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Theme

Study of risk factors and predictive markers of Chronic kidney disease (CKD) in Djamaa Hemodialysis Patients, and assessment of water quality effect (major risk factor) on kidney function in rats Wistar.

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إهـداء

بسم الله الرحمن الرحيم: "قل اعملوا فسيرى الله عملكم ورسوله والمؤمنون" (التوبة-105-) صدق الله العظيم

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Abstract

Chronic kidney Disease(CKD) is recognized as a major health problem, Faced with these problems, this study aims to identify some predictive and risk factors of CKD and to evaluate some biological and oxidative stress markers in HD patients of Djamaa (El-Oued) region, on the other hand in this work we are evaluated the water quality of the Djamaa region and study its effect on some markers of renal function in rats .

Our socioeconomic and clinic risk factors study was conducted on 77 voluntary individual divided into 41 persons reserved as a control and 36 HD patients are recruited from HD service of Hospital Saad Dahleb Djamaa .They are represented by the mean age 46,32 years and their origin cover all Djamaa region. For biological markers study of HD patients , We are selected 21 control with mean age 39.00 ± 3.41years and 20 patients with mean 51.40 ± 3.64 years on which some biochemical, Hematological and oxidative stress markers were estimated. To test the effect of Tap water on renal function we used 3 groups of rats.

Also We are relied the analysis of Odds ratio, student analysis, correlation ratio analysis, and Rook analysis for the statistical study of this work.

Our results of Socioeconomic and clinical factors study illustrate the high relationship of CKD and Diabetes, urinary problem and arterial hyper pressure as a frequently risk factors also renal herbal medicine, drugs nephrotoxic and Disease before CKD are the very important risk factors OR(62.00 - 25.45) while that additive soft drink, spices and amount of water are significant ($P<0.05$) protective factors against CKD when OR (0.232 - 0.352).

Our biological study demonstrate a significant variations ($P<0.05$) in biochemical parameters , Hematological markers , electrolytes levels and oxidative stress markers which represented an important significant($P<0.05$) specificity of GSH(32%,AUC=31%), ORAC and FRAP activities(87%,AUC=77% and 73%,AUC=85%) respectively. also we notice a significant correlation between oxidative stress markers and some biochemical parameters of kidney function.

In addition, we found a significant deference in some minerals and electrolytes levels between some spring ,tap and filtered water of deferent areas of Djamaa region which represented a significant effects on renal function shown in a remarkable changes of biological markers of rats drink water during 60 days of the experiment where the TW represented a high risk for kidney dysfunction while it contributes to significant variation on oxidant stress markers as MDA level and antioxidant enzymes as GSH, CAT, GST and SOD

also biochemical and hematological markers illustrate an significant modifications which indicate to the renal disorder and anemia consequents while that the FW is represented a significant effect on renal function and biological markers studied but did not very deferent with TW results.

Finally, we conclude that there are a most socioeconomic and clinical risk factors for CKD also tap water and filtered water are an important risk factor for renal function while there may contribute to renal dysfunction and CKD in Djamaa population. In addition, GSH, ORAC and FRAP activities represent very important predictive factors for the disease studied where its can suggested in prognostic parameters of CKD.

Key words: Chronic kidney disease , Hemodialysis , oxidative stress , Tap Water. .

الملخص

يعتبر مرض القصور الكلوي مشكل يهدد الصحة العمومية ،و من اجل ذلك أجريت هذه الدراسة و التي تهدف إلى تحديد بعض عوامل الخطر وعوامل التنبؤ لمرض القصور الكلوي وتقييم بعض المعايير البيولوجية ومعايير الإجهاد التاكسدي للمرضى الخاضعين لتصفية الدم في منطقة جامعة (الوادي) , من ناحية أخرى قمنا في هذا العمل بتقييم جودة المياه في منطقة جامعة ودراسة تأثيرها على بعض المعايير البيولوجية لوظيفة الكلى لدى الفئران.

تم إجراء دراسة عوامل الخطر الاجتماعية و السريرية على 77 متطوعًا موزعين على قسمين 41 شخصًا سليم و 36 من مرضى غسيل الكلى تم اختيارهم من مصلحة تصفية الدم لمستشفى سعد دحلب جامعة حيث متوسط عمرهم 32,46±2.90 سنة و يمثلون جميع مناطق جامعة, و من اجل الدراسة البيولوجية لمرض القصور الكلوي تم اختيار 21 شخص سليم متوسط عمرهم 3.41 ± 39.00 سنة و20 شخص مريض بالقصور الكلوي المزمن متوسط عمرهم 3.64± 51.40 حيث تم تقدير بعض المعايير البيوكيميائية مثل (اليوريا ، الكرياتينين) و مستوى بعض الشوارد (الصوديوم ، البوتاسيوم والكلوريد) وعناصر مكونات الدم و كذا معايير الإجهاد ألتأكسدي لدى جميع الفئات المدروسة في هذا العمل. كما اعتمدنا على تحليل نسبة الترجيح و تحليل الطالب و تحليل نسبة الارتباط و تحليل رووك من اجل الدراسة الإحصائية لهذا العمل.

النتائج المتحصل عليها في هذه الدراسة توضح أن مرض السكري المزمن، والمشاكل البولية وارتفاع ضغط الدم الشرياني هي عوامل خطر كبيرة لمرض القصور الكلوي كما توضح أيضا أن استعمال الأعشاب الطبية والأدوية الخاصة بأمراض الكلى والإصابة بالأمراض المزمنة هي عوامل خطر أيضا للإصابة بمرض الفشل الكلوي المزمن بقيم OR متفاوتة (P<0.05) (25.45 - OR(62.00 كما أوضحت الدراسة أن المشروبات الغازية و استعمال التوابل و شرب كميات كبيرة من المياه تعتبر عوامل حماية و وقاية ضد المرض بقيم (0.352 - 0.232) OR <1.

بالنسبة للدراسة البيولوجية أظهرت النتائج تباينات كبيرة في مستوى المعايير البيوكيميائية و في مكونات الدم ومستوى الشوارد في المصل قبل و بعد عملية غسيل الكلى و كذلك ف معايير الإجهاد التاكسدي مما يظهر تأثير المرض على الحالة الفيزيولوجية للكلى .كما بينت النتائج ظهور معايير خاصة لتنبؤ المرض (P<0.05) (32%, AUC = 31 %) GSH (87%, AUC = 77%) و ORAC(73 % , AUC = 85٪ و FRAP على التوالي وأكد ذلك العلاقة المعنوية بين هذه العلامات وبعض المعايير البيوكيميائية الخاصة بوظيفة الكلى التي ظهرت في نتائج تحليل نسبة الارتباط الإحصائي.

أما فيما يخص الدراسة التحليلية للماء أظهرت النتائج اختلالا كبيرا في مستويات المعادن و الشوارد في مياه الصنابير لمختلف أنحاء منطقة جامعة و المياه المصفاة لنفس المنطقة مقارنة بالمياه المعدنية الطبيعية. هذا الاختلال ظهر جليا في نتائج دراسة تأثير تلك المياه على وظيفة الكلى لدى الفئران حيث أظهرت اختلالا وظيفيا للكلى أكدته تغيرات المعايير البيوكيميائية و مكونات الدم و معايير الإجهاد التاكسدي مما يوضح التأثير السلبي لاستعمال مياه الصنابير و المياه المصفاة على وظيفة الكلى لدى استعمالها للشرب .

في الأخير نستنتج من هذا العمل أن بعض السلوكات الاجتماعية و السريرية هي عوامل مهمة للإصابة أو الوقاية من الفشل الكلوي و أن مياه الشرب هي عامل رئيسي للإصابة بالمرض في منطقة جامعة بالإضافة إلى ذلك تمثل معايير GSH ORAC, FRAP عوامل بيولوجية جديدة تسهم في التنبؤ بالإصابة بمرض القصور الكلوي المزمن حيث يمكن اقتراحها ضمن معايير تشخيص هذا المرض.

كلمات مفتاحية: القصور الكلوي المزمن , غسيل الكلى ,الإجهاد التاكسدي , مياه الصنبور.

Abbreviation list

ACR: Albumin-Creatinine Rate.

ADE: Algerie d'eau (Algeria water).

AER: Albumin-Excretion Rate.

AGE_s: Advanced Glycation End-products

Ang II: Angeotensine II.

APC: Antigen presentin cells.

AV: Arteriovenouse.

BHT: Butylate dhydroxytoluene.

CAT: Catalase

Cd: Cadmium.

CDNB:1-chloro-2-4-dinitrobenzene.

CKD: Chronic Kidney Disease.

CKDu**:** Chronic Kidney Disease unkonow.

Cl: Chlorine.

Co: Cobalt

Cr: Chromium

CRF: Chronic Renal Failure**.**

CRP: C-reactive protein

CTI: chronic tubule-interstitial injury.

CVD: Cardiovascular Disease.

CVM: cardiovascular morbidity**.**

DNA: Deoxyribonucleic acid.

DTNB:5,5' Dithiobis(2-nitrobenzoic acid)

EPO: Erythropoietin.

EDTA: Ethylenediaminetetraacetic acid.

ESA: erythropoiesis-stimulating agent**.**

ESRD: End Stage Renal Disease.

F: Fluoride.

Fe: iron.

FRAP: Ferric Reducing Antioxidant Power

GFR: Glomerular Filtration Rate.

GSHas: Reduced Glutathion oxidase**.**

GST: Glutathion S Transferase.

HB: Hemoglobine.

HCT: Hematocrit.

HD: Hemodialysis.

Hg: Mercury

HLA.DR: Human Leukocyte Antigen – antigen D Related

HPS 700-11: Hyperspers 700-11.

HTA: Hypertension.

IL1: interleukin-1.

IL6: interleukin-6

ILa: interleukin a

K: potassium.

KDOQI: kidney Disease Outcome Quality Initiative

LDL: Low Density Lipoprotein**.**

MDA: Malondialdehyde.

Na: sodium..

NADPH: Nicotinamide Adenine Dinucleoide Phosphate.

NBT: Nitro-Blue Tetrazolium**.**

NF-KB: Nuclear Factor-Kappa B.

Ni: Nickel

O_2: Oxygen.

OD: Optical Density.

OR: Odds ratio.

ORAC: Oxygen Radical Absorbance Capacity.

OS: Oxidative stress.

PAD: Patients After Dialysis.

Pb: Lead**.**

PBD: Patients Before Dialysis.

PIH: Pregency Induced Hypertension.

Pmp: Per million population.

RA: Rheumatoid Arthritis**.**

RBC: Red Blood Cells.

ROS: Reactive Oxygen species.

SOD: Superoxide Dismutase.

TBS: Tris Buffer Saline.

TCA: Trichloroacetic acid**.**

TNF-a: tumor necrosis factor-a

WBC: White Blood Cells.

WHO: World Health Organization.

UTI: Urinary tract infection.

UV: Ultraviolet.

Zn: Zinc.

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SUMMARY

Bibliographic part

Experimental part

Introduction

Introduction

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem **(**Levey et *al*, 2007). During the past three decades, the incidence and prevalence of end stage renal disease (ESRD) have risen progressively. For example, annual new cases of ESRD increased from approximately 14,500 in 1978 to 100,359 in 2002; during the same period, the number of individuals on dialysis and with kidney transplants increased from 42,000 to 431,000(Anton et *al*, 2006). There is a wide spectrum of kidney disease, which can be rapid onset (acute) or longer term (chronic) (Public Health England , 2014).

The global CKD prevalence was reported to be 13.4% , in USA the prevalence was 13.6% , in Europe is lower than USA and more homogeneous and in some asian countries higher than USA but the Africa ,the lowest prevalence was 4% in northern Africa macro area, the highest 16.5% in west and central west Africa and the average prevalence in the entire Africa continent was 10.1% **(**AbdElhafeez et *al*,2018), also the burden of CKD prevalence in North Africa shown 650 pmp in Egypt,323 pmp in libya,734 pmp in Tunisia,300 in morocco and 475 in Algeria (Rashad , 2013). In addition, the total number of ESRD patients receiving renal replacement therapy in Algeria with population of 37 100 000 in 2001 reached 17000 in 2011 the prevalence and incidence of ESRD is 100 pmp and 109 pmp respectively (Lydia, 2014).

Chronic kidney disease (CKD) has emerged as a global public health burden for its increasing number of patients, high risk of progression to end-stage renal disease (ESRD), and poor prognosis of morbidity and mortality (Shang-Jyh et *al*, 2010).

It attracts worldwide attention to its epidemiology, risk factors, treatment plans and preventive.

In order to identify the risk factors of renal disease, An individual's genetic and phenotypic make up puts him/her at risk for kidney disease .factors such as smoking, exposure to heavy metals, excessive alcohol consumptionand the use of analgesic medication (Rumeyza , 2013). Moreover, CVD , hypertension, diabetes and obesity are traditional risk factors (Ibrahim et *al*, 2014). In addition, environmental pollution including air and water contamination causer or aggravates many acute and chronic human disease **(**Sunil et *al*, 2016). Indeed Drinking water pollution is a relatively new problem and increases the stress arising as a result of unprecedented population growth, urbanization, and industrialization since 1990s (Chen, 2002; Velea et *al*.,2009).

Many of recent landmarks in scientific research have shown that in human beings, oxidative stress has been implicated in the progression of major health problems by inactivating the metabolic enzymes and damaging important cellular components (Rahman et *al*, 2012), it is as a consequence of increase a reactive oxygen species and decrease in antioxidant defenses in prevalent in many health problems like CKD (Atieh et *al*, 2015).

So the oxidative stress to have a central role in the pathophysiological process of uremia and its complications. However ,there is little evidence to suggest how early oxidative stress in a starts developing during the progression of CKD (Evangelia et *al*, 2006).

Faced with these problems, this study aims to identify some predictive and risk factors of CKD and to evaluate some biological and oxidative stress markers in HD patients of Djamaa (El-Oued) region, on the other hand in this work we are evaluated the water quality of the Djamaa region and study its effect on some markers of renal function in rats.

BIBLIOGRAPHIC PART

Kidney anatomy and CKD

I. Generality

I.1. Kidney anatomy:

The kidney is a pair of bean shaped , reddish brown organs about the size of your fist . It measures 10 – 12 cm the length(Studymode,2011) .5,5 cm the width and 3 cm thickness. Each kidney in an adult weighs about 150 g(Course Hero,2018).If the kidney is sectioned , tow regions are seen (figure 01):

I.1.1. Renal cortex: an outer part of the kidneys where most enthrones is located.(Ebneshahidi , 2006)

I.1.2. Renal medulla: an inner part of the kidneys where some anthrones is located, also where urine is collected to be excreted outward.(Ebneshahidi , 2006)

I.1.2.1. Renal pyramids: The medulla has many basically triangular regions with a striped appearance, the renal, or medullary pyramids; the broader base of each pyramid faces toward the cortex while its tip, the apex, points toward the inner region of the kidney. (Marianne , 2017)

I.1.2.2. Renal columns: The pyramids are separated by extensions of cortex-like tissue, the renal columns.(Marianne, 2017)

I.1.2.3. Renal pelvis: Medial to the hilum is a flat, basinlike cavity, the renal pelvis, which is continuous with the ureter leaving the hilum. .(Marianne, 2017)

I.1.2.4. Renal artery: which branches off the descending aorta.(Marieb et *al.*,1994)

I.1.2.5. Renal vein: drains blood from each kidney, entering into the inferior vena cava. These vessels enter / exit the kidney in the indented medial region of the kidney called the **renal hilum** .(Marieb et *al.*,1994)

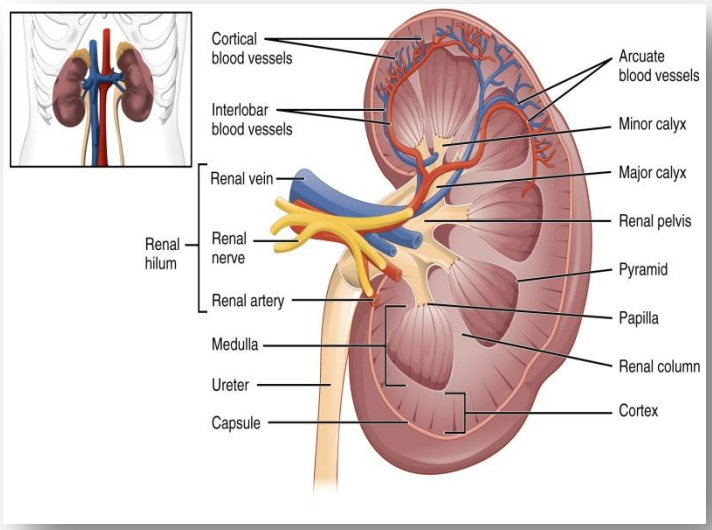


Figure 01: Kidney structure. (Kim et *al*, 2011)

I.1.1. Nephron

I.1.1.1. Definition of nephron:

The kidney's basic work units are the nephron ,apprpximately 1.2 million nephrons are contained in each kidney and form the urine (Miriama, 1998)**.** It represents two types of nephron which are distinguished by the location of their glomeruli:(Sands and Verlander, 2010)

- **The cortical nephron;** has a short loop of henle descending partially into the medulla and the majority type. .(Lawrence et *al*, 2018).
- **The juxtamedullary nephron 15%;** has a very long loop of henle and has a higher glomerular filtration rate, as its associated glomerulus is pro-portionally larger than that of the cortical nephron .(Lawrence et *al*, 2018).

I.1.1.2. Nephron structure and function

This functional unit of kidney is consist by two parts :renal corpuscle and renal tubules(figure 02).**(**Lawrence et *al*, 2018).

I.1.1.2.1. Renal corpuscle:

I.1.1.2.1.1. Glomerulus; connected to a complicated and twisted tubule that finally drains into a collecting duct**. (**Kriz and Elger, 2010).

I.1.1.2.1.2. Bowman's capsule; Double membrane cup-shaped structure that surrounds the glomerulus**.**(Lockwood et *al*, 2018)

I.1.1.2.2.Renal tubular : Consists of

I.1.1.2.2.1. proximales convoluted tubules; The proximal tubule reabsorbs 50– 60% of the total filtered load of inorganic solutes and water, whereas organic solutes.(Pablo et *al*, 2002)

I.1.1.2.2.2. Distal Convoluted Tubule; The tight junctions of the cells lining the distal tubule are "tight," so water and electrolytes cannot diffuse across the tubule and the filtrate remains hypotonic. In the early portion of the distal tubule, an apical Na^{+}/Cl^{-} transporter causes further reabsorption of ions. Thiazide diuretics block this reabsorption.(Seely and Blankenship, 2018)

I.1.1.2.2.3. Loop of Henle; It is U shaped middle portion of renal tubules. It is composed of ascending and descending loop. Ascending loop is thick walled and impermeable to water while descending loop is thin walled and permeable to water.(karki, 2017)

I.1.1.2.2.4. Collecting Duct; Determines final concentration of urine also Normally impermeable to water reabsorption (Hackenmueller , 2013)

I.1.2. vessels blood

I.1.2.1. Afferent Arteriole; The afferent arteriole receives blood rich in oxygen from the renal artery. This blood is transported to theglomerulus of the nephron where it is pressure filtered .(Tapan , 2017)

I.1.2.2. Efferent arteriole; is smaller in diameter than the afferent arteriole.(Tapan , 2017) so pressure difference occurs between the two ends of the glomerulus. This causes the filtration of blood plasma into the space of the Bowman's capsule. Since the blood plasma filtration occurs under high pressure, it is called ultra-filtration or the high pressure-filtration.(Lakna, 2017)

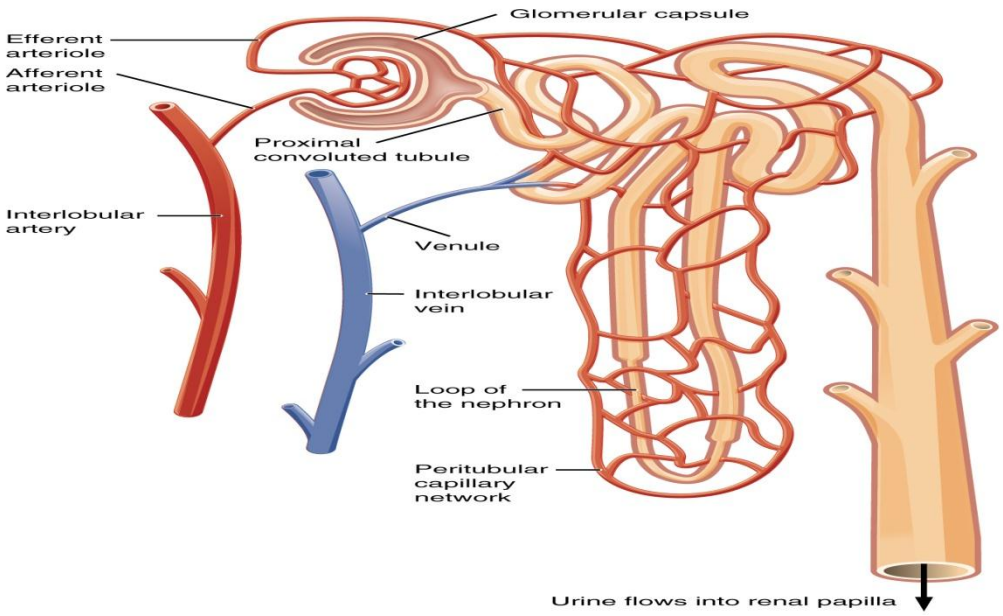


Figure 02: Nephron anatomy (Kim et *al*, 2011).

