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Risk of Kidney Failure Associated with the Use of Acetaminophen, Aspirin, and Non-steroidal Anti-inflammatory Drugs

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Abstract

People who take analgesic drugs frequently may be at increased risk of end-stage renal disease [ESRD], but the extent of this risk remains unclear. Purpose: To investigate the relationship between non-steroidal anti-inflammatory drugs[NSAIDs] and kidney failure and to confirm the effect NSAIDs and kidney failure. We studied 424 persons(298 patient 166 male and 132 female)treated for ESRD of different ages from Hail region and 126 healthy person(23male and 103 female) . The study done by questionnaire, we asked them about their past use of medications containing paracetamol, aspirin, and others non-steroidal drugs. For each analgesic if it was taken routinely, as needed, and for more than 1 year or less. Heavier acetaminophen (paracetamol) use was associated with an increased risk of ESRD. In the study population we found that 52.59% of sick persons used paracetamol and 17.69% not used it. Also we found that 28.77% of sick persons used aspirin and 41.51% not used it. In addition to that we found that 34.43% of sick persons used other NSAIDs and 35.85% not used them.

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16.51%of sick person confirmed that they had renal failure due to drugs, 49.53 %said no and 4.25 not answered. 14.39 % of healthy person confirmed that drugs caused renal failure , 14.86% said no and 0.4% not answered using SPSS analysis. People who often taken acetaminophen were associated with an increased risk of ESRD more than those often take aspirin or other NSAIDs.

Keywords: Kidney; failure; NSAIDs; acetaminophen.

1. Introduction

1.1. Acute renal failure [ARF]

ARF is characterized clinically by an abrupt decrease in renal function over a period of hours to days, resulting in the accumulation of nitrogenous waste products [azotemia] and the inability to maintain and regulate fluid, electrolyte, and acid–base balance [1].

1. 2.Chronic kidney disease [CKD]

This is often not reversible and describes the continuum of kidney dysfunction from early to late-stage disease [2].

Estimated glomerular filtration rates [eGFR] range from 90 mL/minute/1.73 m^2 in the early stages to 15 mL/minute/1.73 m^2 in the late stages of disease. The most severe stage occurs when the eGFR is less than 15 mL/minute/1.73 m^2 and is known as end-stage renal disease [ESRD] [2]. Patients with ESRD require renal replacement therapy in the form of dialysis or transplantation to sustain life.

The presence of protein in the urine [defined as proteinuria, albuminuria, or microalbuminuria based on protein type and amount] is an early and sensitive marker of kidney damage.

1.3. Actions and pathophysiological role of prostaglandins [PGs] on kidney

PGE_2 and PGI_2 increase water and K+ excretion and have a diuretic effect. PGI_2, PGE_2 and PGD_2 evoke release of renin [3].

1.4 .The objective of this study

To investigate the relationship between NSAIDs and kidney failure and to confirm the effect of NSAIDs and kidney failure.

2. Literature review

Analgesic nephropathy was first described in the 1950s [4]. In patients on long term NSAIDs without acute or chronic renal failure, subclinical renal dysfunction such as reduced creatinine clearance and impaired urine concentrating ability has been shown to be present. This dysfunction is reversible on withdrawal of NSAIDs.

Even with a wide range of NSAIDs at our disposal, a renal safe NSAID is yet to be discovered [5].

There was previous study for causes of chronic kidney disease in 300 patients in Hail region and they found that 23% of this population screening was due to hypertension and diabetes .This mean that people in Hail region are of high risk if they use NSAIDs and may be precipitating factor of renal failure [6].

2.1. Non-steroidal anti-inflammatory drugs [NSAIDs]

NSAIDs are used as pain relievers, reduce inflammation and lower fevers. They prevent blood from clotting. However; they have adverse effects that can develop an ulcer. They also may interfere with kidney function [3].

The pharmacological action of NSAIDs is due to reducing the production of prostaglandins [PGs] which are chemicals that promote inflammation, pain, and fever.

