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**Original Research**

# Combinatorial multiplicity of cardiometabolic and inflammatory markers in gum arabica modality of CKD CAM: Part 2

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**Abstract**

**Aim:** A combinatorial multiplicity of molecular blood markers were assessed using ELISA colorimetric determinations in this prospective cohort study of the impact of guar gum arabica (GA) use on kidney function parameters of chronic kidney disease (CKD) in consumers (cases) vs. non consumers (age- and CKD stage- matched controls). **Results:** Mean age of study participants was 68.12 (±SD 10) years with homogenous sex distribution in both study arms and comparable levels of eGFR, sCr, ESR, CRP, HbA1c, FPG, UA and fasting lipid profiling parameters (P value >0.05). Consistently in study population of recruits; mean CKD duration was 6.94 years (±SD 7.8) and CKD stage IV (37.6% of total study population) was of predominant incidence, followed by stages IIIa and IIIb (20.4% and 19.4%, respectively). Despite the negative glucosuria in 75% of CKD patients; hypertension (92.5%), dyslipidemia (64.8%) and diabetes mellitus (54.8%) were prevalent in a descending order of predominance. GA consumption mean duration was 1.3±1.1 (range 0.25-6) years with a mean dose of 1.7±1.0 (range 0.5-6) spoons per day. Remarkably plasma concentrations of resistin (P value =0.047), and nesfatin-1 in cases were substantially greater (P value =0.005) but obestatin (P value =0.018), kisspeptin (P value =0.006), and vascular endothelial growth factor (VEGF) (P value =0.003) were found of pronouncedly lower blood levels in cases in comparison to those of controls. Invariably, human asymmetric dimethylarginine (ADMA), zinc alpha 2-glycoprtein, alpha klotho, ghrelin, and C-reactive protein (CRP) lacked any significant discrepancies in plasma levels in cases vs. those of controls (P value >0.05). In CKD cases on GA modality, ghrelin had substantial inverse correlations with dialysis duration, FBS and uric acid in CKD cases. Pronounced proportional associations of sCr levels were found with ghrelin, hsCRP and resistin in the same pool of cases. eGFR disproportionally correlated with cases' hsCRP and resistin. In GA-naïve-CKD controls; sCr related proportionally and significantly with asymmetric dimethylarginine (ADMA) and Zinc alpha 2-glycoprtein. **Conclusively:** interventional studies are much justifiably needed.

**Keywords:**

1. ADMA (asymmetric dimethylarginine), alpha klotho, chronic kidney disease (CKD), C-reactive protein (CRP);
2. Ghrelin, gum Arabica, kisspeptin, nesfatin, , resistin;
3. zinc alpha 2-glycoprtein, , Obestatin, Vascular endothelial growth factor (VEGF)

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## INTRODUCTION

Recurrently chronic kidney disease (CKD) patients suffer anorexia and cachexia symptoms frequented with decreased quality of life and increased mortality. Hence, chronic inflammation is the pathophysiology in CKD of ensuing and progressing of anorexia, cachexia, and renal osteodystrophy, with increased cardiovascular disease (CVD) risk.[1a-e] Early-stage CKD biomarkers, such as proteinuria, microalbuminuria and reduced glomerular filtration rate (GFR) can be critically under-detected.[2] Due to irreversibility of CKD; the unmet need for early diagnosis and treatment can be more challenging to overcome these limitations in translational medicine. Effectively, CKD markers in clinical practice and experimental settings can be categorized as those of endothelial dysfunction, tubulo-glomerular damage, oxidative stress and vascular injury. As of translational relevance and evidence; the addition of these biomarkers to clinical and experimental settings may substantially identify higher risk of eGFR decline in persons with early or advanced CKD and significantly improve discrimination for the renal outcome in diabetic and sickle cell nephropathies (DN and SCN, respectively).[3a,b]

Most challenging is collaborative approach to standardize the use of promising biomarkers in complementary combinations





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to refine their clinical utilities in progressive kidney damages and repairs.[4a,b] Suggestively, emerging technology of urinary proteomics, metabolomics, and transcriptom can serve as a novel strategy to improve the diagnosis, prognosis and treatment of diabetic nephropathy[1c,d,e, 5a-d] thereby paving the way for molecular biomarkers not used routinely in clinical practice or prospective clinical trials. Most of the CAM-related self-management practices were closely linked to chronic illnesses.[6a,b] Remarkably, in a retrospective cohort of CKD-diabetic patients; GA (gum acacia) ameliorated eGFR, fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) (but not lipid profile or proinflammatory C-reactive protein (CRP)) vs. those of nondiabetic subjects.[7] Principally, a limited number of studies were conducted on patients with small sample size and short duration.[7,8a-m] Even more so limited studies were mainly done on arabic gum in animal models and rodents. Meanwhile, our study includes CKD patients at stages II-V who are not on dialysis which will be sufficiently powered with comprehensive assessment of CKD clinical outcomes in correlation with a complementary combination of multiple molecular biomarkers of CKD ensuing and progression.

