**Myocardial Injury in Metabolic Acidosis of Non- Dialysis Dependent CKD Patients.**

T.S. Rashaad1, S. H. Abdel Aziz1, A. T. Mahmoud1, H.G. Abdel Salam1and E.L. El-Shahawy1.

Internal Medicine and Nephrology, Dept., Faculty of Medicine, Benha Univ., Benha, Egypt 1

E-Mail: ahmed2356@gmail.com

**Abstract:**

Correction of metabolic acidosis (MA) by using oral sodium bicarbonate therapy (OSBT) in non-dialysis dependent chronic kidney disease (CKD) patients with MA has a positive effect on myocardium as it improves the functional parameters and delay worsening of the structural parameters through modification of risk factors as correction of MA leads to increase of eGFR, decrease of uremia, decrease of serum uric acid level, better control of DM, improvement of lipid profile, thyroid profile and malnutrition inflammation complex syndrome (MICS). **Aim of the work:** To assess the association between myocardial injury and MA in non-dialysis dependent CKD patients and the impact of the correction of MA on myocardium. **Patient and Methods**: The study was carried out at nephrology unit, internal medicine department, at Banha University Hospitals on 6 months' duration, where 50 patients were selected. Echocardiography, arterial blood gases, anion gap, e GFR, serum uric acid, lipid profile, urine analysis, troponin I, CK-MB, serum creatinine, HA1C, serum albumin and CRP were measured before and after OSBT. **Results**: Mean blood PH statistically significant increased from 7.26±0.03 to 7.35±0.003 (p value < 0.001). Mean serum HCO3¯ statistically significant increased from 13.65±1.19 to 23.56±0.74 (p value < 0.001). Mean LVESD statistically significant decreased from 3.86±0.47 to 3.78±0.54 cm (p value 0.035). Mean LVESD no statistically significant difference from 5.62±0.43 to 5.63±0.42 (p value 0.76). Mean EF% statistically significant increased from 52 to 57 % (p value < 0.001). **Conclusion:** OSBThas a positive effect on myocardium by improvement of the functional parameters and delay worsening of the structural parameters.

**Keywords:** MA, CKD, OSBT, echocardiography changes. (OSBT) Oral sodium bicarbonate therapy, (CKD) chronic kidney disease, (MA) metabolic acidosis

1. **Introduction**

Abnormalities of kidney structure or function, present for >3 months, with implications for health is defined as chronic kidney disease (CKD) (1)

CKD is one of the most common worldwide diseases and it is increasing in incidence and prevalence***(2).***

The leading cause of morbidity and mortality in CKD patients is cardiovascular disease (CVD), it occurs at the earliest CKD stages without manifest vascular disease. A graded increase in CVD risk occurs with worsening renal function (3).

There is an increase of prevalence of concomitant chronic heart failure (HF), cardiac arrhythmias (most common atrial ﬁbrillation), ischemic heart disease and calciﬁcation of the valves in CKD patients (4).

According report published in 2013 to the U.S. Renal Data System, CKD patients with CVD, HF was estimated in 43% of patients, and 15% had acute myocardial infarction (AMI) (5).

Traditionally MA is defined as a decrease in serum bicarbonate (HCO3-) concentration, often cause a reduction in PH of blood, is a common association of progressive CKD (6).

Observational studies have shown that if the GFR decreases below 25 ml/min/1.73 m2, MA develops. Bu, it occurs earlier in CKD specially, if associated with defects in acid excretion by renal tubules as in collecting duct damage or hyporeninemic hypoaldosteronism (7).

The decrease in serum bicarbonate is almost mild to moderate in degree varying between 12 and 23 mEq/l, pH of the blood >7.2, and variable anion gap. Severe MA is unusual if there is no concomitant increase in production of endogenous net acid or losses of bicarbonate (8).

In CKD patients with moderate and advanced disease, U-shaped is an association between all-cause mortality and serum concentration of HCO3. patient's serum bicarbonate concentration of 26-29 mEq/l had the lowest rate of mortality but, patient's serum HCO3- levels of < 22 mEq/l had the highest rate of mortality. In patients with serum HCO3- levels >29 mEq/l had an increase in mortality (9).

Many adverse effects occur with CKD patients with MA, as altered skeletal metabolism (10), resistance of insulin (11) and fastening of kidney disease progression (12).

Fall of myocardial Na + - k-ATPase action, caused by MA, prompt decrease in myocardial contractility and HF. Also, acidosis has a role in the inﬂammatory response of vascular endothelial cells (13).

An increased rate of atherosclerosis in CKD patients occurs due to chronic inﬂammation. As increases in endothelin and aldosterone levels is associated with acidosis. An increased risk of cardiovascular disease is associated with high aldosterone. MA causes increase in atherosclerosis, inﬂammation and increased aldosterone and endothelin levels that cause change in left ventricular thickness (14).

Administration of oral sodium bicarbonate for Thirty days in CKD patients with mildly eGFR leads to reduce plasma endothelin-1 and aldosterone levels (15).

