**Archives of Nephrology**

**ISSN: 2639-3573**

**Volume 3, Issue 2, 2020, PP: 1-13**

# Effect of Caffeinated Coffee Consumption on Renal Function in Health and Diabetes: A Double-Edged Sword

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## Abstract

***Introduction:** Evidently, caffeinated coffee (CCAF) consumption is associated with decreased risk of diabetes mellitus, however, its effect on the kidney in diabetes and health is yet to be thoroughly researched and ascertained. This formed the focus of the present study.*

***Methods:** Sixty (30 male and 30 female) animals were divided into 12 groups (6 pairs) (n=5 per group). Animals in group 1 served as normal control (NCTRL) and were given standard feed and water only. Group 2 animals received standard feed plus CCAF. Group 3 was the diabetic (DIA) alone group while groups 4, 5, and 6 were DIA plus CCAF treatment. After 4 weeks of treatment, the animals were sacrificed and blood obtained and analyzed for the biochemical indices of renal function and carbohydrate metabolism using standard methods.*

***Results:** The consumption of CCAF was not associated with any significant change in serum creatinine (SCr) and electrolyte levels in the CCAF control group compared with the NCTRL group. However, SCr levels increased significantly in DIA alone and DIA plus CCAF groups compared with the NCTRL group. Serum urea increased and decreased significantly in DIA alone and DIA plus CCAF treatment groups respectively. Serum glucose, insulin and HOMA-IR increased and decreased significantly in DIA alone group and DIA plus CCAF treated groups respectively compared with NCTRL and CCAF control groups.*

***Conclusion:** CCAF consumption may not adversely affect renal endpoints in healthy persons; however, those with diabetes mellitus and impaired renal function should avoid CCAF consumption.*

**Keywords:** *Caffeine, Coffee, Renal endpoints, insulin, Diabetes*

## Introduction

The coffee plant is a widely distributed evergreen shrub belonging to the Rubiaceae family of flowering plants. Coffee tea which is produced from the roasted coffee bean is adjudged as one of the most widely consumed beverages in the world probably due to its nutritional and other health benefits.[1-3] It is estimated that about 500 billion cups of coffee are consumed annually worldwide,[4] thereby making coffee second to water in terms of the frequency of consumption,[5] and is a major beverage in daily life.[6]

Coffee has rich and varied bioactive constituents including macro-nutrients (carbohydrates, lipids, and proteins), electrolytes, (magnesium ($Mg^+$) and potassium ($K^+$)), vitamins (niacin and vitamin E), phytochemicals (tannins and polyphenols). Other bio-constituents include phenolic acids (chlorogenic acids (CGAs), caffeic acid, melanoidin, trigonelline, diterpenes, cafestol, and kahweol),[7] hydroxyhydroquinone, [6] β-carboline, harmani and caffeine (1, 3, 7-trimethyl xanthine). Caffeine is considered as the most pharmacologically active constituents of coffee. In some countries such as North America, coffee consumption forms the major source (about 75%) of dietary caffeine in adults.[1,8] Although caffeine content of coffee may vary according to the product brand, methods of preparation (e.g.,

roasting) and size of the serving cup,[1] moderate to heavy intake of caffeinated coffee are required to achieve the physiological level of plasma caffeine (2-10micrg/ml) in human. Caffeine is posited to mediate most, if not, all its effects through the blockade of adenosine A1 and A2 receptors Tofovic et al.,[9] who cited Sawynok.[10] Although it is the most commonly consumed stimulant worldwide, caffeine consumption is associated with several detrimental health effects including gastrointestinal, respiratory, central nervous and cardiovascular system toxicities. Likewise, several health benefits are associated with moderate coffee consumption including a reduction in the incidence of gallstone,[11] renal stone, poor memory,[12] Alzheimer's disease and Parkinson's disease.[13]

Other benefits include a lower risk of diabetes mellitus [14] and cardiovascular disease risk. Although several studies have been conducted to unravel the effect of caffeinated coffee (CCAF) consumption on renal endpoints and carbohydrate metabolism in health and disease, this does not mean that the effect of coffee on the kidney is understood to the fullest degree or that it can be fully duplicated. Also, being the most widely consumed beverage in the world, and given the limitations/drawbacks of previous studies including low power and inconsistent results, more researches are needed for a better understanding of its effect on some vital organs in healthy persons, and patients with chronic diseases such as the kidney in diabetes, given that they share many risk factors. Currently, there is no consensus on the effect of coffee consumption on the renal endpoints in patients with diabetes mellitus. The present study aimed to assess the effect of CCAF consumption on markers of renal function and carbohydrate metabolism in healthy and diabetic rats.

## Materials and Methods

### Animal Care and Use

Sixty (30male and 30 female) Wister Albino rats weighing between 200gm and 250gm were used for this study. They were kept in five well-ventilated cages for one week to acclimatize to the environment and were adequately cared for according to the principle of Laboratory Animal Care and use (National Institute of Health 2011) including allowing access to food and water ad libitum. They were fed with rat chow (Vital Feeds, Grand Coral Ltd. Jos).

### Segregation of Animals

#### *Segregation and Treatment of Animals*

The animals were randomly divided into 12 groups (6pairs) (n=5 per group) for male and female animals.

