ASSOCIAÇÃO ENTRE A INTERLEUCINA-17A E OS PARÂMETROS BIOQUÍMICOS EM PACIENTES COM DOENÇA RENAL CRÓNICA.

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Resumo:
A interleucina-17A (IL-17A) parece desempenhar um papel importante no sistema imunitário humano, e o desequilíbrio desta citocina está envolvido em muitas doenças, como a aterosclerose, a hipertensão e a nefropatia diabética. O presente estudo tem como objetivo analisar a associação entre os níveis de IL-17A e parâmetros renais/bioquímicos em indivíduos com ou sem doença renal crônica (DRC). Noventa e dois indivíduos foram divididos em dois grupos, de acordo com sua taxa de filtração glomerular [(TFG); mL/min/1,73m2]: TFG > 90,0 (controlo; n=21) ou TFG < 60 (indivíduos com DRC; n=71). A IL-17A foi avaliada por citometria de fluxo e os testes renais e bioquímicos foram determinados por espetrofotómetro, no soro. Os níveis séricos de IL-17A estavam aumentados nos indivíduos com insuficiência renal e esta citocina apresenta uma associação positiva com a creatinina, a ureia, o potássio, o fósforo e o colesterol total. Por outro lado, os níveis de IL-17A correlacionam-se negativamente com a TFG, a albumina e o colesterol HDL, mesmo quando se excluem variáveis como a idade, o sexo, a hipertensão e a diabetes. A análise de regressão simples demonstrou que o aumento dos níveis de IL-17A pode ser determinado por níveis séricos elevados de ureia, potássio e creatinina e pela diminuição da TFG, do colesterol HDL e dos níveis de albumina. Níveis elevados de IL-17A podem estar associados a biomarcadores clássicos de doença renal terminal e esta citocina pode desempenhar um papel importante na (des)regulação do sistema renal.

Palavras chave: Bioquímica. Doença renal crónica. Citocina. Taxa de filtração glomerular.

INTERPLAY BETWEEN INTERLEUKIN-17A AND BIOCHEMICAL PARAMETERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE.

Abstract:
Interleukin-17A (IL-17A) seems to play an important role in the human immune system, and the unbalance of this cytokine is involved in many diseases, such as atherosclerosis, hypertension and diabetic nephropathy. The present study aims to analyze the association between IL-17A levels and renal/ biochemical parameters in individuals with or without chronic kidney disease (CKD). Ninety-two individuals were divided in two groups, according to their glomerular filtration rate [(GFR); mL/min/1.73m^2]: GFR > 90.0 (control; n=21) or

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GFR < 60 (CKD individuals; n=71). IL-17A was evaluated by flow cytometry and renal and biochemical tests were determined by spectrophotometer, in serum. Serum IL-17A levels were augmented in individuals with renal insufficiency, and this cytokine shows a positive association with creatinine, urea, potassium, phosphorus, and total cholesterol. Conversely, IL-17A levels negatively correlates with GFR, albumin and HDL cholesterol, even when variables including age, sex, hypertension, and diabetes were excluded. Simple regression analysis demonstrated that increased IL-17A levels can be determined by high serum levels of urea, potassium, creatinine and decreased in GFR, HDL cholesterol and albumin levels. High levels of IL-17A may be associated with classical biomarkers of end-stage renal disease, and this cytokine may play an important role in the renal system (dys)regulation.

Key words: Biochemical. Chronic Kidney Disease. Cytokine, Glomerular Filtration Rate.

ASOCIACIÓN ENTRE LA INTERLEUCINA-17A Y LOS PARÁMETROS BIOQUÍMICOS EN PACIENTES CON ENFERMEDAD RENAL CRÓNICA.