As of inflammation related blood indices; neutrophil/ lymphocyte ratio (NLR) is high in CKD group and is correlated with uric acid and proteinuria, which are known to be associated with atherosclerosis in patients with CKD. Also, a statistically significant relationship was detected between mean platelet volume (MPV) and platelet count, uric acid and fibrinogen but not microalbuminuria/proteinuria.[9] Platelet-related indices and their determination are inexpensive and routinely ordered markers. Effectively, platelet parameters can be risk stratification tools of CKD patients prone to develop coronary artery disease. Markedly attaining statistical significance; the mean values of platelet distribution width (PDW), mean platelet volume MPV, platelet count, plateletcrit and platelet large cell ratio (PLCR) were found to be lower in ESRD (end stage renal disease) receiving hemodialysis. [10]

**α-Klotho** is an anti-aging protein, produced by kidney, brain and placenta; it has been involved in important biological processes, such as calcium/phosphate metabolism, mineral bone density, resistance to oxidative stress, and nitric oxide production in the endothelium. It regulates metabolism via distinct central and peripheral mechanisms.[11] Noticeably in CKD patients, a significant positive correlation between soluble α-klotho and eGFR but a marked negative association of soluble α-klotho and FGF23 were proven Wang et al.,[12]. Rotondi et al.[13] endorsed lower soluble-klotho as mirroring renal transmembrane klotho; such reduction was detectable since CKD stage 2. Besides, it correlated positively with serum calcium and negatively with serum phosphate and PTH. Low expression of α-klotho appears to improve anemia in patients with CKD and has been hypothesized to be a compensatory mechanism to attenuate the effects of CKD anemia.[14] In Sauriasari et al.[15] and Piwkowska et al.[16] reports; soluble α-klotho was highly commended among the novel batch of molecular markers of diabetic kidney disease (DKD). Taken together, klotho has exceptional and potential diagnostic (in AKI and CKD)[17]and therapeutic implications (as in prognosis of progression and extrarenal complications) and as replacement therapy for systemic klotho deficiency in CKD.[18a-c]

Asymmetrical dimethylarginine (ADMA) is predominantly involved in systemic inflammation-induced endothelial dysfunction in atherosclerosis.[19] Endothelial dysfunction in linkage to reduction of bioavailability of nitric oxide (NO) can be among early phases of atherosclerotic CVD. NO-synthase can generate NO from L-arginine. Remarkably, this can be easily blocked by endogenous L-arginine analogues such as ADMA.[20] ADMA was found to accelerate renal cell fibrosis principally under high glucose condition and through signaling pathway of NOX4/ROS/ERK (NADPH Oxidase 4/ reactive oxygen species/ extracellular signal-regulated protein kinase.[21] Besides, ADMA elevations were connected to CKD progression via mechanism involving collagen and TGF-β1 (Transforming growth factor beta1) synthesis[22]and its accumulation in erythrocytes worsened CKD- anemia[23] most probably via induction of impaired response to erythropoietin.[24]Importantly, eGFR levels inversely and markedly associated with ADMA concentrations among elders of both genders.[25] Interestingly ADMA accumulation in erythrocytes could worsen CKD-related anemia.[23] Effectively, ADMA was enlisted among the highly selected novel biomarkers in the diagnosis of CKD and the prediction of its outcome.[26a-e] Suggestively, in totality of selected biomarkers; the combination of ADMA, symmetric dimethylarginine (SDMA), uromodulin, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), miRNA, ncRNA, and lincRNA biomarkers could mirror all types of alterations occurring in the course of this disease.[26]

Ghrelin is a prominent endocrine factor in stress-induced obesity.[27] Outstandingly, kidney degrades ghrelin. Increased total ghrelin levels in CKD are primarily due to the decreased degradation of ghrelin in the kidney. Nevertheless, plasma ghrelin level was not found to be a probable indicator of kidney insufficiency in T2D patients.[28] Maternal serum ratio of ghrelin to obestatin decreased in preeclampsia.[29] Besides, ghrelin levels were associated markedly with inflammatory and nutritional markers and with cardiac and vascular dysfunction parameters in hemodialysis patients.[30] In risk stratification, ghrelin and obestatin plasma levels can be differentially expressed in different stages of CKD patients; hemodialys-CKD patients presented the highest obestatin plasma levels and the lowest ghrelin/obestatin ratio in comparison to those of nonhemodialysis-CKD patients and healthy subjects.[31] Both ghrelin and obestatin were attained as promising CKD biomarkers in children.[32]