Group 1: Animals in this group served as normal control (NCTRL) group and were orally gavaged 2ml of normal saline for 4wks.

Group 2: Animals in this group served as CCAF (Nestle Nigeria) control group and were orally gavaged with medium dose (38.4mg/kg) of CCAF. Medium dose of the CCAF was used as CCAF control given the empirical evidence that showed that moderate coffee consumption is associated with a lower risk of chronic diseases such as diabetes mellitus and diabetes-induced kidney disorders.[15]

Group 3: Animals in this group served as diabetic (DIA) control group.

Group 4: Animals in this group served as DIA plus low dose caffeinated coffee (CAFLD) (19.2mg/kg) group.

Group 5: Animals in this group served as DIA plus medium dose of caffeinated coffee (CAFMD) (38.4mg/kg) group.

Group 6: Animals in this group served as DIA plus high dose of caffeinated coffee (CAFHD) (57.6mg/kg) group.

### Induction of Diabetes

Forty (20 male and 20 female) Wister Albino rats were randomly selected and induced with diabetes as follows: after 18hrs fasting, diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) (65mg/kg-BW) dissolved in a freshly prepared 0.IM citrate buffer, 15 minutes after the intraperitoneal injection of nicotinamide (120mg/kg-BW) dissolved in normal saline was given. Seventy-two hours after the injection of STZ, blood samples were collected from the tail vein of the rats by pricking and used for the estimation of fasting blood sugar (FBS).

After determining the lethal dose ($LD_{50}$) (192mg/kg) of the experimental CCAF, the different doses of the CCAF given to the animals were calculated as 10%, 20%, and 30% for low, medium and high dose groups respectively of the $LD_{50}$. Accordingly, 19.2mg/kg, 38.4mg/kg, and 57.6mg/kg were used as low, medium, and high doses of the experimental CCAF.

## Biochemical Analysis

Markers of renal function tested included electrolytes: sodium ($Na^+$), $K^+$, chloride ($Cl^-$), and bicarbonate ($HCO3^-$). Others include serum urea (Ur), creatinine ($Cr^-$), and uric acid (UA). Serum electrolytes: $Na^+$ and $K^+$ were measured by flame photometry (Jenson PEP 9) Jenson Scientific Limited, Bedfordshire (UK). Serum $Cl^-$ was measured by the ion-selective meter (Orion 730; Orion Research Inc; Boston MA). Serum creatinine (SCr) was measured using Jaffe's method using 0.75 sodium hydroxide and 1% Picric acid (Sigma Chemicals, Perth, Balcatta, India). Serum urea (Ur) and uric acid (UA) were measured using a multi-channel automated analyzer (SYNCHRON, Los Angeles, CA, USA). Serum HCO3 levels were measured by the enzymatic method. The serum insulin level was determined by an enzyme-linked immunosorbent (ELISA) method using a commercially available kit (Clouol-clone corp, Houston USA). Fasting blood sugar was measured by multi-channel automated system lipid pro-TM Model KM-001A; info Pia Co Ltd. South Korea. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as follows; HOMA-IR=[fasting blood glucose (mmol/L) x fasting insulin (μ/U/mol/22.5)].

## Statistical Analysis

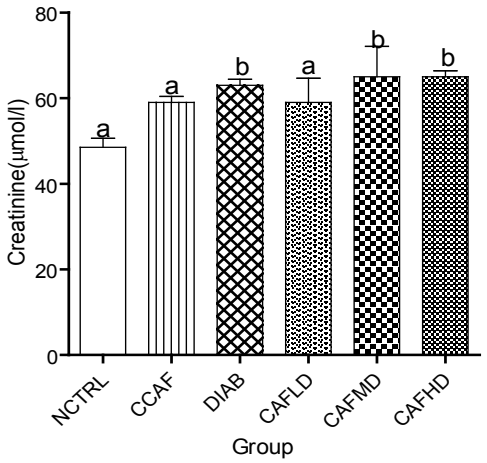
Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS), version 20.0. The one-way analysis of variance (ANOVA) and posthoc Tukey Least Significant differences test were used to analyze the data and determine the significant levels respectively.

Data were express as Mean ± Standard Error of Mean (SEM) and bar charts were used to illustrate the variation in the numerical values across experimental groups. P-values <0.05 were considered statistically significant.

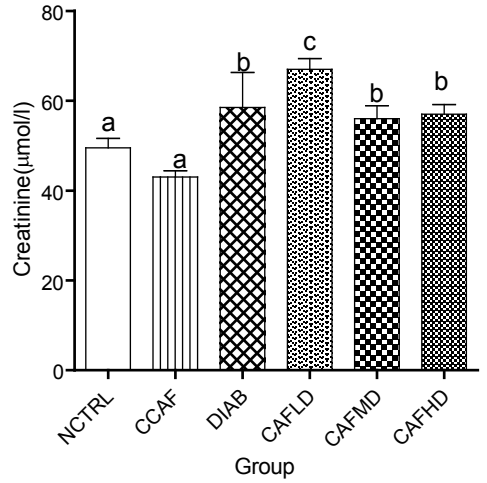
## Results

Results of the present study showed that female animals in CCAF alone group and DIA plus low dose CCAF group had a nonsignificant decrease in SCr levels compared to levels in NCTRL groups, however levels significantly increased in DIA alone, DIA plus medium dose and DIA plus high dose CCAF groups compared to levels in the NCTRL group. In male animals, SCr levels increased significantly in DIA control and DIA plus CCAF groups compared with NCTRL and CCAF control groups (Figures 1a&1b).

