ISSN: (3007-0384)
E-ISSN: (3007-0392)
Journal of Wahj Al-Ulom for Pure Sciences
available online at: https://uomosul.edu.iq/womeneducation/jwups/

The physiological role of Indoleamine 2,3-Dioxygenase and its relationship with obesity in patients with chronic renal failure in Nineveh Governorate

Fatima Muhammad Yunus[1], Rana F. Jasim[2]

[a] **Chemistry Department, College of Education for Girls, University of Mosul, Mosul-Iraq,**
***Corresponding author e-mail:** @student.uomosul.edu.iq

***Keywords*:**
Creatinine,
Glucose,
Obesity,
Smoker,
Triglyceride.

ARTICLE INFO
Article history:
Received : 26/06/2023
Accepted : 03/07/2023
Available online : 01/08/2024
Email: jwups@uomosul.edu.iq

ABSTRACT

The study included the determination of Indoleamine 2,3-dioxygenase (IDO) conc. with other parameters in patients of chronic renal failure (CRF) treated with hemodialysis and comparing with control cases, after separation of serum from blood samples IDO level has been determined in the serum and the conc. of urea, creatinine, Potassium, sodium, glucose, total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), very low-density lipoprotein-cholesterol (VLDL-C), vitamin D, total protein, and GFR value in two groups. The results have been showing that the conc. of IDO in control cases (4.74 ±1.53 ng/ml) and IDO conc. significantly increased in patients compared with the healthy control. It has been found that the level of IDO increased significantly with age and non-smokers CRF patients and control cases. IDO conc. significantly showed an increment with BMI increasing in the two groups. the level of urea, creatinine, Potassium, and glucose showed a significant increase while sodium, total cholesterol, HDL-C, LDL-C, vitamin D, total protein, and GFR values showed a significant decrease in patients compared to control cases. By using linear regression analysis (Pearson correlation coefficient) the results showed a positive correlation between IDO and urea, creatinine, and triglycerides and a negative correlation with total cholesterol, LDL-C, and GFR. We concluded that IDO conc. can be a bioindicator of obesity and could be a promising target to treat and control insulin resistance and obesity.

الدور الفسيولوجي لانزيم اندول امين 2-3 داي اوكسجنيز وعلاقته بالسمنة لدى مرضى الفشل الكلوي المزمن في محافظة نينوى

فاطمة محمد يونس(1)، رنا فاضل جاسم(2)

(2،1) قسم الكيمياء، كلية التربية للبنات، جامعة الموصل، الموصل، العراق

الخلاصة:

تضمن البحث تقدير تركيز انزيم اندول امين 2,3- داي اوكسجينيز لدى مرضى الفشل الكلوي المزمن والمعالجين بالديلزة الدموية ومقارنتها مع مجموعة الاصحاء، فبعد فصل المصل من نماذج الدم التي تم جمعها ، قدر تركيز الانزيم وكذلك تركيز كل من اليوريا والكرياتنين والبوتاسيوم والصوديوم والكلوكوز والكولسترول الكلي والكليسريدات والبروتين الدهني عالي الكثافة وواطئ الكثافة وواطئ الكثافة جداً للكولسترولوالبروتين الكلي وفيتامين دي وقيمة معدل الترشيح الكبيبي، حيث اظهرت النتائج ان تركيز الانزيم لدى الاصحاء بلغ (4.74 ±1.53 ng/ml) ولوحظ ارتفاع معنوي في تركيز الانزيم لدى المرضى مقارنة بالاصحاء. كما لوحظ ارتفاع في تركيز الانزيم مع التقدم بالعمر لدى المرضى والاصحاء. كذلك لوحظ ارتفاع في تركيز الانزيم مع زيادة مؤشر كتلة الجسمt في كلا المجموعتين. وقد اظهرت النتائج ارتفاع معنوي في تركيز اليوريا والكرياتنين والبوتاسيوم والكلوكوز بينما لوحظ انخفاض معنوي في تركيز الصوديوم والكولسترول الكلي والبروتين الدهني عالي وواطئ الكثافة للكولسترول والبروتين الكلي وفيتامين دي ومعدل الترشيح الكبيبي لدى المرضى مقارنة بالاصحاء وباستخدام تحليل الانحدار الخطي (معامل ارتباط بيرسون) فقد ظهرت علاقة معنوية ايجابية بين تركيز الانزيم وبين اليوريا والكرياتينين والكليسريدات الثلاثية بينما لوحظ وجود علاقة معنوية عكسية بين تركيز الانزيم وبين تركيز الكولسترول الكلي والبروتين الدهني واطئ الكثافة للكولسترول ومعدل الترشيح الكبيبي. نستنتج من ذلك ان تركيز الانزيم قد يعد مؤشرا على السمنة وقد يكون هدفا علاجيا واعداً للسيطرة على مقاومة الانسولين والسمنة.