Ingestion of 15 g of acetaminophen may be fatal, death being caused by severe hepatotoxicity [7]. Recent data also implicate acetaminophen in rare cases of renal damage without hepatic damage even after usual doses of acetaminophen [7].

At the usual dosage, aspirin's renal toxicity occur less frequently [7].Other non-selective cyclooxygenase inhibitors include ibuprofen, diclofenac, indomethacin, ketoprofen and mefenamic acid. Selective COX-2 inhibitors are contraindicated in patients with severe renal insufficiency [COX-2 is constitutively active in the kidney].

3. Materials and methods

3.1. Material

This study was done by questionnaire which was developed by the supervisors and students.

3.1.1. Study participants

We studied 424 person, 189 male and 235female .298 patients treated for ESRD of male and female of different ages and different nationalities (Saudi Arabi 293, Sudan 3،Jordan 2) and 126 healthy person male and female.

3.1.2. Data collections

The interviewer explained to participants the objective of the study and asked standards questions. The study participant were interviewed separately in the hospitals (King Khalid hospital(236),Al-Shamli hospital(9),Al-Ghazalah hospital(3) , Moqaq hospital(20) and Baqa' hospital(30) approximately for 15minutes about their part use of medication containing paracetamol , aspirin and other NSAIDs for life time exposure. For each analgesic drug the average use [in pills per year] and the cumulative intake (in pills) examined for an association with ESRD. The case patient had to have ESRD and had to have started long term dialysis between 5 months to 7 years in comparison with 126 healthy person male and female .

3.2. Statistical analysis

The observations for each drug were done using SPSS(cross tabulation and Chi-Square ($X^{2)}$ statistical

Analysis, Phi and cramer' s V) was used to compare the drugs used by the sick and healthy persons and P values less than 0.05 were considered significant. .

4. Results

This study was done in Saudi Arabia in Hail region and we found that many patients using NSAIDs, paracetamol and aspirin thought that these drugs caused renal failure.

A majority of studies participants that taken analgesics drugs either at needed or continuously. The survey covered 298 patient and 126 healthy as shown in table 1, the result shown below according to SPSS analysis (cross tabulation and Chi-Square ($X^{2)}$ statistical analysis) .

Table 1: The population frequency of distribution in comparison to idea of causes of renal failure (n= 424)

Patterns	**Frequency/percentage** **n (%)**	**Mean**	**Standard error of mean**	**Standard deviation**	**P-value**
1.Sex		1.55	0.024	0.498	P<0.05
Male	189(44.6%)				
Female	235(55.4%)				
2.Age		1.3	0.022	0.461	P<.001
10-30	295(69.6%)				
31-60	129(30.4%)				
3.Status		1.3	0.022	0.458	P<0.001
Sick	298(70.3%)				
Healthy	126(29.7%)				

4.1. Effect of drugs and renal failure

In this study we found that 16.51% of sick persons confirmed that there was relationship between intake of analgesic drugs and the causes of renal failure ,49.53% said no and 4.25%not answered .For healthy 14.39% said yes ,14.86 said no and 0.4% not answered .

4.2. Effect of paracetamol and renal failure

In this study we found that 52.59% of sick persons confirmed the use of paracetamol and 17.69% not used it. For healthy persons 15.09% used paracetamol and 14.62% not used it.

For the use of paracetamol, the percentage of sick persons was 52.59% , who took it continuously was 14.62 % , who took it at need was 38.44% and 17.22% not answered, in a dose of one tablet was 33.02%,2 tablets was 12.50% and more than 2 tablets was 5.66% and 19.1% not answered, in a duration of less than 6month was 20.05% , less than one year was 4.7% and more than one year was 28.07%.and 17.45% not answered as shown in figures 1,2 ,3and 4($P < 0.001$) .