II. Chronic kidney disease

II.1. Definition

CKD is defined as the presence of kidney damage manifested by abnormal albumin excretion(Robert et *al*, 2008) or decreased kidney function(Angela et *al*, 2016)(shown by glomelural filtration rate GFR<60 ml/min/1.73m^2 for 3 months or more(Robert et *al*, 2005) which is less than half of normal value in young adult men and women of approximately 125 ml/min/1.73m^2(Kidney Disease: Improving Global Outcomes KDIGO.,2013) and the ACR >30 mg/g (Ki-Chul et *al*, 2019).

The glomerular filtration rate (GFR) is the best overall index of kidney filtration in healthy and disease(*Claudio and Lakhmir* , 2019) when the volume of plasma that is filtred by the glomeruli per unit of time,it is measured by the clearance of inulin or creatinine (*Kent et al., 2015)*also the age and gender are used to estimate the GFR. It become normal when it's number is more 90 ml/min (National kidney foundation[NKF],2013) but in kidney damage it divided depending the CKD stage whereas it become less than 15 ml/min in ESRD.(Douglass, 2008**)** a consequently the acute renal failure or acute kidney injury (AKI) is associated with acute decline of GFR (Matthieu and Didier, 2011).

II.2. Classification of CKD

Nearly ten years ago nephrologists began using a system of classification for CKD which was established in 2002 by the kidney Disease Outcome Quality Initiative (KDOQI) (Syed and Gerard ,2012) where the determination of CKD stages should be based on the combination between the kidney function indices (estimated GFR) and kidney damage (albuminuria-proteinuria)whatever the underling diagnosis**.**(David ,2012)

We can identify any stage of CKD by their estimated GFR as (David et *al* ,2017) study which shown :

- **Stage 1;** is a kidney damage with normal or increased GFR >90 ml/min/1.73m^2 .
- **Stage 2;** is a kidney damage with mildly decreased GFR 60 to 89 ml/min/1.73m^2
- **Stage 3;** is divided into 3a and 3b which are distinguished by the mildly to moderately decreased GFR 45 to 59 ml/min/1.73m^2 and moderately to severely decreased GFR 30 to 44 ml/min/1.73m^2 respectively, and the severely stages as study of (Kidney Disease: Improving Global Outcomes[KD:IGO],2005)
- **Stage 4;** there is a severe decreased GFR 15 to 29 ml/min/1.73m^2
- **Stage 5;** a kidney failure so GFR <15 ml/min/1.73m^2 or dialysis .

Each stage be to linked to a specific action plans and have a related terms us (albuminuria stage, early or late or end stage renal disease) also this classification based on a specific treatment as dialysis and transplantation.

There is the albuminuria categories in CKD represented in table 01 according the (Allan et *al*, 2016) study the nephrotoxic syndrome AER>2200 mg/24h and ACR>220 mg/mmol.

Table 01: Albuminuria categories in CKD **.**(Allan et *al*, 2016)

Category	AER(mg/24h) or (mg/g)	terms
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased
A3	>300	Severely increased

II.3. Risk factors and progression

The determination of factors predisposing an individual to CKD is essential in terms of personal and community health as some risk factors which can be non modifiable including; age ,gender ,ethnicity and family history.(Rumeyza,2013) In addition, a number of independent risk factors have been identified that may be modified by pharmacotherapy or

lifestyle changes to reduce the rate of CKD progression such as Diabetes ,hypertension , inflammation ,anemia (Rainer,2006) and smoking ,obesity , physical activity.(Sadia et *al*,2012), also metabolic syndromes , dislipidemia, agricultural occupation and contact with agrochemicals can lead to kidney disease.(Carlos et *al*, 2011)**.**

Feurthmore, The contamination of water resources has important repercussions for the environment and human health (Emmanuel et *al*, 2009; Muhammad et *al*, 2011). While that Drinking water contamination with different chemicals and heavy metals, released from different anthropogenic sources has become a global concern. (Rapant and Krcmova, 2007) Generally, drinking water containing different anions and heavy metals including Cd, Cr, Co, Hg, Ni, Pb, Zn etc, has significant adverse effects on human health either through deficiency or toxicity due to excessive intake .also the water which is showed in study of(Helmut, 2007) who's only confirmed that of the potential adverse effects of chronic low fluoride supplementation of drinking water on normal or decreased kidneys is insufficiency. while. the kidneys are the target organs for fluoride toxicity.(Djouadi and Derouiche, 2017) .

II.4. Symptoms of chronic kidney disease

The symptoms that one can experience during kidney failure change according to several factors. Any person with kidney failure will display a few symptoms as Reduction in the amount of urine passage(Pramod et *al*, 2018)**,** fatigue, dry skin, frequent urination, loss of appetite, nausea, swelling of the hands or feet, numbness in the hands or feet, trouble concentration and darkening of the skin or muscle cramps.(Kidney Function Guide, 2018).

II.5. Diagnosis of chronic kidney disease

Kidney damage is usually identified by abnormality in the blood , urine, imaging tests and if needed by kidney biopsy (Amy and Craig, 2011) so the following diagnosis evaluation tests for CKD are always indicated repeating serum, urea, creatinine electrolytes, eGFR and albumin within 1 week and fasting lipids and glucose , urine microscopy and culture and renal ultrasound scan(David, 2013)**,** also we selected diagnostic testing including hematology , body condition score and blood pressure.(Andrew et *al*, 2016).

II.6. Management Modality of chronic kidney disease

II.6.1. Medical treatment;

The modalities of renal replacement therapy available for the treatment of end stage renal disease (ESRD) include peritoneal dialysis, hemodialysis and renal transplantation. (United States Renal Data System[USRDS], 1999).

- **Kidney transplantation;** has become the preferred treatment for qualified patients with ESRD while kidney transplantation is more cost-effective than maintenance dialysis and more importantly(figure 03), it provides better quality of life and prolongs.(Rubin, 2014).

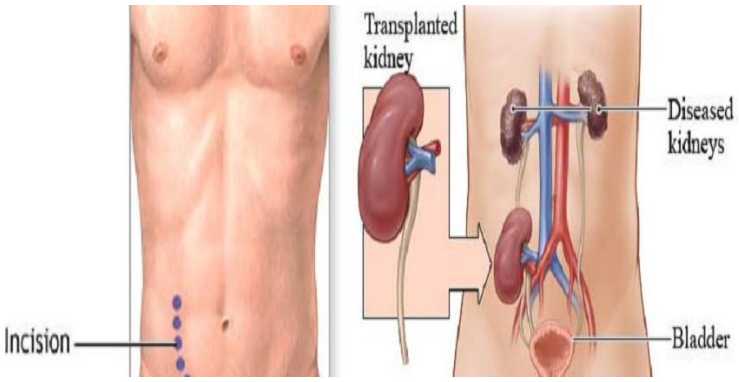


Figure 03: kidney transplant anatomy (Mark, 2013)

- **peritoneal dialysis;** works using the body's peritoneal membrane as a filter, this form of dialysis is very gentle on the body and it can protect the remaining kidney function also it's able to be successfully incorporated into most lifestyles.(Kidney Health Australia, 2016)(figure04)**.**

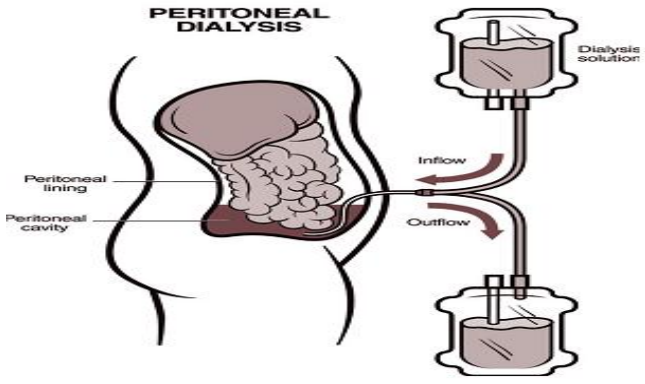


Figure 04: peritoneal dialysis options (National Kidney Foundation[NKF],2006).

- **Hemodialysis modality;** is a complex process requiring a skilled health care team and an appropriate educational process that can be individualized for patients and their supports

(figure05). (Brendan et *al*, 2018), it has been used since the 1940 to treat people with kidney disease when the kidney can't performed their function as a excretion water and regulation the level chemical elements in blood, dialysis can help keep the body. (Carissa Stephens.,2018)

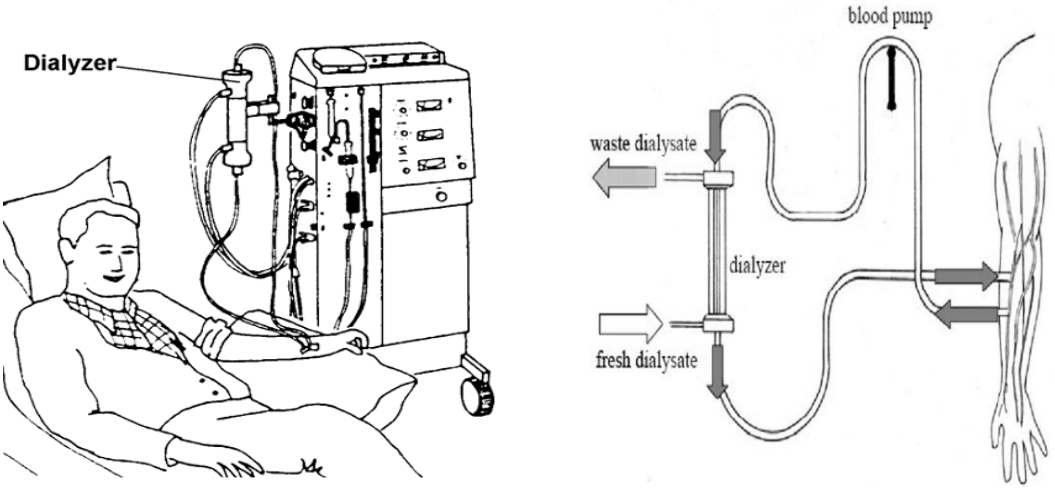


Figure05: hemodialysis operation (Hasan , 2008; Health Information Translations, 2008).

To get the blood to flow the artificial kidney, it must to create an entrance point (vascular access) in to blood vessels, there is three types of entrance point**:** (Carissa Stephens.,2018)

Arteriovenous(AVF) fistula; is created by making a surgical connection between one of your arteries and one of your veins. Most of the time, a fistula is created in your non-dominant arm, but it can also be placed in your leg if the arteries and veins in your arm are not large enough or healthy.(Azura vascular car,2017)

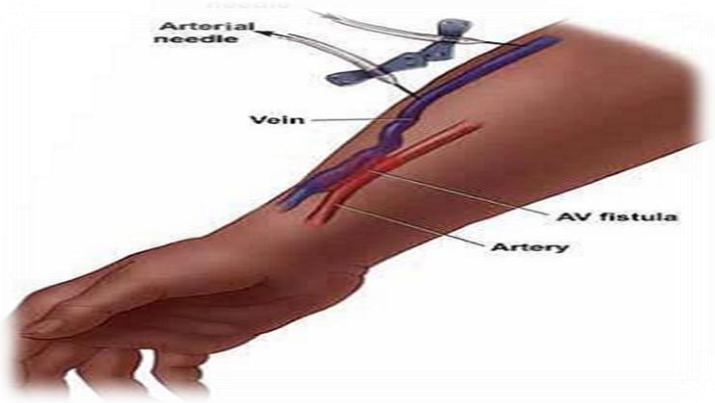


Figure 06: Arteriovenous fistula(Larry, 2013).

- ✓ **Arteriovenous graft;** is the second most common vascular access of choice in hemodialysis patients ,This type is a surgically created anastomosis between an artery and vein via prosthetic conduit(figure07)**.**(Nagadarshini et *al*, 2016).

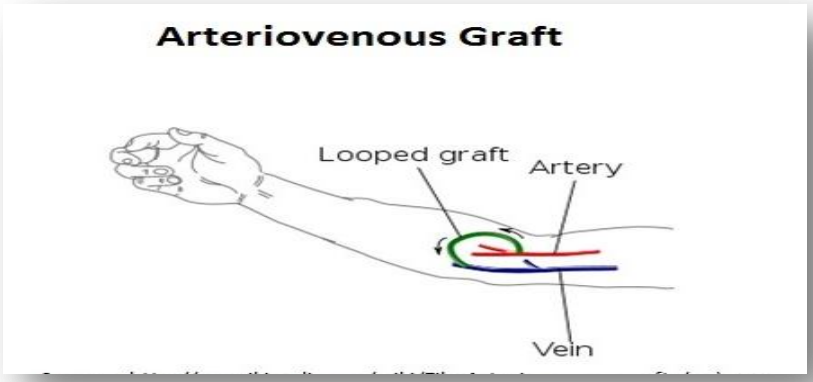


Figure 07: Arteriovenous graft (*Lynn* et *al*, 2015)

- ✓ **Vascular access catheter;** is placed in a branch vein in the arm, neck, or just beneath the collarbone(figure08).(Vascular Access Procedure,2005).

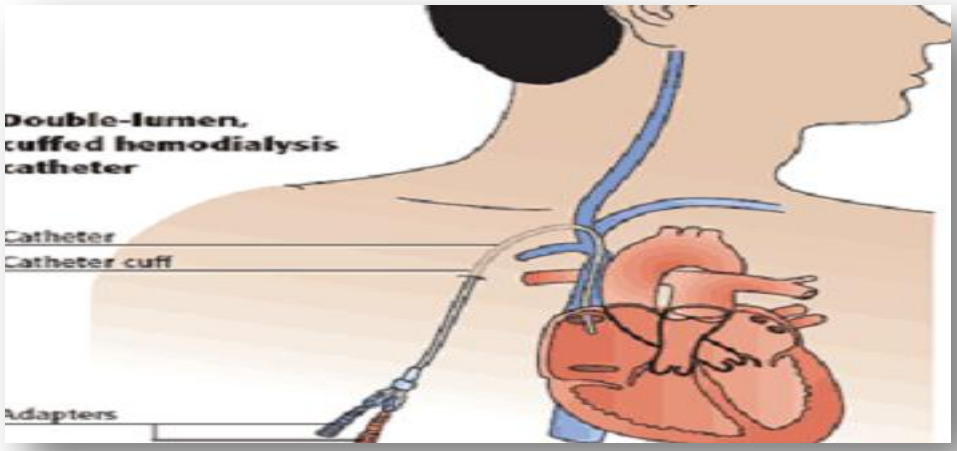


Figure 08: Vascular access catheter option(Eileen et *al* ,2007**).**

II.6.2.Supplementing treatment:

The supplementing treatment of CKD consists treatment of underling cause if possible, aggressive treatment of high blood pressure , cessation of smoking , use of pharmacological drugs and other symptoms**.**(Gohil et *al*, 2013).

II.7. Prevention of chronic kidney disease

The CKD can to decline by lifestyle modification such as diet control , weight reduction and exercises (Aminu et *al*, 2005)**,** also try to reduce the number of people with prediabetes,

diabetes and hypertension ,the most common precursors of CKD and begin to address some of social, economic and other factors that negatively impact health.(Ann et *al*, 2016).

III. kidney disease and Oxidative stress

The kidney is a highly energetic organ. This makes it more vulnerable to damage caused by OS . In turn, OS is associated with kidney disease progression. Furthermore, several complications of chronic kidney disease (CKD) such as inflammation , the major cause of death in patients with CKD, are also linked to increased levels of OS.(Kristien et *al*, 2018).

The kidneys maintain persistently high levels of mitochondrial oxidative phosphorylation and arterial blood flow, making them an environment in which ROS formation is expected (Agarwal, 2003).

In ERSD patients the antioxidant-pro-oxidant balance is shifted toward an increased oxidative stress. Several antioxidant systems have been shown to be deficient in patients with chronic renal insufficiency. Reduced levels of vitamin C are present, in part due to a dietary restriction of fresh fruits and vegetables to avoid hyperkalemia, and vitamin E intracellular levels are low, selenium levels are reduced, and there is a deficiency in the glutathione system (Davis et *al*, 2005).

The imbalance in pro- and anti-oxidant capacities in these patients results in excess production of ROS in the blood (Nguyen et *al*, 1985) , and neutrophils in uremic patients produce more ROS when stimulated (Davis et *al*, 2005).

The oxidant stress in dialysis patients causes increases in malondialdehyde, oxidized LDL, and increases in antibodies against oxidized LDL (Locatelli et *al*, 2003).

V. Inflammation in Hemodialysis patients and oxidative stress

Oxidative stress in renal failure has been associated with hypertension endothelial dysfunction , decreased erythrocyte lifespan , and atherosclerosis and inflammation (Davis et *al*, 2005).

The inflammatory cells are then a source of free radicals in the forms of reactive oxygen and nitrogen species, although reactive oxygen species (ROS) are considered the most common. The highly reactive ROS are capable of damaging various structures and functional pathways in cells (Small et *al*, 2013). Moreover the inflammation is a redox-sensitive mechanism, as oxidative stress is able to activate transcriptor factors such as NF-kB, which regulates inflammatory mediator gene expression. NF-kB is a dimer factor maintained inactivated in the cytoplasm by binding to inhibitory proteins (members of I-kB family).(Victoria et *al*, 2008).

Kidney anatomy and CKD

The causes of inflammation in dialysis patients include both factors arising from dialysis itself (efficiency and biocompatibility issues) as well as others that are non-dialysis related, such as advanced age and diabetes, renal disease and uremia perse (Vassilis et *al*, 2009).

ESRD patients have increased levels of inflammation-related proteins, such as interleukin-6 (IL-6), tumor necrosis factor-a (TNF-a) and C-reactive protein(CRP) and are subjected to enhanced oxidative stress as aresult of both insufficient anti-oxidant defence mechanisms and excessive generation of oxidant compounds (Spittle et *al*, 2001).

Components of the inflammatory response associated with hemodialysis (HD) method include neutrophil activation due to interaction between blood and dialysis membranes with consequent increased synthesis and release of pro-inflammatory cytokines (IL-1â, IL-6, TNF-a), poor quality of dialysis water, back filtration of contaminated dialysate to the blood compartment, intravenous iron therapyand presence of foreign bodies (access graft, centralvenous hemodialysis catheter) (Francesco et *al*, 2003).

In addition, there is a strong relationship between inflammation and oxidative stress in this patient population, as both are related to endothelial dysfunction, and reactive oxygen species (ROS),lipid and protein oxidation products as well as advanced glycation end-products (AGEs) are generated in response to inflammatory stimuli (Mezzano et *al*, 2001).

EXPERIMENTAL PART

Materials and Methods

Materials and Methods

I. Materials and Methods

Part 1: Patients study

I.1.1. Risk factors study

I.1.1.1.The study duration

The duration of this study was taken 8 month which was started from September 2018 to april 2019 at hemodialysis service of Saad Dahleb hospital (Djamaa) and medical analysis laboratory of the hospital of Saad Dahleb in Djamaa , Bachir Ben Naser –El-Oued and biological laboratory of science of nature and life faculty at university of Echahid Hamma Lakhdar El-Oued**.**

I.1.1.2.Region of the study

Theregion of Oued Righ is a valley situated in the North east of the Algeria sahara. It covers a South North axis whose latitude is 32°,54' to 39°,9'North and longitude 05°,50 to 05°,75 east.this region is divided naturally into bloks called trios: upper Oued Righ **(Touggort),** in the middle**(Djamaa)** and in lower of this region **(M'gheir region**) (Abdelkader and Hamid, 2012).

Our study was conducted in the Middle of Oued Righ**(the Djamaa region).** which is limited to the North by El M'gheir, East by Oued Souf to the west by Ouled Djellal and in the south by Touggourt region(Abdelfatah , 2008)(figure09).