hsCRP (highly sensitive C-reactive protein) is involved in immunometabolism.[33]Increase in serum albumin concentration is associated with prediabetes development and progression to overt diabetes independently of metabolic syndrome.[34] In reference to this frame of hsCRP/albumin ratio and urine albumin/creatinine ratio,microalbuminuria is a known early predictive factor for renal and cardiovascular diseases, not only in patients with diabetes mellitus or hypertension but also in the general population. Reportedly, the presence of hypertension and hyperglycemia was associated with microalbuminuria. Especially hemoglobin A1c was associated

with microalbuminuria regardless of weight status.[35] The urine albumin-to-creatinine ratio (UACR) is a useful predictor of cardiovascular (CV) events in adults. As endothelial dysfunction may mediate the link between obesity-related insulin resistance and early microalbuminuria; UACR was remarkably ascribed as an early marker of endothelial dysfunction independent of glycemia.[36] 25-(OH)D independently associated with albuminuria in T2D patients but not associated with β-cell function or insulin resistance.[37] The high-sensitivity C-reactive protein (hs-CRP)/albumin ratio has recently been tested as a prognostic marker for mortality in sepsis[38] and acute kidney injury. The hs-CRP/albumin ratio has more value than either test alone for predicting prognoses in various clinical settings thereby serving as a surrogate marker of disease severity.[39] Additionally, hsCRP/albumin ratio (CAR) was recognized as a validated robust prognostic indicator with a discriminatory ability for patients with operable tumors.[40a-,b] Exceptionally, plasma concentrations of 25(OH) D independently associated with both CRP and albumin. This comes in with consistency with the systemic inflammatory response as a major confounding factor in determining vitamin D status.[41]

Kisspeptin has a diagnosis utilityin prediction of pregnancy complications.[42] Metabolic regulation of kisspeptin presents principally the link between energy balance and reproduction.[43] Shoji et al.,[44] showed that expression of kisspeptin and kisspeptin receptor are altered in the kidney tissues of chronic renal impairment, raising the possibility of their pathophysiological roles in CKD. The circulating levels of kisspeptin, among other several markers of inflammation; may have prognostic significance and underlying pathophysiology in CKD patients. Kisspeptin levels were elevated in the serum of critically ill patients at admission to the ICU, when compared to healthy controls, and remained increased after 72 hours of ICU treatment. Notably, kisspeptin levels were independent of the presence of sepsis and etiology of critical illness. In line, serum concentrations of kisspeptin were not correlated to concentrations of inflammatory cytokines or established sepsis markers. Serum kisspeptin correlated inversely with the glomerular filtration rate (GFR). Kisspeptin levels did not correlate with adipokines measured in serum, including leptin, resistin, ghrelin, or adiponectin.[45] Andreozzi, et al.,[46] stated that plasma kisspeptin levels are associated with insulin secretion in nondiabetic individuals. kisspeptin concentration was significantly and positively correlated with age, blood pressure, and 2-h post-load glucose, and inversely correlated with BMI, and waist circumference. There was an inverse relationship between kisspeptin levels and oral glucose tolerance test (OGTT)-derived indexes of glucose-stimulated insulin secretion. Additionally, studies in animal models reported that expression of kisspeptin and/or KISS1R is altered in chronically impaired kidneys.[47] In the frame of this reference, it suppresses metastasis of urogenital carcinomas, besides the possible therapeutic potential of this finding, tissue and tumour-stage-specific alterations in kisspeptin and KISS1/KISS1R expression could potentially be used as biomarkers for the diagnosis and prognosis of urogenital carcinomas.

Nesfatin-1peptide protects rat renal epithelial cells substantially against high glucose and $H_2O_2$ induced injury via inhibition of oxidative stress, apoptosis and fibrosis.[48] Nesfatin-1 protects against diabetic cardiomyopathy in diabetic mouse model via the p38-MAPK pathway.[49] Importantly downregulation of nesfatin-1 expression was reported in vitro in cultured cells and in acute kidney injury in vivo in Wistar rats. [50] Moreover, it is an anorexic neuropeptide, a biomarker of CVD inhibiting the development of obesity and metabolic syndrome. [51] Furthermore, nesfatin-1exerted antioxidant and anti-inflammatory activity in diabetic mice, as shown by decreased reactive oxygen species (ROS), oxidative lipid product malondialdehyde (MDA) levels, increased superoxide dismutase (SOD) and glutathione (GSH), decreased cardiac and plasma interleukin-1 β (IL-1β) and tumor necrosis factor-α (TNF-α) levels. [49] In patients with T2D, circulating nesfatin-1 associated with microalbuminuria independent of other established risk factors of DKD. [52]