For healthy person 2.36% used it continuously,13.44% when need and 13.92% not answered in a dose of one tablet was 6.6% ,2tablet was 7.08% and more than 2 tablet was 1.18% and 14.86% not answered in a duration of less than 6month was 6.6% , less than one year was 2.36% and more than one year was 5.9% and 14.68% not answered as shown in figures 1,2 ,3and 4($P < 0.001$) .

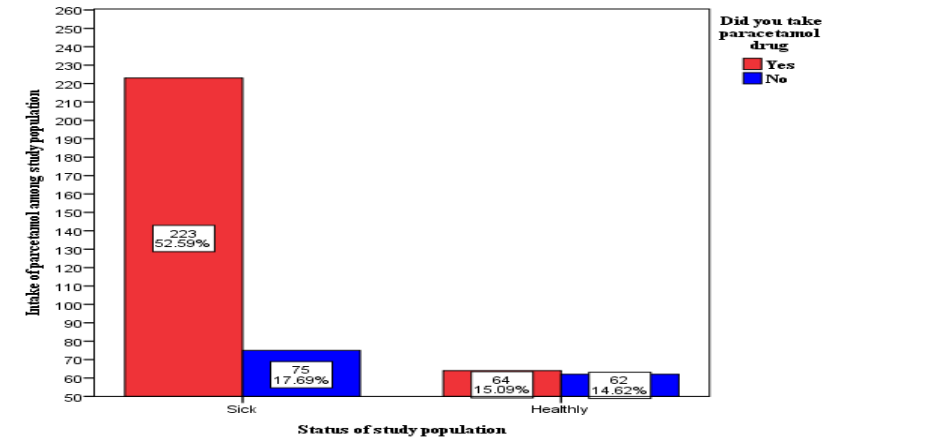

Figure 1: Intake of paracetamol by sick persons with ESRD and healthy persons

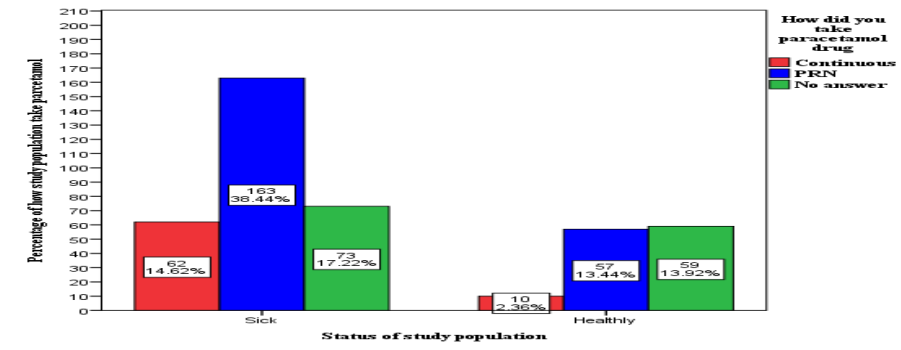

Figure 2: Intake of paracetamol when needed or continuous by sick persons with ESRD and healthy

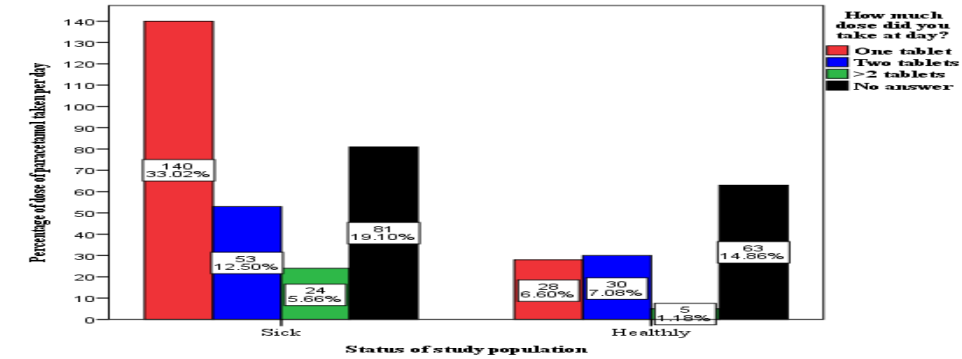

Figure 3: Intake of paracetamol doses per day by sick persons with ESRD and healthy persons

