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Effect of Niacin in the Prevention of Acute Kidney Injury after Cardiac Surgery by Measuring Urine QPRT and Albumin/Creatinine Ratio

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Abstract

Background—Acute kidney injury is a risk factor for mortality in cardiac surgery patients. Nicotinamide adenine dinucleotide (NAD+) is a cofactor for numerous enzymes involved in cellular energy metabolism, and for adaptive responses of cells to bioenergetics and oxidative stress and is now a major player in aging and age-related diseases. Urine Albumin/Creatinine/Ratio have an important role in the early diagnosis of renal injury post-cardiac surgery, urinary QPRT may have a role in detecting niacin deficiency

Method:

Using cohort - study design based on 90 subjects all patients subjected to open-heart surgery, were divided into two groups according to the dosing of niacin (vitamin B3) we measured Urine QPRT and Albumin/Creatinine/Ratio at baseline, before surgery, 1 day after surgery, one week after surgery.

Results:

Urine Albumin/Creatinine/Ratio significantly elevated ($p \leq 0.05$) in the control group (subjects who didn´t receive vitamin B3 supplement from baseline while those who receive vitamin B3 supplement show stable Urine QPRT and Albumin/Creatinine/Ratio level.

Conclusion:

vitamin B3 (niacin) has a beneficial role in renal protection after cardiac surgery.

Introduction :

Niacin was first discovered in 1873 by Hugo Weidel chemist and isolated by Casimiro Funk, but believed to have been thiamine, and was found to be the third water-soluble vitamin that has become known as vitamin B3(1).

NAD+ has an essential role as a cofactor for many metabolic pathways such as glycolysis, b-oxidation fatty acids, and a tricarboxylic acid cycle. In anaerobic glycolysis and mitochondrial-oxidant phosphorylation (OXPHOS), a reduced NAD+ form is a primary contributor to hydrides for ATP production diseases (2).

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Nicotinic acid, nicotinamide, riboside, and tryptophan are the synthetic components of NAD+ in the diet(3).Two enzymatic reactions produce NAD+ from nicotinamide and nicotinamide riboside, while the Preiss-Handler pathway produces NAD+ from nicotinic acid and consists of three steps. The longest NAD+ biosynthesis pathway is the kynurenine pathway, in which tryptophan is catabolized by kynurenine to produce quinolinic acid, which is then converted to nicotinic acid mononucleotide, an intermediate in NAD+ metabolism. The Preiss-Handler pathway then produces NAD+ from nicotinic acid mononucleotide(Figure 1) (3).