Obestatin the diverse and complementary effects of ghrelin and obestatin were found[53] in linkage to obesity and diabetes.[54] Remarkably obestatin, encoded by the same gene as ghrelin, is described as a physiological opponent of ghrelin. As ghrelin and obestatin, negatively related to renal function, seem to be promising inverse indicators of nutritional status in children with CKD, potential therapeutic implications in terms of optimization of their removal in patients on hemodialysis can be suggested.[32] Hemodialysis patients showed elevated serum leptin, ghrelin, and low obestatin levels compared with healthy volunteers (vs. nondialysis controls). Besides, inverse correlations between obestatin and body mass index (BMI), waist circumference, and C-reactive protein were evident (vs. nondialysis controls).[55]

Resistin elevated levels in CKD were pronouncedly associated with inflammation as well as decreased GFR.[56] Reportedly, increased resistin concentrations had the clinical utility in risk stratification and prognostication among heart failure patients with prediabetes and type 2 diabetes (T2D)[57] though it was not a likely mediator of insulin resistance or obesity.[58] Of interest, resistin contributes to endothelial dysfunction, vascular smooth muscle cell (VSMC) proliferation, and atherothrombosis demonstrating effects on the development of hypertension and coronary artery disease (CAD).[59] Moreover, cardiovascular death is thought to depend on the accumulation of uremic toxins when glomerular filtration rate falls. Nevertheless, resistin among others (IL-10, leptin, and adiponectin) were not considered uremic toxins.[1b] Considerably, resistin's contribution to cardiovascular (CV) risk in CKD male patients was highly signified.[60] Surprisingly, such a relationship between resistin and CV risk was substantially modifiable by plasminogen activator inhibitor 1 (PAI-1) concentrations.[60] Outstandingly, resistin was also a marked predictor of CV hospital admissions and renal deterioration in diabetic patients with CKD.[61] Moreover, specifically resistin and urine albumin-to-creatinine ratio (UACR) were independent predictors of progression to ESRD.[61]

Vascular endothelial growth factor (VEGF)involvement in kidney development, microvascular maintenance and

pathophysiology of renal disease can be signified advertently.[62a,b] It was considered substantially as a new therapeutic target for CKD-related hypertension.[62] Surprisingly, Shye et al.[63] found considerably substantial worsening of proteinuria and renal function being appreciably linked to post-intravitreal vascular endothelial growth factor blockade for diabetic proliferative retinopathy. Meanwhile, targeted VEGF neutralization via macrophage polarization could induce long-term renal recovery in CKD.[64] Also, it is taken for a growth factor specific for vascular endothelial cells inducing angiogenesis via binding to vascular endothelial growth factor receptor. Its physiology involves mitogenesis, angiogenesis, and endothelial survival; effects of VEGF on bone marrow cells and hematopoiesis incurs enhancement of vascular permeability and hemodynamic effects.[65] Its pathophysiology is ascribed to solid tumors, hematological malignancies, intraocular neovascular syndromes, inflammatory disorders and brain edema, besides pathology of the female reproductive tract.[65] The levels of SCr, BUN and VEGF in the CKD group were significantly higher compared to respective those of healthy non-CKD controls and VEGF levels associated substantially and proportionally with CKD severity.[66] In effect, a low urinary VEGF-A165b level reflects renal dysfunction in the CKD. Conversely; a high circulating VEGF-A165b level cannot be attributed to decreased renal clearance.[67]

Zinc-α2-glycoprotein (ZAG) promotes lipid metabolism and glucose utilization, and regulates insulin sensitivity.[68] Broadly among other angiogenic factors,[69] ZAG can role as an instrumental cardiovascular protective factor with a favorable metabolic profile for hemodialysis patients[70a,b] predicting associated mortalities[71] and ESRD (End Stage Renal disease) patients.[72] Remarkably, ZAG could inversely associate with pro-atherogenic factors linked to systemic inflammation and oxidative stress. Moreover, plasma ZAG concentrations impartially associated with VCAM-1 (vascular cell adhesion molecule 1)[70] and decreased in CAD patients.[73] It was identified with a novel antifibrotic role as a negative regulator of fibrosis progression- a unifying feature of CKD.[74] Recently, elevated ZAG levels in fibrotic kidney disease were ascribed beneficial effects in an exquisite linkage to tubular cell lipid metabolism, and highly unprecedented avenues in CKD treatment.[75] Exquisitely in T2D patients' ZAG as an adipokine it could be as attained as the early biomarker affinity of diabetic nephropathy.[76] Serum ZAG correlated significantly and positively with estimated GFR (eGFR) but remarkably and negatively with serum creatinine (SCr), HbA1c, Total serum cholesterol, triglycerides, LDL-cholesterol, and urinary albumin-to-creatinine ratio (UACR).