**Female**




**Male**




**Figures1a &1b.** *Effect of caffeinated coffee and diabetes on SCr levels in (A) Female and (B) Male rats.*

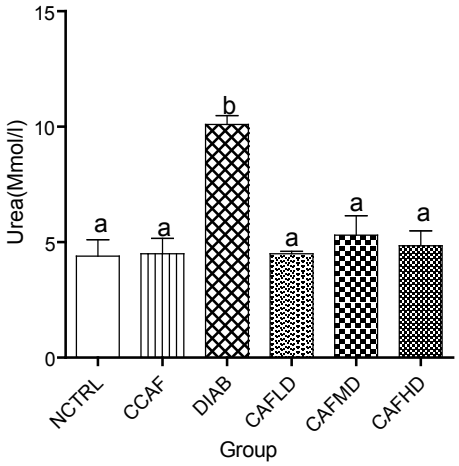
*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

*Different letters indicates significance while similar letters represent non-significance.*

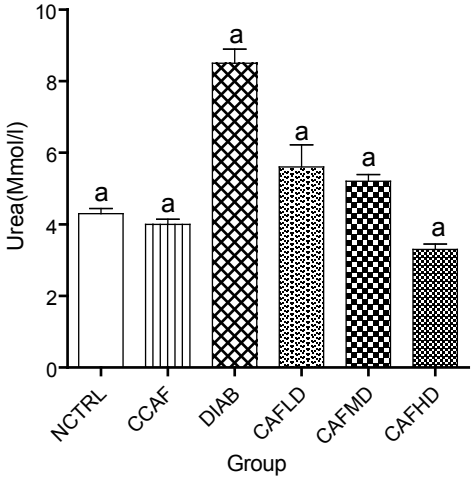
## Serum Urea

Serum Ur levels increased significantly in DIA control groups compared with NCTRL and CCAF control groups in both male and female animals. However, treatment with different doses of CCAF caused significant decreases in serum Ur levels compared with the DIA control group and a nonsignificant decrease compared with NCTRL and CCAF control groups (Figures 2a&2b).

**Female**




**Male**




**Figures2a & 2b.** *Effect of caffeinated coffee and diabetes on serum Ur levels in (A) Female and (B) Male rats.*

*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

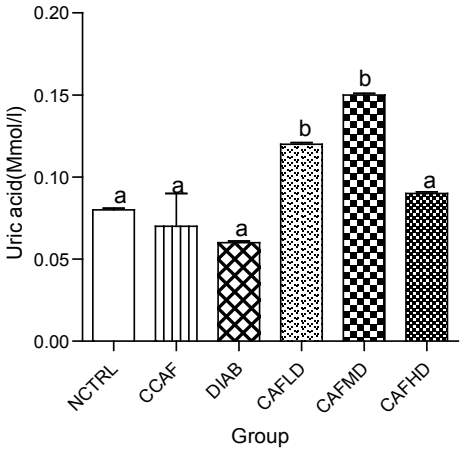
*Different letters indicates significance while similar letters represent non-significance.*

## Serum Uric Acid

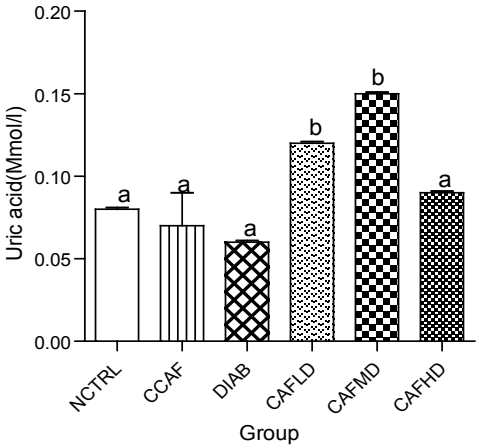
Figures 3a & 3b show that in female animals, serum UA increased significantly in the CCAF control and DIA plus high dose CCAF groups, while nonsignificant decreases in serum UA level were found in DIA plus low dose and DIA plus medium-dose groups compared with the NCTRL group.

In male rats, serum UA level increased significantly in DIA plus low dose and DIA plus medium-dose groups compared with the NCTRL group. However, a nonsignificant change was observed in serum UA of animals in CCAF alone, DIA alone, and DIA plus high dose groups compared with the NCTRL group.