Resumen:
La interleucina-17A (IL-17A) parece desempeñar un papel importante en el sistema inmunológico humano, y el desequilibrio de esta citocina está implicado en muchas enfermedades, como la aterosclerosis, la hipertensión y la nefropatía diabética. El presente estudio tiene como objetivo analizar la asociación entre los niveles de IL-17A y los parámetros renales/bioquímicos en individuos con o sin enfermedad renal crónica (ERC). Noventa y dos individuos fueron divididos en dos grupos, de acuerdo con su tasa de filtración glomerular [(TFG); mL/min/1,73m2]: TFG > 90,0 (control; n=21) o TFG < 60 (individuos con ERC; n=71). La IL-17A fue evaluada por citometría de flujo y las pruebas renales y bioquímicas fueron determinadas por espectrofotómetro, en el suero. Los niveles séricos de IL-17A estaban aumentados en los individuos con insuficiencia renal y esta citocina presenta una asociación positiva con la creatinina, la urea, el potasio, el fósforo y el colesterol total. Por otro lado, los niveles de IL-17A se correlacionan negativamente con la TFG, la albúmina y el colesterol HDL, incluso cuando se excluyen variables como la edad, el sexo, la hipertensión y la diabetes. El análisis de regresión simple demostró que el aumento de los niveles de IL-17A puede ser determinado por niveles séricos elevados de urea, potasio y creatinina, y por la disminución de la TFG, el colesterol HDL y los niveles de albúmina. Niveles elevados de IL-17A pueden estar asociados a biomarcadores clásicos de enfermedad renal terminal y esta citocina puede desempeñar un papel importante en la (des)regulación del sistema renal.

Palabras clave: Bioquímica. Enfermedad renal crónica. Citocina. Tasa de filtración glomerular.

Introdution

Chronic kidney disease (CKD), is a pathological condition defined according to the glomerular filtration rate (GFR), being less than 60 mL/min per 1.73 m^2 of body surface area, for 3 or more months (Levey *et al.*, 2011). CKD reached almost 700 million people in 2017, including patients classified in the five stages of this disease (Bikbov *et al.*, 2020). This

condition is either a risk factor and a consequence for cardiovascular events (Rao *et al.*, 2007). The increased prevalence and severity of obesity, diabetes, metabolic syndrome and the inadequate control of elevated blood pressure, are conditions frequently simultaneously observed with the impaired GFR, and they further contribute to cardiovascular risk among CKD individuals (Tripathi *et al.*, 2010).

Inflammation has been recognized since the late 1990s as an essential part of renal dysfunction, when it was linked to cardiovascular disease occurrence and the mortality rates within these individuals (Stenvinkel *et al.*, 1999; Zimmermann *et al.*, 1999). Indeed, a growing body of evidence demonstrates that inflammation is a contributor to CKD development and severity and, therefore, inflammatory markers may provide additional tools to verify the severity of renal dysfunction (Ernst & Resch, 1993; Hwang *et al.*, 1997; Ridker *et al.*, 2000a; Ridker *et al.*, 2000b). With this regard, inflammation markers such as C-reactive protein (Ridker *et al.*, 2000a) and interleukin-6 (IL- 6) (Ridker *et al.*, 2000b) have been described as independent predictors of increased mortality in individuals with chronic renal failure.

Multiple factors can contribute to immune environment in CKD (Stenvinkel, 2001). Among them, higher circulating levels of proinflammatory cytokines and dysregulated cytokine metabolism (Amento *et al.*, 1991; Ross, 1999) are consistently observed in individuals with CKD. Interleukin-17 (IL-17), is a cytokine which elicits inflammatory responses by inducing the expression of chemokines, proinflammatory cytokines and matrix metalloproteases (Dong *et al.*, 2008; Cortvrindt *et al.*, 2017). This cytokine is majority produced by the T helper 17 (Th17) cells, a subset of CD4+ T cells. The best characterized and biologically most potent member of the family is IL-17A, and this isoform represents the founder member of a cytokine family that includes 6 isoforms of IL-17, classified from A to F. IL-17A binds mainly to the receptors IL-17RA and IL-17RC (Turner *et al.*, 2010). Interestingly, IL-17A is also involved in the pathogenesis of hypertension (Zhang & Crowley, 2015), diabetic nephropathy (Yu *et al.*, 2016), fibrosis (Peng *et al.*, 2015), glomerulonephritis (Qiao *et al.*, 2015), nephrotic syndrome (Shao *et al.*, 2009).

Several studies have demonstrated the contribution of IL-17A to CKD. However, most of these evidences come from *in vitro* studies (Hirai *et al.*, 2012; Hot, Lenief & Miossec, 2012; Krueger & Brunner, 2018) or, alternatively, from experimental animal models (Kitching & Holdsworth, 2011; Yu *et al.*, 2016). The initial evidence for the modulatory importance of IL-17A in renal inflammation was provided in 2009, in a murine model of

glomerulonephritis (Paust *et al.*, 2009). Thereafter, Gan *et al*. (2010) showed a crucial role for IL-17 mediating renal tissue damage in a murine model of vasculitis. Currently, the consensus is that increase IL-17A, produced by effector memory T cells results in a significant immune activation in individuals with CKD (Cortvrindt *et al.*, 2017).