## AIM

Our utmost aim was to investigate the impact of gum arabica CAM on the novel plasma biomarkers of renal damage in Jordanian CKD patients. Therefore the current study is to explore the potential of novel biomarkers plasma levels (namely; resistin, vascular endothelial growth factor, zinc-α2-glycoprotein, ghrelin, kisspeptin, obestatin, highly sensitive C-reactive protein, nesfatin, asymmetrical dimethylarginine and α-klotho) for risk stratification and prognostication, for refining diagnostic and preventive/therapeutic approaches and describe some obstacles that still need to be overcome. We highlight the importance of a collaborative/complementary approach to standardize the integrative use of promising new biomarkers. Finally, we outline the limitations of conventional markers of renal damage as extensions of the pathogenic process occurring at the level of the organ and its functional subunits, with a discussion of the expected pattern of clinical and biochemical progression among CKD patients.

## METHODS

Following obtaining the Institutional Review Board (IRB) approval for conducting this prospective cohort study at the Jordan University Hospital (JUH) (169/2019)/nephrology outpatient clinics; all patients fulfilling the inclusion criteria were recruited after explaining the purpose and the nature of the study and signing an informed consent form. Blood samples (in lithium heparin used for single determinations) were obtained from CKD patients. Forty five patients consuming gum arabica in the past 6 months (cases) and 48 non-gum arabica consumers (controls; age- and CKD stage-matched to cases) were included (Figure 1 of study recruitment flow chart). Inclusion criteria were a) Adults 18-90; b) Stable CKD stages II--V at the baseline visit; c) Attend nephrology clinic regularly for follow up. Exclusion criteria were a) Pregnant ladies; b) Patients on renal replacement therapy; c) Patients treated by complementary and alternative medicine (CAM) other than gum arabica. Urinalysis for proteinuria and glucosuria was conducted routinely at clinics and clinical chemistry analysis was frequented regularly for 2 or 3 successive visits for serum creatinine (sCr), glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG), uric acid, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) as well as fasting lipid profile parameters. Plasma levels of CKD molecular biomarkers were measured by ELISA kits with intra- and inter-assay accuracy and precision CV% 10-12% (kisspeptin, zinc alpha2 glycoprotein, alpha klotho, human asymmetric ADMA, nesfatin-1 from MyBioSourse, USA; resistin, obestatin, ghrelin, CRP and VEGF from Abcam, USA).

### Statistical Analysis

Was performed using SPSS. The independent sample t test, paired t-test, Chi Square and Fisher's exact analyses were performed as appropriate where P values<0.05 were considered significant. Spearman or Pearson ranking of potential cross-correlations were assessed for the clinical and demographic parameters with investigated set of kidney function biomarkers.

## RESULTS

### Clinicodemographic characteristics of the study sample

This study is a part of the previously published cohort study of effect of GA on biomarkers of kidney damage in Jordanian CKD patient (citation).Baseline demographic and clinical