Theoretically, worsening of vascular calciﬁcation result from alkali therapy, but no study has performed in humans to confirm this side effect (16)

But, chronic administration of sodium bicarbonate may result in side effects, as hypercapnia, hypokalemia, ionized hypocalcemia, a rise in the urinary excretion of sodium, prolongation of the QTc interval and may cause worsening of vascular calcifications n administration (17)

Administration of oral sodium bicarbonate to reach levels of serum bicarbonate in pre-dialysis at 24 mEq/ L, cause decreasing in exacerbation of secondary hyperparathyroidism in CKD patients complaining of high bone turnover, also stimulating bone turnover in patients complaining of low bone formation. Treatment of MA leads to increase parathyroid glands sensitivity to calcium leads to decrease in PTH after year of alkali therapy (18)

 MA treatment improves the insulin signaling and decreases breakdown of muscle (19).

Administration of oral sodium bicarbonate decreased the rate of GFR loss also, decreased the progression to end-stage renal disease (ESRD) needing dialysis (20).

 High diet animal protein, has a large dietary acid load. In contrast to, fruits and vegetables diet rich contains larger quantities of base precursors so, increasing consumption of fruit and vegetable cause raising of serum bicarbonate level (21).

1. **Patient and Methods:**

This prospectively study was carried out at nephrology unit, internal medicine department, at Banha University Hospitals on 6 months' duration, where 50 patients were selected after approval of the local Ethics Committee and obtaining written informed consents.

**Inclusion criteria included** male and female patients**,** age ˃ 18 years, patients who are non- dialysis dependent chronic kidney disease, patients with CKD with MA. **Exclusion criteria included** age < 18 years, patients with chronic kidney disease on hemodialysis and pregnancy

**Methods:**

For each patient was admitted to nephrology unit who is non- dialysis dependent chronic kidney disease patient with metabolic acidosis Patients were received oral sodium bicarbonate 650 mg tablet (twice to three times per day) till HCO**3-**> 22 mEq/L& the following was done:

***1-History****:* Age, Sex, Cardiovascular history.

***2-Clinical examination****:* blood pressure was measured by sphygmomanometer, Measurement was obtained before during and after OSBT, Cardiovascular examination if there was a lower limb edema

***3-Radiological study:*** Echocardiography: It was used in determining cardiac function (ejection fraction, LVESD and LVEDD), cardiac dimensions (LV dimension).

**4-Laboratory assessment:** Before& after OSBT we measured arterial blood gases, serum sodium, serum potassium, serum chloride, anion gap= (Na**+** + K**+**) – (HCO3¯+ Cl¯), e GFR measured using modification diet in renal disease (MDRD) study equation, serum calcium, serum phosphorus, PTH, serum uric acid, lipid profile (total cholesterol, HDL, LDL and triglyceride), urine analysis (specific gravity, PH), 24h urinary albumin, troponin I, CK-MB, blood urea, serum creatinine, serum albumin, CRP.

***5-ECG***

**2.1. Statistical methodology**

**Data management**

The clinical data were recorded on a report form. These data were tabulated and analysed using the computer program SPSS (Statistical package for social science) version 20 to obtain:

**Descriptive data**

Descriptive statistics were calculated for the data in the form of:

1. Mean and standard deviation Median and inter-quartile range (IQR) for quantitative data.
2. Frequency and distribution for qualitative data.

**Analytical statistics**

 In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests: -

1. test: - Used to compare mean of two groups of quantitative data of parametric and non-parametric respectively.
2. Paired t test and willcoxon test: Used to compare mean of variables in different time periods of quantitative data of parametric and non-parametric respectively.
3. Student's *t-*test and Mann-Whitney 3-Inter-group comparison of categorical data was performed by using chi square test (*X2-*value) and fisher exact test (FET).



Correlation coefficient: - Pearson and spearman correlation

1. To find relationships between variables parametric and non-parametric respectively.

A *P* value <0.05 was considered statistically significant while >0.05 statistically insignificant P value <0.01 was considered highly significant in all analyses.

1. **Results**

A total of 50 CKD patients, stage 3B-5 with MA were enrolled in the study including 58% (n=29) females and 42% (n=21) males. The median age was 54±10 years; average estimated glomerular filtration rate (eGFR) using modification diet in renal disease (MDRD) was 25.06±6.05 ml/min/1.73m2 table (1).

The cause of CKD was DM &hypertension 40% (n=20), DM12% (n =6), hypertension 8% (n=4), glomerulonephritis 16% (n=8), APKD 12% (n=6) & recurrent stone former 12% (n=6) were included into final analysis table (2).

blood PH and serum HCO3¯ levels were statistically significant increased&anion gapwas statistically significant decreased after OSBT as p value was (< 0.001, < 0.001 and < 0.001 respectively) table (3).

eGFR was statistically significant increased & serum creatinine &blood urea was statistically significant decreased after OSBTas p value was (< 0.001, < 0.001 and < 0.001 respectively) table (3).

Serum sodium was statistically significant increased & serum potassium &serum chloride was statistically significant decreased after OSBT as p value was (< 0.001, < 0.001 and < 0.001 respectively) table (4).

Serum albumin was statistically significant increased & serumCRP wasstatistically significant decreased after OSBTas p value was (< 0.001 and < 0.001 respectively) table (4).

High sensitive troponin I &CK-MB levels were statistically significant decreased after OSBTas p value was (< 0.001 and < 0.001 respectively) table (4).