Despite the importance of IL-17A in CKD has been established, the relationship between IL-17A and classical biomarkers of end-stage renal disease have not yet been completely identified. Thus, the aim of the present study is to analyze the association between IL-17A levels and biochemical parameters in individuals with or without chronic kidney disease (CKD).

Methods

Subjects

This cross-sectional study was conducted in control subjects or individuals with stage 3 to 5 CKD, according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group., 2013). Individuals with CKD were recruited in the Center of Nephrology of Barra do Garças, and individuals without CKD were recruited in the local public health system from Brazil.

The volunteers signed an informed consent form before entering the study, which was approved by the Research Ethics Committee from the Federal University of Mato Grosso (Protocol Number CAAE: 34568114.9.0000.5587). Informed consents were obtained in written forms from individuals and all clinical investigation was conducted, according to the principles expressed in the Resolution number 466, of the National Health Council.

Initially, 428 individuals pre-diagnosed with CKD were investigated. The individuals were divided in two groups, according their glomerular filtration rate [(GFR); mL/min/1.73m^2]: GFR > 90.0 (control) or GFR < 60.0 (CKD individuals). Inclusion criteria to individuals pre-diagnosed with CKD were: individuals older than 18 years-old; GFR < 60.0 mL/min/1.73m^2 for 3 months or more; hypertension or diabetes as the main cause for CKD diagnostic; in treatment for a period exceeding six months; do not display hospitalization history, for at least three months prior blood collection; do not make use of catheter for dialysis; and individuals with arteriovenous fistula (individuals from stage 5), that this surgery was conducted for at least 3 months before blood collection. All individuals in stage 5 of CKD (GFR < 15 mL/min/1.73 m^2) performed renal function replacement by hemodialysis procedure and blood sample from these individuals were collected before

dialysis procedure. Inclusion criteria to the control group were: GFR > 90.0 mL/min/1.73m^2, older than 18 years-old, without renal impairment, history of cardiovascular disease, hypertension, diabetes or hospitalization within 6 months prior to study.

After analyzing the inclusion criteria, 71 individuals with CKD, who attended the inclusion criteria were available to this study, along with 21 control individuals. Blood samples were collected in control subjects and CKD individuals (8-10 hours fasten).

GFR evaluation

GFR was determined by the CKD-EPI equation, using the age, sex and serum creatinine as variables as following: CKD-EPI equation: 141 x min (SCr/k, 1)$^{\alpha}$ x max (SCr/k, 1)$^{-1.209}$ x 0.993^{Age} [x 1.018 if female] [x 1.159 if black], where SCr is serum creatinine (mg/dL); k is 0.7 for females and 0.9 for males; α is -0.329 for females and -0.411 for males; min is the minimum of SCr/k or 1; and max is the maximum of SCr/k or 1.

Biochemical tests

Serum measurements of creatinine, urea, albumin, glucose, total cholesterol, high density lipoproteins (HDL) cholesterol, potassium, calcium and phosphorous were performed. Biochemical tests were performed by specific laboratory kits and readings were obtained through semi-automatic spectrophotometer (Bioplus® 2000).

Quantification standard cytokines

The cytokine level was conducted using a flow cytometer (FACS Calibur, BD Bioscience, USA). The IL-17A cytokine dosage was performed in a single serum sample (BD Cytometric Bead Array - CBA / Human Th17 Cytokine Kit, BD Biosciences, San Jose, CA), following the technical guidelines contained in the protocols recommended by the manufacturer.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) and were analyzed by Student's t-test. Categorical variables are reported in absolute numbers and percentages were compared using chi-square test. The normality test was conducted by Shapiro-Wilk for all evaluated parameters. Correlations between IL-17A and biochemical parameters were performed using the Pearson's correlation coefficients (r) and simple linear regression analyses (R^2 Ajusted) were performed for IL-17A cytokine as dependent variable and biochemical parameters as a independent variables. Statistical analyses were performed using IBM SPSS version 22.0.0 (SPSS Inc., Chicago, IL). Differences were considered significant when $P < 0.05$.

Results

Blood samples from 92 individuals were collected and classified according their GFR (mL/min/1.73m^2): GFR > 90.0 (control, n=21) and GFR < 60.0 (CKD, n=71), as presented in table 1. The gender distribution was similar among the two groups, but CKD group participants were older than those in the control group (47.76 ± 11.5 and 63.73 ± 15.67, respectively, p<0.001). The proportion of cases with hypertension and diabetes in individuals with CKD was 83.1% and 50%, respectively. Consequently, CKD group presented higher levels of systolic and diastolic blood pressure and hyperglycemia, when compared with control group.