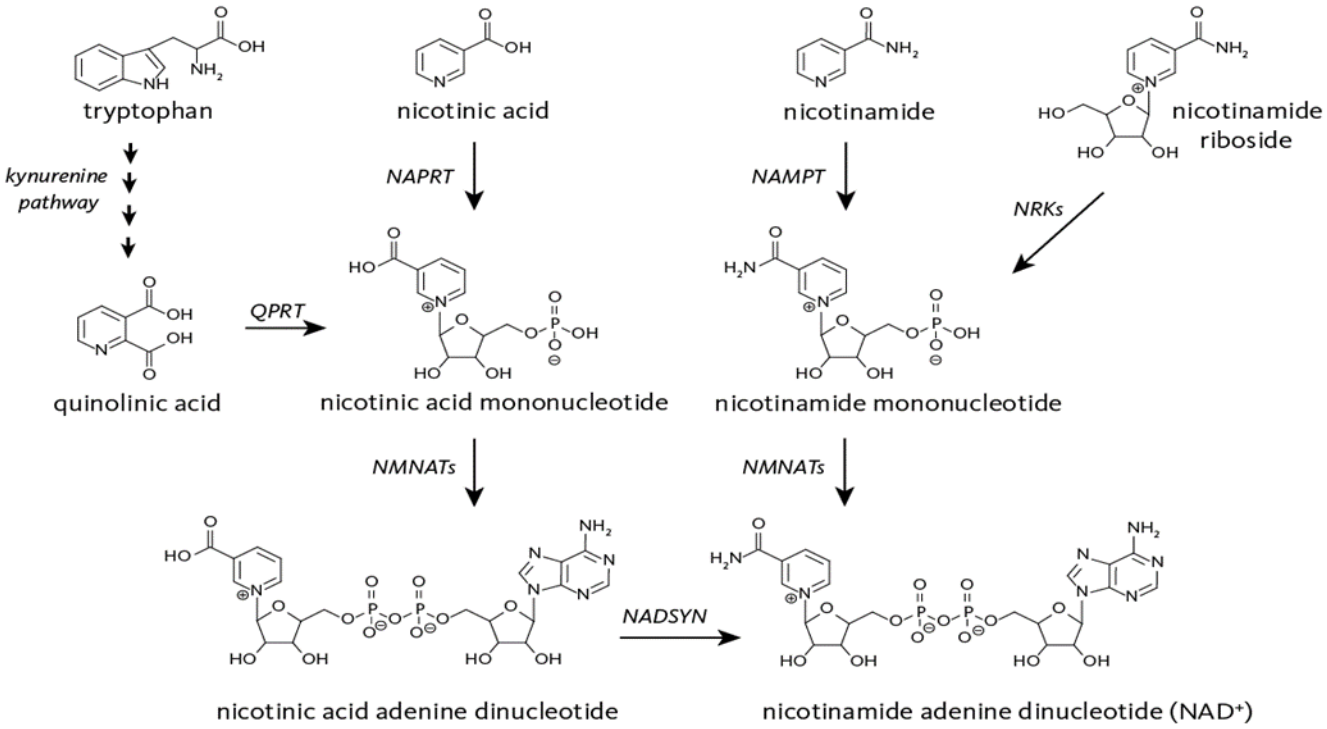

Figure (1) synthesis of Nicotinamide Adenine Dinucleotide (NAD+)

Niacin acts as a coenzyme in electron-transfer reactions, niacin coenzymes, NAD, and NADP, are required by over 400 enzymes, primarily to accept or donate electrons for redox reactions (4) like the isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and malate dehydrogenase complexes(5).NAD and NADP appear to support distinct functions.

Quinolinatephosphoribosyltransferase (QPRT) is a key enzyme in de novo nicotinamide adenine dinucleotide (NAD+) synthesis from tryptophan. Via the salvage and de novo pathways, in which QPRT plays a key role, cells become dependent on NAD+ synthesis. QPRT has been shown to improve glioma brain cancer cells' resistance to radiation and oxidative stress by initiating an NAD+ salvage pathway (6).

In all prokaryotes and eukaryotes, (QPRT) is a member of the phosphoribosyl transferase (PRT) family and is active in de novo NAD biosynthesis using quinolinic acid (QA) as a precursor (7).

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Acute kidney injury (AKI) is one of the most frequent major complications of cardiac surgery, with increased risk of morbidity and mortality(8)(9)Cardiovascular death is 10–20 times more common in patients with renal impairment, and CVD is responsible for more than 40% of deaths of patients with end-stage renal disease (10)Even a slightly to severely reduced renal function increases the risk of CVD mortality and morbidity (11).

Injury of renal tubular epithelial cells is a universal feature of acute kidney injury, including the fact that the cause is unknown. Despite several clinical trials using a variety of treatments, finding a safe way to avoid acute kidney failure remains a challenge (12)

Subjects and Methods:Study design:

This cohort-design study was conducted during the period from September 2019 to November 2020, the subjects were selected from Ibn Al-Bitar center for cardiac surgery in Baghdad –Iraq. The study is based on 90 subjects; 48 Male and 42 females; with age range (30-60 years) all subjects had cardiac problems and were subjected to open-heart surgery, they were divided into two groups according to the dosing of niacin (Vit B3).

These 90 patients dived into two groups: first group 45 subject dosing with niacin (50 mg).

The dosage schedule was based on giving the patient niacin aweek before the operation and one week after it,at a rate of one tablet (50 mg/day). While the rest 45 patient were considered as the control group (without any niacin dosage) 110 patients were collected but the study relied on 90 patients only to match the number that fits the number specified by ELISA kits(96) and some of the patients refuse to continue dosing of niacin. The daily dose of niacin (500 mg) started as it is the dose available in Iraq but this dose caused the emergence of side effects for the patients such as redness and itching, so it was reduced to the amount (50 mg/day) which was important by the researcher and was better tolerated.

This last dose was approved after it was also tested by the researcher, supervisor, and the researcher´s relative for a week, and to make sure that no side effects appeared when it has been given to study´s subjects, they were carefully followed for the side effects.

Serum: vitaminB3 and urine: QPRT, Albumin/Creatinine Ratio was measured for all subjects in the basal level, one day before surgery, one day after surgery and after 7 days after surgery. (4 times of same measurements for all subjects, start dosing patients with vitamin B daily for 7 days before the date of the operation).