***□*** Serum Ca, serum P, PTH& serum uric acid levels were statistically significant decreased after OSBTas p value was (< 0.001, 0.006, < 0.001 and < 0.001 respectively) table (5).

Triglyceride, total cholesterol, HDL-C &LDL-C were statistically significant decreased after OSBTas p value was (< 0.001, < 0.001, 0.001 and < 0.001 respectively) table (5).

Thyroid dysfunction was considered if patient's thyroid hormones fall outside the reference range; free T3 (3.0– 6.8 pmol/L), free T4 (10.0–25.0 pmol/L) and TSH (0.25– 5 mIU/L). Euthyroid was considered if thyroid hormone levels fall within reference range. Overt hypothyroidism was defined as TSH > 5 mIU/L and free T3 < 3.0 pmol/L and free T4 < 10.0 pmol/L. Subclinical hypothyroidism was considered if TSH > 5 mIU/L and free T3 and free T4 within reference range. Subclinical hyperthyroidism was defined as TSH < 0.25 mIU/L and free T3 and freeT4 within reference range. Sick euothyroid syndrome was considered if free T3 < 3.0 pmol/L and free T4 within reference range or < 10.0 pmol/L and TSH < 0.25 mIU/L or within reference range.

Thyroid dysfunction was found in 64% (n=32), the most common thyroid dysfunction is being subclinical hypothyroidism in 30% (n=15) followed by sick euothyroid syndrome in 16% (n=8), followed by overt hypothyroidism in 14% (n=7), followed by subclinical hyperthyroidism in 4%(n=2).

After alkali therapy, total patients that had achieved complete improvement were 56% (n=18). Total patients that had achieved partial improvement were 34.5% (n=11). Total patients that had achieved no improvement were 9.4% (n=3) table (6).

FT3&FT4 levels were statistically significant increased & serum TSH was statistically significant decreased after OSBTas p value was (< 0.001, < 0.001 and < 0.002 respectively) table (7).

24h urinary albumin was statistically significant decreased after OSBTas p value < 0.001 table (7).

Specific gravity of urine was statistically significant increased &PH of urine was statistically significant decreased after OSBTas p value was (< 0.001and < 0.001 respectively) table (7).

There was no statistically significant difference in QT-C (ms), ST segment depression & t wave inversion before and after OSBT as p value was (0.052and 1.0 respectively) table (7).

There was no statistically significant difference in LA, IVS and PW between the studied group before and after OSBT as p value was (0.63, 0.83 and 0.35 respectively) table (8).

EF% was statistically significant increased &LVESD was statistically significant decreased after OSBTas p value was (< 0.001 and 0.035 respectively) & there was no significant difference in LVEDD between the before and after OSBT as p value was 0.76table (8).

**Table (1):** The mean of the age and eGFR and sex in the studied group

|  |  |
| --- | --- |
|  | **The studied group (50)** |
| **Age /year**  mean ±SD (range) | 54.06±10 (32-70) |
| **Sex** no (%)MaleFemale  | 21 (42.0)29 (58.0) |
| **eGFR**ml/min/1.73m2 mean ±SD (range) | 25.06±6.05 |

**Table (2):** CKD causes in the studied group

|  |  |
| --- | --- |
|  | **N (%)** |
| **CKD Causes**APKD DM HTN DM&HTN GN Recurrent stone former  | 6(12.0)6(12.0)4(8.0)20(40.0)8(16.0)6(12.0) |

**Table (3):** Comparison between pre-treatment and post-treatment in the treatment group according to PH, HCO3¯, anion gap anion gap, e GFR, serum creatinine and blood urea

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Pre-treatment** | **Post-treatment** | **P value** |
| PH  | Mean ± SD | 7.26±0.03 | 7.35±0.003 | <0.001 |
| HCO3(Meq/l) | Mean ± SD | 13.65±1.19 | 23.56±0.74 | <0.001 |
| Anion gap (mmol/l) | Mean ± SD | 19.67±2.02 | 13.25±1.10 | <0.001 |
| e GFR ml/min/1.37 m2 | Mean ± SD | 25.06±6.05 | 26.44±7.65 | <0.001 |
| Serum creatinine (mg/dl) | Mean ± SD | 2.47±0.56 | 2.39±0.65 | <0.001 |
| Blood urea(mg/dl) | Mean ± SD | 127.14±19.02 | 122.72±20.98 | <0.001 |

**Table (4):** Comparison between pre-treatment before and post-treatment in the treatment group according to serum Na, serum K and serum Cl, CRP, serum albumin, high sensitive troponin I and CK-MB

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Pre-treatment** | **Post-treatment** | **P value** |
| Serum Na (Meq/l)  | Mean ± SD | 136.46±1.75 | 137.5±1.74 | <0.001 |
| Serum K (Meq/l) | Mean ± SD | 4.59±0.35 | 4.33±0.38 | <0.001 |
| Serum Cl (Meq/l) | Mean ± SD | 108.11±1.94 | 105.1±1.28 | <0.001 |
| CRP (mg/dl) | Mean ± SD | 26.96±7.75 | 19.56±7.94 | <0.001 |
| Serum albumin (g/dl) | Mean ± SD | 3.72±0.19 | 3.86±0.19 | <0.001 |
| High sensitive troponin (ng/l)  | Mean ±SD | 30.33±9.19 | 22.21±10.34 | <0.001 |
| CK-MB (ng/ml) | Mean ± SD | 21.27±9.85 | 18.3±7.91 | <0.001 |