As expected, renal parameters in CKD individuals were impaired, with reduced of GFR and albumin level, along with pronounced serum creatinine and urea levels, when compared to controls (Table 1).

A significant increase in serum glucose, potassium, phosphorus and total cholesterol, as well as, lower HDL cholesterol levels were observed in individuals with CKD, compared to the control group. No difference in calcium serum levels was verified between groups (Table 1).

Serum concentration of IL-17A was increased in individuals with CKD compared to the control group (Figure 1A). Interestingly, serum IL-17A levels negatively correlates with GFR **[(**r = -0.671; p<0.001); Figure 1B].

The Pearson´s correlation analysis between serum IL-17A with the biochemical and renal parameters was performed in the CKD group (Figure 2). High levels of IL-17A revealed a moderate correlation with factors such as creatinine (r = 0.426; p = 0.011; Fig. 2A), urea (r = 0.611; p<0.001; Fig. 2B), potassium (r = 0.513; p = 0.002; Fig. 2C), phosphorus (r = 0.460; p = 0.005; Fig. 2D) and total cholesterol (r = 0.351; p = 0.03; Fig. 2E). Conversely, serum IL-17A levels showed an inverse association with albumin (r = -0.613; p<0.001; Fig. 2F) and HDL cholesterol (r = -0.553; p<0.001; Fig. 2G).

The above-mentioned IL-17A associations may be confounded by variables which are determinants of renal function changes. After the adjustment of age, sex, diabetes and hypertension, the biochemical and renal parameters analyzed still are significantly associated with IL-17A levels.

Table 1: Characteristics of the study population with or without chronic kidney disease.

		GFR > 90.0 (mL/min/1.73m^2) n=21	**GFR < 60.0** (mL/min/1.73m^2) n=71	**IC95%**	**p value**
General parameters					
Sex	Male	9 (43%)	43 (61%)	-	0.118
	Female	12 (57%)	28 (39%)	-	
Age (years)		47.76 (±11.5)	63.73 (±15.67)	-23.30 to -8.64	<0.001*
Medical history					
Hypertension		0 (0%)	59 (83.1%)	-	-
Diabetes		0 (0%)	36 (50.0%)	-	-
Systolic blood pressure (mmHg)		118.8 (±6.2)	152.9 (±16.4)	43.32 to 58.97	0.012*
Diastolic blood pressure (mmHg)		74.5 (±12.1)	85.4 (±27.6)	8.65 to 17.34	0.008*
Renal parameters					
GFR (mL/min/1.73m^2)		95.88 (±5.60)	20.62 (±17.96)	70.88 to 81.25	<0.001*
Creatinine (mg/dL)		0.97 (±0.11)	6.91 (±4.91)	-7.24 to -4.63	<0.001*
Albumin (mg/dL)		4.52 (±0.21)	3.71(±0.23)	0.67 to 0.93	<0.001*
Urea (mg/dL)		28.05 (±7.72)	104.26 (±53.58)	-90.13 to -62.29	<0.001*
Biochemical parameters					
Glycemia (mg/dL)		78.0 (±12.0)	135.0 (±38.0)	3.78 to 7.65	0.026*
Calcium (mg/dL)		7.68 (±1.07)	8.03 (±0.66)	-0.87 to 0.16	0.170
Potassium (mmol/L)		3.76 (±0.31)	4.68 (±0.68)	-1.17 to -0.65	<0.001*
Phosphorus (mg/dL)		3.45 (±0.37)	4.81 (±1.01)	-1.68 to -1.02	<0.001*
Total cholesterol (mg/dL)		149.40 (±18.92)	188.88 (±31.88)	-56.83 to -22.12	<0.001*
HDL cholesterol (mg/dL)		58.03 (±17.76)	38.25 (±11.93)	11.65 to 27.91	<0.001*

Categorical variables were expressed as frequencies n (%) and compared using the chi-square test ($\chi 2$). The results of the renal parameters and biochemical parameters were expressed as mean (±standard deviation) and compared using Student's t-test. *p < 0.05. Abbreviations: GFR= glomerular filtration rate, HDL= high density lipoproteins.