**Female**




**Male**




**Figures3a & 3b.** *Effect of caffeinated coffee and diabetes on serum UA levels in (A) Female and (B) Male rats.*

*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

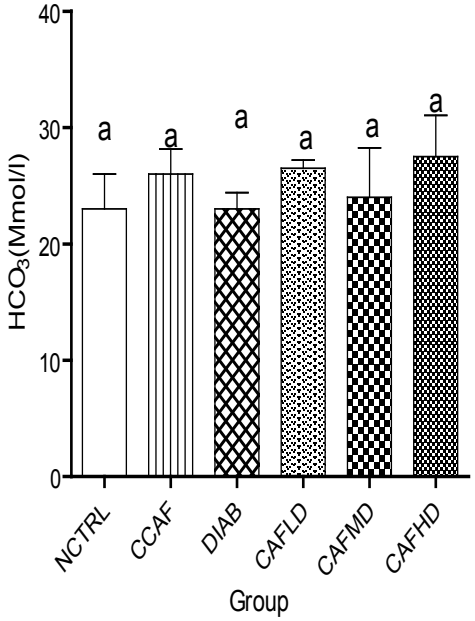
*Different letters indicates significance while similar letters represent non-significance.*

## Electrolytes

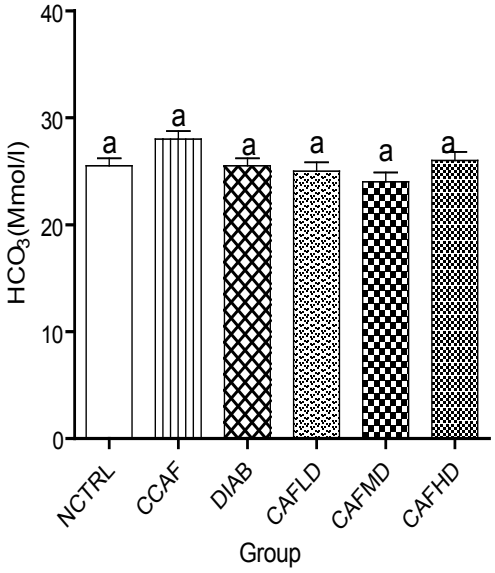
### *Serum Sodium ($Na^+$)*

Serum $Na^+$ levels showed a nonsignificant change in all treatment groups in both male and female animals compared with NCTRL and CCAF control groups, except that in male rats, a significant decrease in serum $Na^+$ concentration was observed only in DIA control group Figures 4a&4b).

**Female**




**Male**




**Figures4a & 4b.** *Effect of caffeinated coffee and diabetes on serum HCO3- levels in (A) Female and (B) Male rats.*

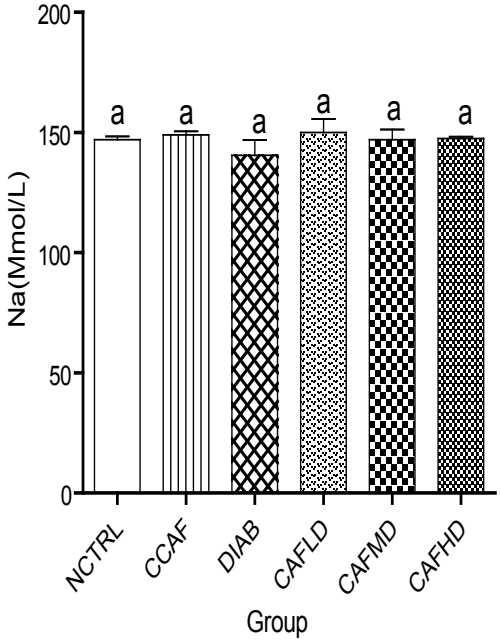
*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

*Different letters indicates significance while similar letters represent non-significance.*

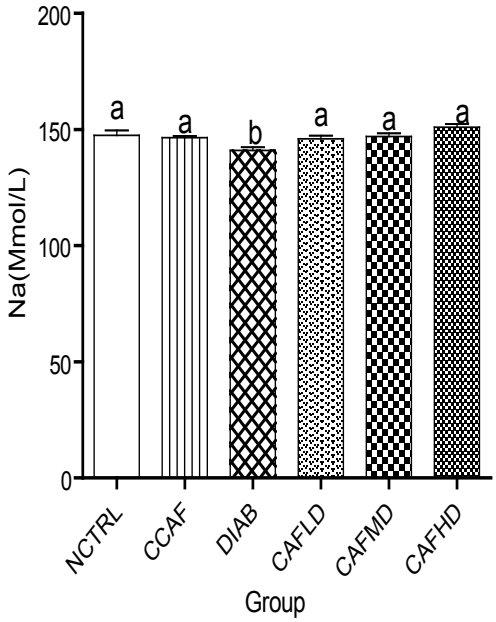
## *Serum Potassium, Chloride and Bicarbonate*

Serum $K^+$, Cl & HCO3 levels were not significantly different when compared across the different study groups in both male and female animals (Figures 5a & 5b, 6a & 6b, 7a & 7b).