Statistical analysis:

Variables were expressed as mean ± SE, students t-test was employed to compare the mean of normally distributed studied variables between two groups, parson´s correlation (r). was used to determine if the studied parameter were related to changes in other study's parameters in the same group.

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The significant level which was dependenton differences and correlations is ≤0.05, more than it was considered as depended (not-significant).

A receiver operating characteristic curve (ROC) curve is frequently used to show in a graphical way the connection trades between clinical sensitivity and specificity for every possible cut-off for a test or a combination of tests (SPSS, version 26 was used)

Results

The successful matching of groups in terms of matching their general status by mating (non-significant difference with p>0.05) subject´s age, sex, Serum: Vitamin B3, and Urine QPRT, albumin /creatinine Ratio.

Table (1): Mean ± SE of age, sex, Serum: Vitamin B3, and Urine QPRT, albumin /creatinine Ration of patients with a cardiac problem who subjected to open cardiac surgery for both groups whom will dosing (basal level) with vitamin B3 and not.

Parameter	Patient with cardiac problem subjected to open cardiac surgery will not be treated with Vit B3 No.45 **Mean ± SE**	Patient with cardiac problem subjected to open cardiac surgery will be treated with Vit B3 No.45 **Mean ± SE**	**t.test Sig**
Age (30-60) years	51.06 ± 1.64	52.82 ± 1.27	P > 0.05 N.S
Sex	1.45 ± 0.5	1.36 ± 0.49	P > 0.05 N.S
S.vit B3 (ng/ml)	14.70 ± 1.34	16.26 ± 1.33	P > 0.05 N.S
Urine .QPRT (ng/ml)	1.13 ± 0.17	1.25 ± 0.13	P > 0.05 N.S
urine Albumin /Creatinine Ratio (mg/mmol)	19.21 ± 0.7	20.57 ± 0.6	P > 0.05 N.S

Start dosing patients with vitamin B3 (50 mg/day) for the first group for 7 days before the date of operation, and all parameters were followed for 7 days in the two groups and it was measurement a second time before the day of the operation.

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A significant difference was found in the level of serum vitamin B3 which showed significant elevation in group dosing with vitamin B3, as it was expected due to dosing (24.02 ±1.06 vs 14.70 ± 1.34 ng/ml) as shownin table (2)

Table (2): Mean ±SE of Serum: Vitamin B3, and Urine QPRT, albumin /creatinine ratio of patients with a cardiac problem who subjected to open cardiac surgery for both groups will dosing (1 day before operation) with vitB3 and not.

Parameter	Patients with a cardiac problem who was not dosing with vitamin B3 after 7 days No.45 **Mean ± SE**	Patients with a cardiac problem who dosing with vitamin B3(50mg) after 7 days No.45 **Mean ± SE**	**t.test Sig**
S.Vit B3 (ng/ml)	14.70 ± 1.34	24.02 ± 1.06	P≤0.05 S
Urine .QPRT (ng/ml)	1.14 ± 0.12	1.11 ± 0.11	P > 0.05 N.S
urine Albumin /Creatinine Ratio (mg/mmol)	19.23 ± 0.61	16.51 ± 0.65	P > 0.05 N.S

S = Significnt (P≤0.05) , N.S = Non significnt (P>0.05)

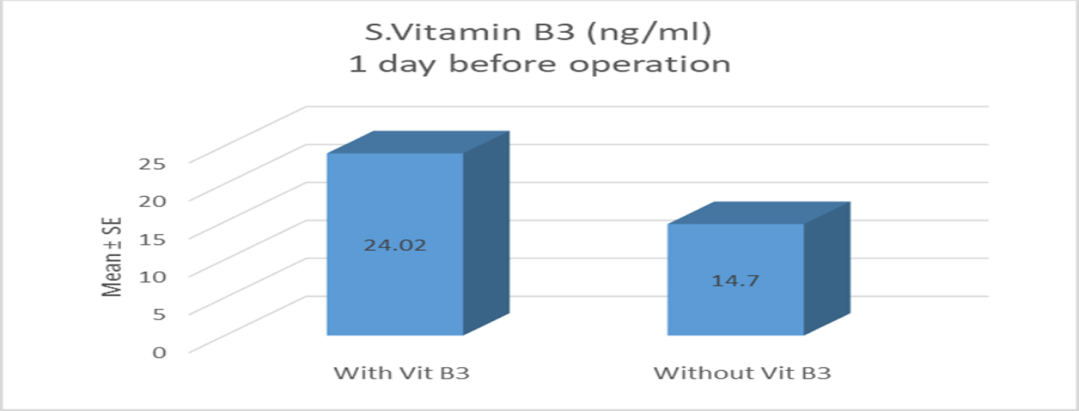

Figure (2): Mean difference between Patients with cardiac problem whom dosing with vitamin B3(50mg) after 7 days & Patients with a cardiac problem who was not dosing with vitamin B3 after 7 days according to vitamin B3(P ≤ 0.05).