Figure 1

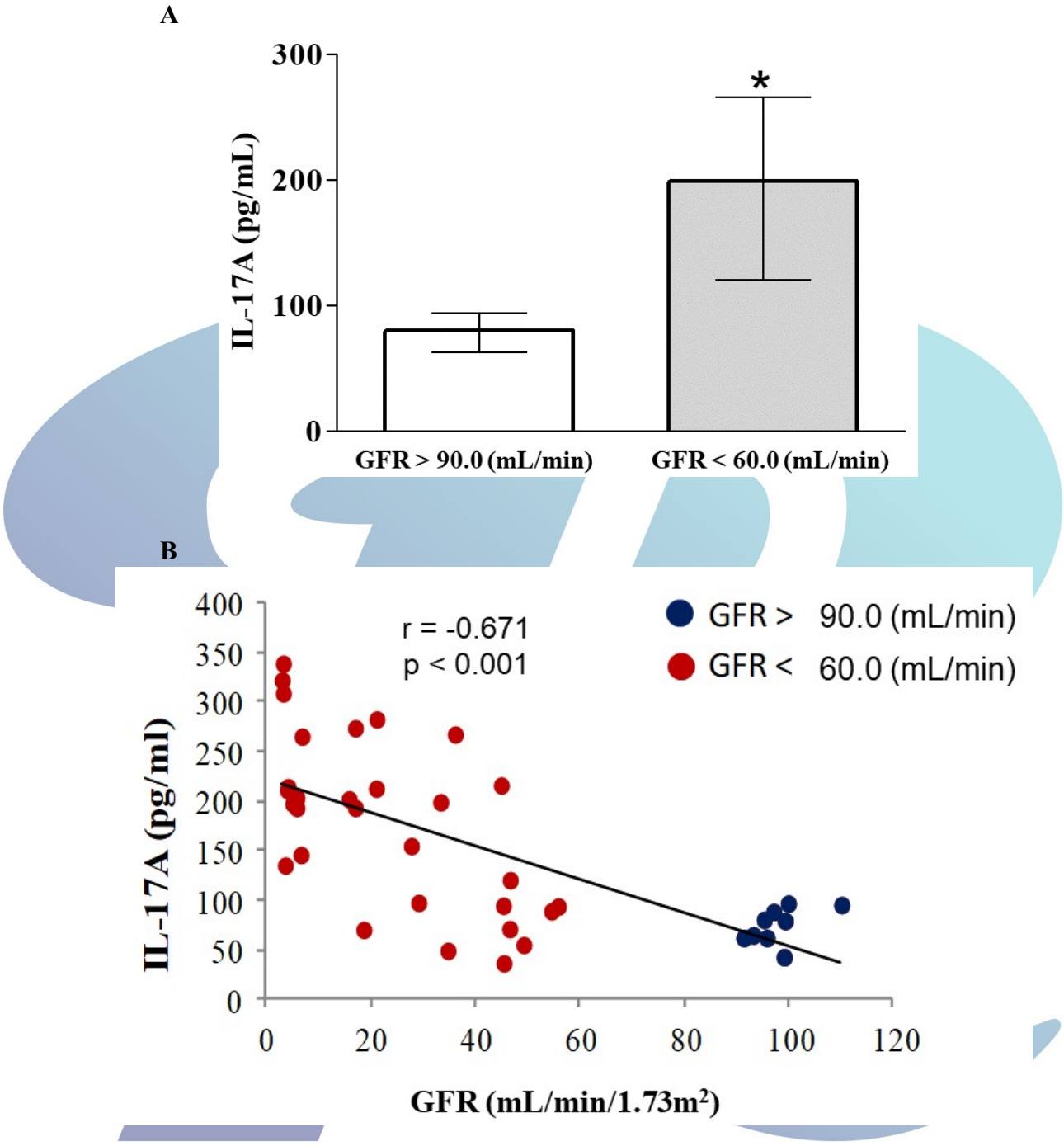