الكلمات المفتاحية: الكرياتينين، الكلوكوز، السمنة، المدخنين، الكليسريدات الثلاثية.

1-INTRODUCTION:

The damage of the kidney or the glomerular filtration rate (GFR) decreasing lower than 60 mL/min/1.73m^2 over three months is known as Chronic renal failure (CRF). The disease progresses with age, diabetes, high blood pressure, high concentration of elements and glomerulonephritis [1], [2]. The important role of the kidney is the expel and eliminate waste products from the body and regulate acid-base balance and the level of water and electrolytes[1] Imbalance of electrolytes and acid-base are the key Causes associated with demineralization of bone, muscle catabolism, increasing the risk of CRF and Cardiovascular diseases, and mortality. As kidney disease develops it has to deal with the imbalance of electrolytes: sodium, potassium, phosphate, magnesium and calcium [2], [3]. Indoleamine 2،3-dioxygenase (IDO) is an intracellular cytoplasmic enzyme that stimulates and maintains immunosuppression. It looks almost linked to several immune cells, including macrophages, dendritic cells, and monocytes. However, IDO affects mainly lymphocytes[4]. IDO is the major catalyzer enzyme of the kynurenine pathway (KP), and it has a wide range of immunological action in inflamed areas, ranging from activation to immunosuppression. Innate immune cells express IDO1 leading to local tryptophan (TRP) catabolism and kynurenine generation, both mechanisms that contribute to the immunosuppressive effect[5]. The enzyme also inhibits metabolism in many biological systems, which include the reproduction of mammals, viruses, stem cells and the digestive system[6]. IDO associates in reciprocal relationship with chronic renal failure disease, where the enzyme had been found in glomerular filtration, tubular cells and nephritis as well as IDO is associated with diabetic nephropathy and renal fibrosis. IDO affects kidney inflammation which is a sign of the beginning of kidney damage[7].

Obesity is associated with kidney disease, which leads to glomerular hypertrophy, changes in blood circulation, kidney hyperfiltration in addition to increased hyperalbuminemia, Obesity promotes a variety of disorders, including metabolic syndrome, high blood pressure, and diabetes, which are the leading causes of chronic renal disease[8].

2-AIM OF THE RESEARCH:

In the last few years, chronic renal failure and obesity increased in Iraq and there were limited studies on indolamine 2,3-dioxygenase and obesity, so we suggested studying the relationship between the enzyme and obesity in the patients and the correlation of the enzyme with some clinical variables.

3-MATERIAL AND METHODS:

Blood samples were collected from 88 healthy people, including 44 males and 44 females with age (15->70 years), also blood samples from 74 patients of CRF, including 45 males and 29 females with age (15->70 years) and treated with hemodialysis were collected from Ibn Sina Teaching Hospital-Nephrology Unit in Mosul city of Iraq, and the following variables were estimated in sera:

IDO conc. was determined by WUHAN Fine Biotech Co., Ltd Kit (China) using Enzyme-Linked Immunoassay Technology. The conc. of Urea, creatinine, total protein, glucose, TC, TG and HDL-C were estimated using a BIOLABO kit (France), also the conc. of sodium and potassium were determined by BIOSYSTM Kit (Spanish), and Vitamin D3 conc. was estimated using the BIOMERIEUX kit (France), while LDL-C conc. and VLDL-C conc. calculated by Friedewald equation:

LDL-C (mmol/L) =Total cholesterol – HDL-C– (TG/2.2) [9],

and the equation: VLDL-C (mmol/L) =TG (mmol/L)/2.2 [10] respectively.