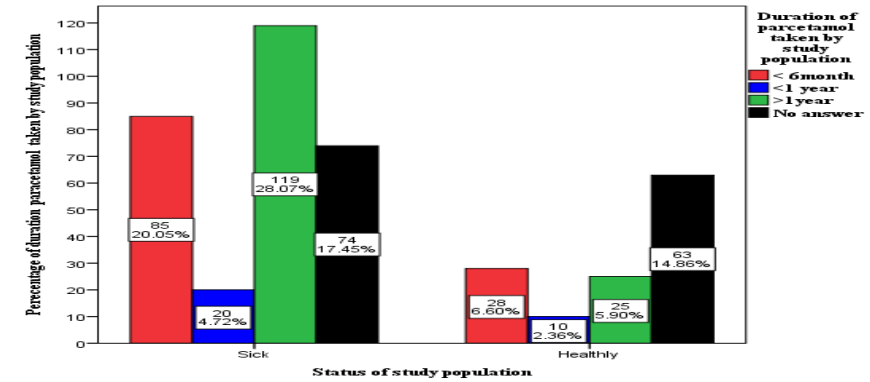

Figure4: Intake of paracetamol doses duration by sick persons with ESRD and healthy persons

Values were expressed as frequency percentages P < 0.001 * highly significant difference from healthy**

4.3. Effect of aspirin and renal failure

For the use of aspirin in this study 29.77% of sick person confirmed that used it, 41.51% not used it .

For healthy persons 5.9% used it ,23.58%not used it and 0.24% not answered.

For the use of aspirin the percentage of sick persons was 29.77%, who took it continuously was 18.63%,who took it at need was 10.61 % and 41.04% not answered, in a dose of one tablet was 22.64%, 2 tablets was 2.59% and more than 2 tablets was 2.12% and 42.92% not answered, in a duration of less than 6month was 5.44% , less than one year was 5.67% and more than one year was 17.73%.and 41.37% not answered as shown in figures 5,6,7 and 8(P < 0.001) .

For healthy person 3.54% used it continuously, 3.07% when need and 23.11% not answered in a dose of one tablet was 3.77% ,2tablet was 0.94% and more than 2 tablet was 0.4% and 24.53% not answered, in a duration of less than 6month was 2.36% , less than one year was 0.71% and more than one year was 2.13% and 24.59% not answered as shown in figures 5,6 ,7 and 8(P < 0.001) .

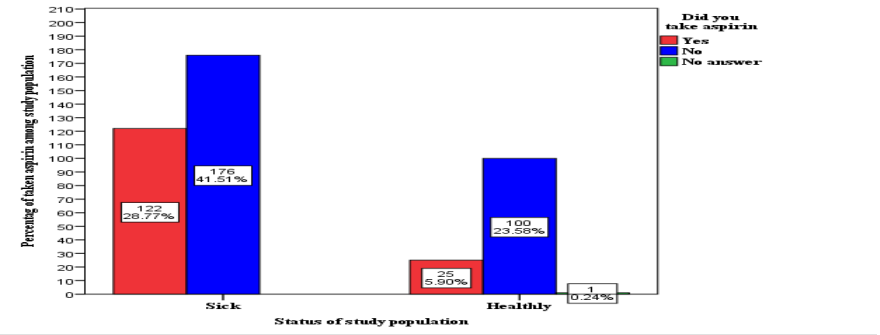

Figure 5: Intake of aspirin by sick persons with ESRD and healthy persons

Values were expressed as frequency percentages P < 0.001 * highly significant difference from healthy**