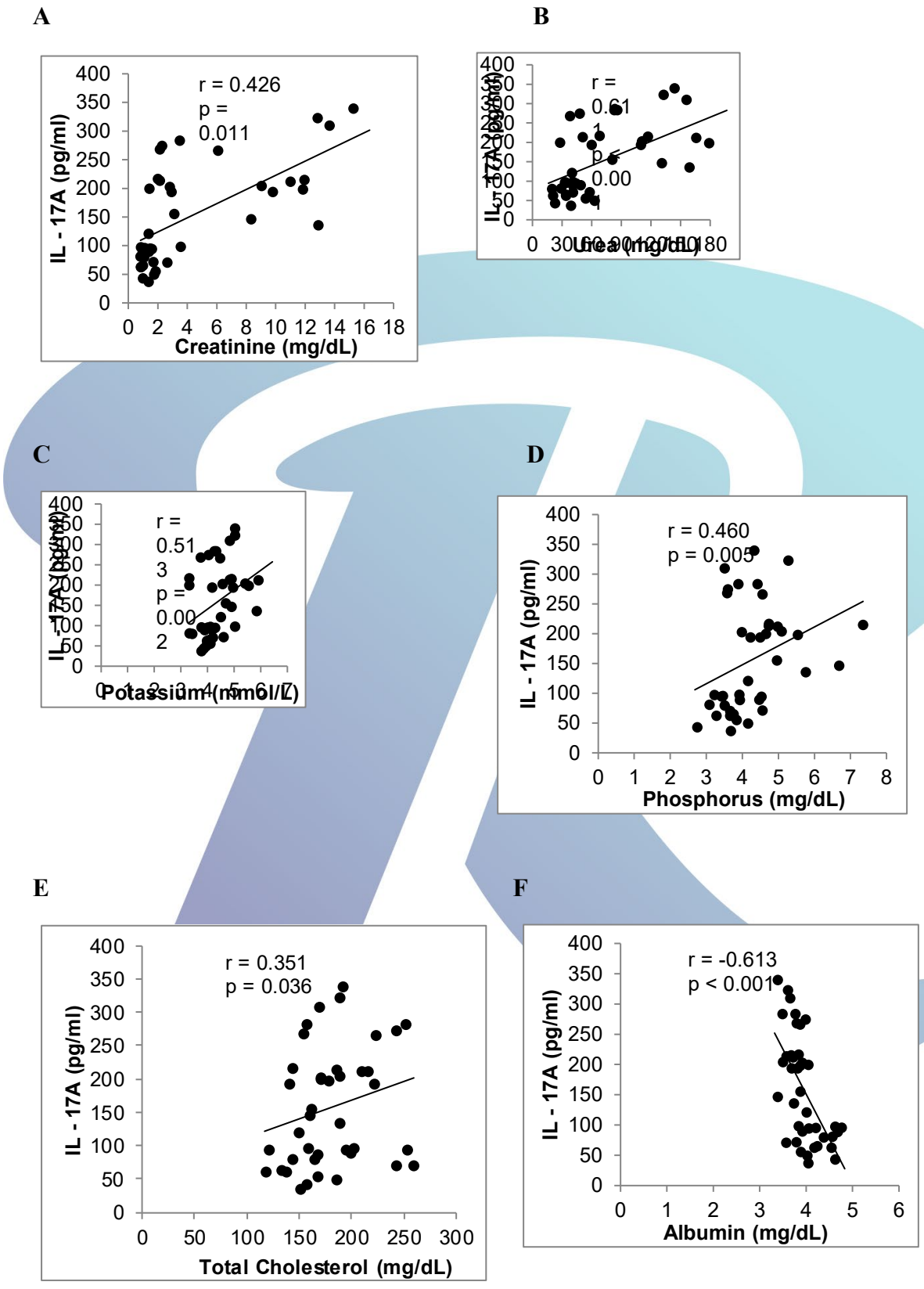