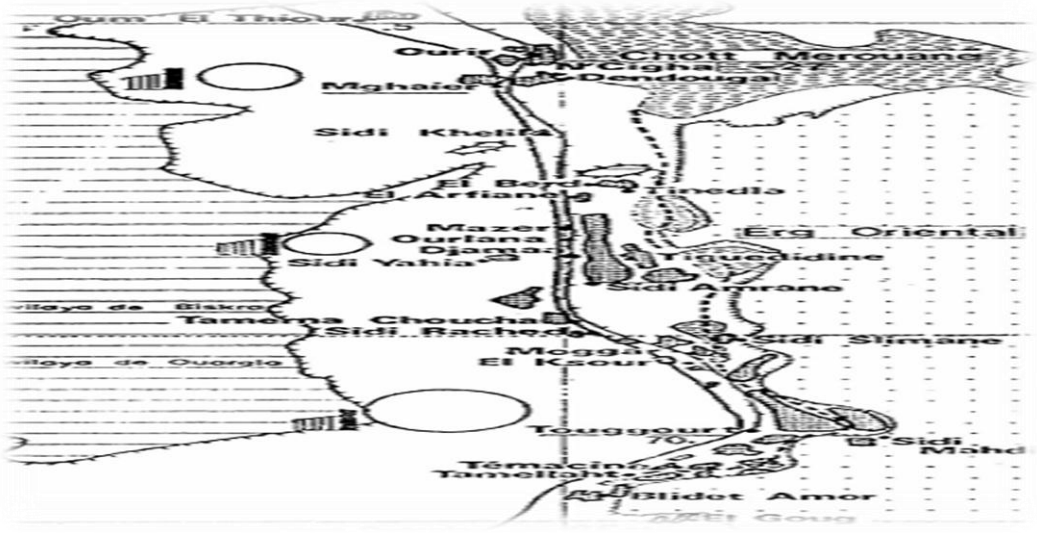


Figure09 : Maps of OuedRigh and Djamaa region(Abdelfatah , 2008).

Materials and Methods

I.1.1.3. Epidemiological study and questionnaire

Concerning a questionnaire (annex01) and statistical study, our work was conducted on 77 voluntary individual divided into 2 groups, group 1 (41 persons reserved as a control recruited from our entourage) and group 2 (36hemodialysis patients) represented mean the age 46.32 years their origin cover all Djamaa region. This population are recruited by Hemodialysis service, they are represented CKD confirmed by the diagnosis kidney echography (Annex 38) and nephrologists doctor of Hospital SAAD SAHLEB Djamaa.

I.1.2. Biological study

Our biological study is carried out on 41 volunteers person of mean age 45.05 ± 2.65 years ,were divided into 21 healthy control with mean age 39.00 ± 3.41 years , the other group of 20 hemodialysis patients of hospital Saad Dahleb –Djamaa with mean age 51.40 ± 3.64 years.

- **Inclusion criteria**
  - ✓ Voluntary persons live in the Djamaa region.
  - ✓ The control voluntary does not have any kidney pathology.
  - ✓ Hemodialysis patients diagnosis by nephrography.
- **Exclusion criteria**
  - ☒ Voluntary live in other region.
  - ☒ Control less than 18 years.
  - ☒ Control has a previous renal or other diseases**.**

I.1.2.1. Reagents

Sodium chloride (NACL), Hydrochloridacide (HCL), Hydrogene peroxide (H_2O_2), Thiobarbituricacide (TBA), Methanol, Coomassie Blue, Butylatedhydroxytoluene(BHT), Trichloroacetic acid (TCA), Phosphate-buffered (KH_2PO_4, K_2HPO_4), Ascorbic acid, Ethylenediamintetraaceticacid (EDTA), Coppersulphate($CuSO_4$) , $Fecl_3$ and potassium fericianure.

I.1.2.2. Methods

I.1.2.2.1. Data collection

For epidemiological study, we have distributed for all volunteers our questionnaire which contains some social and clinical data that can show us different factor associated with CKD .

Materials and Methods

I.1.2.2.2. Sample collection

For biological study, blood sampling is done in the morning for both groups, whether for control or hemodialysis, but for the last group their sampling is done before and after dialysis, after this operation we collected the samples blood in two types of tubes**:**

- In anticoagulant (EDTA) tubes for hematological (FNS) and oxidative stress (MDA , GSH, Catalase) markers assay.
- In dry tubes, samples are centrifuged at 3000 rpm for 10 minutes to obtain the serum and utilized for urea, creatinine, calcium, ionogram analysis and ORAC activity assay.

Part 2: Qualitative study of water in different area of Djamaa region

I.2.1.Samples collection

to obtained some comparatives informations of drinking water quality, a snapshot study was done on 3 drinking water samples of 29 samples divided between 12 the spring water, 13 tap water (TW) and 4 filtered water (FW) which obtained from deferents regions in Djamaa according to an orderly sampling method, these regions were represented in Djamaa maps.

this experimental study was conducted in the ADE laboratory in El Oued unite since 6 month (September 2018 to February 2019)

I.2.2. Methods of testing

I.2.2.1. Conductivity measurement

It is measured by electric method to the conductivity of water determination where The results are displayed directly by the conductimetere an µS with the temperature measured(Determination of electrical conductivity**,**NA 749).

I.2.2.2. Sodium (Na) And Potassium (K) assay

Flame atomic absorption spectrometry for the sodium and potassium dosing in drinking water, raw water, and spring water. The results are displayed directly by the spectrometer in mg/l of Na or K

I.2.2.3. Chloride (Cl) and Calcium (Ca) assay

Titrimetric method for the determination of chlorides dissolved in water with $AgNO_3$ and K_2CrO_4 (Mohr's method,ISO 9297 – NA 6917) and of the calcium by Sodium Hydroxide and EDTA(1984 (F) Calcium Assay - EDTA Titrimetric Method ISO 6058), the results measured by formula:

$$\textbf{Cl (mg/l)} = \frac{VS - Vb}{Va} . Cf$$

$$\textbf{Ca (mg/l)} = \frac{C1 . V1 . A}{V0} .Fc.10^3.F$$

I.2.2.4. Iron (Fe) assay

A specifies spectrometric method for phenantroline for the determination of iron in water.
The intensity of the staining is proportional to the amount of the iron and the results are displayed directly by the spectrometer in mg / l of iron.(Determination of iron ,ISO 6332)

Part 3: Effect of water on renal function in rats

I.3.1. Animals and treatment

Nine females rats with weight (181.74± 6.96) were bought from animals service of Pasteur institute in Algeria , they are installed in faculty SNV ,university of El Oued, Algeria in plastic cages divided in three groups of 3 rats of each. They kept in the animals breeding house for adaptation.

The animals were adapted to laboratory condition photoperiod (12 h of night/12h of Light), an ambient temperature of 22 ± 03 °Cand humidity of (63.2 ± 14)% for two weeks. The standard diet and water are free for the animals during period of adaption.

I.3.2.Experimental Design

After the duration of adaption (2 weeks) ,we are distributed the rats an three groups and distinguished between its by three types of drinking water which are the axis of this study during 60 days.

- **group1 ;**rats receive the mineral water in drinking as control.
- **group2;**rats receive the tap water (TW)
- **group3;**rats receive the filtered water (FW) contained " Hypersperse 700-11"which is a viscous solution as the interscalant product we are prepared it by dilution method 1/20 by original solution.

this product is used in the deminiralisation station of the water during the filtration stages to avoid the precipitation of chlorine in the tubes of the installation.

The evaluation of body weight was controlled during the eight weeks of the experiment.

I.3.3. Blood collection and tissue preparation

At the end of 8th week of experiment the animals were fasted for 16 h, anesthetized by chloroform inhalation then sacrificed by decapitation. The blood was collected in EDTA tubes for hematological analysis and in dry tubes for urea, creatinine, calcium and electrolytes levels assay.

The serum was obtained by blood centrifuging at 3000 rpm for 10 min and frozen at 20 °C until the use.

In addition, One gram of kidney from each rat of the different experiment groups was used. The tissues were milled and homogenized in 9 ml of buffer solution of TBS (50 mM Tris, 150 mM NaCl, pH 7.4). The tissue suspension was centrifuged at 9 000 rpm for 15 min at 4 °C the supernatant obtained was stored at -20 until use for the oxidative stress marker assay.

I.3.4. Measurement of biological Markers

I.3.4.1. Biochemical parameter assay

Serum urea , creatinine, calcium parameters levels were determined by autoanalysis(BIOLIS24j) use commercial kit from spinreact , spain (ref: urea-20141 , creatinine-20151 , calcium-20051) .

I.3.4.2. Method of Hematological analysis

Hematological analysis (FNS) is performed by the hematology autoanalyzer (Sysmex) .

I.3.4.3. Method of electrolytes analysis

Determination of the ionogram parameter (Sodium , potassium and chlorine) by Automatic electrolyte analyzer (Easylute) .

Materials and Methods

I.3.4.4. Method of estimating oxidative stress parameter

I.3.4.4.1. Preparation of erythrocyte homogenate

After displacement of the blood sample, the spittoons are made up to 50 ml with SLR (10 mM Tris-HCl pH 7.5, 10 mM NaCl) and incubated for 30 minutes in the freezer. then centrifuged at 3900 rpm for 20 min and obtained supernant (erythrocyte homogenate) was used for the determination of antioxidant activity .

I.3.4.4.2. Leukocyte separation

After separation of the erythrocytes, the previous operation (removal of the supernatant) is repeated almost twice. if red blood cells persist in the pellet, carry out an additional washing with a lysis buffer until the leucocyte coupling and then recover to perform the stress tests and protein concentration .

I.3.4.4.3. Determination of protein concentration

principle

protein concentration was measured according to the method of Bradford M.M., 1976 that uses comassie blue complex (the appearance of the blue color reflects the degree of ionization of the medium and the intensity corresponds to the concentration of the proteins).

Operating mode

- Take 0.04mlof leukocyte homogenate.
- Add 2ml of Coomassie Blue.
- Waiting 5 min for color stabilization.
- Read the opical density at595nm,
- The obtained optical density is reported on a calibration curve previously drawn.

The concentration of the protein is determined by comparison with a standard range of bovine serum albumin (1mg/ml) previously carried out under the same conditions.(annex.02.)

I.3.4.4.4.Determination of malondialdehyde level

The malondialdehyde was measured according the method of (YAGI,1976), The method is based on the reaction between the carbonyl compounds of malondialdehyde with thiobarbituric acid to give absorbent pink chromophores at 532 nm. MDA level was expressed as nmol of MDA/mg prot.

I.3.4.4.5. Reduced glutathione (GSH) level assay

The level of reduced Glutathion is determined according the WEAK and CORY (1988).by measuring the optical density results from the formation of 2-nitro-5-mercocapturic acid from the reduction of dithio-bis-2-nitrobenzoic acid, which is called Ellman reagent with SH groups exist in GSH briefly.

- 800µl of homogenate samples are add to 200µl of salicylic acid (0.25%).
- The mixture was centrifuge at 1000 rpm for 5 min.
- Take 500 ml of supernatant and mixed with 1000µl of tris buffer(tris 0.4mol,0.02mol NaCl ,Ph =8.9) and 25 µl of DTNB (0.01 mol/L).
- Read the absorbance at 412 nm after 5 min of incubation .

$$\mathbf{GSH\ (nM/mg\ of\ Hb\ )} = \frac{(\mathbf{OD \times 1 \times 1.525})}{\mathbf{13133 \times 0.8 \times 0.5 \times} \boldsymbol{mg\ of\ pr}}$$

OD : Optical Density.

1.525 : total volume of blend an ml.

13133: Absorption constant of SH groups at 412 nm.

0.5 : volume of solution float an ml.

1 : volume of protein mixture .

0.8: volume of homogeneous solution without protein exists in 1 ml.

GSH : concentration of glutathione.

I.3.4.4.6. Glutathione-S-transferase (GST)Activity assay

GST activity was measured spectrophotometrically by the method of (Habig et *al*,1974) . based on the formation kinetics of a complex between a GST substrate: 1-chloro-2-4-dinitrobenzene (CDNB) and GSH. 50 µl of CDNB(0.02M) was mixed with 850µl and 830 µl of phosphate buffer in blank and test tube respectively, then 100 µl of GSH(0.1M) was added to mixture , 20µl of homogenate was puted test tubes. results are measured each1 min during 5 min. The complex formed can be visualized by increasing the optical density at a 340 nm. The GST activity was expressed as nmol CDNB /min/mg prot

$$\mathbf{GSTs(nM\ /min/\ mg\ of\ pro)} = \frac{\boldsymbol{DO\ sample/min} - \mathbf{DO\ blanc/min}}{\mathbf{9.6} \times \boldsymbol{mg\ of\ pro}}$$

I.3.4.4.7. Determination of superoxide dismutase activity assay

The assay method of SOD activity using the NBT by the superoxide anion ($O_2^{\cdot}$), is used as a basis for detecting of presence of SOD by measuring the spectrophotometrically absorbance at 560 nm.(Beauchamp and Fridovich,1971)

Collect in tubes	Blank (In the dark)	Sample(Illuminated tube)	Concentration in the reaction medium
EDTA-Met	1000µL	1000µL	0,1mM EDTA
Phosphate buffer	892,2µL	892,2µL	13mM Met
Sample	0	50	/
Phosphate buffer	1000µL	950µl	50Mm
NBT	85,2µL	85,2µL	75µM
riboflavin	22,6µL	22,6µL	2µM

Expression of results :

$$\mathbf{SOD} = \frac{\boldsymbol{DO\ blanc} - \mathbf{DO\ sample}}{\boldsymbol{DO\ blanc}}$$

I.3.4.4.8. Determination of enzymatic activity of catalase

The catalase activity consists in measuring the catalase-induced loss of H2O2 contained in the sample by measuring the absorbance of H2O2 at 560 nm using a UV /visible spectrophotometer. Briefly In test tubes mix 1 ml of phosphate buffer (KH2PO4, 0.1 M, pH 7.2), 0.975 ml of freshly prepared H2O2 (0.091 M) and 0.025 ml of the enzyme source (homogenate). The absorbance is read at 560nm each minute for 2 minutes.

$$\boldsymbol{CAT(UI/g)} = \frac{\left(\left(\frac{\mathbf{2.3033}}{\mathbf{T}}\right) \times \left(\frac{\mathbf{logA1}}{\mathbf{logA2}}\right)\right)}{\boldsymbol{g\ of\ protein}}$$

Materials and Methods

A1: Absorbance at the first minute.

A2: Absorbance at the second minute.

T: Time interval in minutes

I.3.4.4.9. Determination of antioxidant power ORAC

a. principle

The total antioxidant power of the serum,its capacity to absorb free oxygen radicals (ORAC: Oxygen Radical Absorbance Capacity), is estimated by the ability of red blood cells to resist free radical-induced hemolysis in vitro in the presence of plasma according to the method of Oyaizu, M. (1986). This method is based on the time-dependent monitoring of red blood cell hemolysis induced by a free radical generator..

b. Treatment of redbloodcells

• Centrifuge donor blood at 2000 rpm for 10 min and remove plasma.

• Wash gently 1 volume of the pellet with 2 volumes of physiological saline (without lysing the RBCs), then centrifuge again at 2000 rpm for 5 min.

c. Operating mode

- **Control tube**

• Add 1 ml of RC: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30%) and 2 ml of physiological saline, then stir gently.

Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.

• Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.

• Repeat this operation every 10 minutes for 1 hour.

- **Standard tube**

• To 1 ml of RC are added: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30%) and 2 ml of physiological saline, and 20 µl of vitamin C (400 µM) and then stir gently.

Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.

• Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.

• Repeat this operation every 10 minutes for 1 hour.

➢ **Test tube**

• To 1 ml of RC are added: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30%) and 2 ml of physiological saline, and 20 µl of serum (400 µM) and then stir gently.

Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.

• Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.

• Repeat this operation every 10 min for 1 hour (t0, t10, t20, t30, t40, t50, t60, and average the latter:

• ΣDO = Σ (t0, t10, t20, t30, t40, t50, t60) / 7

• To calculate the total antioxidant power using two methods.

Calculate method

$$ORAC(UI) = \frac{\Sigma(ODcontrol - ODsample)\Delta t}{\Sigma(ODcontrol - ODstandard)\Delta t}$$

I.3.4.4.10. Determination of ferric reducing antioxidant power(FRAP)method.

500µl of serum and 1.25 ml of buffer solution 6,6 (0.2M) add to 1.25 potassium fericianure and incubation 20 min in Bain Marie at 50 C°.also, 1.25 ml of aqueous TCA solution is added to stop the reaction and centrifugation 3000rpm/10 min .after we add:

- 1.25 ml of supernatant
- 1.25 ml of distilled water
- 1.25 ml of $FeCL_3$(0.1%)

And reading an UV visible at 700 nm against a blank

Blank: similarly prepared but replace the sample with distilled water to calibrate the device.

Statistical analysis

The statistical evaluation was carried out by the student's t test using Minitab 14 statistical packagen ,OR risk factored regression analysis using SPSS statistics 25 and the Excel 2007 (Microsoft). The values were given as mean±SEM .Statistical significance was defined as $P<0.05$

Results

Results

II. Results

II.1. patients study

II.1.1. Description of study population

In our study we are chose population are characterized by many different characters are shown in table 02 (age, weight, sex ,social case, job, education level, blood group).We are selected 36 hemodialysis patients and 41 controls , after statistical analysis we are obtained the results showed in table below.

Table (02) : Description of study population

		control	Patients
Age		**46.61 ± 2.84**	**46.03 ± 2.95**
Body weight		**61.20 ± 2.09**	**59.96 ± 2.62**
sex	Men%	16.88	23.38
	Women%	36.36	23.38
Social case	Married%	29.870	29.870
	Single%	23.376	15.584
job	Worker%	19.480	14.285
	unemployed%	33.766	32.467
Educational level	primary%	5.194	25.974
	medium%	7.792	5.194
	High school %	19.480	12.987
	High education%	20.779	2.597
Blood group	A%	18.181	7.791
	B%	10.389	10.388
	AB%	7.791	3.896
	O%	16.882	18.181

Results

II.1.2. Study of socioeconomic and clinic factors

Odds ration (OR) values for Socioeconomic factors (table 03) and Clinic-pathological factors (table 03) show that Diabetes ,urinary problems and Arterial hyper pressure are shown to be significant risk factors for chronic kidney disease(OR= 5.135; P= 0.003),(OR= 6.607;

p=0.001),(OR= 8.276 ; P= 0.000) respectively .In addition, Rheumatoid (OR= 14.375 ; P= 0.004) , History of kidney disease (OR= 20.000 ; P= 0.000), Renal herbal medicine (OR=25.455 ;P= 0.000),Drugs nephrotoxic (OR = 62.857 ; P= 0.000) and Disease before CKD (OR= 62.857; P= 0.000) are also very important risk factors of chronic kidney disease in our study population by highest OR values . While that, Additive soft drinks, spices ,Amount of water and Salty foods are protective factors for CKD in study population (OR ranging from 0.232 to 0.352 ; P ≤0.032) .In contrast, our results indicate that Passive smoking , Tea , Coffee , Food additive and dyes , Red meat , Exposure to chemical , Work in a polluted place , Drugs , Long-term incontinence , Sport , Sweet foods , Sleep disorder, Digestion disorder, Calming, Antibiotic, Using paracetamol drug, Phytotherapy, Using drug, Drugs products, Family history of the disease and Industrial area are not considered as risk factors of CKD in our population since the OR values obtained are not significant

Table (03): Socioeconomic factors of Chronic Kidney Disease (N= 77)

	Control %	Patient %	OR	$CI_{95\%}$	P
Amount Water			**0.362**	0.143- 0.913	**0.025**
Positive	48.051	25.974			
Negative	7.792	20.779			
Tea			0.893	0.344- 2.326	0.504
Positive	18.181	15.584			
Negative	32.467	31.168			
Coffee			0.690	0.245- 1.943	0.330
Positive	15.584	10.389			
Negative	37.662	36.363			
Spices			**0.232**	0.89- 0.604	**0.002**
Positive	36.363	15.584			
Negative	16.883	31.168			
Food additive and dys			0.620	0.200- 1.919	0.292
Positive	12.987	7.792			
Negative	40.259	38.969			
Additive soft drinks			**0.350**	0.132- 0.925	**0.027**
Positive	25.974	11.688			
Negative	27.272	35.064			
Exposure to chemical			0.545	0.179- 1.665	0.213