**Table (5):** Comparison between pre-treatment and post-treatment in the treatment group according to serum total Ca, serum P, PTH, serum uric acid FBG, 2HPP, HA1c, TG, total cholesterol, HDL-C and LDL-C

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **pre-treatment** | **post-treatment** | **P value** |
| Serum total Ca (mg/dl) | Mean ± SD | 8.34±0.41 | 8.46±0.38 | <0.001 |
| Serum P(mg/dl) | Mean ± SD | 4.53±0.46 | 4.46±0.43 | 0.006 |
| PTH (pg/dl) | Mean ± SD | 457.98±176.6 | 436.98±175.78 | <0.001 |
| Serum uric acid (mg/dl)  | Mean ± SD | 8.9±0.57 | 8.16±0.49 | <0.001 |
| TG (mg/dl) | Mean ± SD | 198.68±24.16 | 189.68±28 | <0.001 |
| Total cholesterol (mg/dl) | Mean ± SD | 247.58±17.4 | 237.4±20 | <0.001 |
| HDL-C(mg/dl) | Mean ± SD | 41.82±2.14 | 43.52±2.32 | <0.001 |
| LDL-C (mg/dl) |  Mean ± SD | 170.1±12.27 | 162.76±11.36 | <0.001 |

**Table (6):** Thyroid profile in the studied group

|  |  |
| --- | --- |
|  | **n (%)** |
| Thyroid profile Euthyroid Subclinical hypothyroidism Sick euthyroid Overt hypothyroidism Subclinical hyperthyroidism  | 18(36.0)15(30.0)8(16.0)7(14.0)2(4.0) |
| Improvement\* No improvement Complete improvement Partial improvement  | 3(9.4)18(56.2)11(34.3) |

**Table (7):** Comparison between pre-treatment and post-treatment in treatment group according to TSH, FT3, FT4, 24hour urinary albumin, QT-C, ST segment depression & t wave inversion

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **pre-treatment** | **post-treatment** | **P value** |
| TSH(UIU/ml) | Mean ± SD | 5.09±2.78 | 4.59±2.6 | 0.002 |
| FT3(pmol/l) | Mean ± SD | 3.32±0.80 | 3.7±0.73 | <0.001 |
| FT4(pmol/l) | Mean ± SD | 11.95±3.05 | 13.26±2.79 | <0.001 |
| 24h urinary albumin(mg/l) | Mean ± SD | 655.12±558.62 | 565.62±535.09 | <0.001 |
| Specific gravity of urine | Mean ± SD | 1016.88±2.38 | 1020.88±2.37 | <0.001 |
| PH of urine | Mean ± SD | 5.5±0.36 | 6.46±0.26 | <0.001 |
| QT-C | Mean ± SD | 429.22±30.21 | 423.42±32.34 | 0.052 |
| ST segment depression & t wave inversion | 25(50.0) | 25(50.0) | 1.0 |

**Table (8):** Comparison between pre-treatment and post-treatment in the treatment group according to LA, IVS, PW LVESD, LVEDD and EF%

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **pre-treatment** | **post-treatment** | **P value** |
| LA/cm | Mean ± SD | 3.66±0.24 | 3.65±0.26 | 0.63 |
| IVS/cm | Mean ± SD | 1.16±0.12 | 1.16±0.10 | 0.83 |
| PW/cm | Mean ± SD | 1.04±0.13 | 1.05±0.11 | 0.35 |
| LVESD/cm | Mean ± SD | 3.86±0.47 | 3.78±0.54 | 0.035 |
| LVEDD/cm | Mean ± SD | 5.62±0.43 | 5.63±0.42 | 0.76 |
| EF% | Mean ± SD | 52.7±5.7 | 56.02±6.7 | <0.001 |

1. **Discussion**

The leading cause of morbidity and mortality in CKD patients is CVD, it occurs at the earliest CKD stages without manifest vascular disease. A graded increase in CVD risk occurs with worsening renal function (3).

Fall of myocardial Na + - k-ATPase action, caused by MA, prompt decrease in myocardial contractility and HF. Also, acidosis has a role in the inﬂammatory response of vascular endothelial cells (13).

There is an increase of prevalence of concomitant chronic heart failure (HF), cardiac arrhythmias (most common atrial ﬁbrillation), ischemic heart disease and calciﬁcation of the valves in CKD patients (4).

Treatment of CKD patient with calcium supplementation, calcitriol, insulin &uric acid lowering drugs remained unmodified, but antihypertensive drug was increased in 16 patients as there was increase of systolic blood pressure by 15 - 25 mmHg from pretreatment values and 5 – 10 mmHg increase of diastolic blood pressure from pretreatment values while the remaining of patients experienced no dose modification.

Mild lower limb edema appeared at start of treatment in 13 patients and small dose of diuretics needed for 2 weeks, but no longer need for diuretics as lower limb edema subsides in follow up period.