To follow up the kidney status of the patients, all measurement was made again one day after operation .it was found that patient whom dosing with (50 mg/day) of vitamin B3 had a significant urine albumin/creatinine ratio (19.75 ± 0.6 vs 20.42 ± 1.24 mg/mmol) consequently when compared with a control group, while the urinary QPRT showed a non-significant difference, with p>0.05.

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Table (3): Mean ±SE of age, Serum: Vitamin B3, and Urine QPRT, albumin /creatinine Ration of patients with a cardiac problem who subjected to open cardiac surgery for both groups whom dosing (after 1 day of surgery) with vitamin B3 and not.

Parameter	The patient underwent open cardiac surgery whom dosing for 7 days with vitamin B3 after 1 day No.45 **Mean ± SE**	Patients underwent open cardiac surgery without any dosing of vitamin B3 after 1-day No.45 **Mean ± SE**	**t.test Sig**
S.VIT B3 (ng/ml)	20.26 ± 1.33	13.17 ± 0.85	p≤0.05 S
Urine .QPRT (ng/ml)	1.96 ± 0.3	3.19± 1.3	p>0.05 N.S
urine Albumin /Creatinine Ratio (mg/mmol)	19.75± 0.6	20.42± 1.24	p≤0.05 S

S = Significant (P≤0.05), N.S = Non significant (P>0.05)

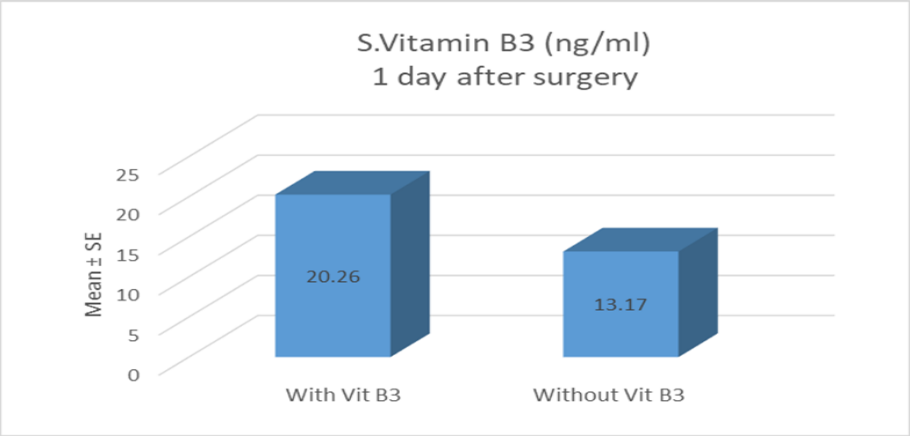

Figure (3) Mean difference between Patient who underwent open cardiac surgery whom dosing for 7 days with Vit B3 after 1 day & Patients with underwent open cardiac surgery without any dosing of Vit B3 after 1-day according to Vitamin B3 (P≤0.05).

To follow up on the occurrence of acute kidney injury in those patients, and to shed light on the role of vitamin B3 dosing in the prevention of renal failure all measurements were repeated after 7 days of the surgery while continuing to give the same dose of vitamin B3 (50 mg/day) for 7 days. It was found that patients who underwent open cardiac surgery whom dosing for 7 days with vitamin B3 had a significant (with p≤0.05) and significant decrease in urine

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albumin/creatinine ratio when compared with patients when underwent open cardiac surgery without any dosing of vitamin B3. (27.47 ± 0.8 vs 13.23 ±1.02 ng/ml), and (18.87 ± 0.63 vs 26.39 ± 1.7 mg/mmol) consequently.

While urine QPRT showed no significant differences between the studied groups (1.91 ± 0.34 vs 2.61 ± 0.35 ng/ml) consequently Table (4)

Table (4): Mean ±SE of age, Serum: Vitamin B3 and Urine QPRT, albumin /creatinine Ration of patients with a cardiac problem who subjected to open cardiac surgery for both groups whom will dosing (after 7 days of surgery) with vitB3 and not.