Furthermore, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is used to compute the Glomerular Filtration Rate (GFR)[11]:

For female(with creatinine < 62 µmol/L):

$$GFR(mL/min/1.73\ m^2) = 144 \times (Cr/61.6)^{-0.329} \times (0.993)^{Age}$$

For female(with creatinine > 62 µmol/L):

$$GFR(mL/min/1.73\ m^2) = 144 \times (Cr/61.6)^{-1.209} \times (0.993)^{Age}$$

For male(with creatinine < 80 µmol/L):

$$GFR(mL/min/1.73\ m^2) = 141 \times (Cr/79.2)^{-0.411} \times (0.993)^{Age}$$

For male(with creatinine > 80 µmol/L):

$$GFR(mL/min/1.73\ m^2) = 141 \times (Cr/79.2)^{-1.209} \times (0.993)^{Age}$$

3-1 Data analysis:

SPSS was utilized to analyze our study data, and conventional statistical procedures were applied to obtain mean and standard division. The T-test was used to compare two variations, ANOVA one way was used to analyze more than two variants, and Pearson correlation coefficient (r) was used to identify the relationship between different parameters, with $P \leq 0.05$ regarded as statistically significant [12].

4- The Results and Discussion:

4-1 IDO concentration in CRF patients and control group:

The normal conc. of IDO is (4.74 ±1.53 ng/ml) in healthy control group, it was consistent with[13] who found the conc. (4.78±0.15 ng/ml) of IDO and close to the conc. (2.60 ± 1.29 ng/ml) found by[14], as shown in Table (1).

Table (1): IDO conc. in CRF patients and control group

IDO conc. (ng/ml) mean ± S. D	
Control	**Patients**
4.74 ±1.53	13.02 ±4.88***

*** Significant variance if p≤ 0.001, S. D= stander division

As showed in figure (1), we found that IDO conc. significantly increased in patients of CRF compared with control group and This result was consisting with[15], [16].

Inflammation, insufficiency immune response and immune imbalance is clear features of CRF. IDO play essential role in immune regulation and control of inflammation, and increased level of IDO is an indicator to impaired in immunoregulation ability in CRF, also, IDO conc. indicate to hypoxia and renal ischemia [16].

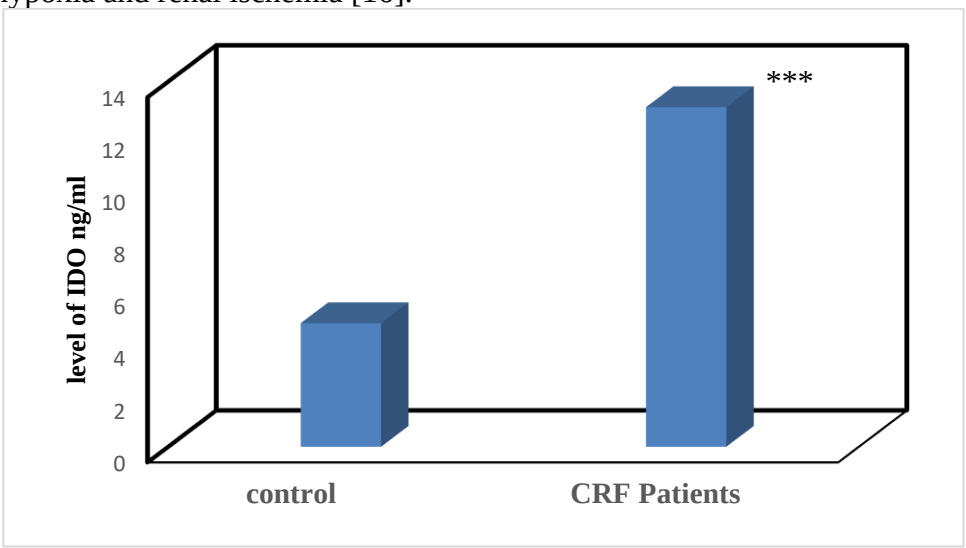

Figure (1): IDO level in CRF patients compared with control

*** Significant variance if p≤ 0.001

4-2 IDO level in CRF patients and control group according to the age:

The results a significant increase in IDO level with age in each group as illustrated in Table (2), this result was in agreement with [16].