Results

Positive	14.285	7.792			
Negative	38.961	38.961			
Work in a polluted place			3.145	0.571- 17.325	0.165
positive	2.597	6.493			
Negative	50.649	40.259			
Industrail area			2.353	0.204- 27.093	0.451
Positive	1.298	2.597			
Negative	51.948	44.155			
Smoking			1.364	0.499-3.728	0.363
Positive	12.987	14.285			
Negative	40.259	32.467			
Drugs			1.143	0.063- 18.958	0.720
Positive	1.299	1.299			
Negative	51.948	45.454			
Long – term			0.446	0.177- 1.108	0.063
incontinence	20.779	10.389			
Positive	32.376	36.363			
Negative					
Sport			0.593	0.238- 1.482	0.187
Positive	25.974	16.883			
Negative	27.272	29.870			
Sweetfoods			0.442	0.177-1.108	0.063
Positive	29.870	16.883			
Negative	23.376	29.870			
Saltyfoods			**0.341**	0.121- 0.957	**0.032**
Positive	22.077	9.090			
Negative	31.168	37.662			
Daily mouvement			0.412	0.141- 1.189	0.085
Positive	44.155	31.168			
Negative	9.090	15.584			
Redmeat			0.432	0.171- 1.090	0.059
Positive	28.571	15.584			
Negative	24.675	31.168			
Agricultures Works			0.243	0.048- 1.228	0.067
Positive	10.390	2.597			
Negative	42.857	44.155			
Antecedent disease			**62.857**	7.741-	**0.000**
before CKD	1.298	28.571		510.434	
Positive	51.948	18.181			
Negative					
History kidney disease			**20.000**	2.445-	**0.000**
Positive	1.298	15.584		163.622	
Negative	51.948	31.168			
Family history of the			1.375	0.467- 4.048	0.380
disease	10.389	11.688			
Positive	42.857	35.064			
Negative					
Sleepdiorder			1.313	0.534- 3.223	0.358
Positive	25.974	25.974			

Results

Negative	27.272	20.779			

OR>1 and P<0.05 indicate a risk factor

OR<1 and P<0.05 indicate a protective factor

Table(04) : Clinic-pathological factors of Chronic Kidney Disease (N= 77)

	Control %	Patients %	OR	$CI_{95\%}$	P
Drugs produits			0.258	0.029-2.324	0.199
Positive	1.298	6,493			
Negative	51.984	40,259			
Hypertension Arterial			**8.276**	2.439-28.079	**0.000**
Positive	5.194	22.077			
Negative	48.059	24.675			
Diabete			**5.134**	1.6346-	**0.003**
Positive	6.493	10.389		16.182	
Negative	46.753	36.363			
Usingdrugs			0.668	0.270- 1.656	0.261
Positive	25.974	18.181			
Negative	27.272	28.571			
Phytotherapy			0.593	0.238- 1.482	0.187
Positive	25.974	16.883			
Negative	27.272	29.870			
Renal herbal medicine			**25.455**	3.135-	**0.000**
Positive	1.298	18.181		206.705	
Negative	51.948	28.571			
Using paracétamol			0.462	0.181- 1.179	0.081
Positive	25.974	14.285			
Negative	27.272	32.467			
UsingAntibiotic			0.462	0.181- 1.179	0.283
Positive	9.090	11.688			
Negative	44.155	35.064			
Drugs			0.579	0.229- 1.461	0.177
Positive	24.675	15.584			
Negative	28.571	31.168			
Rheumatoid			**14.375**	1.670-	**0.004**
Positive	19.480	25.974		123.701	
Negative	33.766	20.779			
Digestion disorder			1.789	0.724-4.423	0.150
Positive	23.376	27.272			
Negative	29.870	19.480			
Urinaryproblems			**6.607**	1.939-22.516	**0.001**
Positive	5.194	19.480			
Negative	48.051	27.272			

OR>1 and P<0.05 indicate a risk factor

OR<1 and P<0.05 indicate a protective factor

Results

II.1.3. Biological Study

II.1.3.1. Biochemical markers

Concerning the biochemical markers presented in table 05,The results revealed that a significant increase ($p<0.01$) in urea and creatinine concentration before dialysis and a significant increase ($p<0.001$)of GRF level in patients with CKD Before dialysis (BD) and after dialysis (AD) compared to control. But no change of urea concentration in PAD.

Table(05): Biochemical markers in serum control and serum patients groups.

Paramètre	**Reference**	**Control N= 21**	**PBD N= 18**	P	**PAD N= 18**	P
SerumUrea(g/l)	0.15 - 0.45	0.17 ± 0.01	0.90 ± 0.06	**0.000**	0.24 ± 0.04	0.115
Serum Creatinine (mg/l)	7 - 13	7.96 ± 0.27	87.49 ± 5.46	**0.000**	26.68 ± 3.02	**0.000**
GFR (ml/min/1.73m^2)	>90	92.96 ± 3.31	6.240 ± 0.417	**0.000**	29.77 ± 4.72	**0.000**
$\frac{urea}{creatinine}$		21.89 ± 1.50	10.67 ± 0.64	**0.000**	8.02 ± 0.80	**0.000**

The results are presented by mean± SEM

II.1.3.2. Electrolytes levels

Regarding the electrolytes levels the results obtained in table 06 represent a significant decrease ($p<0.001$) in serum sodium and potassium concentration in PBD and PAD respectively and a significant increase($p<0.01$)in sodium and potassium in PAD and PBD respectively compared to control.

Also, our results obtained a significant increase ($p<0.001$) in calcium level concerning the group of PAD compared to control. This significant variations are compared with control and did not go outside the reference values except the potassium level .

Results

On another side, there is no significant changes of Chlorine concentration in PBD and PAD and of calcium levels in PBD compared to control.

Table (06):serum Electrolytes and calcium levels of control and patients groups.

Parameters	Reference values	Controls N=16	PBD N=18	P	PAD N=18	P
Serum Na(mmol/l)	135-155	138.53±0.66	135.37±0.40	**0.000**	140.15 ±0.56	**0.007**
Serum K(mmol/l)	3.60-5.50	4.69 ± 0.19	5.59 ± 0.19	**0.000**	3.18 ± 0.20	**0.000**
Serum Cl (mmol/l)	95-105	10.86 ±1.26	103.05 ±1.31	0.545	104.84 ±1.03	0.351
SerumCa (mg/l)	85-105	78.59± 2.23	82.93 ± 6.00	0.479	104.66 ±2.48	**0.000**

The results are presented by mean± SEM

II.1.3.3. Hematological markers

The results of the hematological markers are presented in table 07, the results obtained show that the Erythrocyte line (RBC,HGB,HCT) are significantly decreased ($p<0.001$) in patients with CKD as compared to control group and reference values. Results of Leucocyte lineage (WBG,Granulocyte) show that are significant increased ($p<0.001$) in the patients group compared to the control group. Moreover our result illustrate that the lymphocytes and Platelet line no significant differences ($p>0.05$) in patients with CKD compared to the control group .

Table (07): Hematological parameters of control and patients groups.

parameters	Reference values	Controls N=20	Patients N=20	P
Red blood cell (10^6/l)	**3.50-5.50**	4.75 ± 0.18	3.48 ± 0.22	**0.000**
Hemoglobin	**11-16**	13.07 ± 0.405	9.83 ± 0.46	**0.000**

Results

(g/dl)				
Hematocrit (%)	**34-45**	37.73 ± 1.26	29.73 ± 1.51	**0.000**
Platelet (10^3/l)	**182-369**	249.1 ± 23.3	238.2 ± 19.4	0.581
White blood cell (10^3/l)	**3.98-10.04**	4.86 ± 0.48	6.34± 0.31	**0.000**
Lymphocytes (10^3/l)	**1.18-3.74**	1.33 ± 0.16	1.28± 0.19	0.782
Granulocytes (10^3/l)		3.28 ± 0.44	4.57 ± 0.33	**0.001**

The results are presented by mean± SEM

II.1.3.4. Oxidative Stress markers

According to the result of the table 08 , the analysis of the oxidative stress status reveals a significant decrease ($p<0.001$) in leukocyte catalase activity and in erythrocyte GSH level and a significant increase ($p<0.001$) in erythrocyte MDA level in patient group compared to control. However, no significant change in leukocyte GSH and MDA concentration.

Table(08): Reduce glutathione (GSH) concentration , Malondialdehyde (MDA) level and catalase activity in leukocyte and Erythrocyte of control and patients groups.

Parameter		**Control N = 19**	**Patients N = 18**	**p**
Leukocyte	**GSH (nmol/mgpr)**	0.43 ± 0.04	0.49 ± 0.04	0.211
	Catalase (UI/g pr)	11.19 ± 1.01	10.06 ± 0.24	**0.000**
	MDA (nmol/mgPr)	5.12 ± 0.58	5.12 ± 0.36	0.946
Erythrocyte	**GSH (nmol/mg HB)**	0.42± 0.06	0.24± 0.06	**0.005**
	MDA (nmol/mg HB)	11.00 ± 0.37	12.89 ± 0.64	**0.006**

The results are presented by mean± SEM

Also, our results obtained in table 09 show that a highly significant increase ($p<0.001$) of ORAC and FRAP activity in serum of PAD and PBD respectively but no significant change in other groups

Table (09): Serum ORAC and FRAP activity in control and patients groups.

Paramètre	Control N= 17	PBD N= 17	P	PAD N= 17	P
ORAC(UI)	0.41 ±0.10	0.53 ± 0.09	0.223	0.94 ± 0.08	**0.000**
FRAP (%)	96.12 ± 0.48	98.18 ± 0.78	**0.001**	96.89 ± 0.70	0.119

The results are presented by mean± SEM

II.1.3.5. Predictive factors of oxidative stress factors

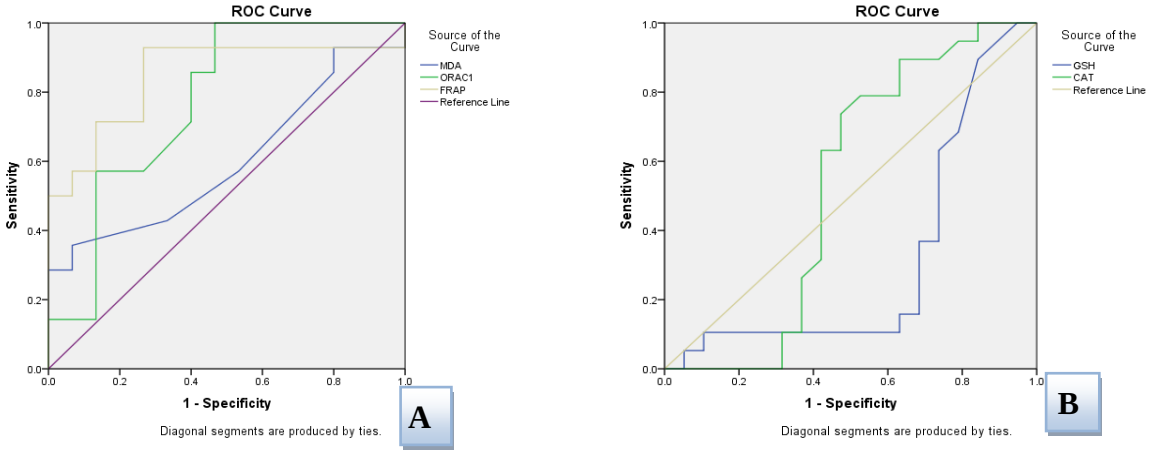
Our results obtained in table 10 demonstrate that the serum FRAP activity has the highest percentage of sensitivity and important significant of specificity (AUC=85%) with ($p<0.01$) also an important significant sensitivity in serum ORAC level and higher percentage specificity(AUC=77%) with ($p<0.05$) .Moreover, there is a low significant sensitivity and specificity in erythrocytes GSH level (AUC=31%) .

In addition, but high percentage sensitivity and low percentage specificity in erythrocytes MDA level (AUC=60%) also an important percentage of sensitivity and specificity(AUC=53%) in catalase in leucocytes but it was not significant results($p>0.05$)

Table(10) : Area Under the Curve.

Test Result Variable(s)	Area	sensitivity	specificity	Std Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
MDA	.600	71%	33%	.109	.359	.387	.813
ORAC1	.771	43%	87%	.090	**.013**	.596	.947
FRAP	.848	79%	73%	.079	**.001**	.692	1.000
GSH	.314	16%	32%	.094	**.050**	.129	.499
CAT	.528	58%	58%	.103	.770	.326	.729

Results



Figure(10):ROC curve for serum ORAC and serum FRAP,RBC MDA level (**A)** and GSH level in erythrocytes and leukocytes catalase activity in leucocytes**(B).**

II.1.3.6. correlation between oxidative stress markers and biochemical parameters

Our correlation results between oxidative stress markers and biochemical parameters represented in table11which clarify a significant positive correlations ($p<0.05$) between catalase activity with creatinine level and between GSH (RBC) with Ca concentration in control group but a significant negative correlation ($p<0.01$) between MDA(WBC) with Na level and between ORAC with Na level in the same group

Concerning patients group there are a significant positive correlations ($p<0.05$) between catalase activity, MDA(WBC)and ORAC with Na level A and MDA(RBC) with creatinine B and GFR B, also between GSH (RBC) with GFR B and GFR A. Furthermore a significant negative correlations ($p<0.05$) between catalase activity with creatinine A and K level B,MDA(WBC) with cratinine B and A also between MDA(RBC) with urea/creatinine and K level A, finally GSH(RBC) with Ca concentration in the same group. while that the MDA(WBC) with K level B in both groups.

Table (11):correlation results between oxidative stress markers and biochemical

Parameters.

Correlation		Control		Patients	
		R	P	R	P
Catalase	Creatinine A	0.398	**0.001**	-0.300	**0.027**

	Na A	-0.018	0.940	0.485	**0.000**
	K B	-0.149	0.543	-0.272	**0.047**
MDA (WBC)	Creatinine B	-0.160	0.489	-0.404	**0.002**
	Creatinine A			-0.350	**0.009**
	Na A	-0.901	**0.000**	0.351	**0.009**
	K B	-0.404	**0.002**	-0.273	**0.045**
MDA (RBC)	Creatinine B	-0.125	0.589	0.280	**0.041**
	Urea/creat B	0.216	0.089	-0.293	**0.032**
	GFR B	-0.023	0.885	0.269	**0.022**
	K A	-0.189	0.438	-0.392	**0.003**
GSH (RBC)	GFR B	-0.305	**0.050**	0.485	**0.003**
	GFR A			0.338	**0.044**
	Ca A	0.357	**0.006**	-0.329	**0.015**
ORAC	Na A	-0.718	**0.000**	0.331	**0.014**

II.2. Qualitative study of water in different area of Djamaa region

For the assessment of the role of water as a risk factor for CKD, In our experimental analysis of water we notice a significant elevated in the chloride and sodium levels in spring water of Rano and Sidi Omran compared to others studied spring water and control where a low level , We found that the extreme calcium and potassium concentrations have been recorded in Zaouia spring water compared to control and different study areas while all areas study represented a low iron and conductivity levels than control.

On the other hand , there is a significant increase in the chloride level in the Djamaa, Zawaliya and Sidi Omran area and the electrical conductivity in Djamaa and Tendla region compared to control ,other studied areas .

Results

In addition , high concentration of calcium ,sodium and potassium was recorded in Zawaliya, Zaouia, Tendla, Djamaa ,Tmerna and Marara areas than controls and FW but at close levels between regions there is no significant difference unlike SidiOmran have a highest calcium level compared to there. Also There was a few presence of iron in Marara area compared other region , but its concentration does not exceed the control.

Generally filtered water contains a very lower levels of electrolytes compared to control and all study areas .