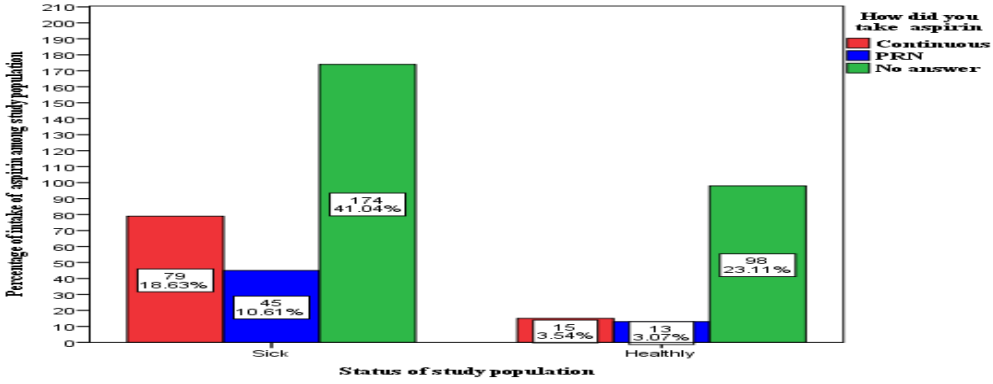

Figure 6: Intake of aspirin when needed or continuous by sick persons with ESRD and healthy persons

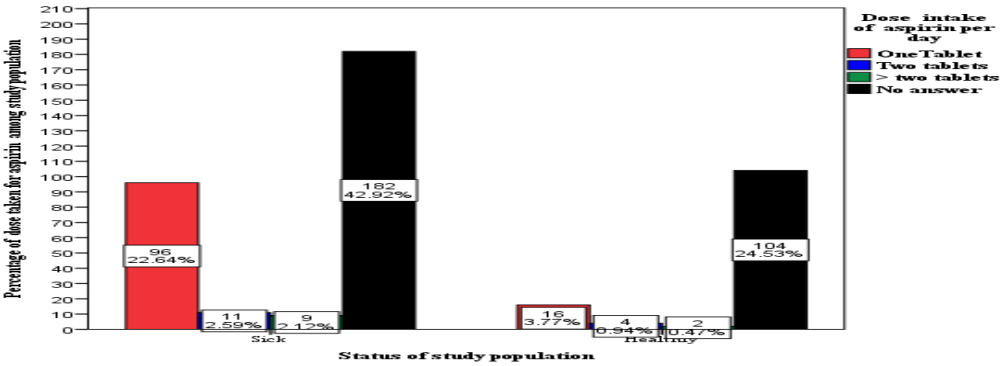

Figure 7: Intake of aspirin doses per day by sick persons with ESRD and healthy persons

Values were expressed as frequency percentages P < 0.001 * highly significant difference from healthy**

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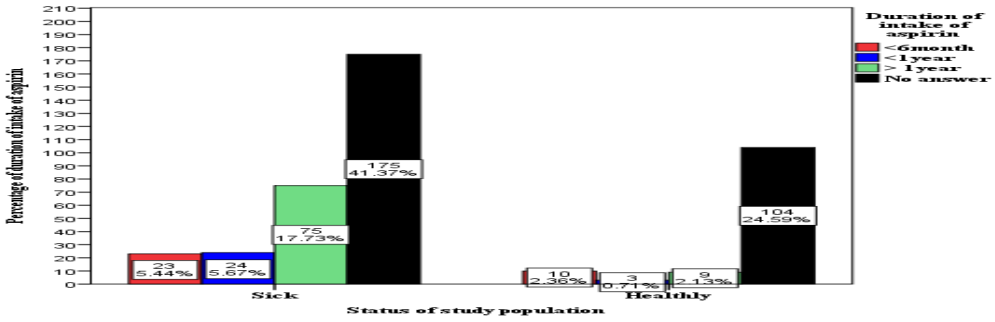

Figure 8: Intake of aspirin doses duration by sick persons with ESRD and healthy persons

Values were expressed as frequency percentages P < 0.001 * highly significant difference from healthy**