Parameter	The patient underwent open cardiac surgery whom dosing for 7 days with vitamin B3 after 7 days of dosing No.45 **Mean ± SE**	Patients underwent open cardiac surgery without any dosing vitamin B3 after 7 days No.45 **Mean ± SE**	**t.test Sig**
S.VIT B3 (ng/ml)	27.47 ± 0.8	13.23 ± 1.02	p≤0.05 S
Urine .QPRT (ng/ml)	1.91 ± 0.34	2.61 ± 0.35	p>0.05 N.S
urine Albumin /Creatinine Ratio (mg/mmol)	18.87 ± 0.63	26.39 ± 1.7	p≤0.05 S

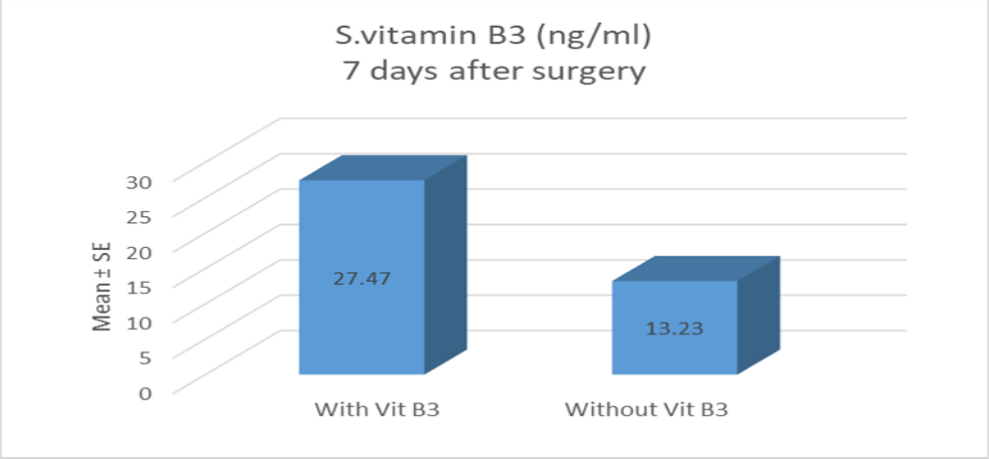

Figure (4) Mean difference between Patient who underwent open cardiac surgery whom dosing for 7 days with vitamin B3 after 7 days & Patients with underwent open cardiac surgery without any dosing of vitamin B3 after 7 according to vitamin B3 (P≤0.05).

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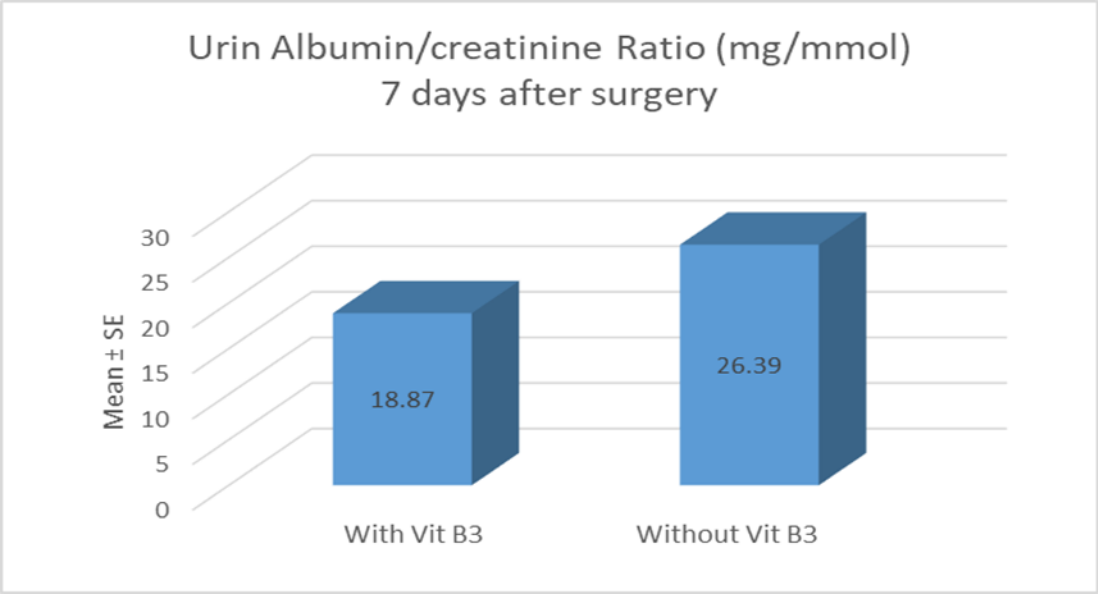

Figure (5) Mean difference between Patient who underwent open cardiac surgery whom dosing for 7 days with vitamin B3 after 7 days & Patients with underwent open cardiac surgery without any dosing of vitamin B3 of after 7 according to Albumin/Creatinine Ratio (P≤0.05).