II.2.1. Spring water analysis

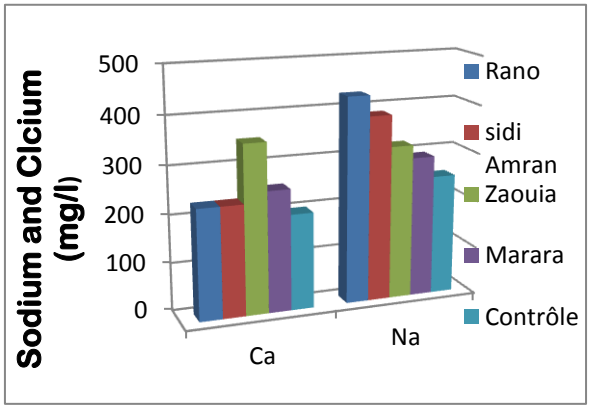


Figure11:sodium and calcium levels in Spring water

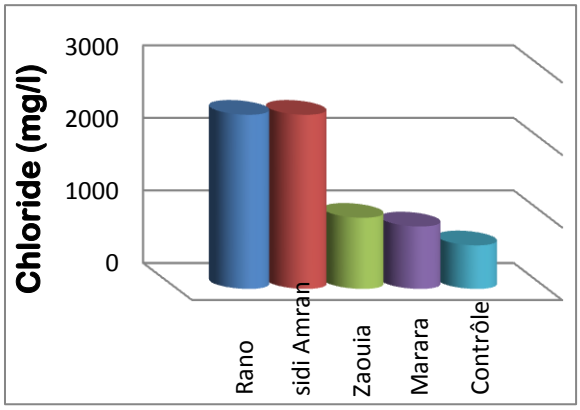


Figure12: Chloride level in spring water

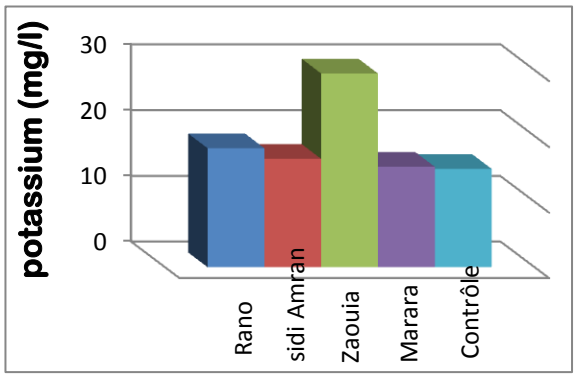


Figure 13: potassium level in spring water

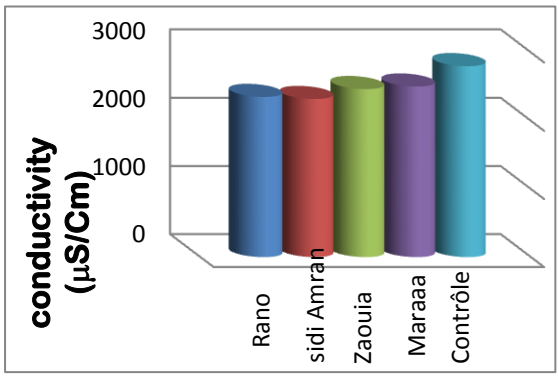


Figure14: conductivity values of spring water

Results

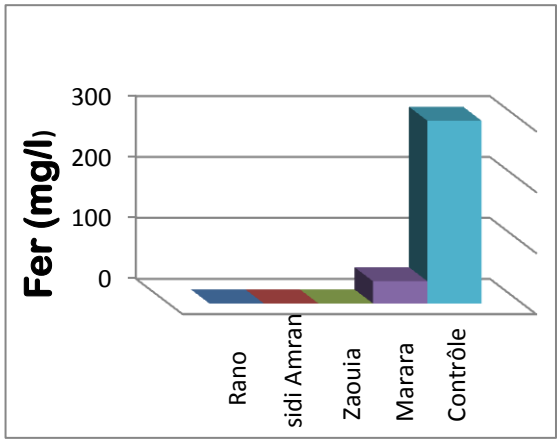


Figure15: Iron level in spring water

II.2.2. Tap and Filtered water

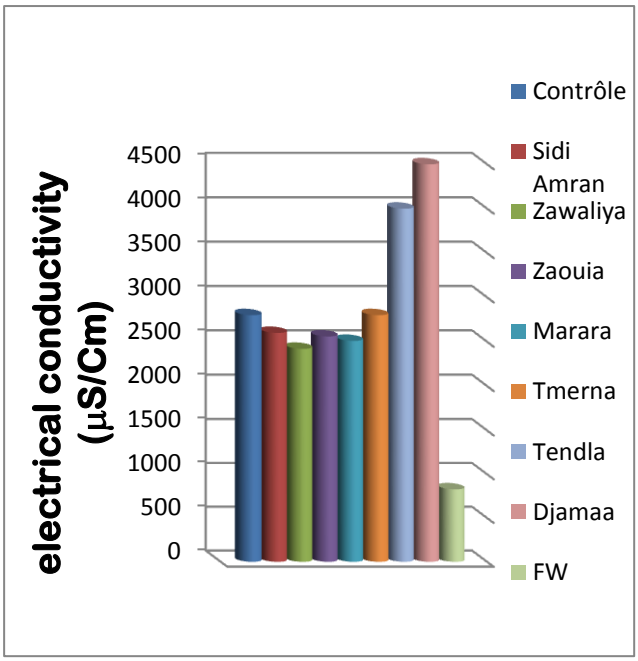


Figure16: electrical conductivity of TW and FW

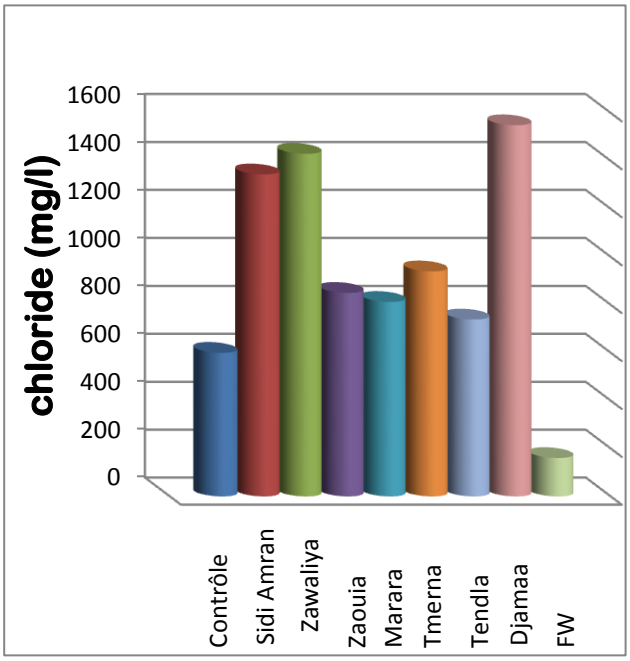


Figure17: chloride level of TW and FW

Results

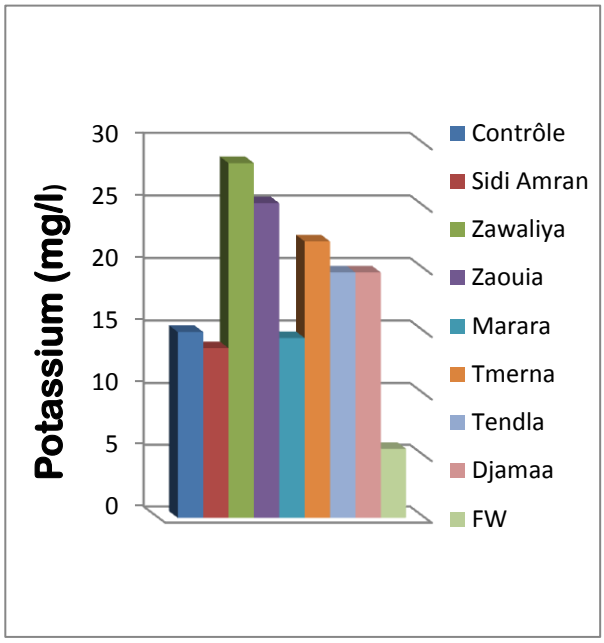


Figure18: potassium level in TW and FW

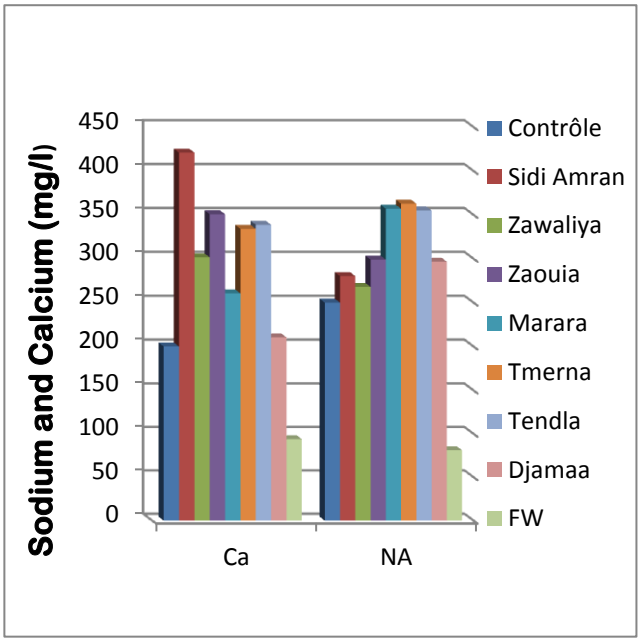


Figure 19:sodium and calcium levels in TW and FW

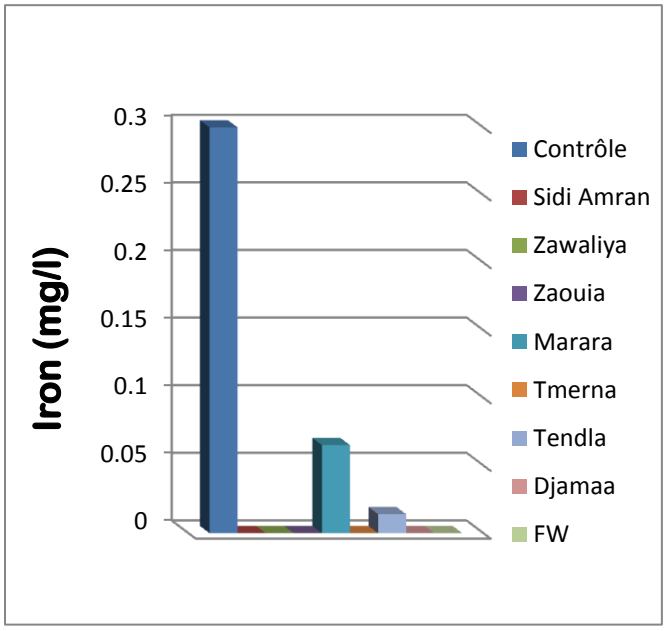


Figure20: Iron concentration in TW and FW

Results

II.3. Effect of water on renal function in rats

II.3.1. Biochemical markers

Concerning the biochemical markers results obtained show that a significant increase ($p<0.05$)of urea and creatinine levels and a decrease of urea/creatinine report in experimental groups compared to control except FW group there is no significant change in urea concentration compared to control.(Figure21).

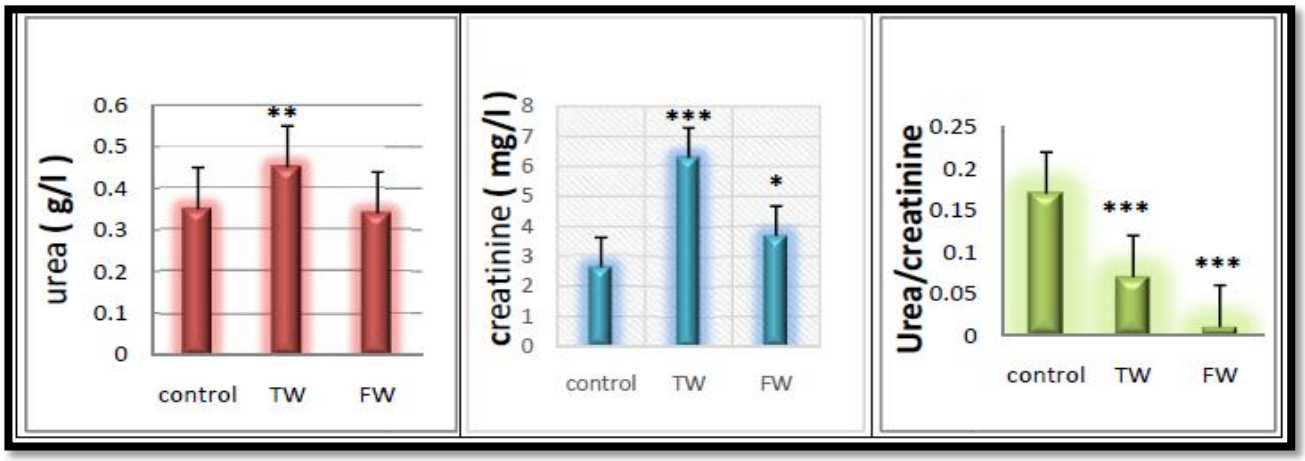


Figure21: urea and creatinine concentration in serum rats of control and experimental groups. Comparison from control ($P<0.05$, $P<0.01$, $P<0.001$).

Regarding the electrolytes level , our results showed a significant elevation ($p<0.05$) in serum sodium level in TW group against control and a significant decrease ($p<0.05$) in serum potassium and chlorine levels in TW and FW groups against controls, But there is no significant changes ($p>0.05$) in serum sodium level in FW group than the controls (Figure22).

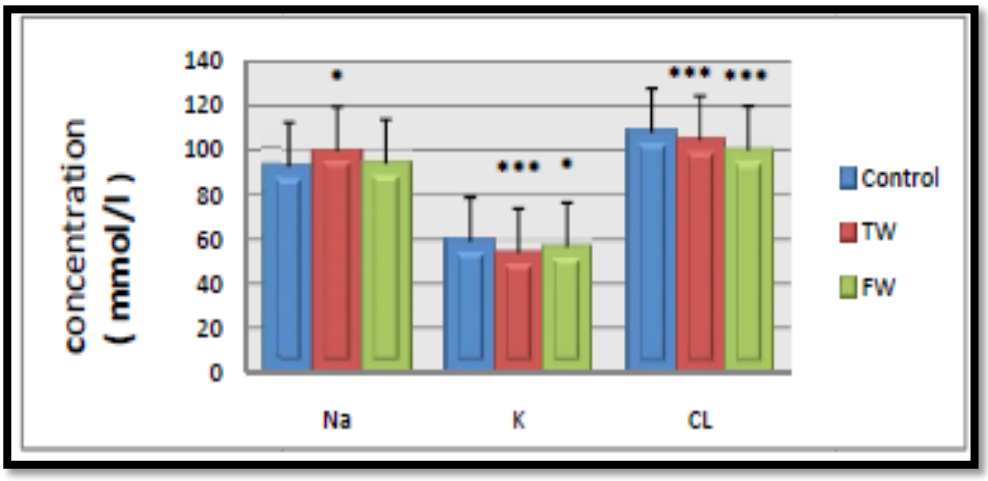


Figure22: Electrolytes levels in serum rats of control and experimental groups.

Comparison from control ($P<0.05$, $P<0.01$, $P<0.001$).

Results

II.3.2. Hematological markers

On the basis of results obtained in Figures (23)shows a significant decrease ($p<0.05$) of RBC, Hemoglobin, WBC and platelet level in TW group compared to control . However, in FW group the WBC and platelet levels are decreased compared to control but no significant variation concerning erythrocytes line.

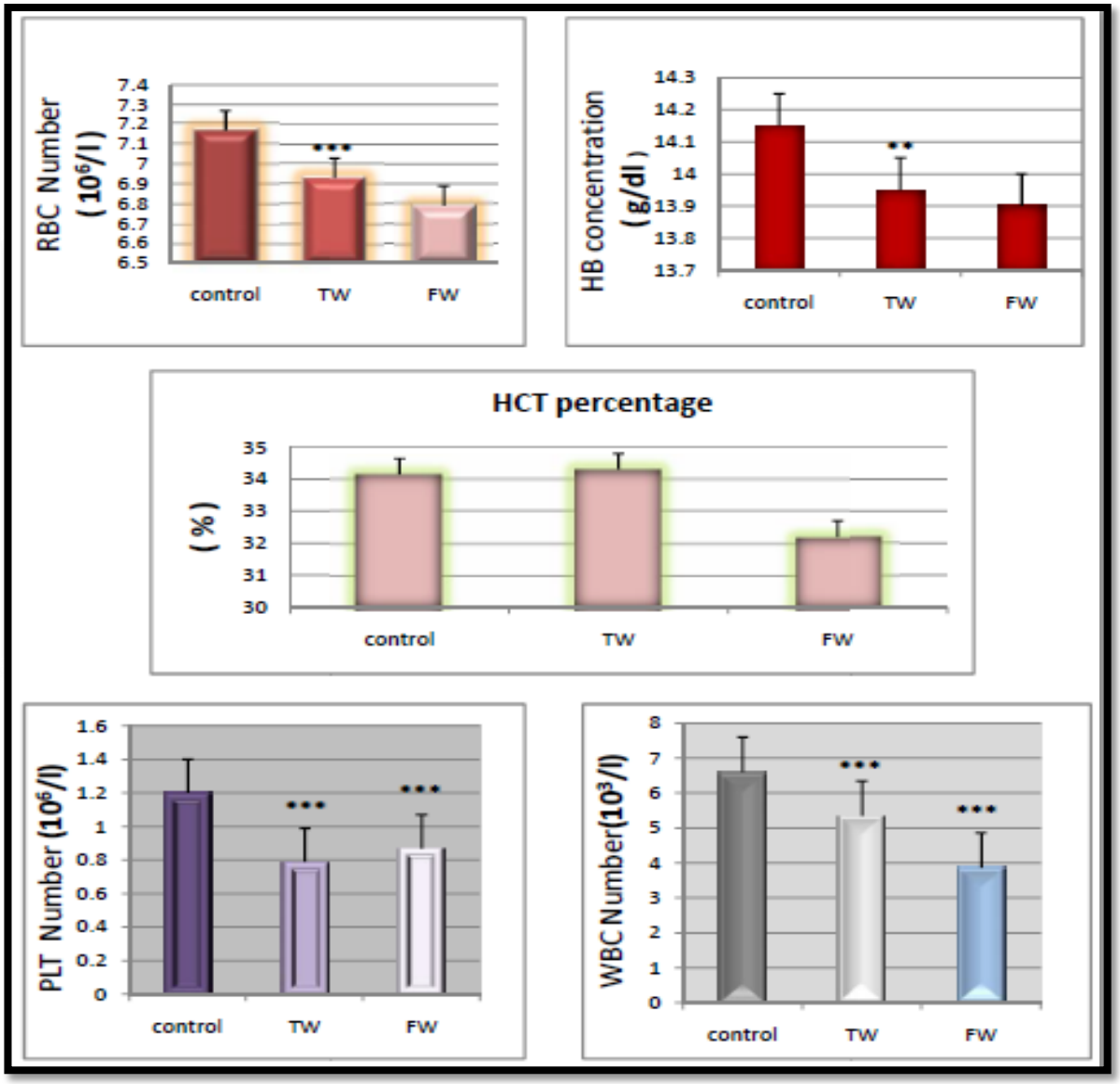


Figure23: Hematological markers Numbers in rats of control and experimental groups. Comparison from control ($P<0.05$, $P<0.01$, $P<0.001$)

Results

II.3.3. Oxidative stress markers

Our results (figures 24.25.26) show that a significant increase ($p < 0.001$) of MDA level and decrease ($p<0.05$) of GST and SOD activities in TW and FW groups and a significant decreased ($p<0.05$) of GSH concentration and catalase activity in TW and increase for catalase activity only in FW group compared to control.

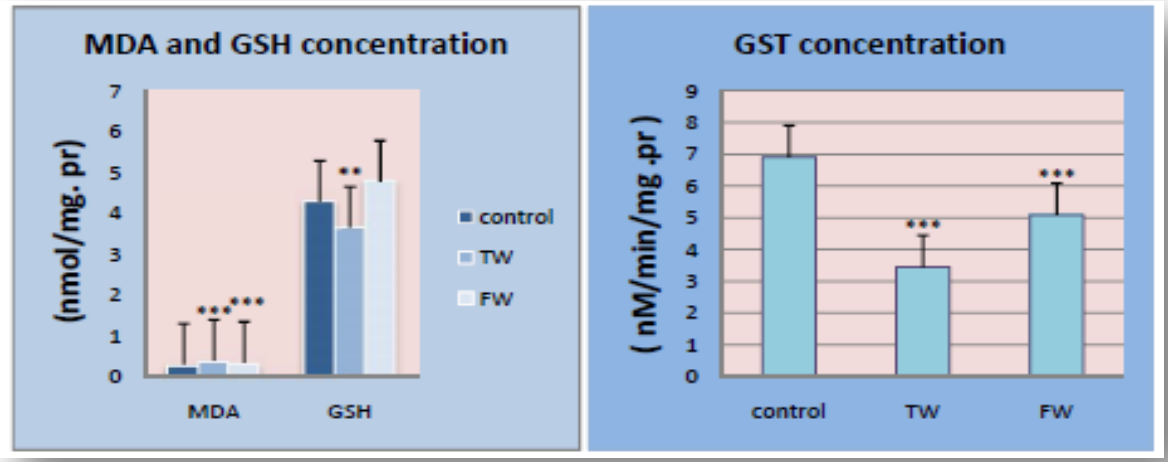


Figure24:MDA and GSH concentration in kidney of control and experimental rats groups.

Figure25: GST activity in kidney of control and experimental rats groups.

Comparison from control (P<0.05, P<0.01, P<0.001).

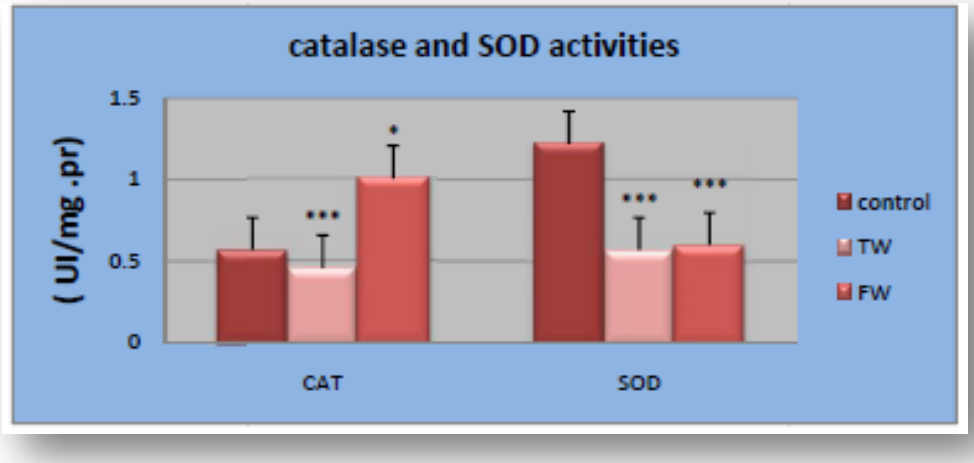


Figure26: catalase and SOD activities in kidney of control and experiment rats groups.

Comparison from control(P<0.05, P<0.01, P<0.001).

Discussion

III. Discussion

III.1. Patients study

III.1.1. study of protective and risk factors of chronic kidney disease

Our study obtained some risk factors are associated with chronic kidney disease. Where show that the diabetes and hypertension are a principals causes for the chronic kidney disease , as study of Hwang *et al* (2010) which based on National Health Insurance(NHI)databased showed diabetes, hypertension were associated with a higher risk of developing CKD .

Diabetes mellitus (43.2%) and hypertension (8.3%) are major underling renal disease of ESRD in 2007,according to the registry of Turkish society of nephrology diabetic patient constitute 37.3% of hemodialysis population in turkey and depend on the USRDS data, half of the new ESRD patient in the united states have diabetic nephropathy (Kazanciog,2013). So, Diabetes mellitus has become the first leading cause of ESRD by outnumbering CGN since 2000 (Hwang *et al*,2010), Approximately 30% of patients with diabetic nephropathy eventually progress to end-stage renal failure, and the rest usually die from cardiovascular disease before reaching end stage (Atkins ,2005).

The relation sheep between hypertension and renal disease is showed in a direct consequence of altered renal development (Valerie *et* al,2010) and progression loss of kidney function If hypertension is superimposed on intrinsic kidney disease, (Janice *et* al, 2002) or a cumulative process resulting from other effects programming such as diabetes which superimposed to reduced nephron number (Valerie *et al*,2010) . It is possible that diffuse arteriosclerosis which is associated with hypertension can have a direct influence on the kidney to decrease filtration and indirect influence on the kidney by way of decreased defusion which can result in elevated creatinine level and increased risk (Shulman *et al*,1989)

Concerning rheumatoid arthritis we obtained that rheumatoid arthritis is higher risk factor for chronic kidney disease ,such as in study of Karie*et al* (2008) who said the chronic kidney disease was highly prevalent in there population of RA patients, nearly half of RA patients are presenting a kidney disease according NKF classification . in addition, Hsien-Yi Chiu *et al* (2015) study is investigated for the cause of renal disease in RA patients, it is demonstrate that the risk of development the CKD , GN and ESRD are attributable to nephrotoxic pharmacotherapy and chronic inflammatory state as demonstrated by elevation of various growth factors, inflammatory mediators, and/or inflammatory markers, such as C-reactive

protein (CRP), interleukin-6, tumor necrosis factor alpha (TNF-α) and renal amyloidosis (Hyun Woo *et al*,2014).