**Female**




**Male**

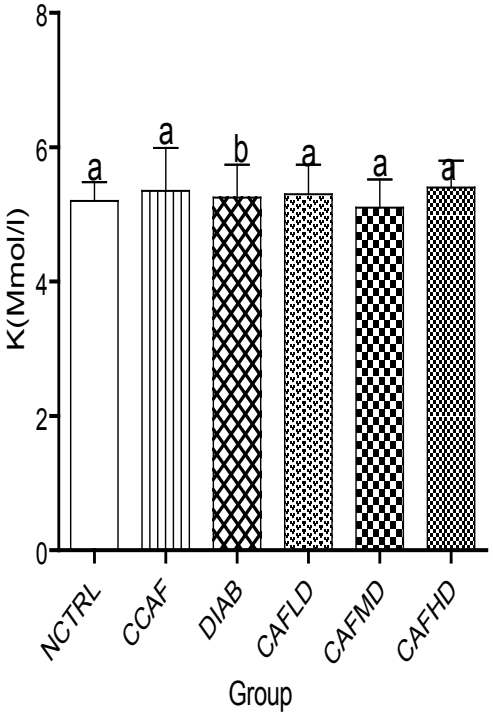



**Figures5a & 5b.** *Effect of caffeinated coffee and diabetes on serum Na+ levels in (A) Female and (B) Male rats.*

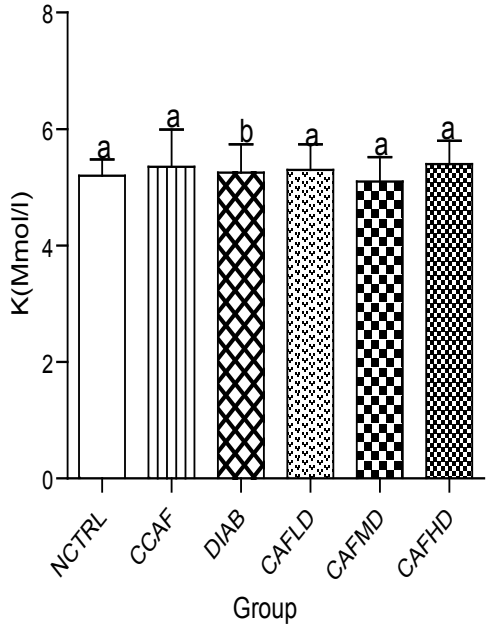
*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

*Different letters indicates significance while similar letters represent non-significance.*

**Female**




**Male**

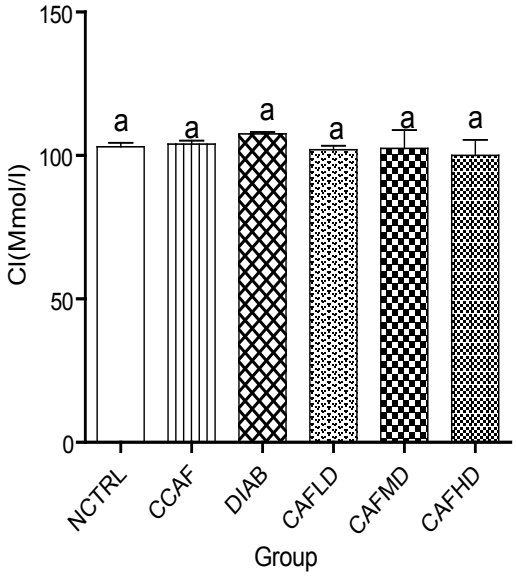



**Figures6a & 6b.** *Effect of caffeinated coffee and diabetes on serum K+ levels in (A) Female and (B) Male rats.*

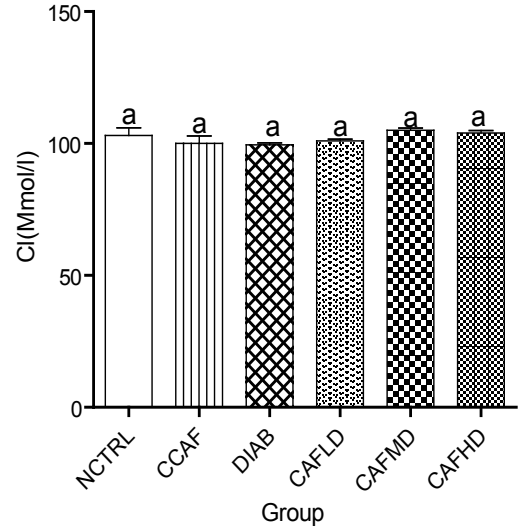
*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

*Different letters indicates significance while similar letters represent non-significance.*