Serum Vitamin B3 showsa significant negative correlation with urine QPRT (r= -0.308, p≤0.05), as shown in figure (6), It was found that Serum vitamin B3 had no-significant correlation (p>0.05) with Albumin/Creatinine Ratio (r= 0.054 p> 0.05).

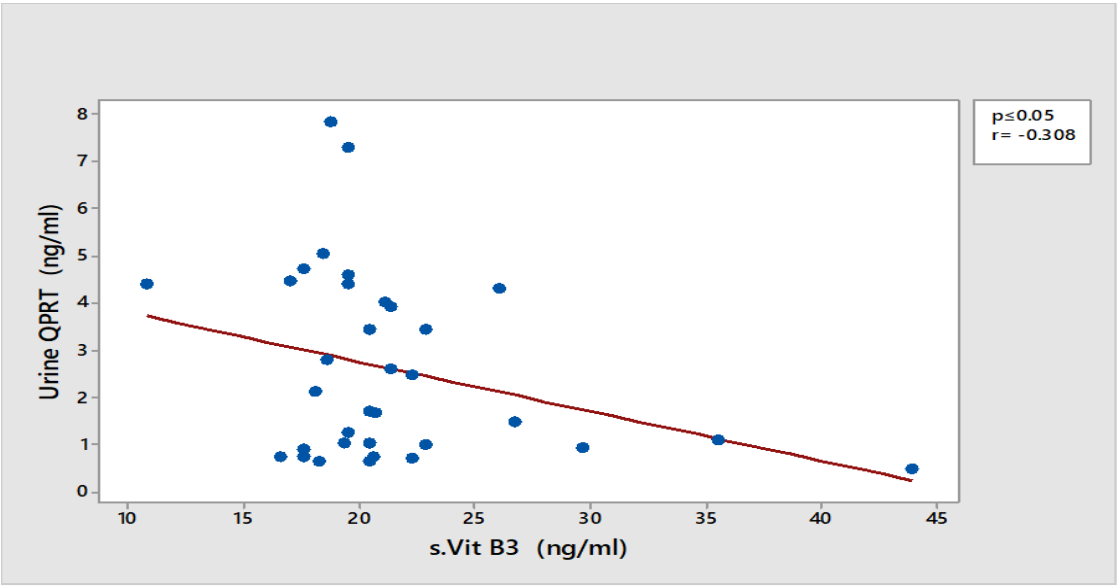

Figure (6): Person's correlation (r) between serum vitamin B3 and Urine QPRT.

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Receiver operating characteristic which is frequently used to show graphically the connection /trade-off between clinical sensitivity and specificity for every possible cut – off for a test or a combination,In addition, the area under the ROC curve givesan idea about the benefit of using the test in diagnosis, As is evident urine albumin/creatinine ratio it is still the most useful diagnostic tool of early renal failure that it has a sensitivity (87.9 %) which is more than the sensitivity of urine QPRT (48.48%). while urine QPRT showed the most specific tool in the diagnosis of early renal failure (78.79%) which is more than urine albumin/creatinine ratio (63.6%).

Table(5): Sensitivity and specificity, an area under and cut-off point of studied kidney markers (Urine albumin/creatinine ratio and QPRT).

Parameter	sensitivity	Specificity	AUC	Cut-off
Urine.Alb/Cre.Ratio	87.9	63.6	80	≤ 23
Urine QPRT	48.48	78.79	61	>2.098