The study of Latony a *et al* (2014) is combined between RA disease characteristics and CVD associated factors which appear to play a role in reduced kidney function

Our study showed that the urinary problems and History of kidney disease is a health risk factor for chronic kidney disease .Holmgren *et al* (1987) concluded that with staghorn caculi , urinary infection and impairment of renal function are at risk of development of terminal renal failure. Concerning study of Eleftheria *et al*(2014) said the CKD is results by other causes as glomerulonephritis , interstitial nephritis , polycystic KD .

Urinary tract infection (UTI) is a bacterial infection of the urine (> 10^5 colony-forming units/ml of urine) .Which may Involve the kidney (pyelonephritis) . Whose patients have an increased risk of associated kidney damage scarring which can result in renal failure (David *et al*,2011) . Pyelonephritis is still one the major causes of end-stage renal disease (ESRD) although bacterial infection has become of lesser importance in this respect in the last 10-15 years (Holmgren *et al*, 1987).Suma *et al* (2003) resulted that kidney stone may play a role in the development of chronic kidney disease .According to Kidney Foundation of Canada [KFC] (2015) that a kidney stone can develop when certain chemicals in the urine from crystals that stick together , larger stones may block the flow of urine or irritate the liming of the urinary tract . It's factors risk of CKD characterized by multiple cysts in both kidney (Edgr *et al*,2015) .

Glomerulonephritis stands out as the major cause of renal failure (Kincaid-Smith.,1980).These disorders which cause inflammation and damage the kidney ase the third in line of ailments that cause CKD (Edgr *et al*, 2015). However the alternative in progressive forms of glomerulonephritis is death from renal failure (Kincaid-Smith,1980) .

Tubulo-interstitial nephritis describes a range of pathological processes that are at least partly responsible for progression of renal disease of nearly all etiologies(Colin *et al*, 1992). According to Choi *et al* (2000) chronic tubule-interstitial injury (CTI) including tubular atrophy and interstitial fibrosis represents one major determinant for the progression renal chronic disease regardless of cause .

Nephrosclerosis is an umbrella term definig changes in all compartements of the kidney these lesions are accompanied by tubule-interstitial inflammation and fibrosis that predict the decline of renal function (Alain,2014) .

Discussion

With regard to Disease before CKD are higher risk factor for CKD as study of Eleftheria*et al* (2014) showed the major causes of ESRD was diabetic nephropathy (19.5%), hypertensive nephropathy (13.8%), chronic interstitial nephritis (11.4%).

Hypertension also accounts for up to one fifth of end-stage renal disease in developing countries, and for chronic kidney disease affecting 7% of the world 's population, and at even greater proportions in developing countries. (Kemi*et al*,2014).the prevalence of hypertension is significantly higher in people with CKD (50-60%) (Couser*et al*, 2014), this disease may cause renal disease or may accelerate the loss function in kidney by several changes of morphology nephrosclerosis (Saulo, 2015).Previous studies have also show a link between insulin resistance hypertension which are represent a higher risk of developing CKD (Ophius *et al* , 2013), the insulin resistance plays a central role in a metabolic syndrome and is associated with increased risk for CKD (Leyking *et al*,2014).

The metabolic syndrome and its components are associated with the development of CKD, microalbuminuria, and overt proteinuria (Leyking *et al*,2014).The presence of microalbumin in urine is a now recognized as a risk marker for CKD and its complication in humans (Ophius *et al*, 2013),also the risk of mortality ,myocardial infraction and progression to kidney failure associated with a given level of eGFR are independently increased in patients with higher levels of proteinuria (Brenda *et al*, 2015).

In addition , we obtained for the Renal herbal medicine and drugs nephrotoxic are important risk factors for the chronic kidney disease .Within study to Bagnis *et al* (2004) Herbal medicine may be a risk for the kidneys, various renal syndromes were reported after the use of medicinal plants. powdered plant extracts may be intentionally adultered by other drugs.

The active Principe of herbal drugs derived from aristolochia species is aristilichic acid (AA) which was shown to be nephrotoxic in humans and rabbits (Stefanovi, 2002).so the toxic effects of aristolochic acid have been inferred from effects see in a result of using herbal containing aristolochia species (IARC ,2002)

The study of Perazella (2009) show Renal injury and clinical renal failure can occur through a variety of mechanisms after administration of different therapeutic agents. Also, Most forms of parenchymal kidney injury can progress to CKD. Focusing on chronic tubulointerstitial nephritis, several agents are more commonly associated with CKD, including combination analgesics (phenacetin, NSAIDS, caffeine), 5-ami-nosalicylic acid (mesalamine), aristolochic acid-containing herbal remedies.(Perazella, 2003)

Discussion

Our result obtained that salty foods is protective factor from chronic kidney disease . depend on Nephron Dail Transplant ,(*1998*). The responses from the 2400 nephrologists were in favor of sodium for all patients ; 33% patients with excessive weight gains and 38% for only a few selected patients . Sodium profiling is a technique used by nephrologists regarding patients with side effects during dialysis.(Stiller *et al*, 2001)

In our study it was observed that the soft drinks is a protective factor. Where it can be source of clean water , carbohydrates and other nutrients in many parts of the world whose human body require about 1 to 2 liters of water a day for good health and basic survival(Shachman ,2004).In addition to that soft drinks can hydrate as well as water and other beverages , who to help your body retain water (regular tap water),The citrate contained in soda help to inhibit the formation of kidney stones. (Paramita R., 2017).

Our result showed that spice is a protective factor for chronic kidney disease . According to Fazel*et al* (2011) Curcumin treatment at the doses of 10 and 20 mg/kg (intraperitoneally) showed significant nephroprotective effects. The study results by Tirkey *et al* (2005) and Bayrak *et al* (2008) showed that curcumin through an antioxidant activity effectively salvaged Cs A nephrotoxicity . such as in study the Anurag *et al* (2007) who said curcumin treatment significantly and dose-dependently restored renal function , reduced lipid peroxidation and enhanced the levels of reduced glutathione and activities of superoxide dismutase and catalase .In general, herbals and spice have high antioxidant concentration that have the potential to inhibit the oxidation of LDL (Tapsell *et al*, 2006).

III.1.2. Biological parameters study

III.1.2.1. Biochemical markers

Urea is the waste product made in the body breaks down proteins(Kidney Health Australia ,2018) and creatinine is product of dephosphorylation of creatine during the muscle contraction and filtred by proximal tubule and secreted out by kidney in urine(Andrew et *al*, 2013),the loss of kidney filtrations declines of GFR and less excretion of wastes results an accumulation of urea and creatinine in blood (Renal Resource Centre, 2012).HD is one of the renal replacement therapy where body waste product like urea, creatinine and free water are removed from the blood, when the kidneys are impaired. by the diffusion of solutes through a semi permeable membrane(Amin et *al*, 2014).

Our results showed a significant increase of serum urea and creatinine levels and very decrease in GFR before dialysis and clear reduction of serum creatinine after dialysis but the serum urea no significant decrease.

Discussion

During dialysis urea and creatinine being small molecules flow through membrane into the sterile solution and is removed due to the counter-current flow of blood and dialysate and removed more urea and creatinine from the blood.(Mahomoodally and Nugessur, 2014), also other study showed that HD not only failed to lower blood ammonia from hydrolysis of urea ,it significantly increased its blood level post dialysis by a mechanisms currently unknow (Vaziri et *al*, 2016), so according to the serum urea level cannot be used to monitor the renal function in CKD patients but may be indicate non renal influence.(Annamala et *al*,2016)when several conditions studied which lead to protein breakdown and resultant increased urea excretion, whether it be feeding a protein-rich diet was associated with increases in all five urea cycle enzymes proportional to the increase in urea synthesis(Robert , 1963). Routinely used for diagnosis of CKD are serum creatinine and urea levels but they are considered as late indicators because a 33% decrease in Glomerular filtration rate (GFR) (Divya et *al*, 2015).

When elevated levels of serum creatinine usually indicates reduced GFR so serum creatinine rises in CKD patients and reduced GFR is relatively higher proportion (Supatra,2013).Moreover, the rate of decline in glomerular filtration and progression of CRF is related to underlying disorder as protein urinary excretion and hypertention (Lippincott,2007).

III.1.2.2. Electrolytes level study

Our study obtained a significant increase in serum Na and Ca levels before and after dialysis and serum K level increasing before dialysis but it decreased after dialysis in patients group compared to controls. The kidney plays an important role in regulation electrolytes, when it is impaired electrolytes imbalance appears (zhengfalei, 2013), the ability of the kidney to excrete Na decrease, salt sensitivity increase so the most end stage renal disease (ESRD) patients are hypertensive while the Na is the dominant factor of hypertension in ERSD (Seoung , 2012). So the disequilibrium syndromes were maintenance hemodialysis patients preferred and vocif various by attributed to electrolytes imbalance (Michael, 2000)when the difference of Na concentration between plasma and dialysate occurs because plasma water constitus only 93% of total plasma whereas it is 100% of total dialysate volume (Flavio et *al*, 2004). Moreover, the determination of dialysate Na concentration is one of the challenges of dialysis prescription, where too low dialysate sodium is responsible for interdialytic intolerance symptoms.(Antonio et *al*, 1999) therefore the high sodium intake has been directly related to high water consumption and consequently to expension of extracellular volume and high levels of interdialytic weight gain(Sibel et *al*.,2017). Add to the Na is impermeable solute which induced the movement of water loss across cell membrane where the net water loss and

hypertonic sodium gain so cellular dehydration (Horacio and Nicolaose, 2000).In addition, the relatively high Na and lactate content of some dialysis solution with various tonicities and electrolytes composition predisposes to hypernatremia and alkalosis(Henry et *al*,1971).

Moreover the prevalence of hyperkalemia in hemodialysis patients was reported to be about 8.7-10% depending on individual center (Choi et *al*, 2013), most patients with ESRD depend HD to maintain levels of serum K and other electrolytes within a normal range,(Adriana et *al*, 2015)during dialysis the cause of hypokalemia was a rapid shift of K from the extracellular to intracellular space secondary to correction of acidosis (Leopoldo and Carl , 1981),also the dialysate's K concentration is lower the blood K levels, serum K leave the blood and enter the dialysate or bath by crossing over the dialyser membrane where the serum K level to drop(Donna, 2006).A consequently hypokalemia can occur in HD patients post dialysis treatment and is a life threatening condition as it may cause ventricular dysarrhythmias (Jennifer et *al*, 2012).

Concerning the increased serum Ca level after dialysis was revealed by dialysate and dialysis solution Ca concentration and it occurs in pathogeneses of arrhythmias during dialysis (Najla and Amar , 2016) when the manipulations of dialysate Ca concentration enable alteration in Ca blood which impact on serum Ca, phosphate, PTH and most likely soft tissue calcification(Nigel et *al*, 2006). The most cases of hypercalcemia among patients with ESRD are introgenic as a result of treatment with Ca containing phosphate binders and vitamin D receptor activating medication(Charles, 2015). Add to hypercalcemia occurs in up 10% to15% in abnormal glomerular and tubule and nephrolithiasis patient, where macrophage within sarcoid granulomas can to synthesize calcitriol by activating vitamin D.(Moysés-Neto et *al*, 2006).

III.1.2.3. Hematological parameters

According to our results which showed that a significative decrease in RBC, HB and HT and a significant increase of WBC and Granulocytes number as study of Abdullah and Abbas, 2012) which demonstrated a significant lower number of RBC,HB and HT in CKD patients compared to controls. Anemia in ESRD is almost universal can be caused by erythropoietin, iron and vitamin deficiency or blood loss and shortened red cell life span (Haythem et *al*, *2014).* Moreover it is a common and often early complication in CKD (Karra et *al*, 2019)when mostly due to diminished production of erythropoietin (EPO) which is a primary regulator of RBC and mostly produced by renal epithelial cells(Suresh et *al*, 2012)so the decrease of EPO production caused by destruction of EPO producing fibroblasts of kidney interstitial fibrosis

and the overall reduction of renal mass(Zhian et *al*, 2009), also the RBC show increased membrane lipid peroxidation, reduced membrane fluidity and increased osmotic fragility which contributed to low grade hemolytic anemia (Paul et *al*,1995) or the low iron and vitamin B12 or folate levels can caused anemia in HD patients because they are needed to make their HB and RBC by its(National Kidney Foundation [NKF], 2012).

In addition, the malnutrition, oxidative stress and inflammation when the contact the blood and dialysis membrane during HD where the release of cytokins (TNFa,$IL_{6,}$IL1) and hypo-responsiveness of erythropoiesis-stimulating agent(ESA)all implicate in the pathogenesis of anemia.(Andreas et *al*, 2018). On another side, the activation of immune system during HD treatment with various dialyser membrane as a inflammatory statue which contributed by WBC elevation(Azar and Hamid , 2006).Furthermore, in HD patients the increased level of HLA.DR expression on APC as(macrophage, B cells and dendritic cells) often found in response to stimulation and therefore also is a marker for immune stimulation (Elı´sio et *al*, 2010).

III.1.2.4. Oxidative stress study

Our study obtained a significant variation of oxidative stress parameters when GSH level and Catalase activity have an estimated decreasing with significant specificity of GSH(32%, AUC=31%) and increasing of MDA in erythrocytes of CKD patients against to controls. Oxidative stress is contribute to development and progression of CKD and the associated complications including atherosclerosis, cardiovascular disease, erythropoietin-resistant anemia, immune deficiency(Yonova et *al*, 2018).Study of Mehryar and Omid (2015) proposed that a loss or inactivation of antioxidant factors as GSH is coupled with increased of lipid peroxidation in erythrocytes of HD patients where the MDA was increased significantly in CKD so it a good indicator for oxidative stress evaluation(Ramchandra et *al*, 2012) a especially in erythrocytes which is well know as a marker of ROS overproduction and increased lipid peroxidation (Jacek R et *al*, 2013)while that the MDA is a end product of it. also, studies have demonstrated that patients with other disease have a higher level of MDA in erythrocytes than in plasma..(Jung Won et *al*, 2010) when the level of lipid peroxidation was significantly increased in erythrocytes membrane in nephropathy patients. (Anuradha andSelvam,1989). The elevation of lipid peroxidation in erythrocyte membrane induce to decrease of erythropoietin(EPO) levels and their antioxidative effect (Zorica et *al*, 2012). Add to decreased of antioxidant enzymes which contributed by a significant delay in elimination of ROS could be the reason of high MDA level in erythrocytes of HD patients (Farzaneh et *al*, 2012). Moreover oxidative breakdown of biological phospholipids occurs in

most cellular membrane RBC while the toxicity of lipoperoxidation products in kidney of mammals involves nephrotoxicity (Marisa and *al*, 2012).

Furthermore, reduced GSH is the most important intracellular scavenger of free radicals as a reductant in oxidative reactions.(Hale et *al*, 2005)and catalase is a tetrameric peroxidase enzyme which converts H_2O_2 to water and molecular oxygen.(Ram et *al*,2004).

The antioxidants agents such as (catalase ,GSH) were decreased in CKD patients as a diabeteic complication(Noori et *al*, 2017), a diminished both enzymatic (catalase) and non enzymatic antioxidant (GSH) in plasma of CKD patients below the normal level may indicated the disturbance of cellular redox-status so the risk of oxidative damage.(Vinothkumar et *al*, 2017)when this oxidative status was in kidney tissus (reduction in GSH and catalase)and increase in MDA level lead to activating apoptosis so there are played important role in development and progression of CKD (Abdelaziz et *al*, 2015). part of the oxidation burden originates in inadequacy of body's key antioxidant enzymes such as (catalase) with reduced function in kidney disease which causes oxidative stress leads to inflammation ,at same time increased superoxide production occurs related to increased NADPH enzyme activity.(Richard ,2006).

On another side, several assay that can measured total antioxidant capacity of serum such as FRAP and ORAC (David , 2010), its can measured the antioxidant capacity of foods and water soluble antioxidant compounds can interact with different ROS sources (David and Seema, 2010), also FRAP assay a powerful test for determination of total serum antioxidant capacity in the body.(Mohammad et *al*, 2007).

Our results represented a significant ORAC and FRAP increasing in patients groups with high significant specificity (87% ,AUC= 77% and 73% ,AUC=85%) respectively compared to control but a significant increase in ORAC of after dialysis patients and in FRAP of before dialysis patients which demonstrated for the presence of oxidant stress status before and after dialysis , as Antolini et *al* (2004) study which showed that to total antioxidant power measured with FRAP and ORAC paradoxically increased in CKD patients. So the chronic renal failure (CRF)was characterized by a peroxidant state and deferent value of antioxidant compounds as vitamin C which increased in plasma of HD patients (Clermont et *al*,2000). Moreover, recent report demonstrated that the predialysis FRAP was higher in patients compared with healthy controls and it decreased after HD than perdialysis.(Jacek et *al*, 2009)a consequently of our results there is a oxidant stress status after dialysis because before dialysis due to relatively higher antioxidant level as (uric acid , vitamin E and GSH) where a balance of oxidants and antioxidants but after dialysis, the removal of antioxidants, an imbalance occurs which is a major cause of cellular oxidation (Kadkhodaee et *al*, 2008).

Furthermore, the water soluble metabolic antioxidants (uric acid, bilirubin)eliminated during dialysis can increased of antioxidants concentration and modified the equilibrium of oxidized and reduced states also lipid and water soluble antioxidants.(Malliaraki et *al*, 2003) however, it caused by semipermeable dialyser bioincompatible membrane during dialysis which associated with uremia, production inflammation ,leucocytes activating , pro-inflammatory cytokines and secretion of myeloperoxidase and $NADP^+$ so ROS increasing production (Adeyemi et *al*, 2018).

III.1.2.5. Study of correlation between biological markers

Our correlation results between oxidative stress markers and biochemical parameters represented in table10which clarify a significant positive correlations ($p<0.05$) between catalase activity and creatinine level and between GSH (RBC) and Ca concentration in control group but a significant negative correlation ($p<0.01$) between MDA(WBC) with Na level and between ORAC and Na level in the same group

Concerning patients group there are a significant positive correlations ($p<0.05$) between catalase activity, MDA(WBC)and ORAC with Na level A and MDA(RBC) with creatinine B and GFR B, also between GSH (RBC) with GFR B and GFR A. Furthermore a significant negative correlations ($p<0.05$) between catalase activity with creatinine A and K level B,MDA(WBC) with cratinine B and A also between MDA(RBC) with urea/creatinine and K level A, finally GSH(RBC) with Ca concentration in the same group. while that the MDA(WBC) with K level B in both groups.

Regarding our correlation results between oxidative stress markers and biochemical parameters which clarify a significant correlation in control and patients groups which prove by Significant correlation between plasma hypatocyte growth factors which its elevation may have a renal origin that aims to protect kidneys from necrosis in patients and creatinine may suggest the presence of a relation between the renal function and plasma oxidative stress statue with the hypatocyte growth factors production(Maryam et *al*,2010).In addition, Serum creatinine level was significantly elevated in hypertensive patients when the marker of oxidative stress was increased in the same group (Farzana et *al*, 2015), an example in Pregnancy Induced Hypertension (PIH) patients PIH associated with increasing in MDA level and decreasing in calcium ,creatinine ratio which associated with endothelial cell dysfunction (Babli et *al*,2014).

Concerning the electrolytes imbalance is as a result of oxidative stress damaging the erythrocytes which in turn reduce the activity of Na^+ ,K^+ ATPase in ESRD which is the main enzyme regulating the movement of electrolytes between serum and RBC's affected due

to a raise in the oxidant stress damaging the erythrocytes membrane (Jaiprakash,2014). In fact, The increasing lipid peroxidation and oxidative stress as well as they reflected electrolytes imbalance hence increased MDA serves as a significant marker for the identification of disease(Mahmood et *al*,2018) whereas Sodium depletion increased several renal antioxidant enzymes consistent with a stress response to increased ROS production(Michael et *al*,1999).Moreover a positive relationship of CAT and MDA and negative relationship between CAT ,MDA and increased K^+ level where the repairing of damage due to oxidative stress was associated in the deferent antioxidant enzymes in optimum K^+ levels and MDA , CAT levels are decreased (Hosseinet *al*, 2010).

Furthermore, The inflammation is associated with oxidative stress when found in MDA level augmentation in progression of CKD (Meenakshiet *al*,2013). Reduced eGFR was associated with higher systemic CRP and IL6 concentration (Elisabet, 2012) which are a markers of systemic inflammation which leads to endothelial dysfunction and tissues damage by increased lipid peroxidation and MDA level(Rohitaet *al*, 2014). Also When renal GSH concentration diminished the renal parameters measured suffered deleterious modification while that the fall in GSH tissue levels was accompanied by parallel reductions of GFR (Adrianaet *al*,1986).