4.4. Effect of other NSAIDs

Also for NSAIDs users we *found that 34.43% of sick persons used other NSAIDs* , 20.28% was take them continuously and 14.39% was take them at needed and 35.61% not answered in a dose of one tablet was 20.99%, 2 tablets was 8.02%, for more than two tablets was 4.25% and 37.03% not answered in a duration of less than sixth months was 9.67%, for less than one year was 3.5% and for more than one year 20.75% and 36.32% not answered as shown in figures 9,10(P < 0.05) and 11 (P < 0.01). For healthy person 4.95% used it continuously, 8.73% when need and 16.04% not answered in a dose of one tablet was 5.42% ,2tablet was 4.25% and more than 2 tablet was 1.89% and 18.16% not answered, in a duration of less than 6month was 6.84% , less than one year was 0.71% and more than one year was 4.48% and 17.69% not answered as shown in figures 9,10(P < 0.05) and 11 (P < 0.01).

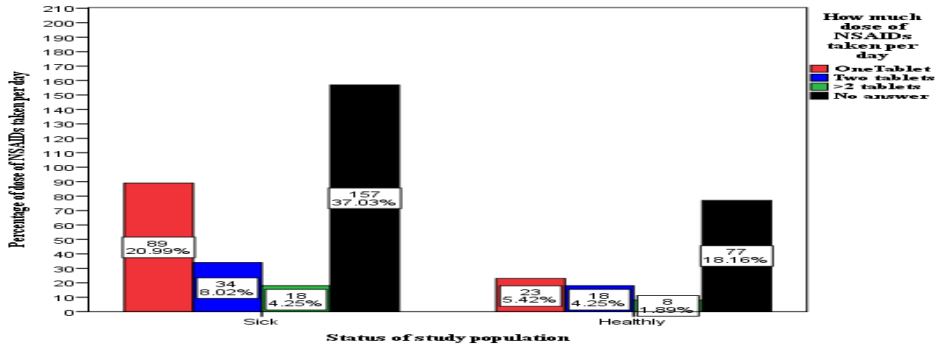

Figure 9: Intake of other NSAIDS when needed or continuous by sick persons with ESRD and healthy **persons.Values were expressed as frequency percentages P < 0.05* significant difference from healthy**

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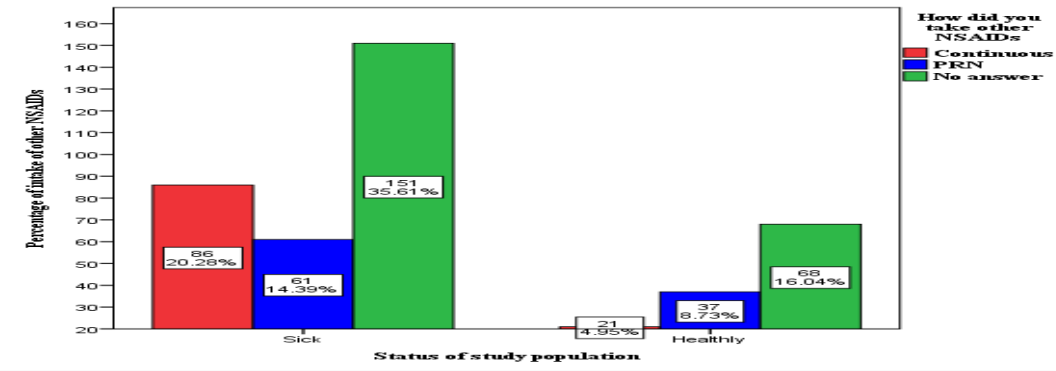

Figure 10: Intake of other NSAIDS doses per day by sick persons with ESRD and healthy persons