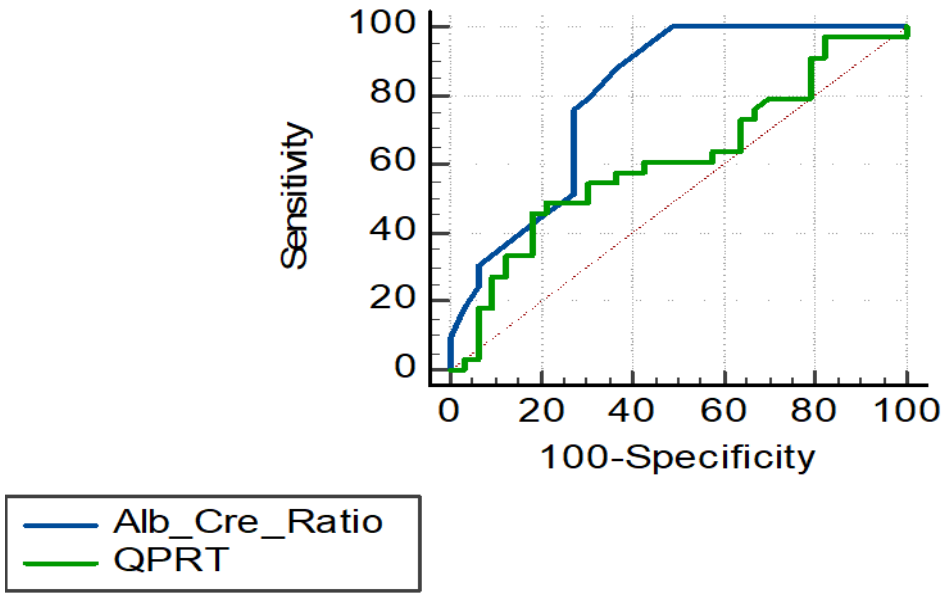

Figure (7): ROC curve of sensitivity and specificity, the area under and cut-off point of (urine albumin/creatinine ratio and QPRT)

Discussion:

In the table (3-1), the subject's age and sex-matched that acute kidney injury (AKI) was affected by age and sex, that subjects more than 65 years old are at high risk of developing AKI

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(Davidsons edition 23, 2018).Many research (13) reported that women have a slower decline in renal function,and for that causes the present study matched subject's ages and no of sex.

In table (3-2) serum vitamin B3 level showed to be significantly increased ($p \leq 0.05$) in subjects who received vitamin B3 supplements for one week before cardiac surgery and this result is considered to be normally occurring after dosing.

Vitamin B3 (niacin) has an important role in maintaining normal renal functionthrough different mechanism including energy production by mitochondria whichpresent in the heart and kidneys in the highest numbers and they are among thegreatest oxygen consumers of all organs in the body(14). Energy production ismaintained in these organs through the oxidative metabolism of a range of fuels,substrate metabolism is strongly tied to the pyridine dinucleotide, nicotinamideadenine dinucleotide (NAD+), this essential metabolite serves as a key cofactor inmitochondrial metabolic processes that facilitate energy production(15)and also have several other important cellular functions(16).

It was noticed that after a day of the open cardiac surgery, the patients who were not dosed with vitamin B3 (table 3-3) showed an increase in the level of urine albumin/creatinine ratio which indicates a defect in the function of the kidneys,while QPRT within normal. This may be related that a healthy kidney can greatly increase its work capacity. With two healthy kidneys each kidney performs 50% of the normal kidney function, if one kidney is lost, the other kidney can enlarge and provide up to 75% of the normal kidney function(17).

The increase in urine albumin excretion in Patientswho underwent open cardiac surgery is usually attributed to renal vascular damage however, it is thought to be related to inflammation, increased glomerular permeability in the renal vascular system(18)

In the table (3-4) after 7 days of dosing with the same dose of the vitamin B3, it was observed that a percentage of patients who were not dosed had acute kidney injury through the elevation in the test serum level of urine albumin/creatinine ratio showed to be significantly increased ($p \leq 0.05$).

Recently, the albumin to creatinine ratio (ACR), measured from a random urine sample, was suggested to be an effective surrogate to 24-hr urine collection for detecting microalbuminuria (19). ACR is convenient to perform and is less affected by variation in urine concentration because it is a ratio between two measured substances. Also, serum creatinine has been widely used as a marker of GFR, but it is not sensitive enough to detect decreased renal function. Therefore, various plasma low molecular weight proteins have been suggested as valuable markers of decreased renal function in place of serum creatinine (20).