Moreover , the perturbation of Ca^+ homeostasis is considered a very important aspect of chemically induced cell injury and it correlated with a variety of cellular characteristic including changes in cell surface and permeability ,GSH and protein thiol status and loss of activity mitochondrial dysfunction due to permeability transition(Donald,1997) as well as the hyperthyroidisme as a result of damaged mobilization of Ca^+ which leads to reduced blood Ca^+ rat which induced dysfunction of the respiratory chain in mitochondria when lead the generation of free radical that will lead to oxidant stress (Niko R et *al*.,2016).

III.2.Qualitative study of water in different area of Djamaa region

With regard to the electrical conductivity are very high level in the water of the study area and the center distribution of water , with a value superior to the WHO standard 2500 µS/cm which about 4000 µS/cm. As study of Idir et *al* (2018) showed waters in the Djamaa region are in contact with a lithology rich in evaporates, reveal an excessive mineralization, expressed by very high electrical conductivity values, oscillating in most cases between 2520 and 11970 $\mu S.cm^{-1}$, Significant and variable levels of mineral elements have been observed. According to Houari and Nezli (2018) **,** The extreme values of electrical conductivity have been recorded in Djamaa (8300 $\mu S.cm^{-1}$) . Conductivity reflects the mineralization of water

(Benrabah et *al*, 2016) and has the higher level of ionic concentration activity due to excessive dissolve solid(Yirdaw et *al*, 2016) **.**

Our results obtained have a very high calcium level which is very higher compared to the WHO standard 200 mg /l . As study of Zobeidi et *al* (2013) the calcium levels show high concentration exceeding potable standards (204 to 260 mg/l),it is the main urinary risk for calcium stone. Extremely hard water (hardness > 500 mg/l) is also unifit for consumption because the constituent mineral such as Ca^{+} can depsit inside the body if present in high amounts leading to kidney stone (Mahajan et *al*, 2006)where the Calcium stone is most common type of kidney stone which occurs in about 70% -80% of case . they are usually composed of Ca^{+}(Edgar et *al*, 2015).

In addition , we obtained for the Sodium is a high level in the water of the study area with ranging from 208 to 428.5 mg/l . As recording to Tifrani et *al* (2016) the measured sodium concentration exceed 200mg/l WHO approval , with values obtained at an average of 263 mg/l . In fact, High sodium intake may also exert direct effects on CKD progression , independent of blood pressure(Wang Yu et *al*, 2011). This is consistent with our experimental study on rats , there is a significant increase in serum sodium level in the group that drank the tap water (TW) compared to the control group. The study of Neri et *al* (1985)show the high level of sodium is a big risk factor of CVD . According to Thomas et *al* (2008) the several cardiovascular risk factor associated with CKD are unique to patients with this disease. High level of serum sodium could also affect endothelial function via TGF-$\beta_1$which play an important role in the progression of CKD (Ying et *al* (1998).

In our study it was observed that the potassium is a high level in the major water of study area and the center distribution of water with ranging from 29.48 to 15.33. As recording to Sekkoum et *al* (2012) show that the potassium is not in the standards of potability of water , with values obtained at an average of 29 mg/l . However, filtered water contains a low potassium level on average 5.36 mg/l when the Potassium plays a crucial role for sufficient functioning of the heart(Palmer et *al*, 2016). Infants and older may be at higher risk for high potassium levels**(**Water Health Organization[WHO] 2009)**.** High potassium is a risk factor of CVM , arrhythmia and heart failure(Liesa et *al*, 2018).

In our experiments on rats we observed that there was a slight decrease in the level of potassium when the rats group drank filtered water at an average 56.46mmol/l compared to the control group (58.91 mmol/l) , but extreme decrease recorded in the tap water group (53.87 mmol/l)while study of Checherita et *al* (2011) show that 70,11% present arrhythmias

in hyperkalemia groups and 75,92% in hypo K cases and conclude that K below on above normal represent the major cause in arrhythmias appearance also The study of David Weinr (1997)show that the ventricular arrhythmias are a second cardiovascular side –effect of hypokalemia . Arrhythmias is a risk factor for cardiovascular diseases (Paul et *al*, 2011).Hypokalemia has been associated with an increased frequency of ventricular arrhythmia (Philip, 1990). Furthermore, Potassium deficiency changes the function of many organs and significantly affects many organs in the body as well as kidneys. Hypokalemia also impairs the kidneys ability to concentrate the urine maximally(Mujais et *al*, 1992)when hypokalemia is accompanied by enhanced renal cystogenesis and many lead to interstitial scarring and renal insufficiency (Torres et *al*, 1990).

With regard to the chloride is a very high level in the water of the study area and the center distribution of water , with a value superior to the standard norm Algerian of 500 mg/l which about 2400 mg/l. As recording to Zobeidi et *al* (2013**)**, the measured chloride concentration exceed 250mg/l WHO approval , with values obtained at an average of 320 to 1264mg/l.

In addition , we obtained for the Iron is a very low level in the water of study area with ranging from 0 to 0.065 mg/l . As recording to WHO (1996) the health concentration of iron in the water should be no more than 0.3 mg/l . The iron is an essential element in the human body where it installs oxygen transport proteins such as hemoglobin or myoglobin (Do Well et *al*, 2003). The primary causes of iron deficiency include low intake of bioavailable (Nazanim et *al*, 2014).Through the results obtained by Rebrcca (2012) , we conclude that ground water can provide an inexpensive and sustainable source of bioavailable iron. Based on Dutra et *al* (2007) study and the results obtained , water is an essential element of iron in the body and improves as well as growth. Perutz (1982) concluded that iron is essential to hemoglobin structure and function.

III.3. Effect of water on renal function in rats.

III.3.1. Biologicals markers study

The results of animal study indicate a low level the HB in two groups TW and FW compared to control. The study of Jeffery L.M (2013) show that hemoglobin is the most iron-containing protein in the red blood cells . therefore anemia is characteristic of iron deficiency when Hemoglobin induced anemia may cause renal dysfunction caused by low oxygen delivery , which exacerbates renal dysplasia wich in turn leads to interstitial renal injury and

fibrosis (Mehdi et *al*, 2009).Studies indicate that low levels of Hb in patients with anemia may increase the risk of kidney disease (New JP et *al*, 2008).

Our study showed a significant variations in oxidative stress markers where the quality of drinking water has a major influence on public health and prolong exposure to contaminated water has been known to increase the risk of disorders in kidney (Wasana et *al*,2017).Among the common environmental toxins associated with CKD are heavy metals while The kidney is a target organ in heavy metal toxicity for its capability to reabsorb and concentrate divalent ions and metals, the acute kidney injury (AKI) by heavy metals diverge from CKD for the mechanism of toxicity(Paolo et *al*,2017),so industrial environmental contamination of groundwater recognized as an important source of exposure that may result in kidney disease(Peter et *al*,2010). Heavy metal and their salts are considered as very important group of environmental pollutant such as the water who it's toxicity has been attributed to oxidative stress (Iwan et *al*,2015)which may be caused by excess contaminant water exposure and its toxicity such as a lead exposure which produce toxic effects on animal tissue (Derouiche et *al*,2017). The environmental pro-oxidant pollutants induce free radical formation which contribute to oxidative stress which can produce major interrelated derangements of cellular metabolism, damage membrane permeability and destruction of cells by lipid peroxidation (Balahoroğlu et *al*,2008).

Our results represent a significant increased in MDA level and decreased in antioxidant parameters such as GSH concentration, GST, SOD and catalase activities in TW group these results are in agreement with results of Inkielewicz. et *al* (2008)that found The concentration of GSH and CAT, SOD activities are decreased in kidney of experimental animals exposed to some toxic products in their drinking water. Several study showed that a mineral of fluore produce a decrease in activity of antioxidant enzymes such as (GSH, GST, SOD and catalase) when the free radical produced(Iwonaand Narcyz,2012) and oxidative stress which have been implicated in the pathogenesis of toxic elements such as fluor intoxication by increase of lipid peroxide level and decrease of SOD and catalase activities in kidney(Ranjan et *al*,2009).Moreover, other toxic products of drinking water (disinfectants) may induce to oxidative stress in mammalian cells and occure intracellular imbalance more susceptible to oxidative damage(Jing et *al*,2006).

Discussion

In addition ,The increase in conductivity and richness in inorganic ion (K^{+}, K^{+2}, Na^{+} and Mg^{+2}in TW influences metal bioavailability and toxicity and water chemistry parameters strongly influence toxicity of metals to organisms(Oluwafikemi et *al*,2017)where the ionicity in drinking water by deferent electrolytes is one of the risk factors which cause CKDu (Kumari et *al*,2016). However The high calcium intake in tap water increases the urinary calcium concentration such as enhanced risk for renal stones also indicated by increased of calcium citrate index(Vincenzo et *al*,1999). Furthermore, least part of hyperosmotic stress lead to proteins and DNA damages which are caused by secondary oxidative stress when the hyperosmolality increases ROS and carbonylation in renal inner medulary cells(Dietmar,2004; Zhang et *al*,2004). Also the sodium fluoride caused oxidative stress and apoptosis in soft organ which was accompanied by increasing ROS and MDA levels and decreasing mRNA expression levels and activities of SOD, CAT, GSH and GST(Azab et *al*,2018).The increased of oxidative stress in water pollutant patients which demonstrated by increased levels of MDA and inhibition of antioxidant enzymes when the accumulation of ROS contributed the renal insufficiency and necrosis(Wasana et *al*,2016).

Concerning FW group which contained hypersperse 700-11(HPS) as a xenobiotic demonstrated a significant increasing of MDA levels and catalase activity and deceased in GST, and SOD levels against the control. where Mohammad et *al* (2004) explain that the stimulation of free radical production induced lipid peroxidation and disturbance of total antioxidant capability of human and animals body are mechanisms of toxicity in most xenobiotics which are chemical compounds foreign to the body such as drugs, food additives and environmental pollutants (Dibyajyoti, 2014). The exposition of a xenobiotic toxic, the antioxidant enzymes decreased when the ROS increased which modulates the generation of oxidative stress (Derouiche et *al*,2017).

Also the study of Iwona and Narcyz (2012) demonstrated a greater risk of oxidative stress and kidney damages during exposure to xenobiotics in drinking water. Currently the water borne xenobiotics can be uptake via deferent tissues and capable to contribute to oxidative stress when overexpression of ROS and inhibition of antioxidant enzymes activity and associated with cell dysfunction (Mario et *al*,2017). The defense mechanisms of antioxidant (GSH, CAT, GST and SOD) can be subverted by xenobiotics that induce the production of excessive of untimely free radicals and result in damage to macromolecules including DNA(Rana,1997).So xenobiotics can induced oxidative stress results in decreasing the antioxidant capacity GST and SOD and increasing in lipid peroxidation and catalase activity

by alteration the expression of antioxidant enzymes which leading to disruption of the cell function(Sapna et *al*,2015).

Conclusion and prospects

Conclusion

Chronic kidney disease is a worldwide public health problem with a high prevalence and continuity, so it is necessary to determine the main cause and find means of early diagnostic and prevention against this disease. In our study we investigated several risk factors to limit which one is most likely to cause CKD.

Our socioeconomic and clinical risk factors study demonstrated Diabetes, urinary problems, HTA , history of kidney disorder, renal herbal medicine, nephrotoxic drugs and disease before CKD are considered to be a very important risk factors for CKD Which inspire us to prevent and maintain the health status of the individual while that additive soft drinks, spices ,Amount of water and Salty foods are protective factors for CKD in study population.

The variation of creatinine and electrolytes levels after dialysis indicates for ineffectiveness of hemodialysis where it have a directly effects of dialysate solution and dialyser membrane on cellular osmolarity. Also we found a variation of hematological parameters where the decreasing of erythrocytes line and increasing of white blood cells and granulocytes while its favor the anemia and immune response appearance as CKD complication.

As consequently, creatinine and hematological parameters are a most prognostic markers and hemodialysis is not only and effective solution of treatment the CKD.

Other results illustrate a variation of catalase activity and GSH level where indicates a existence of oxidative stress status which contribute to imbalance of antioxidant defense system and overexpression of free radicals and leads to cells membrane alteration and disease progression.

Therefore, the erythrocytes GSH level ,serum ORAC and FRAP activities are shown to be a prdictive and a new reliable markers for CKD ,while that it demonstrated in our study by the significant correlation between oxidative stress and biochemical parameters of kidney disease where we can suggested and insert this markers into the analytical diagnostic list for prediction of disease concerned. And include the antioxidant treatment in the list of treatment and prevent of CKD.

On the other hand, our results showed a variation on electrolytes levels and some minerals concentration on some types water of deferent areas in Djamaa region which indicates that this variation depending nature of area and the quality of water installation.

As conclusion the use of tap water and filtered water affects the biochemical and hematological parameters and even the renal stress parameters in rats which shows the effect of this type of water as a major risk factor for kidney failure.

Prospects

based on the results of our study, we hope to take these results into account:

- Conduct in-depth studies on other specific risk factors.
- Reduce the use of the types of water studied in our work and find an alternative.
- The inclusion of certain biological parameters studied in the diagnosis of CKD.

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Bibliographical references

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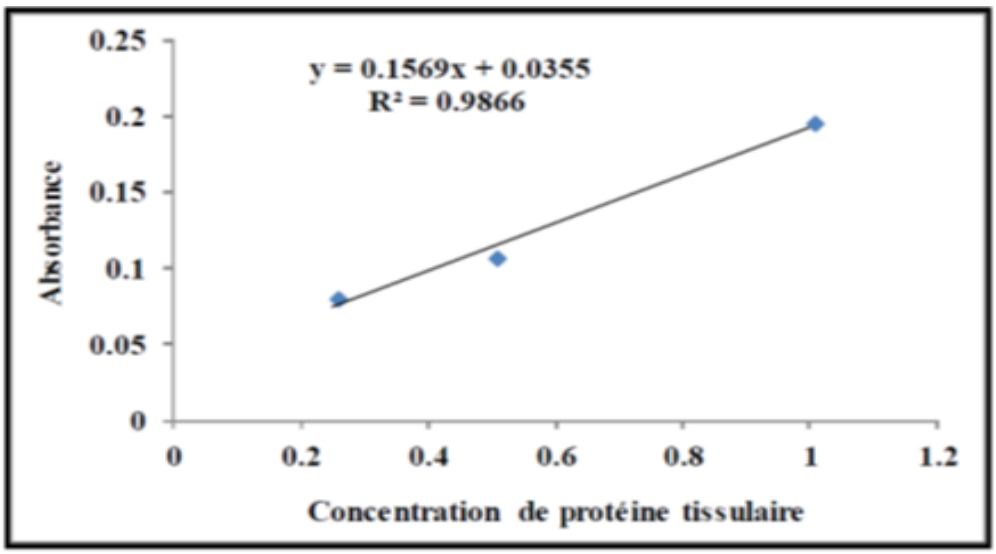
Annexes

Annex 01 : Questionner for patients

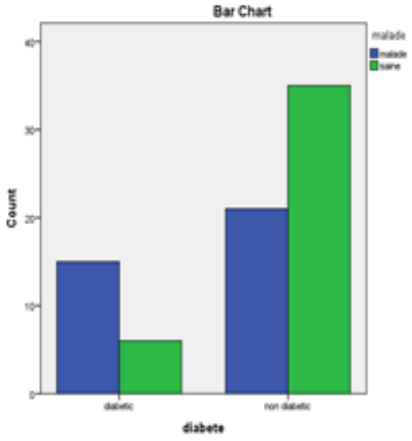
	العمر: الوزن: الطول: المهنة: الجنس:	مكان السكن: الحالة المدنية: فصيلة الدم: المستوى التعليمي:

الرقم	السؤال		نعم	لا	ملاحظات
01	هل مستوى الدخل ضعيف-متوسط-جيد				
02	هل تشرب ماء الحنفيه او نوع اخر اذكره				
03	هل تشرب الماء كثيرا				
04	هل تشرب الشاي بكثرة . و كم مرة في اليوم				
05	هل تشرب القهوة بكثرة .وكم مرة في اليوم				
06	هل تستعمل البهارات بكثرة				
07	هل تستعمل المضافات و الملونات الغذائيه بكثرة				
08	هل انت مدمن على المشروبات الغازيه				
09	هل تتعرض للمواد الكيميائيه بكثرةمثل المبيدات الحشريه				
10	هل تعمل في مكان ملوث				
11	هل تسكن بمنطقه صناعيه او قرب منطقه صناعيه				
12	هل انت تدخن او احد من العائله يدخن				
13	كم سيجارة تدخن في اليوم				
14	هل تعاني من اضطرابات في الهضم				
15	هل تتناول ادويه مخدرة او مهدئه				
16	هل تتناول ادويه لعلاج الكلى او عسر البول قبل المرض				
17	هل تعاني من امراض مزمنه كالقلب و ضغط الدم والسكري				
18	هل تعاني من التهاب المفاصل				
19	هل تعاني من مشاكل في المسالك البوليه				
20	هل تمارس الرياضه من قبل				
21	هل انت حركي في حياتك اليوميه				
22	هل اصيب احد من افراد العائله بنفس المرض				
23	هل تعاني من امراض الكلى من قبل				
24	متى تم اكتشاف مرضك بالكلى				
25	هل اصبت بمرض الكلى بسبب مرض اخر اذكره				
26	متى تم اكتشاف مرضك الاخر قبل مرضك بالكلى او بعد				
27	هل مرضك يتطلب تصفيه الدم				
28	كم مرة في الاسبوع تقوم بالتصفيه وكم ساعه في اليوم				
29	هل كنت تتناول اي نوع من المخدرات				
30	هل تستعمل الادويه بكثرة عند اي مرض ولو بسيط				
31	هل تستعمل الاعشاب الطبيه بكثرة لعلاج المشاكل الصحيه				
32	هل استعملت الاعشاب الطبيه لعلاج مشكل الكلى				
33	هل تستعمل البراسيتامول بكثرة				
34	هل تستعمل المضادات الحيويه بكثرة				
35	هل تستعمل ادويه مسكنات الالم بكثرة				
36	هل تتناول الاغذيه المالحه او تحب زيادة الملح بكثرة				
37	هل تتناول السكريات بكثرة				
38	هل تحبس البول عادة لمدة طويله				
39	هل تاكل اللحوم الحمراء بكثرة كم مرة في الاسبوع				
40	هل انت نصبي في حياتك اليوميه				
41	هل تعاني من اضطراب في النوم				

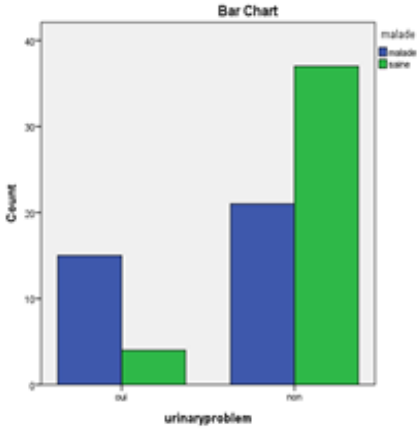


Annex 02 : Calibration curve used BSA (1 mg / ml) for the determination of tissue proteins

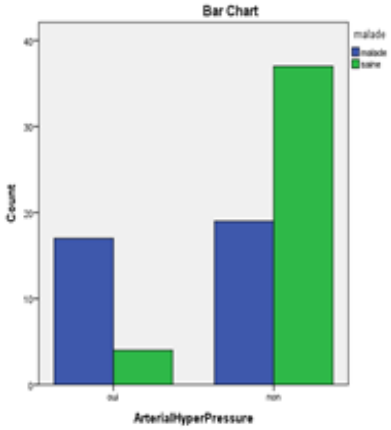
Riskfactors :