Table (2): IDO level in CRF patients and control group according to the age

Age(year)	IDO level (ng/ml) mean ± S. D	
	Control	Patients
15-35	2.65 ±1.15	10.03 ±3.27
36-56	6.257 ±1.86 *	14.95 ±2.34 **
57-77	7.200 ±2.06 **	18.09 ±5.43 ***

* Significant variance vertically at p≤ 0.05, ** if p≤ 0.01, *** if p≤ 0.001
S. D= stander division

Pro-inflammatory cytokines increased with Aging and can cause many diseases related to age such as CRF. Also, IDO levels increased in inflammation and autoimmune disorders [17].

4-3 IDO level in CRF patients and control group according to the Smoking:

As shown in Table (3), The level of IDO in smokers decreased significantly compared with non-smokers in each group and this result was consistent with[18].

Table (3) IDO level in CRF patients and control group according to the **s**moke

Smoke	IDO level (ng/ml) mean ± S. D	
	Control group	Patients
non-smokers	6.26±2.24	15.94±5.37
Smokers	2.98 ±1.01*	9.79 ± 2.34 **

* Significant variance vertically at p≤ 0.05, ** at p≤ 0.01.

Cigarette smoking reduces the activity of IDO, consequently, attenuates the immunosuppressive effects of IDO. Many studies showed that tobacco decreases dendritic cell number in an animal's lung tissue, and tobacco has an immunosuppressive influence on dendritic cell functions. Also, Nicotine affects receptors in dendritic cells leading to defect Th1 response and reducing interferon IFN-γ production, a potent inducer of IDO. So, Smoking may have an indirect effect on IDO via lowering IFN- levels[19].

4-4 IDO level in CRF patients and control group according to the BMI:

The data in Table (4) revealed a significant increase in IDO levels with increasing body mass index in each group, and this was consistent with[7].

Table (4): IDO level in CRF patients and control group according to the BMI

BMI	IDO level (ng/ml) mean ± S. D	
	Control group	Patients
Normal	3.31±1.86	9.13±3.19
Obesity	7.0±1.77 **	13.42±2.90*
Over obesity	8.63±2.27***	17.12 ±5.12**

* Significant difference vertically at p≤ 0.05, ** at p≤ 0.01, *** at p≤ 0.001.

Body mass index (BMI) activates the immune enzyme IDO as well as CKD, Obesity is linked to abnormal metabolism of amino acids particularly, tryptophan (Trp), which metabolize by IDO to kynurenine (Kyn), which is upregulated in the obese subjects. Overexpression of IDO1 depletes Trp and decreases the production of other metabolites of Trp such as serotonin, which involves in the suppression of appetite and generation of satiety [20].

Adipose tissue is a storage of energy that maintains homeostasis of glucose and lipid. Also, it is considered an endocrine organ that secretes many cytokines, such as interleukin-6, adiponectin, and leptin, which can cause obesity. In obese individuals, excessive glucose is transported into adipocytes to synthesise triglycerides and to form lipid droplets that are stored in adipocytes which become hypertrophy and induced to produce proinflammatory cytokines, which can cause insulin resistance [7].

Mature adipocytes are critical for the metabolism of Kyn, in obese subjects. So, the deficiency of IDO in adipocytes decreases Kyn and protects from obesity. the excessive Kyn induces overexpression of the aryl hydrocarbon receptor, which then activated the IL6 signalling, that can cause the development of insulin resistance and obesity. Additionally, vitamin B6 efficiently catalyzes the catabolism of Kyn, reduces the amount of Kyn, and is rescued from obesity. Therefore, prevention the accumulation of Kyn could be a promising to treat insulin resistance and obesity [7], [20].