Figure 1- Serum IL-17A levels increase in individuals with chronic kidney disease and this cytokine is negatively correlated with GFR. Concentrations of IL-17A (pg/mL) in individuals with normal GFR or with chronic kidney disease at many levels. Results are expressed as mean ± standard deviation and compared by *Students t* test. * P <0.05 vs. GFR > 90.0 mL/min/1.73m^2. Abbreviations: GFR - glomerular filtration rate.

Figure 2


A
r = 0.426
p = 0.011
IL - 17A (pg/ml)
Creatinine (mg/dL)
B
C
D
r = 0.460
p = 0.005
IL - 17A (pg/ml)
Phosphorus (mg/dL)
E
r = 0.351
p = 0.036
IL - 17A (pg/ml)
Total Cholesterol (mg/dL)
F
r = -0.613
p < 0.001
IL - 17A (pg/ml)
Albumin (mg/dL)

G

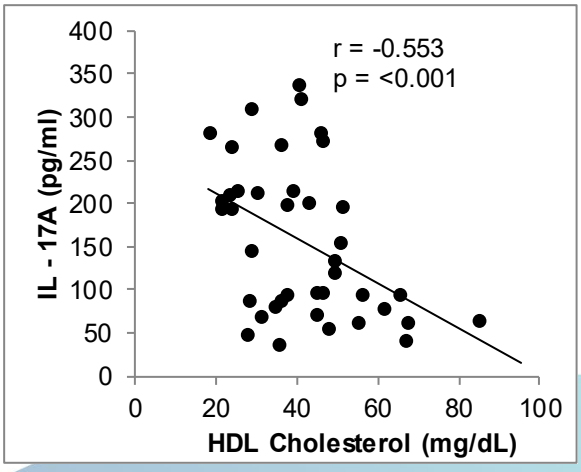


Figure 2 - Correlation between IL-17A and biochemical parameters in individuals with advanced stages of chronic kidney disease. The bivariate correlation of Pearson was used to evaluate the degree of association between the variables tested.

In a simple linear regression analysis (Table 2) showed that increased IL-17A levels can be determined by reduced of GFR (R^2 Ajusted = 0.44, $p < 0.001$), HDL cholesterol (R^2 Ajusted = 0.29, $p < 0.001$) and low serum levels of albumin (R^2 Ajusted = 0.36, $p < 0.001$). Also, IL-17A can be determined by higher serum levels of urea (R^2 Ajusted = 0.36, $p < 0.001$); potassium (R^2 Ajusted = 0.24, $p = 0.002$); phosphorus (R^2 Ajusted = 0.19, $p = 0.005$); creatinine (R^2 Ajusted = 0.16, $p < 0.001$) and total cholesterol (R^2 Ajusted = 0.12, $p = 0.011$, Table 2).

Table 2: Simple linear regression analyses of serum IL-17A level

Parameters	Coefficient β (IC95%)	Standard Error	Ajusted R Square	p value
GFR (mL/min/1.73m^2)	-1.65 (-2.27 to -1.04)	0.31	0.44	< 0.001*
Albumin (mg/dL)	-139.78 (-204. 66 to - 74.90)	31.85	0.36	<0.001*
Urea (mg/dL)	1.02 (0.57 to 1.48)	0.22	0.36	<0.001*
HDL cholesterol (mg/dL)	-2.72 (-4.14 to -1.30)	0.70	0.29	< 0.001*
Potassium (mmol/L)	66.39 (27.09 to 105.69)	19.31	0.24	0.002*
Phosphorus (mg/dL)	43.89 (13.85 to 73.95)	14.76	0.19	0.005*
Creatinine (mg/dL)	8.23 (2.04 to 14.42)	3.04	0.16	0.011*
Total cholesterol (mg/dL)	0.92 (0.65 to 1.76)	0.42	0.12	0.036*

Dependent Variable: IL-17.

Discussion

The most important finds of this study were that individuals with CKD showed increased serum IL-17A levels, and this cytokine is associated with GFR and several biochemical parameters, classically altered during the CKD.

Diabetes and hypertension are relevant fields of investigation as they are the predominant risk factors for CKD globally (Weaver, Fadrowski & Jaar, 2015). Among the CKD individuals from this study, a higher prevalence of hypertension, compared to diabetes, was observed. The relationship between IL-17A and hypertension has been recognized (Madhur *et al*., 2010; Norlander *et al.*, 2016). In line with these findings, blood pressure increased is observed after IL-17A exogenous infusion in mice (Nguyen *et al.*, 2012; Orejudo *et al.*, 2019). One possible mechanism for blood pressure elevation relies that IL-17A can stimulate sodium retention, by activating both NHE3 sodium transporter and NCC exchanger in the nephron (Norlander *et al.*, 2016). Other possibility is that IL-17A induces vascular remodeling in resistance arteries, leading to augmented peripheral vascular resistance (Orejudo *et al.*, 2020).

It is likely that risk factors, such as diabetes, hypertension and advanced age favors the sustained inflammatory activity noted in CKD individuals (Chung *et al.*, 2012). Of importance, even after variables such as age, sex, hypertension and diabetes were removed, IL-17A still displayed associated with GFR and several biochemical parameters, such as, urea, albumin, HDL cholesterol, potassium and phosphorus.