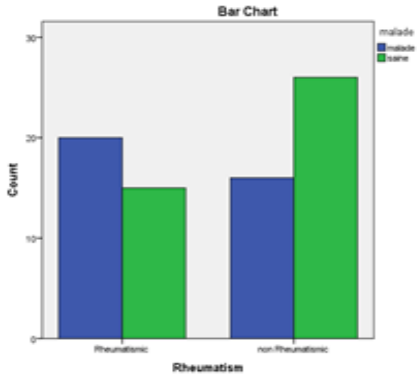
Annex 03: Diabetes



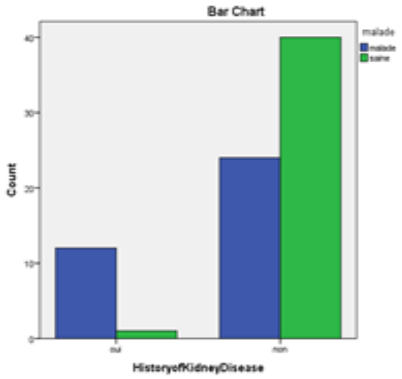
Annex 04: Urinary problem



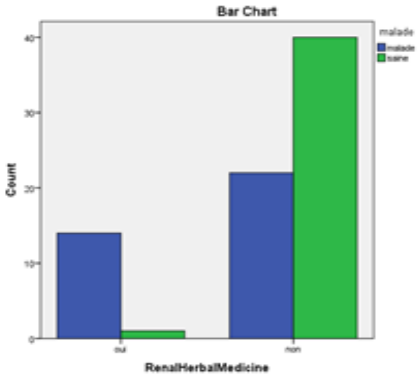
Annex 05: Arterial Hyperpressure



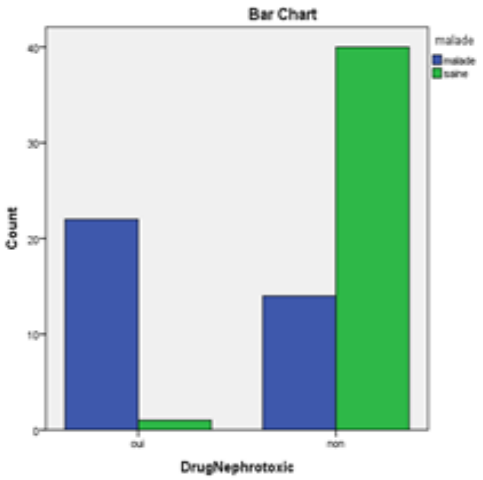
Annex 06 : Rheumatoid



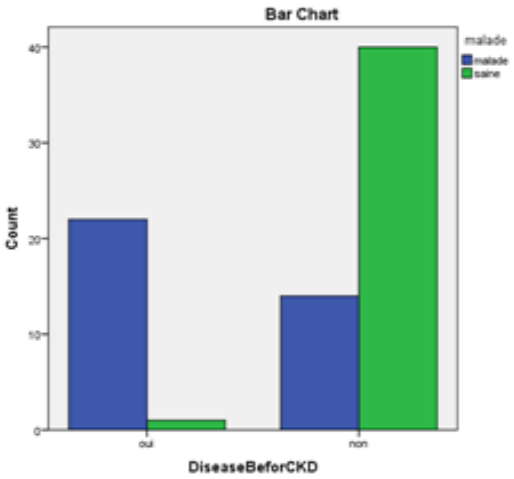
Annex 07: History of kidney disease



Annex 08: Renal herbal medicine

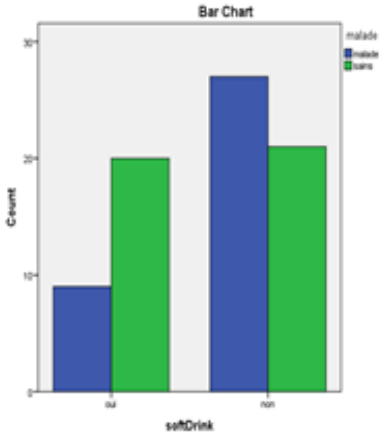


Annex 09 : Drug nephrotoxic

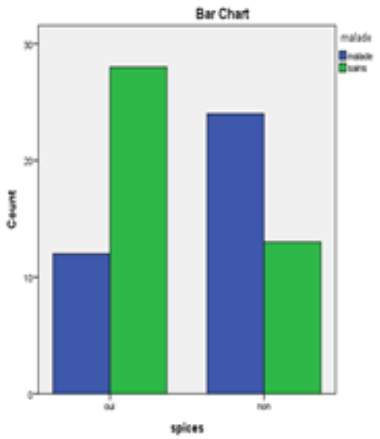


Annex 10 : Disease before CKD

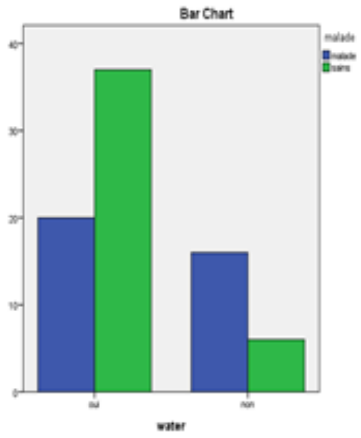
Predictor factors :



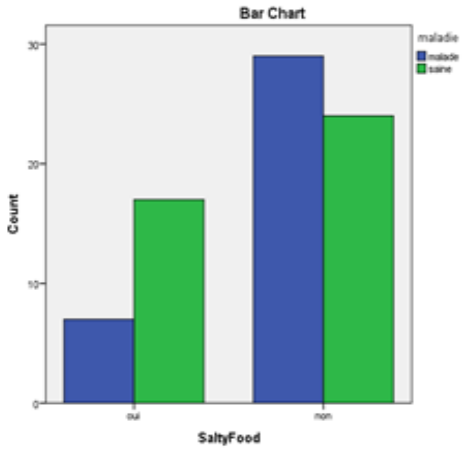
Annex 11: Additive soft drinks



Annex 12: Spices

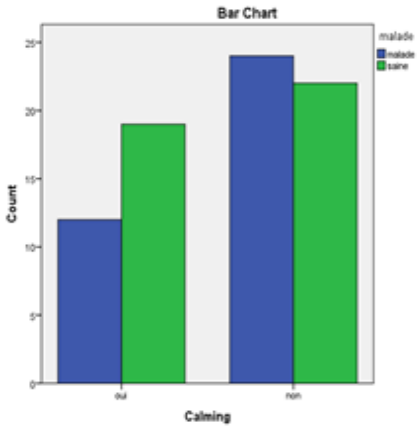


Annex 13: Amount of water

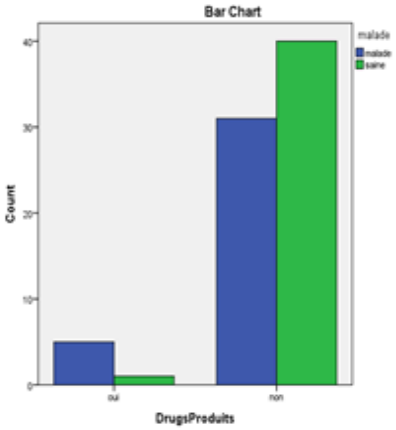


Annex 14 : Salty food

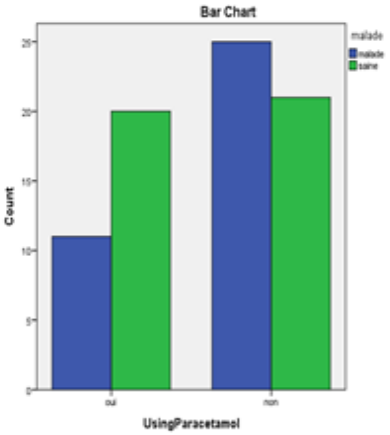
Other factors :



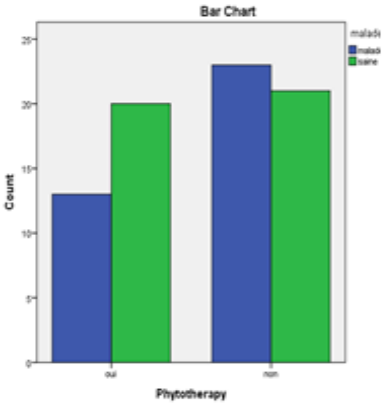
Annex 15: Calmants



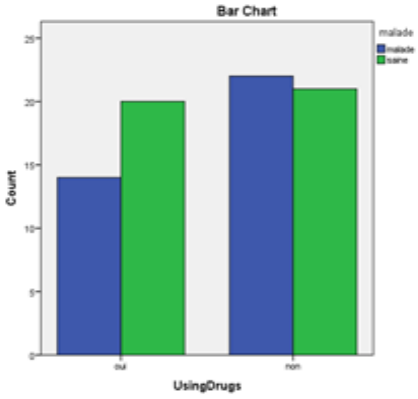
Annex 16: Drug produits



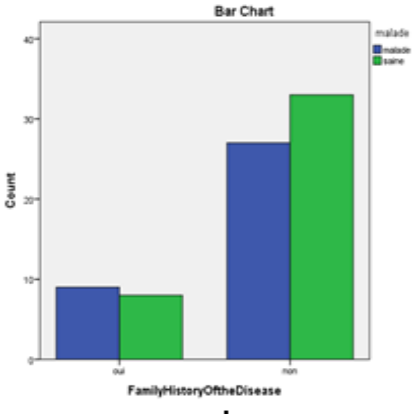
Annex17:Usingparacetamol



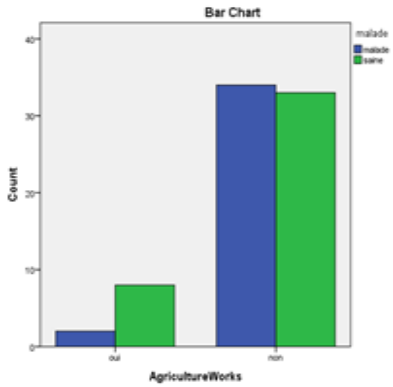
Annex 18: Phytotherapy



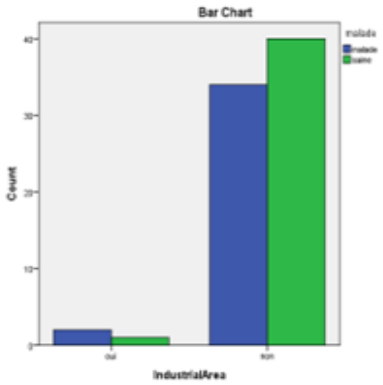
Annex 19: Using drugs



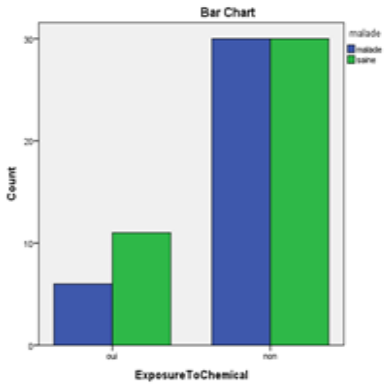
Annex 20: Family histroy of the disease



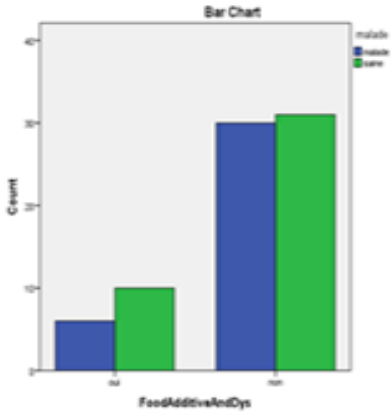
Annex 21 : Agriculture works



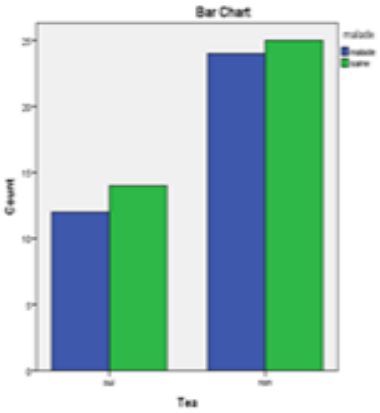
Annex 22 : industrial area



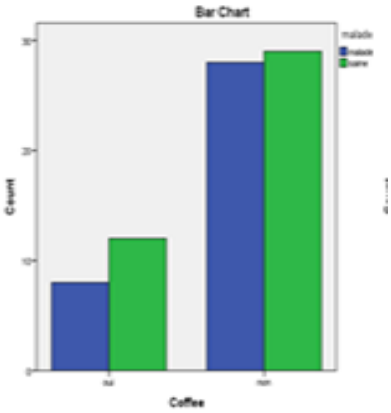
Annex 23 : Exposure to chemical



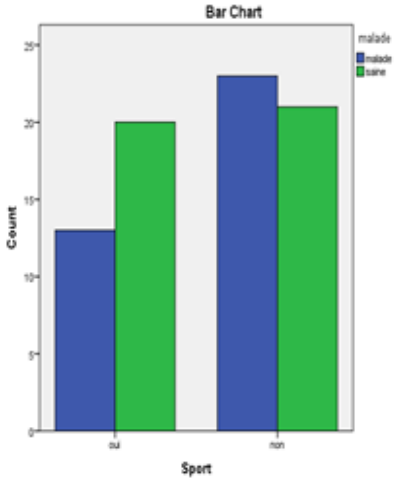
Annex 24: Food additive and dys



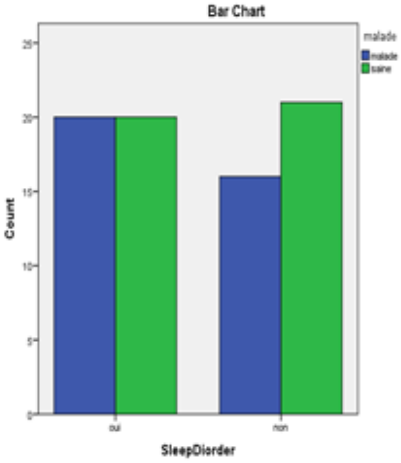
Annex 25: Tea



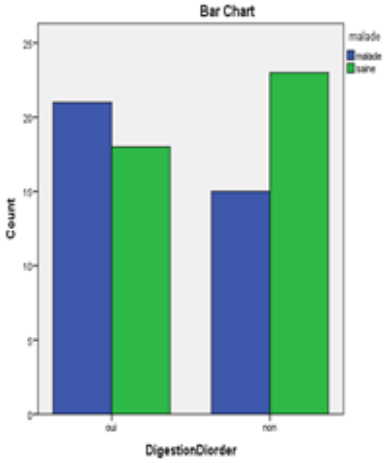
Annex 26: Coffee



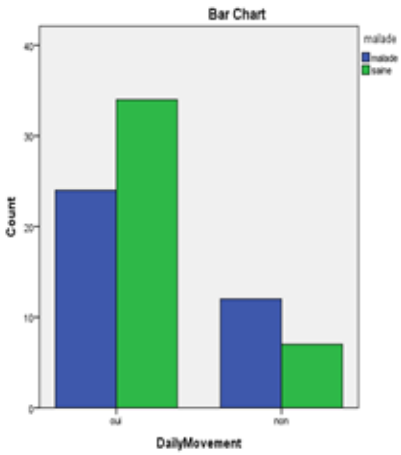
Annex 27: Sport



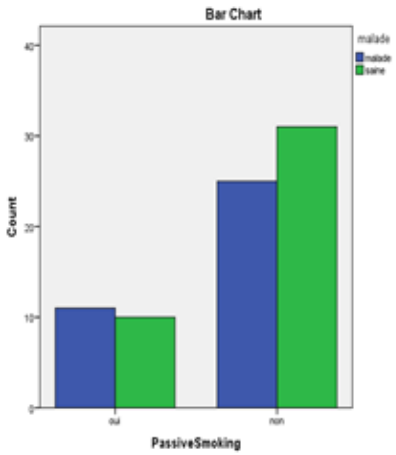
Annex 28 : Sleep disorder



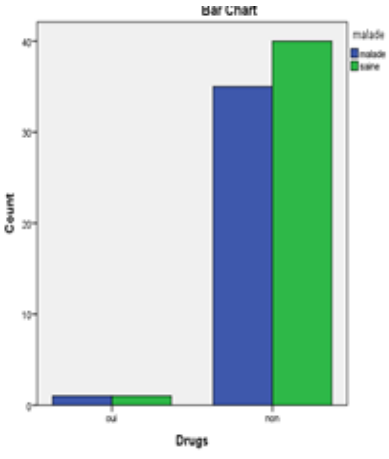
Annex29 : Digestion disorder



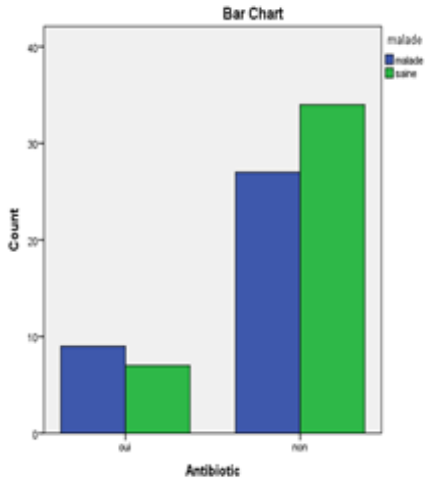
Annex 30 : Daily mouvemant



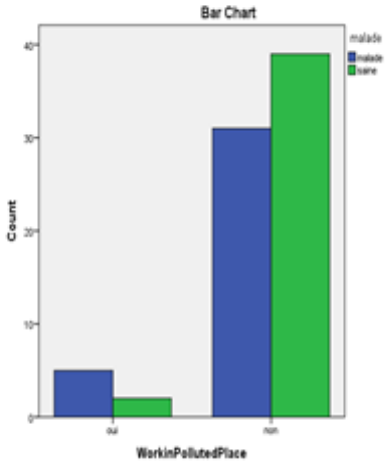
Annex 31 : Passive smoking



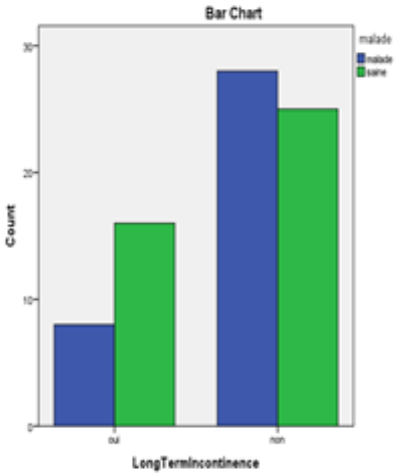
Annex 32: Drugs



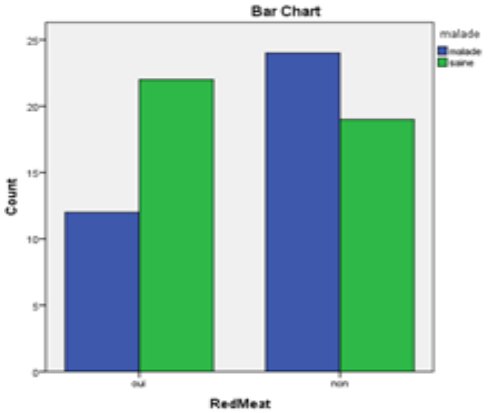
Annex 33 : Antibiotic



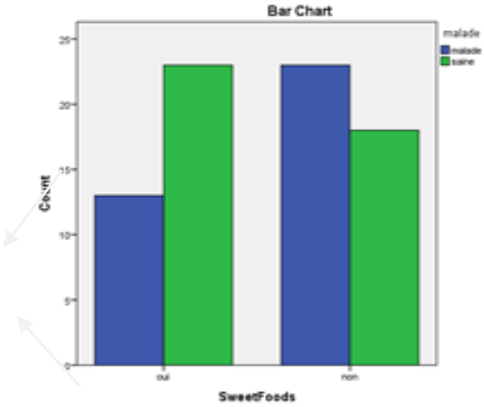
Annex 34 : Work in pollute place



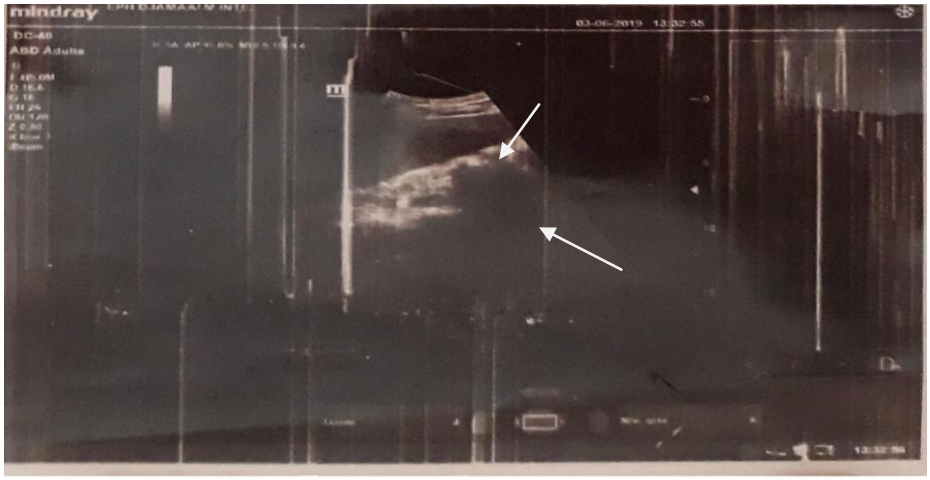
Annex 35 : Long-term incontinence



Annex 36 : Red meat



Annex 37 : Sweet foods



Annex 38: kidney atrophy of patient with CKD screening by kidney echography