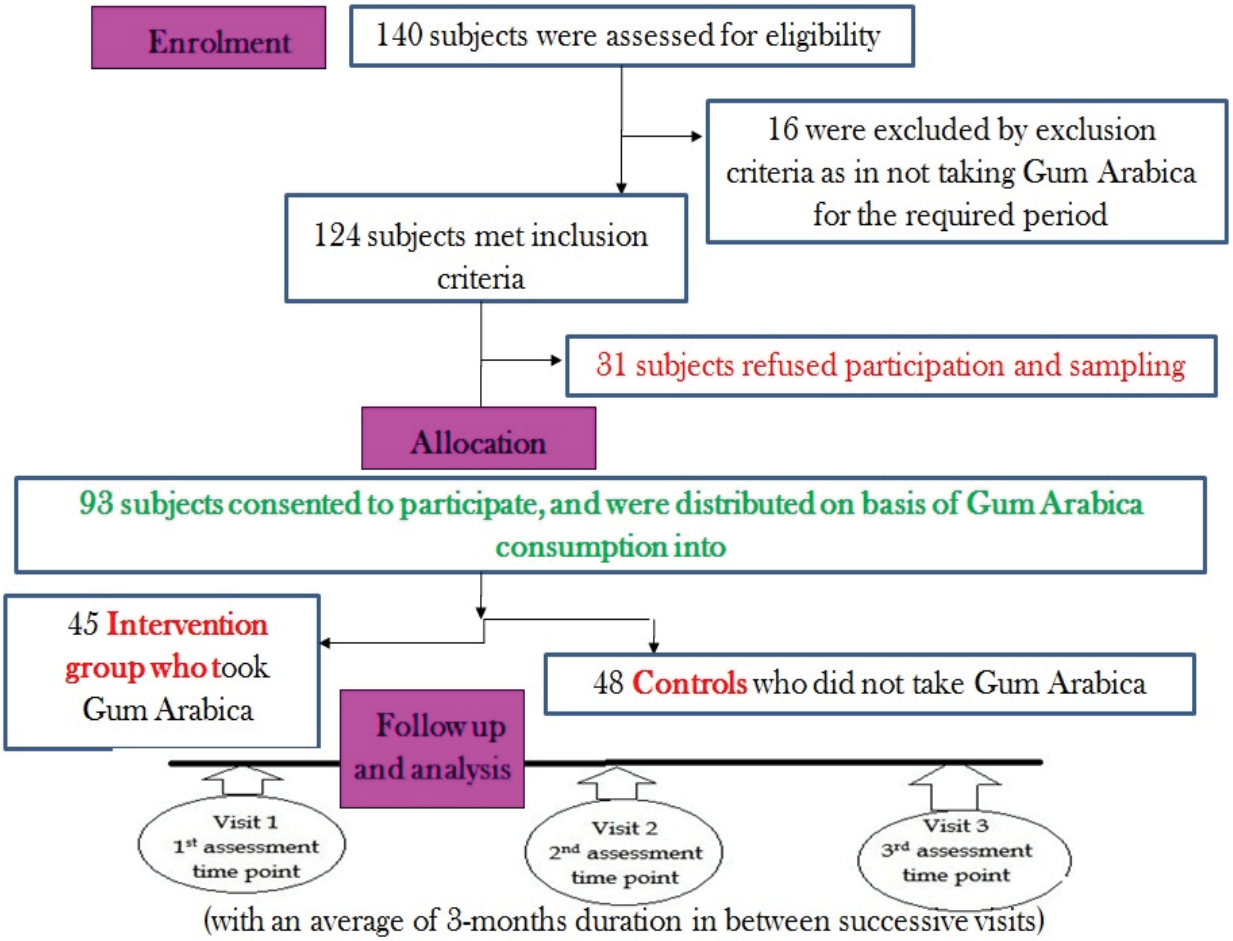


**Figure 1.** Recruitment flow chart

characteristics of study participants with their comparisons between the study groups are shown in Table 1S. Briefly, the study included 93 CKD patients, divided into 45(48.4%) patients who received GA (cases) and 48 (51.6%) patients who did not receive GA (control).The mean age of study participants was 68.12 years, similar for two groups (P value=0.731). Most study participants, 56 (60.2%) were males, and the rest 37 (39.5%) were females, with even gender distribution between the study groups (P value =0.676). Table 1S contains anthropometric and clinical data of study participants. The mean body mass index (BMI) was 31.22 kg/m$^2$; henceforth falling into the obesity category. Cases had significantly higher BMI than the controls (P value =0.048). The most prevalent CKD stage was stage 4 (37.6%) patients, followed by stage 3a (20.4%) and stage 3b (19.4%), with similar distribution between the cases and the controls (P value >0.05).The mean CKD duration was 6.94 years, similar between the two study groups (P value >0.05). Both the frequency and the duration of concomitant conditions (diabetes mellitus, diabetic neuropathy, hypertension, dyslipidemia, coronary artery disease, heart failure and thyroid/parathyroid disorders) were similar between the case and the control groups (P value >0.05 for all). The mean duration of GA use among the cases was 1.3±1.1 (range 0.25-6) years and the mean dose was 1.7±1.0 (range 0.5-6) spoons per day.

**Urinary protein and urine glucose tests results at visit 1**

Table 2S shows the results of urine tests for protein and glucose among the total sample and for the study groups at visit 1. More than quarter of CKD patients (28.6%) had negative test for urinary protein, while relatively similar proportions (ranging between 14.3% and 22.0%) of patients had different degrees of proteinuria. Almost three quarters (74.7%) of CKD patients had negative test for urinary glucose, 14.3% had +1 urinary glucose, and only a minor proportion of patients (ranging between 3.3% and 4.4%) had higher degree of glucosuria (from +2 to +4). There was no significant difference in distribution of proteinuria and glucosuria categories between the cases and the controls (P value >0.05 for all).