A correlation between GFR and inflammation has been clearly demonstrated and accepted everywhere (Goldstein, Leung & Silverstein, 2006; Tripathi *et al.*, 2010; Chung *et al.*, 2012). Different biomarkers of inflammation appear to have a different predictive value in CKD and dysregulated cytokine metabolism is present not only in adult (Amento *et al.*, 1991; Ross, 1999), but also in pediatric individuals with CKD (Goldstein, Leung & Silverstein, 2006). Interestingly, proinflammatory factors were upregulated in kidneys from IL-17A-infused mice (Orejudo *et al.*, 2019), furthermore it has been suggested that IL-17 knockout mice are protected from kidney injury due to impairment of both, the innate and the adaptive arms of the immune response (Gan *et al.*, 2010). Our findings demonstrate an increased serum level of IL-17A in individuals with CKD. Besides that, increase of this cytokine is correlated with classically biomarkers of end-stage renal disease, such as creatinine, urea and albumin, reinforces the current idea that this particular cytokine may be associated to the severity of kidney dysfunction.

In a study conducted with 105 patients receiving haemodialysis, an increased number of Th17 cells was observed, followed by an imbalanced ratio between Th17/Treg cell (Lang *et al.*, 2014). Supporting this findings, IL-17A positive cells, mainly Th17, were found in kidney from individuals with hypertensive nephrosclerosis. Besides that, in a cohort study with 650 healthy elderly individuals, Coto and colleagues analyzed the allele gene rs4819554AA which is part of the IL17RA promoter. The authors showed a significantly higher frequency of allele rs4819554AA homozygotes among individuals with an estimated glomerular filtration rate < 60 mL/min/1.73m^2 (Coto *et al.*, 2015), suggesting that polymorphisms in the IL-17 pathway genes perhaps contribute to the risk of chronic kidney disease.

Our findings suggest that increased IL-17A levels in individuals with CKD, could be determined by reduced of GFR, albumin level and HDL cholesterol, furthermore high levels of this cytokine also could be determined by higher serum levels of creatinine and urea, classically altered during the CKD. These evidences set the idea that IL-17A might be can play an important role in the renal system (dys)regulation.

The possible mechanism of renal dysfunction in individuals with high IL-17A levels can be multifactorial. Th17 cells promote kidney injury since infiltrating Th17 cells locally secrete IL-17, which stimulates resident renal proximal tubular epithelial cells and consequently upregulated expression of numerous pro-inflammatory cytokines and chemokines such as as IL-6, C-X-C motif ligand (CXCL) 1, CXCL8, and CCL2. These inflammatory mediators further enhance the recruitment of neutrophils and the induction of monocyte and Th1 cell-attracting chemokines that promote immune-mediated kidney damage (Turner *et al.*, 2010; Zhang *et al.*, 2015). Significant immune dysregulation has been reported in individuals with end-stage renal disease, when compared with the general population (Tripathi *et al.*, 2010), along with our findings.

In the kidneys, IL-17 also promotes aortic stiffening, possibly through upregulation of type I collagen deposition in the coronary and renal arteries (McMaster *et al.*, 2015). However, numbers of IL-17-producing T cells at the site of inflammation are usually low, at the same time has been suggested a high level of synergism between IL-17A and other pro-inflammatory cytokines and chemokines across various organ systems (Hot, Lenief & Miossec, 2012; Zenobia & Hajishengallis, 2015).

It is likely that IL-17A is part of a complex network of cytokines, at where circulating IL-17A could interact with other cytokines and chemokines in renal tissue to trigger both local and systemic inflammation (Turner *et al.*, 2010; Waite & Skokos, 2012). Therefore, it is

believed that IL-17A is not only a consequence of GFR, but also may acts as a trigger for the progression of CKD and its related complications. At this moment, antibodies targeting Th17 are being tested in mice (Chan *et al.*, 2014) and into clinical practice (Miossec & Kolls, 2012), which suggests that monoclonal antibodies against IL-17A could be a novel interesting therapeutic target to prevent CKD progression.

It is important to mention that even considering the central role of IL-17A in the pathogenesis of kidney diseases, other factors should be taken into consideration. Several diseases, inflammatory factors and biochemical parameters have been associated with GFR and some of these factors seem to be strongly associated with CKD. Besides that, in this study there are limitation that should be considered such as the small sample size and the use of a cross-sectional design, which does not allow the determination of a causal relationship between IL-17A levels and biochemical parameters in individuals with CKD. In summary, further studies are clearly needed to establish a potential link between IL-17A and the pathogenesis of CKD in human.

Conclusion

In this study, we have showed that serum concentration of IL-17A was increased in individuals with CKD and this cytokine is associated with classically parameters, altered during the CKD. Based on these findings, it seems that IL-17A play an important role in the renal system (dys)regulation, and this cytokine might be a useful target to prevent CKD progression.

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