	nr	nr	0.68	nr	AKI	Very low-birth-weight infants
Hanna, 2016[53]	nr[c]	nr	nr	nr	nr	0.97	nr	Stage I AKI	Preterm
	nr	nr	nr	nr	nr	0.86	nr	Stage II/III AKI	Preterm
Sweetman, 2016[54]	2923.2 pg/mL[c]	nr	nr	nr	nr	0.91	nr	AKI	Neonatal encephalopathy
De Freitas, 2016[55]	3 ng/mL[c]	0.85	0.42	nr	nr	0.79	0.65–0.93	GFR < 30 mL/min/1.73 m^2	Preterm and Term newborns
Gupta, 2016[56]	1.75 pg/mL	0.7	0.75	nr	nr	0.75	0.53–0.91	AKI	Treated with hypothermia for hypoxic ischaemic encephalopathy

[a] For under cut-off value.
[b] Adjusted model.
[c] Use multiplexing technique, AUC = area under the curve, AKI = acute kidney injury, CKD = chronic kidney disease, ESKD = end stage of kidney disease, GFR = estimated glomerular filtration rate, HR = hazard ratio unadjusted model, NPT = nephropathy, nr = not reported.

adjusted for the level of urinary Cr, the cut-off values in neonates with AKI were higher, reaching up to 45 ng/mg Cr; where this last value was the one that reported the highest AUC as well as sensitivity and specificity in neonates.[50]

No cut-off points were identified for studies related to AKI, or kidney or bladder cancer, in children or adults.

Discussion

Since its identification in the early 1960s, numerous articles on EGF have been published.

In this study, we carried out a systematic review on the levels of uEGF in kidney diseases in patients of all ages. A significant number of studies were found where a statistically significant alteration was identified in patients with various kidney pathologies, in most cases with a decrease in uEGF levels. Although recent research shows uEGF used as a biomarker of function, in the presence of kidney disease or therapeutic response,[60–62] the measurement of uEGF in routine clinical practice is not performed. Numerous factors may be contributing to this situation with the main one being the lack of a universally accepted cut-off value either to establish the normality of the values or to identify a particular disease. In this review, a significant heterogeneity of uEGF levels could be identified not only in the patients studied but also in the controls, even among patients of the same age range. This problem in establishing a cut-off point may be due to the lack of uniformity in the way of reporting the levels of uEGF and to the different techniques used to measure it.

Most authors reported the levels of uEGF adjusted to the levels of urinary Cr, while another group of researchers evaluated the levels without considering this parameter, which makes it difficult to compare the results since there is no study that evaluates the correlation between the different techniques available for measuring uEGF. Another difference in the report of uEGF values was the sampling method: some authors collected the urine sample for 24 h while others were spot samples. To this regard, it has been reported that there was no significant difference in uEGF according to the way the urine was collected[63,64]; however, in some kidney pathologies, the spot uEGF/creatinine ratio could over or underestimate the 24-h uEGF values, in addition that, in the former method, a high intra-individual variability could be found, requiring serial measurements.[65,66] Age, on the other hand, is a factor that has been identified as intervening in uEGF levels; from neonatal patients where uEGF values showed differences according to gestational age,[55] as well as between children, adolescents, and adults. Other characteristics that vary significantly between studies is the lack of uniformity between the timeline in prospective studies, and the criteria to consider the presence of kidney diseases; and, frequently, it is not established whether to identify its value as a diagnostic or as a prognostic factor.

Regarding the pathologies studied and the way of reporting, it is suggested that in the case of AKI, the adjustment of uEGF values with urinary Cr might not be ideal due to the changes that occur in the latter; so, in AKI, the uEGF levels could be more exact without adjusting.[67]

On the other hand, it was not possible to identify whether any kidney disease was associated with the lowest levels of uEGF, since, as previously commented, when the units were equivalent the age or the technique used to measure was not, so the utility of uEGF for distinguishing between different types of kidney disease is not clear.

In general, we substantiated that in most studies patients of all ages with kidney disease, including cancer, have lower levels of uEGF compared to their controls. The EGF is a growth factor that has been identified in various tissues; however, EGF measured in urine appears to be produced mainly in the kidneys, while in plasma the source of EGF may be more diverse.[68] The predominantly renal origin of uEGF makes it an important marker of kidney homeostasis, and it has been shown to participate in the control of electrolytes, particularly magnesium,[69] and in podocytes, provides an effect repair and protection against noxious stimuli such as hyperglycemia.[70] Although the overexpression of the EGF receptor is widely described in the genesis of cancer including kidney cancer, this receptor has various ligands so a decrease in uEGF in kidney cancer could be explained, according to some authors, by the decrease in the renal production due to epithelial cell damage.[71]

Our study had some limitations. Firstly, we did not use a single criterion to define the various types of kidney diseases that we included in the review. Secondly, we were not able to convert all the uEGF values to a single unit of measurement to be able to make an adequate comparison between all of them since the studies did not report urinary Cr values or uresis in 24 h, so we could only compare between those for which we were able to obtain the equivalent units. Thirdly, other standard early markers such as albuminuria were not reported due to most studies not reporting such findings. Fourth, our study did not include the calculation of a cut-off value for uEGF due to the great heterogeneity between the studies, and we could not establish a normal value among healthy patients. On the other hand, this review provides a reference source for the use of uEGF in the clinical practice, without established cut-off points, the comparison with the levels reported in similar populations may be useful in monitoring uEGF in patients. The prospective cohort studies included in this review show the association of low abnormal levels of uEGF with the progression of the disease and decreased function of kidney, so using the uEGF levels of patients as their own control could be a monitoring strategy in these patients.

In conclusion, uEGF values are decreased in patients with primary and secondary nephropathy, AKI, CKD, and renal or bladder carcinoma; and progression to AKI in patients with risk, or to CKD in patients with primary and secondary nephropathy, were also associated to lower levels of uEGF. It is necessary to establish criteria to standardise the way of evaluating uEGF to be able to use it as a valuable biomarker in clinical practice.

Authors' contributions

MRS, MH and XT designed the study, JABB, II, YD and YC carried out the data collection. MRS, OMC and EMZ analyzed the data. JABB, II, YD, YC and EMZ made the figure and the

tables. MRS, MH, OMC and XT wrote and reviewed the article. All authors agree and have approved this version of the manuscript. We declare that the work has not been previously published and that it is not under evaluation for publication in any other medium.

Conflicts of interest

All the authors declare no competing interest.

Acknowledgements

This research has not received specific aid from public sector agencies, the commercial sector or non-profit entities.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.nefro.2022.10.003.

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