The concentration of some clinical parameters in CRF patients in comparison to the control group:

The results in Table (5) showed a significant increase in the concentration of urea and creatinine in patients compared to the control group and these findings were similar to those in [21], the kidney failed to remove these metabolites from the blood, thereby its concentration increased in the blood[22].

Potassium concentration showed a significant increase while sodium concentration showed a significant decrease in patients compared to the control group, and these results were consistent with [23], [24], Potassium is the cation that is most abundant in intracellular fluid, so the impaired in renal regulatory mechanisms can cause high blood potassium level (hyperkalemia) which is common in CRF patients because of decrease in eGFR and reabsorption [23], Sodium represent the chief mineral in the extracellular fluid that keeps balance of fluids in the body and helps muscles and nerves to work properly. Impaired Kidneys function and dysfunction of the aldosterone and renin-angiotensin system leads to extra losses of fluids, and poor ability to maintain water balance so the patients are more likely to develop hyponatremia[25].

The findings also revealed a significant increase in glucose level in patients and these results were consistent with [26]. The filtered glucose is completely reabsorbed into the circulatory system, which leads to an increase in the conc. of glucose in the blood[27].

A significant decrease had been showed in Table (5) in cholesterol, LDL-C, and HDL these results were identical to those [28], [29], the cause may be due to malnutrition or inflammation which is a complication of kidney disease, the toxins that not removed by dialysis from the body of the patients can interfere with the smell and taste of the patients, so the food loses its appeal [29].

the decrease in HDL indicates the progression of chronic kidney disease because HDL losses the ability to enhance the efflux of cholesterol from macrophages as well as losses antioxidant and anti-inflammatory properties, the cause of the decline in HDL-C level is renal dysfunction and decreased eGFR. Also due to reduced synthesis and increased catabolism of ApoA-I. [30].

The results in Table (3) showed a significant decrease in total Protein conc. in patients compared to the control group, and these results were consistent with those found in[31] because protein leaks through kidney filters to the urine which cais lled proteinuria[32].

Vitamin D_3 showed a significant decrease in concentration in patients, and these results were consistent with those found in [33] this may be due to malnutrition which results from lack of appetite or impaired vit D gastrointestinal absorption, or maybe because of an impaired in the enzyme 1α-hydroxylase that converts 25-(OH)vitamin D into 1,25 dihydroxy-vitamin D (the active form) [34].

The results presented in Table (5) showed a significant decrease in glomerular filtration in patients compared to the control group, and these results were consistent with those in [35], the reason for the decrease is due to poor nephron function and may result from diabetic nephropathy or an increase in protein concentration This leads to an increase in the pressure of the glomerular capillaries[36].

Table (5): some clinical parameters concentration in CRF patients compared to control.

Clinical parameters	Control group mean ± S. D	Patients mean ± S. D
Urea mmol\l	4.68 ± 0.75	24.59 ± 7.99 ***
Creatinine mmol\l	77.80 ± 11.46	909.5 ± 277.2 ***
Potassium mmol\l	3.98 ± 0.244	4.47 ± 0.83 *
Sodium mmol\l	138.9 ± 4.69	129.8 ± 11.27**
Glucose mg/dl	5.03 ± 0.78	7.7 ± 2.69 *
TC mg/dl	4.27 ± 0.94	3.28 ± 0.70 **
TG mg/dl	1.44 ± 0.341	1.76 ± 0.40
LDL mg/dl	2.47 ± 0.77	1.68 ± 0.61**
VLDL mg/dl	0.64 ± 0.26	0.78 ± 0.22
HDL mg/dl	1.16 ± 0.30	0.76 ± 0.16***
Total Protein mg/dl	69.40 ± 3.73	53.61 ± 14.69 ***
Vitamin D_3 ng/ml	30.47 ± 7.26	14.79 ± 4.79 ***
GFR µmol/l	99.13 ± 19.78	5.23 ± 1.66***

* Significant difference vertically at p≤ 0.05, ** at p≤ 0.01, *** at p≤ 0.001.