There was statistically significant increase in blood PH, HCO3 and decrease anion gap in treatment group after OSBT and this is concordant with ***Mathur RP et al 2006*** as they concluded that three months of administration of oral bicarbonate therapy with levels of bicarbonate at 22–26 mEq/L result in significant MA correction and increase in pH serum bicarbonate levels and blood. So, correction of MA leads to increase in PH and HCO3 decrease anion gap in treatment group OSBT.

There was statistically significant increase in eGFR and decrease of serum creatinine and blood urea in treatment group after OSBT this is concordant with ***de*** ***Brito-Ashurst et al 2009*** as they concluded that bicarbonate therapy was a significant lower in a decline in creatinine clearance in the treatment group. Wesson et al 2010 concluded that in CKD with MA, endothelin plays a role in renal acidification by the activation receptors of ET-B, also it activates receptors of ET-A that cause tubulointerstitial injury **(Kovesdy CP., 2012).** Wesson et al 2011**,** concluded that aldosterone and endothelin-1 were decreased after 30 days of bicarbonate therapy in CKD stage 2 with macroalbuminuria **(Wesson DE et al., 2011).** So, correction of MA leads to decrease of endothelin-1 and aldosterone that leads to decrease renal injury, increase in eGFR and decrease in serum creatinine and blood in treatment group after OSBT.

There was statistically significant decrease serum potassium and serum chloride in treatment group after OSBT. This is concordant with ***Susantitaphong et al 2012*** as they concluded that sodium bicarbonate therapy can decrease serum chloride and decrease serum potassium. So, correction of MA lead to increase in decrease serum potassium and serum chloride in treatment group after OSBT.

There was statistically significant increase in serum albumin in treatment OSBT and this is concordant with ***de Brito-Ashurst I et al 2009*** who concluded that serum albumin levels increase in the treatment group after 1 year of bicarbonate therapy.

There was statistically significant decrease in high sensitive troponin & CK-MB in treatment group after OSBT.As the MA cause increasing atherosclerosis, inflammation. Elevated levels of aldosterone, endothelin and angiotensin II that may lead to a change in geometry of left ventricular also, related to cardiovascular disease risk increasement **(Dobre M et al., 2016).** CKD with MA causes enhancing of production of catecholamine, aldosterone and endothelin-1; which leads to changes in left ventricular geometry and mass (**Raj S et al., 2013)**. CKD patients with dyslipidemia and thyroid dysfunction has more increase in CVD risk that contributes to morbidity and mortality (**Khatiwada S et al., 2015)**. Atherosclerotic vascular disease, that increase the risk of CVD events, dyslipidemia with lower HDL and higher LDL cholesterol (**Liu Y et al., 2004)**. Proteinuria associated with CKD, increases risk for CVD as MI as it increased risk for atherosclerotic events and increase mortality of cardiovascular **(Agrawal, V., et al., 2009).** Atherosclerosis is mediated by several process. Inflammation one of the important factors**.** CRP is marker of inflammation **(Menon Vet al., 2005).** CKD causes increase in serum uric acid by enhancing tubular ischemia and glomerular damage through cortical vasoconstriction and glomerular hypertension. Also, uric acid induces in vascular cells inflammatory mediators, including monocyte chemoattractant protein and C-reactive protein and vasoconstrictive factors such as thromboxane **(Kang DH et al., 2005)**. Endothelial dysfunction is associated hyperuricemia and endothelial dysfunction improves with lowering uric acid. Also, hyperuricemia is one of independable risk factor for hypertension (**Zoccali C, Maio R et al., 2006).** Wesson et al 2011**,** concluded Administration of oral sodium bicarbonate for Thirty days in CKD patients with mildly eGFR leads to reduce plasma endothelin-1 and aldosterone levels **(Wesson DE et al., 2011).** Ori et al concluded that the benefit of alkali therapy on inflammation as it decreases IL-10 secretion from mononuclear cells after 1 month of NaHCO3 therapy in CKD patients stage 4 - 5 **(Ori Y et al., 2015).** Also, MA correction in CKD patients causes T3 levels to increase towards normal levels **(Wiederkehr et al., 2004).** Also, Rizzetto et al, concluded that in CKD patients stage 2–4, the use of OSBT for MA correction was associated with a decrease minimally oxidized LDL, a serum levels of LDL (–). These result concomitant with good alkali therapy effect to prevent further LDL oxidation, which has important effect in atherogenesis in patients with CKD **(Rizzetto et al., 2017).** In our study there was decrease of LDL-C, serum uric acid, CRP and improvement in thyroid function (increase of FT3 and FT4) so as a consequence there was decrease in endothelial dysfunction, inflammation and atherosclerosis. so, correction of MA leads to modification of all this factors that contribute to decrease of myocardial injury in treatment group after OSBT.