**Comparison of baseline kidney function and clinical biochemistry tests between the study groups**

At visit 1, there was no significant difference between the two study groups in estimated glomerular filtration rate (eGFR) , with mean of 34.02±17.72 for the cases and 37.01±16.76 in the controls (in mL/min/1.73m$^2$), P value =0.406, as assessed by the Chronic Kidney Disease Epidemiology Collaboration creatinine

equation (eGFR/CKD-EPI, Table 3S). Evidently comparable findings were obtained for both groups for ESR, CRP, HbA1c and FPG.

**The effect of GA on serum creatinine, clinical chemistry parameters and arterial blood pressure**

Serum creatinine (SCr) levels did not differ between the study groups at visit 1 and at the visits 2 and 3 (P value >0.05 for all; Table 3S). Furthermore, the changes in SCr between visit 2 and visit 1, visit 3 and visit 2 and visit 3 and visit 1 were comparable among the cases as well as the controls equally (P value >0.05 for all). Similar findings were essentially obtainable for serum levels of uric acid and fasting lipid profiling parameters. Notably, SBP mean values (visits 2 and 3; respective P values of 0.028 and 0.018) and DBP mean values (visits 2 and 3; respective P values of 0.033 and 0.025) for cases were reported significantly higher than those of controls.

**The effect of GA on blood inflammatory and cardiometabolic biomarkers**

Table 1 demonstrates differences in blood biomarkers of inflammation and cardiometabolic syndromes between the cases and the controls at the end of the study. Remarkably, plasma concentrations of resistin, and nesfatin-1 in cases were substantially greater compared to controls' (respective P values of 0.047 and 0.005). Nevertheless, obestatin (P value =0.018), kisspeptin (P value =0.006), and VEGF (P value =0.003) were found of pronouncedly lower blood levels in cases in comparison to those of controls. Invariably, ADMA, ZAG, alpha klotho, ghrelin, and CRP lacked in intergroup totality any significant discrepancies in plasma levels in cases vs. those of controls (P values >0.05 for these 5 biomarkers).

**The effect of GA on correlations between blood inflammatory and cardiometabolic biomarkers with clinical and kidney function parameters**

Exquisitely plasma levels of α-Klotho, Kisspeptin, Nesfatin-1 Obestatin, Vascular endothelial growth factor or Zinc-α2-glycoprotein lacked appreciable relations with kidney function parameters in CKD cases on GA modality (Table 2). Inherently obtainable were the substantial inverse correlations of ghrelin with dialysis duration, FBS and UA_1. Most outstandingly were the pronounced proportional associations of sCr levels with all ghrelin, highly sensitive C-reactive protein (hsCRP) and resistin in the same pool of cases. eGFR correlated disproportionally with hsCRP and resistin (Table 2). Unequivocally in CKD controls;

**Table 1:** Comparison of blood biomarkers inflammation and cardiometabolic syndromes between the study groups

| Biomarkers N | | Cases | | | Controls | | | p-value* |
|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | N | Mean | SD | | |
| 1 | Alpha klotho (pg/mL) | 45 | 123 | 59.07 | 43 | 131.81 | 43.4 | 0.429 |
| **2** | C-reactive protein(ng/mL) | 45 | 299.04 | 71.24 | 43 | 301.07 | 49.92 | 0.877 |
| **3** | Ghrelin(pg/mL) | 45 | 99.29 | 96.8 | 43 | 66.48 | 71.05 | 0.073 |
| 4 | Human asymmetric dimethylarginine (ADMA) (μmol/mL) | 45 | 0.563 | 0.186 | 43 | 0.565 | 0.156 | 0.946 |
| 5 | **Kisspeptin (pg/mL)** | **45** | **25.7** | **4.33** | **43** | **28.21** | **3.94** | **0.006** |
| **6** | **Nesfatin-1 (ng/mL)** | **45** | **3.68** | **1.43** | **43** | **2.91** | **1.04** | **0.005** |
| 7 | **Obestatin(pg/mL)** | **45** | **49.15** | **14.25** | **43** | **58.97** | **23.08** | **0.018** |
| **8** | **Resistin (ng/mL)** | **45** | **55.38** | **24.05** | **43** | **44.64** | **25.99** | **0.047** |
| 9 | **Vascular endothelial growth factor (VEGF) (ng/mL)** | **45** | **3196.44** | **324.17** | **43** | **3619.35** | **826.17** | **0.003** |
| **10** | Zinc alpha 2-glycoprtein(ng/mL) | 45 | 862 | 937.39 | 43 | 1057.91 | 269.8 | 0.191 |