Correlation between IDO level and some parameters in CRF patients and control group:

Our results in Table (6) showed a significant positive correlation between the level of IDO and the concentration of urea, creatinine, and triglycerides and a significant negative correlation between the level of IDO and the concentration of cholesterol, LDL, and GFR values.

Table (6): Correlation between IDO concentration and some parameters in control group and CRF patients

Clinical Parameters	Control group		Patients	
	r-value	P- value	r-value	P- value
Urea mmol\l	0.56	0.029*	0.715	0.0027**
Creatine mmol\l	0.318	0.247	0.675	0.0080 **
Potassium mmol\l	0.472	0.075	0.106	0.7048
Sodium mmol\l	-0.442	0.098	-0.127	0.6498
Glucose mg/dl	0.238	0.392	0.366	0.1792
TC mg/dl	-0.515	0.059	-0.632	0.0115*
TG mg/dl	0.243	0.382	0.634	0.0111*
LDL mg/dl	-0.497	0.070	-0.531	0.0414*
VLDL mg/dl	0.203	0.467	0.387	0.1537
HDL mg/dl	-0.284	0.323	-0.421	0.1176
Total Protein mg/dl	-0.194	0.486	-0.053	0.8492
Vitamin D_3 ng/ml	-0.346	0.205	-0.362	0.2033
GFR µmol/l	-0.535	0.048*	-0.515	0.0493*

* Significant difference vertically at p≤ 0.05, ** at p≤ 0.01.

Chronic inflammation can increase the level of IDO and causes CRF that the kidneys fails to remove the wastes products from the blood, such as urea and creatinine which leading to increase their concentration in body, with decline in GRF[37].

Inflammation, oxidative stress, malnutrition, and uremic toxins were proposed as risk factors of cardiovascular disease and dyslipidemia in CRF patients which cause increase TG, decrease HDL-C, TC and LDL-C level. Also, Inflammation and oxidative stress induce IDO[38]. IDO level correlates negatively with GFR because of association of IDO level with severity of CRF, since GFR is an important indicator of CRF severity [39].

5-Conclusion:

IDO level could be a marker of inflammation in CRF undergoing hemodialysis, and there was a strong relation between IDO level and oxidative stress thus TRP to KYN ratio may indicate the oxidative stress state in CRF patients.

Acknowledgement

We would like to extend our thanks and gratitude to the University of Mosul, College of Education for Girls for the facilities it provided us to complete the research

Conflict of the interests

The authors assure there is no conflict of interest.

Reference:

[1] G.-C. M. Herber-Gast *et al.*, "Consumption of whole grains, fruit and vegetables is not associated with indices of renal function in the population-based longitudinal Doetinchem study," *British journal of nutrition*, vol. 118, no. 5, pp. 375–382, 2017.

[2] S. Mazzaferro *et al.*, "Focus on the possible role of dietary sodium, potassium, phosphate, magnesium, and calcium on CKD progression," *J Clin Med*, vol. 10, no. 5, p. 958, 2021.

[3] T. Dhondup and Q. Qian, "Electrolyte and acid-base disorders in chronic kidney disease and end-stage kidney failure," *Blood Purif*, vol. 43, no. 1–3, pp. 179–188, 2017.

[4] K. Wiśnicki, P. Donizy, A. Remiorz, D. Janczak, M. Krajewska, and M. Banasik, "Significance of indoleamine 2, 3-dioxygenase expression in the immunological response of kidney graft recipients," *Diagnostics*, vol. 12, no. 10, p. 2353, 2022.

[5] A. Krupa, M. M. Krupa, and K. Pawlak, "Indoleamine 2, 3 Dioxygenase 1—The Potential Link between the Innate Immunity and the Ischemia-Reperfusion-Induced Acute Kidney Injury?," *Int J Mol Sci*, vol. 23, no. 11, p. 6176, 2022.

[6] J. C. Mbongue, D. A. Nicholas, T. W. Torrez, N.-S. Kim, A. F. Firek, and W. H. R. Langridge, "The role of indoleamine 2, 3-dioxygenase in immune suppression and autoimmunity," *Vaccines (Basel)*, vol. 3, no. 3, pp. 703–729, 2015.