There was statistically significant decrease in TSH & increase of FT3 and FT4 in treatment group after OSBT. As, MA cause lowering of serum free T3 and T4levels **(Kalantar-Zadeh K et al., 2004).** Low basal metabolic rates occur in CKD patients with uremia as MA affect levels of thyroid hormone by reducing thyroxine (T4) and triiodothyronine (T3) and elevated levels of thyroid-stimulating hormone. Also, MA correction in CKD patients leads to rise of T3 levels towards normal **(Wiederkehr et al., 2004).** Type 1 5' deiodinase expression inhibited by TNFα and interleukin-1, the enzyme responsible for T4 to T3 conversion in peripheral tissues. This explains how CKD associated with vascular damage and chronic inflammation that interrupt the normal process of T3 synthesis from T4 **(Carrero et al., 2007).** So, correction of MA leads to decrease of inflammation (decrease CRP) after treatment, so leads to increase of FT3, FT4 and decrease of TSH (due to decrease of the feedback inhibition due to increase of FT3, FT4) in treatment group after OSBT.

There was statistically significant decrease of triglyceride, total cholesterol and LDL-C and increase of HDL-C in treatment group after OSBT and this is not concordant with ***Rizzetto F et al*** ***2017.*** Our explanation is there was increase of FT3 and FT4 in treatment group after OSBT. Lipid metabolism affected by thyroid hormones as it enhances lipid substrates utilization, increases mobilization of triglycerides stored in adipose tissue increases lipoprotein-lipase activity and concentration of non-esterified fatty acid ***(Pucci E et al., 2000)***. So, correction of MA leads to improvement in thyroid function (increase of FT3 and FT4) as a result it causes improvement in lipid profile (decrease of triglyceride, total cholesterol and LDL-C and increase of HDL-C) in treatment group after OSBT.

Thyroid dysfunction was found in 64% (n=32), the most common thyroid dysfunction was subclinical hypothyroidism 30% (n=15) followed by sick euthyroid syndrome 16% (n=8), followed by overt hypothyroidism in 14% (n=7), followed by subclinical hyperthyroidism 4%(n=2).

Our study revealed that patients had achieved complete improvement in treatment group after sodium bicarbonate therapy was 56.2% (n=18) was as subclinical hypothyroidism (n=10), sick euthyroid (n= 8) and patients that had achieved partial improvement was 34.5% (n=11) were as subclinical hypothyroidism (n=5), overt hypothyroidism (n=4) and subclinical hyperthyroidism (n=2) and patients that had achieved no improvement was 9.4% (n=3) was of overt hypothyroidismtable(13).

Our study revealed that there was statistically significant increase of serum calcium in treatment group after OSBT and this is not concordant with ***Mathur RP et al 2006,*** as they concluded that after MA correction of MA in CKD patients, there was no significant change in total calcium and phosphorus. Our explanation is as, in CKD patients with MA, urinary calcium excretion is small quantities, but fecal calcium excretion in faces was equaled or exceeded dietary intake. So, Continuous MA correction by NaHCO3 administration causes reducing excretion of both urinary and fecal calcium and produced a daily calcium balance indistinguishable from zero **(Litzow J et al., 1976).** MA correction by NaHCO3 administration increases 1,25(OH)2D3 in vitamin D deficient CKD patients **(Lu K et al., 1995).** So, correction of MA lead to increase of vitamin D level and reduced both urinary and fecal calcium excretion that led to increase of total serum calcium in treatment group after OSBT.

There was statistically significant decrease of PTH in treatment group after OSBT and this is concordant with ***Mathur RP et al 2006,*** as they concluded that after MA correction in CKD patients it attenuates PTH rise, that may prevent bad long-term complications of secondary hyperparathyroidism. MA treatment increase the parathyroid glands sensitivity to calcium so, PTH decreased in the year after alkali therapy was initiated ***(Graham et al., 1997).*** So, correction of MA lead to increase of total calcium also increase the sensitivity of the parathyroid glands to calcium leading to decrease of PTH in treatment group after OSBT.

There was statistically significant decrease serum phosphorous in treatment group OSBT. As, CKD progress, there is decreased phosphate filtration and excretion causing hyperphosphatemia **(Arora k et al., 2018)**. As in this group after OSBT, there was eGFR increasement that causes increase of phosphorous urinary excretion.

There was statistically significant decrease in serum uric acid level in treatment group after OSBT and this is not concordant with from ***Rizzetto F et al*** ***2017*** as they concluded that after oral NaHCO3 therapy for 1 year to reach serum HCO3¯levels > 22 m M concluded that there was no significant differences changes of serum uric acid compare pretreatment and post-treatment. Our explanation is in this study serum uric acid before treatment was not elevated (6.6±1.0 mg/dl) but in our study serum uric acid before treatment was (8.9±0.6mg/dl).As, several hemodynamics and metabolic derangements can affect uric acid renal excretion acid-base imbalance as MA, variation of effective vascular volume such as renin-angiotensin system alteration, low urinary PH and insulin resistance can influence urate renal clearance **(Bruno CM et al., 2016)**, as in our study oral bicarbonate therapy decrease of urinary PH and increase of eGFR so all these factors increase urinary uric acid excretion.