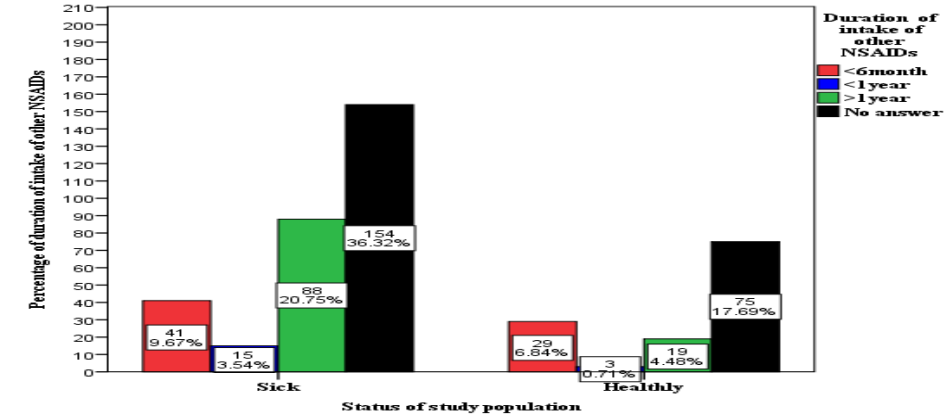

Figure 11: Intake of other NSAIDS doses duration by sick persons with ESRD and healthy persons

Values were expressed as frequency percentages P < 0.01 significant difference from healthy**

5. Discussion

Nephrotoxicity has been observed for all of the NSAIDS and may be due, in part, to interference with the autoregulation of renal blood flow, which is modulated by prostaglandins.

At the therapeutic doses, acetaminophen is considered a safe drug. However, it can cause hepatic necrosis, nephrotoxicity, extrahepatic lesions, and even death in humans and experimental animals when taken in overdose [8, 9].

The results in this study revealed that aspirin, acetaminophen and other NSAIDs caused renal failure when used regularly in some patients and this confirmed by the previous findings of [10] who studies 716 patient treated for ESRD and stated that heavier doses of acetaminophen use associated with an increased risk of ESRD in a dose dependent fashion.

Although paracetamol has apparent COX-2 inhibitory activity [11], it is widely regarded as being safe in patients with risk factors for renal impairment in contrast to patients taking NSAIDs. Experimental proof of this concept is scanty but NSAIDs decreased GFR to a greater extent than placebo or paracetamol in a trial involving stressed kidneys [low sodium diet, dehydration and exercise] [12], and immediately after surgery in elderly patients [13]. The renal safety of paracetamol is also indicated by two studies finding no increase in the risk of hospitalization for heart failure [14] and no worsening of renal function in patients with grades 4–5 kidney disease [15].

Both are conditions in which NSAIDs are expected to worsen renal function. Conversely, in an epidemiological study, [16] reported that paracetamol exacerbated the development of chronic renal failure, although bias could not be excluded in this population study. However all NSAIDs may not have the same renal effect .Similarly, ibuprofen depressed renal function to a greater extent than paracetamol during surgery on sodium-depleted, anaes thetised dogs [17].

Peripheral oedema was also less common in a clinical trial comparing paracetamol and naproxen [18].

Both classes of NSAIDs have been associated with increase in blood pressure [19], more so in patients treated for hypertension than normotensive individuals [20].

6. Conclusion

On the light of the present study we found that 52.59% of sick persons used paracetamol , 34.43% of sick persons used other NSAIDs and 28.77% of sick persons used aspirin. 16.51%of sick person confirmed that they had renal failure due to drugs and 14.39 % of healthy person confirmed that drugs caused renal failure ,using SPSS analysis. People who often taken acetaminophen were associated with an increased risk of ESRD more than those often take aspirin or other NSAIDs **.**

So there is strong association between renal failure, paracetamol, NSAIDs and aspirin. So our result is concur with the Previous research suggest that NSAIDs cause renal damage in persons with renal insufficiency by lowering GFR through an anti-prostaglandins effects.

7. Constraints and limitations

The collection of large numbers of patients with ESRD of the study participant from different areas is difficult and require long time and the time of session of dialysis for most patients at night. Also some patients don't respond easily.

8. Recommendations

Further study needed with large numbers of patients for more nephrotoxic drugs from NSAIDs to confirm the risk of kidney failure and to be more specific because not all NSAIDs have the same renal effect.

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