[7] H.-R. Kim, H.-S. Jin, and Y.-B. Eom, "Identification of Genetic Markers Linked to The Activity of Indoleamine 2, 3-Dioxygenase and Kidney Function," *Metabolites*, vol. 13, no. 4, p. 541, 2023.

[8] E. Nehus, "Obesity and chronic kidney disease," *Curr Opin Pediatr*, vol. 30, no. 2, pp. 241–246, 2018.

[9] L. J. Mundal *et al.*, "Association of low-density lipoprotein cholesterol with risk of aortic valve stenosis in familial hypercholesterolemia," *JAMA Cardiol*, vol. 4, no. 11, pp. 1156–1159, 2019.

[10] S. Hwang *et al.*, "A deep neural network for estimating low-density lipoprotein cholesterol from electronic health records: Real-time routine clinical application," *JMIR Med Inform*, vol. 9, no. 8, p. e29331, 2021.

[11] W.-A. S. Mula-Abed, K. Al Rasadi, and D. Al-Riyami, "Estimated glomerular filtration rate (eGFR): A serum creatinine-based test for the detection of chronic kidney disease and its impact on clinical practice," *Oman Med J*, vol. 27, no. 2, p. 108, 2012.

[12] B. Pan *et al.*, "Correlation of indoleamine-2, 3-dioxygenase and chronic kidney disease: a pilot study," *J Immunol Res*, vol. 2021, 2021.

[13] S. S. Danha and A. L. Hussein, "The Role of Serum Level of Indoleamine 2, 3–dioxygenase 1 (IDO1) in Patients with Prostate Cancer," *Medico Legal Update*, vol. 21, no. 2, pp. 1402–1407, 2021.

[14] Y. Zhang *et al.*, "Associations between expression of indoleamine 2, 3-dioxygenase enzyme and inflammatory cytokines in patients with first-episode drug-naive Schizophrenia," *Transl Psychiatry*, vol. 11, no. 1, p. 595, 2021.

[15] A. Molfino *et al.*, "Fatigue in patients on chronic hemodialysis: the role of indoleamine 2, 3-dioxygenase (IDO) activity, interleukin-6, and muscularity," *Nutrients*, vol. 15, no. 4, p. 876, 2023.

[16] H. Hong, S. Zhou, H. Shi, and M. Li, "Plasma and urine indoleamine 2, 3-dioxygenase activity: promising biomarkers for chronic kidney disease and inflammation status," *J Inflamm Res*, pp. 5129–5139, 2022.

[17] A. Salminen, "Increased immunosuppression impairs tissue homeostasis with aging and age-related diseases," *J Mol Med*, vol. 99, pp. 1–20, 2021.

[18] M. Pertovaara, M. Heliövaara, A. Raitala, S. S. Oja, P. Knekt, and M. Hurme, "The activity of the immunoregulatory enzyme indoleamine 2, 3-dioxygenase is decreased in smokers," *Clin Exp Immunol*, vol. 145, no. 3, pp. 469–473, 2006.

[19] S. Bano, S. B. Hamid, F. Sajid, and H. Sharif, "Gender-Based Effects of Chronic Nicotine Administration on Hypothalamic Pituitary Adrenal Axis and Indoleamine 2, 3 dioxygenase Activity in Rats," 2021.

[20] I. Wolowczuk *et al.*, "Tryptophan metabolism activation by indoleamine 2, 3-dioxygenase in adipose tissue of obese women: an attempt to maintain immune homeostasis and vascular tone," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 303, no. 2, pp. R135–R143, 2012.

[21] D. Pandya, A. K. Nagrajappa, and K. S. Ravi, "Assessment and correlation of urea and creatinine levels in saliva and serum of patients with chronic kidney disease, diabetes

and hypertension–a research study," *J Clin Diagn Res*, vol. 10, no. 10, p. ZC58, 2016.

[22] T. J. Lasisi, Y. R. Raji, and B. L. Salako, "Salivary creatinine and urea analysis in patients with chronic kidney disease: a case control study," *BMC Nephrol*, vol. 17, pp. 1–6, 2016.