**Female**




**Male**



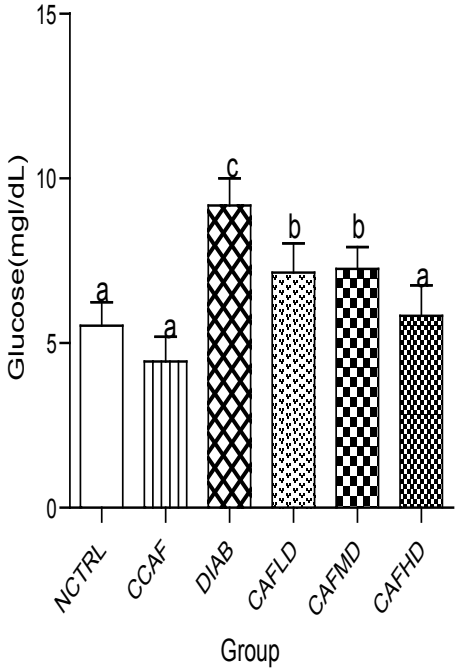

**Figures7a & 7b.** *Effect of caffeinated coffee and diabetes on serum Cl- levels in (A) Female and (B) Male rats.*

*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

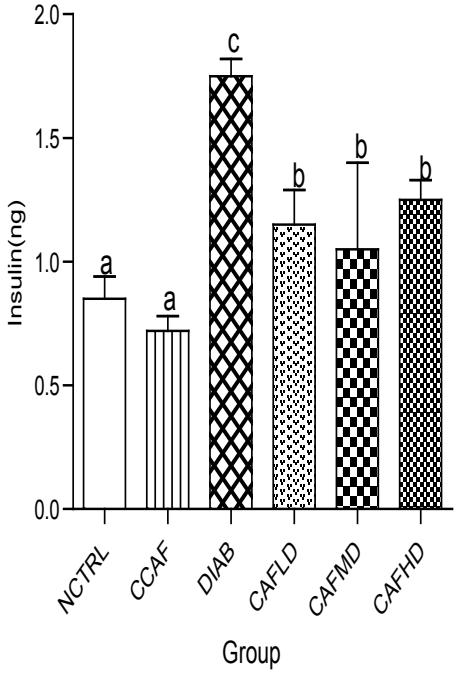
*Different letters indicates significance while similar letters represent non-significance.*

Serum glucose, insulin and calculated HOMA-IR increased significantly in the DIA alone group and decreased significantly in DIA animals treated with different doses of the CCAF compared with NCTRL and CCAF alone groups (Figures 8a & 8b, 9a & 9b, 10a & 10b) respectively.

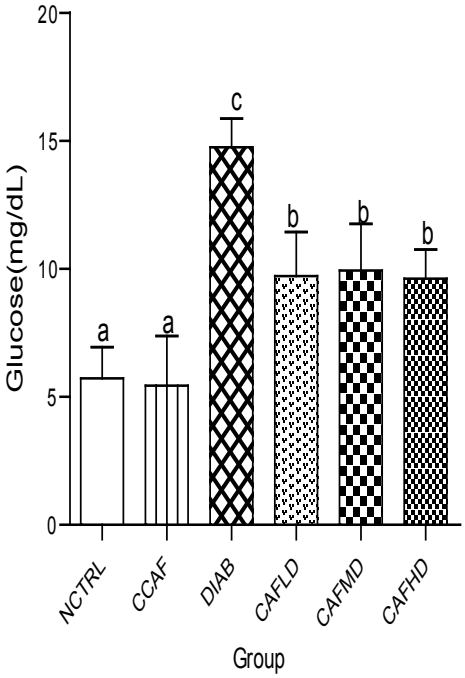
**Female**



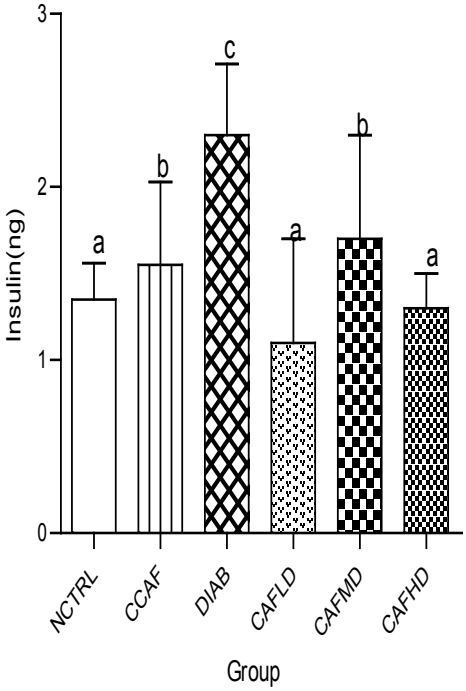

**Female**




**Male**




**Male**




**Figures8a & 8b.** *Effect of caffeinated coffee and diabetes on glucose levels in (A) Female and (B) Male rats.*

*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

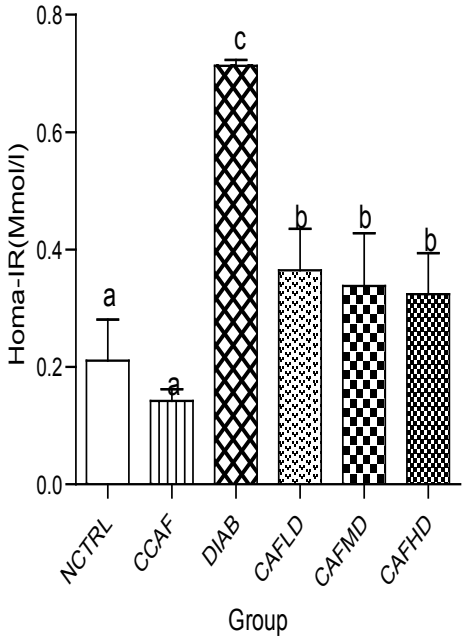
*Different letters indicates significance while similar letters represent non-significance.*

**Figures9a & 9b.** *Effect of caffeinated coffee and diabetes on insulin levels in (A) Female and (B) Male rats.*

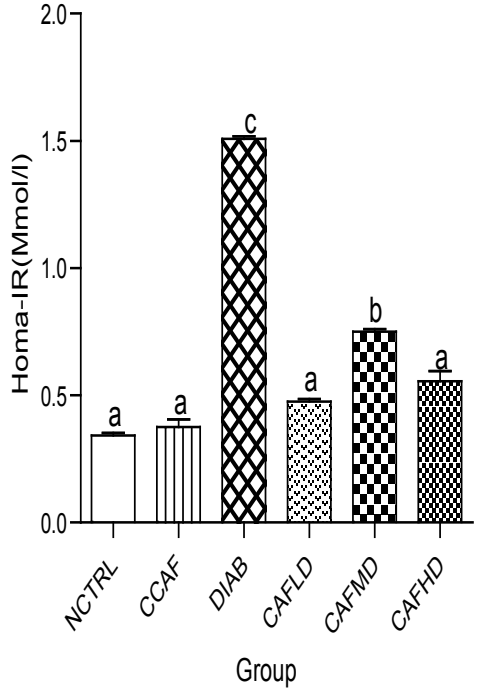
*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