There was statistically significant decrease in 24-hour urinary albumin in treatment group after OSBT and this is concordant with Mahajan et al., 2010concluded that CKD patients who received NaHCO3 had significantly less decreases of the eGFR, slopes in urine endothelin and urinary markers of tubular injury, and albuminuria stabilization. aldosterone/mineralocorticoid receptor (MR) is a major factor causing CKD progression. Aldosterone/MR stimulates injury of glomerular podocytes, leading to glomerular filtration barrier disruption and proteinuria. Aldosterone/MR causes podocytes injury through endoplasmic reticulum stress and oxidative stress **(Yuan Y et al., 2015).** As, MA in CKD patients causes tubulointerstitial fibrosis through increases in levels of ET-1 to increase acid elimination **(Raphael KL, 2019)** Endothelial dysfunction and inflammation are associated with proteinuria **(Fraser SD et al., 2014)**. So, correction of MA leads to decrease inflammation (decrease of CRP) and aldosterone so leads to decrease podocytes injury and decrease of albuminuria in treatment group after OSBT.

There was statistically significant increase in specific gravity of urine and decrease of PH of urine in treatment group after OSBT. As metabolic derangements and several hemodynamics affects renal excretion of uric acid and acid-base imbalance as in MA, effective vascular volume variation such as alteration of renin-angiotensin system, insulin resistance and low urinary PH can affect renal clearance of urate **(Bruno CM et al., 2016)**, as in our study OSBT leads to increase of eGFR and increase uric acid excretion inurine that lead to increase of specific gravity of urine also oral bicarbonate therapy decrease urinary PH in treatment group after OSBT.

There was no statistically significant difference in QT-C interval between pre-treatment and post-treatment and this is not unconcordant with ***Yenigum et al 2016,*** as they concluded that MA correction improves QT interval. Our explanation is as this study included CKD patients whose had normal ECG, normal transthoracic echocardiography with normal left ventricular ejection fraction with 3 months and electrolytes as calcium, potassium and phosphorus within normal range, but in our study there were abnormalities in ECG as ischemic changes, abnormalities in transthoracic echocardiography as LVH and abnormalities in electrolytes as potassium (hyperkalemia) and phosphorus so, in our study there were no significant differences in QT-C interval between pre-treatment and post-treatment.there was no statistically significant difference in ST segment depression &t wave inversion between pre-treatment and post-treatment.

 There was no statistically significant in left atrial (LA) diameter or in interventricular septum (IVS) diameter or in posterior wall (PW) diameter or left ventricular end diastole diameter (LVEDD) between pre-treatment and post-treatment. there was statistically significant decrease of left ventricular end systole diameter (LVESD) and increase of left ventricular ejection fraction (EF%) in treatment group after OSBT. Chronic Renal Insufficiency Cohort study concluded that lower serum HCO3- in CKD patients was associated with more increased in left ventricular mass, left ventricular hypertrophy, diastolic dysfunctionand left ventricular geometry **(Stancu et al., 2018).** Fall of myocardial Na + - k-ATPase action, caused by MA, prompt decrease in myocardial contractility and HF. Also, acidosis has a role in the inﬂammatory response of vascular endothelial cells **(Kovesdy CP., 2012).** One of the risk factors of mortality in CVD is hyperphosphatemia **(Levin A et al., 2007).** Ori et al concluded that the benefit of alkali treatment on inflammation as it decreases IL-10 secretion from mononuclear cells after 1 month of OSBT in CKD patients stage 4 and 5 **(Ori Y et al., 2015).** Also, Rizzetto et al, concluded that in a group of CKD patients with stage 2–4, the use of OSBT for the MA was associated with decrease in both a minimally oxidized LDL and a serum levels of LDL (–). These findings show the benefit of alkali therapy to prevent LDL oxidation, which has important effect in atherogenesis in CKD patients **(Rizzetto et al., 2017).** MA correction in CKD patients leads T3 levels to rise towards normal **(Wiederkehr et al., 2004).** So, correctionof MAleads to improvement of eGFR and thyroid function and decrease of LDL, decrease serum uric acid, decrease serum phosphorous decrease CRP, decrease albuminuria and decrease cardiac enzymes. So, modification of these risk factors decrease inflammation, atherogenesis, endothelial dysfunction, myocardial injury, increase of myocardial contractility and prevent further LVH.