There is an association between the use of cardiopulmonary bypass and the development of AKI, with combined surgical procedures (valve replacement and coronary artery bypass) and prolonged cardiopulmonary bypass times increasing the incidence of AKI in adults(21). The optimal perfusion pressure and flow rates in humans undergoing cardiopulmonary bypass are not

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known, and both higher perfusion pressure and the use of pulsatile flow have failed to improve postoperative renal function(22).The incidence of AKI after cardiac surgery is as high as 30% (23). AKI is associated with increased hospital length of stay, in-hospital mortality, and risk of development of CKD (30). Even mild postoperative AKI may be associated with worse short and long–term outcomes (24)

Serum Vitamin B3 showsa significant negative correlation with urine QPRT (r= -0.308, $p \leq 0.05$), as shown in figure (6)

QPRT is a key enzyme in the catabolism of quinoline is in between the tryptophan and nicotinamide adenine dinucleotide (NAD+) pathway results in the production of nicotinic acid, QPRT catalyzes the Mg2+-dependent transition of QA from tryptophan and 5 phosphoribosyl-1-pyrophosphate (PRPP), resulting in carbon dioxide, pyrophosphate, and nicotinic acid mononucleotide (NAMN), a precursor of nicotinate adenine dinucleotide (NAD), followed by conversion to NAD. QA is the first step in the de novo synthesis of NAD, which is formed by degrading tryptophan through the kynurenine pathway, a metabolic pathway in the brain (7). The kynurenine pathway (KP) of tryptophan degradation is a major pathway for the de novo biosynthesis of NAD + it metabolizes more than 90% of tryptophan (25) (Figure 8)(26)

In the table (3-5) Through the ROC analysis, the ability of urine albumin/creatinine ratio and QPRT as a test to correctly identify patients with a disease was determined bud the results showed that the test had moderate sensitivity for the diagnosis of early kidney failure, while the ability of the tests to correctly identify people without the disease (specificity) also showed that the test had moderate specificity for the diagnosis of AKI. This can also give another explanation for the lack of relationships with the state of kidney failure or its clarity during this period.

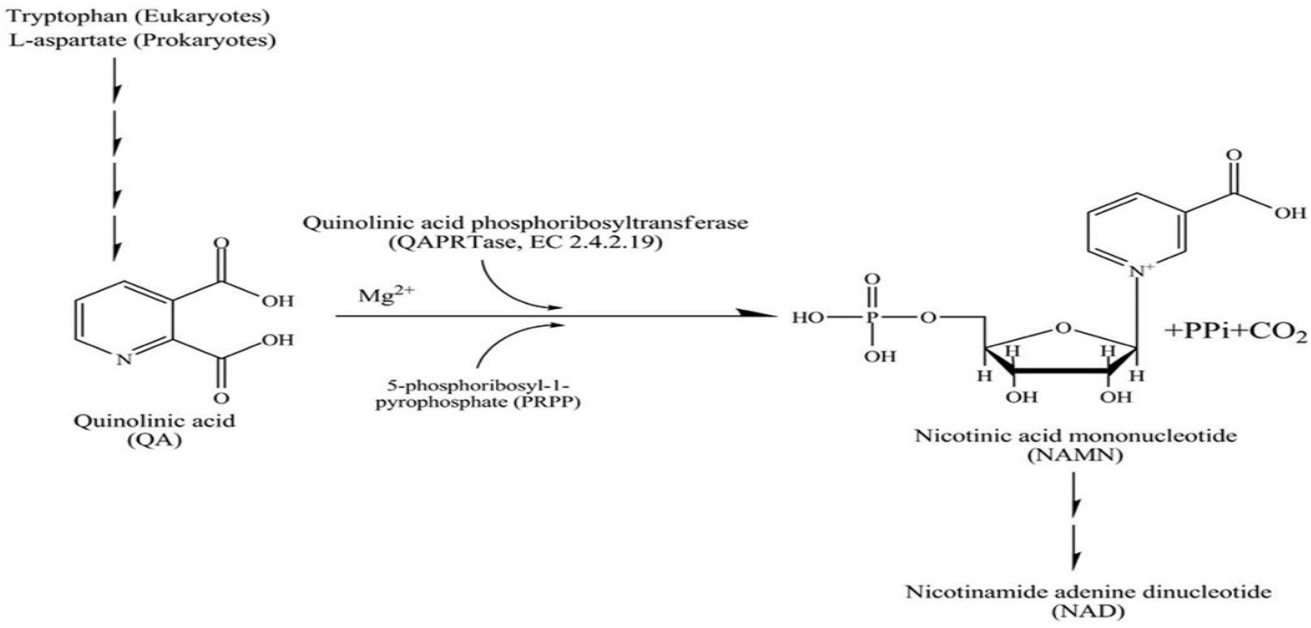

Figure (8) Schematic representation of the reaction catalyzed by QPRTase.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 9901 - 9914
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Conclusion:

vitamin B3 (niacin) shows a significantly beneficial role in renal protection after cardiac surgery by assessing urinary QPRT and Albumin/creatinine ratio level post cardiac surgery.

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