*Different letters indicates significance while similar letters represent non-significance.*

**Female**




**Male**




**Figures10a & 10b.** *Effect of caffeinated coffee and diabetes on calculated HOMA-IR levels in (A) Female and (B) Male rats.*

*Values are expressed as Mean ± SEM at P <0.05 relative to control.*

*Different letters indicates significance while similar letters represent non-significance.*

## Discussion

The results of the present study showed that there were no significant differences in SCr and electrolyte levels between the CCAF control group and the NCTRL group regardless of gender. However, SCr levels increased significantly in DIA alone and DIA plus CCAF treated groups compared to levels in the control groups, probably due to diabetic-induced glomerular hyperfiltration mediated by the associated hyperglycemia and disordered insulin levels in diabetes. Also, the SCr level did not differ significantly between the DIA alone group and the DIA plus CCAF treated groups. The above findings suggest effect modification by diabetes on the association between CCAF consumption and changes in renal endpoints and lend credence to the hypothesis that caffeine consumption has no detrimental effect on renal function and structure in animals with healthy kidney [16] but worsens pre-existing renal disease such as early DIA nephropathy (i.e., glomerular hyperfiltration).[17] Additionally, a significant decrease in serum Ur level was found in DIA plus CCAF groups compared with DIA alone group likely due to the glomerular hyperfiltration-induced decline in serum Ur level [18] and the effect of the biologically active compounds in CCAF. It is interesting to note that glomerular hyperfiltration is a physiologically adaptive mechanism to reduce the post-prandial rise in serum Ur level after a high protein diet by decreasing reabsorption and enhancing excretion. However, in diabetes, glomerular hyperfiltration mitigates reabsorption of Ur from the tubular fluid and leading to more excretion thereby resulting in decreased serum Ur level as observed in the present study. Vasopressin-urea dependent increased glomerular filtration rate is implicated in the diabetic-induced hyperfiltration because this condition is associated with increased plasma vasopressin level and catabolism of protein and hence excretion of Ur.[19]

Histopathological examination of renal tubular epithelium in DIA associated glomerular hyperfiltration showed marked tubular epithelial changes including tubular hyperplasia and hypertrophy. Reduced intra-tubular pressure and hydraulic pressure in Bowman's space were also detected.[20] SCr, Ur, and Cr-based estimation of estimated glomerular filtration rate (eGFR) are the primary variables used in the estimation of renal function in clinical practice. However, serum

Ur is a less specific marker of glomerular filtration rate compared with SCr which more closely fulfills the criteria for use as a marker of renal function.[21,22]

Our findings and notions are consistent with the results of several studies conducted in different parts of the world, including 4 cohort studies conducted in Italy, Japan, and Korea that found no significant association between coffee consumption and chronic kidney disease; although pooled results showed a nonsignificant reduction in the risk of chronic renal disease.[23,24] In other studies, the consumption of CCAF was found to produce either a desirable or undesirable effect on renal endpoints.[25,26,27] The variation in the effect of CCAF on renal function across studies could partly be due to the effect of several confounding factors including differences in the extent of tolerance, genetic polymorphism, gut microbiome, and inter-individual differences in caffeine metabolism which are known to contribute to the variability in the renal hemodynamic responses to caffeine consumption.[28] Mechanistic studies indicate that the inhibitory effect of caffeine on adenosine receptors in the juxtaglomerular cells promotes renin secretion which in turn increased plasma angiotensin II. Angiotensin II is a potent vasoconstrictor causes the vasoconstriction of the renal vascular system including afferent arterioles and leading to decrease renal blood flow and by extension decreased renal endpoints. However, other studies found no effect of caffeine intake on plasma rennin activity[29,30] or a decrease in plasma rennin activity after acute caffeine intake.[31] Interestingly, others found that chronic CCAF intake attenuated the acute increase in plasma rennin activity[32,33] and leading to a null effect on renal endpoints in healthy individuals as observed in the present study.

It is also plausible that the null significant effect observed in the present study may at least in part be due to dose or duration related effect as previously documented. Accordingly, a cross-sectional study of Korean women by Kim *et al.,*[6] showed that the consumption of at least 2cups of coffee per day decreased the odds for renal function impairment compared to those who drank less than 1cup per day. In a parallel study, Herber-Gast *et al.,*[34] found that intake of 6 cups of coffee per day was associated with a better kidney function than the consumption of less than or equal to 1cup per day. Saito *et al.,*[3] also observed that drinking of at least 3cups of coffee per day was significantly associated with increased cystatin C-based eGFR compared with drinking green tea.