1. **References**
2. C. Y. Hsu, J. D. Ordonez, G.M. Chertow, Fan. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int,vol. 74,pp. 101–107,2008.
3. J.Coresh, E.Selvin, L. A. Stevens, Manzi. Prevalence of chronic kidney disease in the United States. JAMA,vol. 298,pp.2038–47,2007.
4. E.DiAngelantonio, R.Chowdhury, N.Sarwar, Aspelund. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study BMJ,vol. 341,pp.c4986,2010.
5. S. P. Sedlis, C. T. Jurkovitz, P. M. Hartigan, Goldfarb. Optimal medical therapy with or without percutaneous coronary intervention for patients with stable coronary artery disease and chronic kidney disease. Am J Cardiol,vol. 104,pp.1647–1653,2009.
6. M. A. Onuigbo. The CKD enigma with misleading statistics and myths about CKD, and conflicting ESRD and death rates in the literature: results of a 2008 U.S population-based cross-sectional CKD outcomes Ren Fail analysis, vol.35(3), pp.338–343,2013.
7. J. A.Kraut, I. Kurtz. Metabolic acidosis of CKD: Diagnosis, clinical characteristics, and treatment. Am J Kidney Dis,vol 45(6),pp.978–993,2005.
8. M.Schambelan, A.Sebastian, E.G. Biglieri. Prevalence, pathogenesis, and functional significance of aldosterone defciency in hyperkalemic patients with chronic renal insufficiency Kidney Int,vol. 17(1),pp.89–101,1980.
9. R.M.Hakim, J.M.Lazarus. Biochemical parameters in chronic renal failure. Am J Kidney Dis,vol. 11(3),pp.238–247,1988.
10. C.P. Kovesdy, J.E. Anderson, K.Kalantar-Zadeh. “Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD,” Nephrology Dialysis Transplantation, vol.24 (4), pp.1232–1237,2009.
11. J.A.Kraut. Disturbances of acid–base balance and bone disease in end-stage renal disease. Sem Dial, vol.13(4), pp.261–266,2000.
12. R.H.Mak. Effect of metabolic acidosis on insulin action and secretion in uremia. Kidney international, vol.54(2), pp.603–607,1998.
13. J.L.Bailey, X.Wang, B.K. England. The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. J ClinInvest,vol. 97(6),pp.1447–1453,1996.
14. A.Chen, L.Dong, N.R Lefﬂer, A.S.Asch. Activation of GPR4 by acidosis increases endothelial cell adhesion through the cAMP/ Epac pathway. PLoSONE,vol. 6(11) e27,pp.586,2011.
15. D.E.Wesson, J.Simoni, K. Broglio, S.Sheather. Acid retention accompanies reduced GFR in humans and increase plasma levels of aldosterone and endothelin. Am J Physiol Renal Physiol,vol. 300(4),pp. F830- F837,2011.
16. D.E.Wesson. Does an Acid-Milieu in Chronic Kidney Disease Contribute to Its Increased Cardiovascular Mortality? Am J Nephrol,vol 43(6),pp.408–410,2016.
17. F.J.Mendoza, I.Lopez, Montes, A.Oca, J.Perez, M.Rodriguez, E.Aguilera-Tejrro. Metabolic acidosis inhibits soft tissue calciﬁcation in uremic rats. Kidney Int. 73(4):407-414,2008.
18. S.A.Al-Abri, T.Kearney. “Baking soda misuse as a home remedy: case experience of the California Poison Control System,”JournalofClinicalPharmacyandTherapeutics,vol. 39(1),pp.73–77,2014.
19. K.A.Graham, N.A.Hoenich, M.Tarbit, M.K.Ward,T.H .Goodship. Correction of acidosis in hemodialysis patients increases the sensitivity of the parathyroid glands to calcium. Journal of the American Society of Nephrology: JASN,vol. 8(4),pp.627–631,1997.
20. R.H Mak. Effect of metabolic acidosis on insulin action and secretion in uremia. Kidney international, vol.54(2), pp.603–607,1998.
21. I.DeBrito-Ashurst, M.Varagunam, M.J Raftery, M.M.Yaqoob. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am SocNephrol,vol. 20(9) 2075,pp.2084,2009.
22. N.Goraya, J.Simoni, C.H.Jo, D.E.Wesson. A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. ClinJAmSocNephrol. 8(3):371-381,2013.
23. I.Łoniewski, D.E.WessonBicarbonate therapy for prevention of chronic kidney disease progression. Kidney International,vol. 85(3),pp.529–535. ,2014.
24. K.Kalantar-Zadeh, R.Mehrotra, D.Fouque, J.D.Kopple. Metabolic Acidosis and Malnutrition-Inflammation Complex Syndrome in Chronic Renal Failure Seminars in Dialysis,vol. 17(6),pp.455– 465,2004.
25. M.Dobre, J.Roy, K.Tao, A.H Androsen, N.Bansal, T.Hostetter. Serum bicarbonate and structural and functional cardiac abnormalities in CKD – a report from the CRIC study. Am J Nephrol,vol. 43(6),pp.411–420,2016.
26. A.Bellasi, L.D.iMicco, D.Santoro. Correction of metabolic acidosis improves insulin resistance in chronic kidney disease BMC Nephrology 17(1),158,2016.
27. F.Rizzetto, D.Mafra, A.B.Barra. One-Year Conservative Care Using Sodium Bicarbonate Supplementation Is Associated with a Decrease in Electronegative LDL in Chronic Kidney Disease Patients: A Pilot Study Cardiorenal Med,vol. 7(4),pp.334–341,2017.
28. Z.C.Yenigun, C.Aypak, D.Turgut. effect of MA in QT intervals in patient with chronic kidney disease .int.jartiforgans,vol. 39(6),pp.272-276. ,2016.
29. R.P.Mathur, S.C.Dash, N.Gupta. Effects of Correction of Metabolic Acidosis on Blood Urea and Bone Metabolism in Patients with Mild to Moderate Chronic Kidney Disease: A Prospective Randomized Single Blind Controlled Trial, Renal Failure,vol. 28(1),pp.1-5,2006.
30. P.Susantitaphong,K.Sewaralthahab, E.M. Balk, B. L.Jaber, vol.17(1),1-58,2013.
31. N. E.Madia. Short- and Long-Term Effects of Alkali Therapy in Chronic Kidney Disease: A Systematic Review Am J Nephrol,vol. 35(6), pp.540–547,2012.