[23] S. L. Seliger, "Hyperkalemia in patients with chronic renal failure," *Nephrology Dialysis Transplantation*, vol. 34, no. Supplement_3, pp. iii12–iii18, 2019.

[24] R. Zhang, S. Wang, M. Zhang, and L. Cui, "Hyponatremia in patients with chronic kidney disease," *Hemodialysis International*, vol. 21, no. 1, pp. 3–10, 2017.

[25] C. P. Kovesdy *et al.*, "Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure," *Circulation*, vol. 125, no. 5, pp. 677–684, 2012.

[26] D. K. Patel and J. Strong, "The pleiotropic effects of sodium–glucose cotransporter-2 inhibitors: beyond the glycemic benefit," *Diabetes Therapy*, vol. 10, pp. 1771–1792, 2019.

[27] J. H. Bae, E.-G. Park, S. Kim, S. G. Kim, S. Hahn, and N. H. Kim, "Effects of sodium-glucose cotransporter 2 inhibitors on renal outcomes in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials," *Sci Rep*, vol. 9, no. 1, p. 13009, 2019.

[28] A. B. Reiss, I. Voloshyna, J. De Leon, N. Miyawaki, and J. Mattana, "Cholesterol metabolism in CKD," *American Journal of Kidney Diseases*, vol. 66, no. 6, pp. 1071–1082, 2015.

[29] H. Shen *et al.*, "Small dense low-density lipoprotein cholesterol was associated with future cardiovascular events in chronic kidney disease patients," *BMC Nephrol*, vol. 17, pp. 1–7, 2016.

[30] A. Gluba-Brzozka, B. Franczyk, and J. Rysz, "Cholesterol Disturbances and the Role of Proper Nutrition in CKD Patients. Nutrients. 2019; 11 (11): 2820."

[31] K. Kalantar-Zadeh *et al.*, "Plant-dominant low-protein diet for conservative management of chronic kidney disease," *Nutrients*, vol. 12, no. 7, p. 1931, 2020.

[32] S. Sharma and B. Smyth, "From proteinuria to fibrosis: An update on pathophysiology and treatment options," *Kidney Blood Press Res*, vol. 46, no. 4, pp. 411–420, 2021.

[33] G. Cianciolo *et al.*, "Vitamin D effects on bone homeostasis and cardiovascular system in patients with chronic kidney disease and renal transplant recipients," *Nutrients*, vol. 13, no. 5, p. 1453, 2021.

[34] V. Brandenburg and M. Ketteler, "Vitamin D and secondary hyperparathyroidism in chronic kidney disease: a critical appraisal of the past, present, and the future," *Nutrients*, vol. 14, no. 15, p. 3009, 2022.

[35] E. Russo *et al.*, "Working Group on UricAcid and Cardiovascular Risk of the Italian Society of Hypertension. Association of uric acid with kidney function and albuminuria: the uric acid right for heart health (URRAH) project," *J Nephrol*, vol. 35, no. 1, pp. 211–221, 2022.

[36] M. Provenzano *et al.*, "Reclassification of chronic kidney disease patients for end-stage renal disease risk by proteinuria indexed to estimated glomerular filtration rate: multicentre prospective study in nephrology clinics," *Nephrology Dialysis Transplantation*, vol. 35, no. 1, pp. 138–147, 2020.

[37] M. A. Aziz, G. H. Majeed, K. S. Diab, and R. J. Al-Tamimi, "The association of oxidant–antioxidant status in patients with chronic renal failure," *Ren Fail*, vol. 38, no. 1, pp. 20–26, 2016.

[38] K. Rosenstein and L. R. Tannock, "Dyslipidemia in chronic kidney disease," *Endotext [Internet]*, 2022.

[39] Y.-S. Bao, Y. Ji, S.-L. Zhao, L.-L. Ma, R.-J. Xie, and S.-P. Na, "Serum levels and activity of indoleamine2, 3-dioxygenase and tryptophanyl-tRNA synthetase and their association with disease severity in patients with chronic kidney disease," *Biomarkers*, vol. 18, no. 5, pp. 379–385, 2013.