The nonsignificant decreased and increased SCr level in the CCAF alone group in the male and female animals respectively compared with the NCTRL group agreed with the results of the aforementioned studies. Likewise, previous studies that showed that the consumption of at least 1 cup of coffee per day was associated with a lower risk of kidney disease compared with the never drinking coffee groups.[35-37]

The non-significant decrease in SCr in DIA female rats treated with a low dose of CCAF as against the significant increase in SCr level in DIA male rats treated with a low dose of CCAF indicate stronger protection for female than male animals, similar to previous reports by Neugarten and Golestaneh,[38] Lew *et al.,*[7] and Hu *et al.,*[23].

Also, the null significant changes in SCr level between CCAF alone group and the NCRTL group could be due to the interaction between the bioactive constituents of coffee tea. This notion agrees with the premise that coffee contains different compounds with opposing systemic effects.[39] For instances, whilst caffeine may inhibit adenosine[40] effect and insulin sensitivity, other coffee biologically active constituents (e.g., chlorogenic acids, caffeic acid, trigonelline, diterpenes, cafestol, kahweol, $Mg^{+}$, vitamin E, and other polyphenolic acids) have the potentiality to enhance adenosine and insulin activities and can attenuate caffeine-induced renal toxicity thereby protecting the glomerular endothelium from oxidative stress due to their antioxidant, anti-inflammatory and immune system modulating effects. Conversely, the significant increase in SCr in DIA alone group and DIA plus CCAF groups compared with the NCTRL group indicates a greater effect of DIA-associated impaired renal (glomerular hyperfiltration) excretory function including the excretion of Cr.

The beneficial effect of CCAF consumption in carbohydrate metabolism was also obvious in the results of the present study showing inverse association with markers of abnormal carbohydrate metabolism including high fasting blood glucose, fasting insulin and HOMA-IR levels in both male and female DIA rats treated with CCAF compared with the DIA alone group. These findings are in good agreement

with results of several other studies in the literature which found an inverse relationship between CCAF consumption and incident type 2 diabetic Mellitus and insulin resistance.[3,41-43]

However, concerns have been raised about the mechanism(s) underlying the association between CCAF consumption and the anti-diabetic and nephroprotective effects. Several speculations have been made regarding these activities. Available evidence indicates that most actions of CCAF are mediated by its bioactive constituents including vitamins (niacin and vitamin E), electrolytes ($Mg^+$ and $K^+$), phytochemicals (tannins and polyphenolic acids (e.g., chlorogenic acid, caffeic acid, melanoidin, trigonelline, diterpenes, cafestol, and kahweol), hydroxyhydroquinone and caffeine. Some of these bioconstituents are known to possess potent antioxidants,[44] anti-inflammatory, [45], and immune system modulating effects,[46] which are known to underline the pathologies driving the onset, progression, and complications of caffeine-induced renal disorders, diabetes mellitus, and diabetic-induced renal disorders. This notion is supported by the growing knowledge that the vast and versatile pharmacological activities of many medicinal plants are dependent on their phytochemical and nutritional constituents.[47]

Results of feeding studies,[48,49] showed a direct correlation between vitamin E supplementation and improvement in markers of insulin resistance and oxidative stress. Coffee, being rich in $Mg^+$ caused increased serum $Mg^+$ levels in a study by Saito *et al.,*[3] A plethora of research reports inverse relationship between serum $Mg^+$ level and insulin sensitivity and onset, progression, and complications of diabetes mellitus. $Mg^+$ deficiency has been shown to cause endothelial cell dysfunction, inflammation, and oxidative stress. $Mg^+$ supplementation improves insulin sensitivity even in non-diabetic subjects,[50] modulate inflammation and immune system dysfunctions and decreased tumor necrosis factor-α expression in cells.[51,52]

Polyphenols mediate antioxidant, anti-inflammatory, and immune system modulating effects.[53] CGA (a phenolic compound with antioxidant properties) reduced insulin resistance, serum glucose level, and glucose absorption in the gut through the reduction of hepatic gluconeogenesis and inflammation[54] and hence the risk of overt nephropathy. Caffeine acid ameliorated the effect of tumor necrosis factor-α induced-inflammatory response in endothelial cells. [55] Likewise, caffeine has been found to enhance glucose homeostasis by inhibiting adenosine-induced hepatic gluconeogenesis as well as stimulating insulin secretion from the pancreatic beta-cell invivo.[56]

Therefore, prolonged consumption of CCAF could be detrimental to renal endpoints in diabetes, but caused improvement in markers of carbohydrate metabolism corollary of the effect of its bioactive constituents. Accordingly, the effects of CCAF consumption on renal endpoints and markers of carbohydrate metabolism in diabetes could be described as a double-edged sword.

## Conclusion

The consumption of CCAF may not have any significant detrimental effect on renal endpoints in healthy individuals, however, high-risk persons for kidney disease such as those with diabetes mellitus and those in a renal compromised state, during vulnerable periods such as during renal dialysis or renal transplant and those on prescription medications known to adversely affect the kidney may avoid CCAF consumption. However, long-term clinical trials and prospective epidemiological studies with a large sample size are needed to enable a more definite conclusion to be made.

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**Citation:** **Ekpenyong, CE, Nwachuku, C, Otokpa, DE.** *Effect of Caffeinated Coffee Consumption on Renal Function in Health and Diabetes: A Double-Edged Sword. Archives of Nephrology. 2020; 3(2): 01-13.*