*by independent sample t-test
SD: standard deviation

**Table 2:** Correlations between plasma biomarkers and other parameters in cases

| Parameters/CKD plasma molecular biomarkers | Ghrelin | | hsCRP (highly sensitive C-reactive protein) | | Resistin | |
|---|---|---|---|---|---|---|
| | r | P value | r | P value | r | P value |
| DM Duration (years) | **-0.461*** | **0.031** | | | | |
| dose of GA (spoons/day) | | | **-0.294*** | | **0.05** | |
| sCr_2 | **0.371*** | | **0.012** | **0.303*** | **0.043** | |
| sCr_3 | **0.331*** | **0.043** | | | | |
| eGFR | | | **-0.325*** | **0.03** | **-0.303*** | **0.043** |
| FBS | **-0.379*** | **0.01** | | | | |
| Uric acid 1 | **-0.447**** | **0.003** | | | | |

r: correlation coefficient; *statistically significant at p≤0.05.

BMI and weight correlated substantially and inversely with nesfatin-1, ghrelin and kisspeptin among the rest of plasma biomarkers.Importantly Human asymmetric dimethylarginine (ADMA) and Zinc alpha 2-glycoprtein related proportionally and significantly with sCr in GA-naïve-CKD controls (Table 3).

**The effect of GA on correlations between blood inflammatory and cardiometabolic biomarkers with clinical and kidney function parameters in successive visitations**

Most notably resistin had substantially inverse correlations (P values<0.05) with SBP_1 and BBP_2, fasting LDL-C_1 and TC_1. Similar outcomes were not evident among the rest of molecular plasma biomarkers of CKD. Exceptionally pronounced disproportional association of vascular endothelial growth factor with HTN duration was reported in CKD cases on Gum Arabica modality. Markedly SBP negatively associated with both α-Klotho and Nesfatin-1 levels while TG correlated significantly with both Kisspeptin and Obestatin. Exquisitely Zinc-α2-glycoprotein had an inverse relation with TG_2 but a direct relation with DBP_3 (Table 4). Principally both Nesfatin-1 and Zinc alpha 2-glycoprtein correlated substantially and proportionally with SBP. While Kisspeptin had significant and direct relation with TC and TG; ghrelin; conversely, associated inversely and markedly with TG in gum Arabica naïve CKD controls (Table 5).

## DISCUSSION

Our study originated from the observation that patients in nephrology clinics are using Arabic gum, which is freely accessible and used by patients, stemming basically from community members suggestions. Within this scope; we signified adopting a collaborative/complementary strategy to standardize the integrative application of fascinating novel biomarkers. Also the expected pattern of clinical and biochemical progression among patients with CKD was highlighted via the shortcomings of traditional markers of renal damage and pathogenic process occurring at the level of the organ and its workable subunits. Obviously many CAM consumers thought that eating Arabic gum would help in cure of their CKD, and less frequently, it

**Table 3:** Correlations between plasma biomarkers and other parameters in controls

| Parameters/CKD plasma molecular biomarkers | Human asymmetric dimethylarginine (ADMA) | | Nesfatin-1 | | Zinc alpha 2-glycoprtein | | Ghrelin | | Kisspeptin | |
|---|---|---|---|---|---|---|---|---|---|---|
| | r | P value | r | P value | r | P value | r | P value | r | P value |
| Wt_kg | | | **-0.411**** | **0.006** | **-0.355*** | | **-0.358*** | **0.018** | **-0.339*** | **0.026** |
| BMI | **-0.433**** | | **0.004** | | **0.021** | | **-0.265** | **0.09** | | |
| SCr_1 | **0.333*** | **0.029** | | | | | | | | |
| SCr_2 | **0.335*** | **0.028** | | | **0.339*** | **0.026** | | | | |
| SCr_3 | **0.310*** | **0.049** | | | | | | | | |

r: correlation coefficient; *statistically significant at P value≤0.05.

**Table 4:** Correlations between plasma biomarkers and clinical parameters in CKD cases

| Parameters/ CKD plasma molecular biomarkers | α-Klotho | | Ghrelin | | Kisspeptin | | Nesfatin-1 | | Obestatin | | Resistin | | Vascular endothelial growth factor (VEGF) | | Zinc-α2-glycoprotein (ZAG) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | r | P value | r | P value | r | P value | r | P value | r | P value | r | P value | r | P value | r | P value |
| HTN Duration (years) | **-0.326*** 0.04 | | | | | | | | | | | | **-0.317*** | 0.036 | | |
| SBP_1 | | | | | | | | | | | | | | | | |
| SBP_2 | **-0.317*** | 0 | | | | | | | | | | | | | | |
| SBP_3 | | | | | | | **-0.413**** | 0 | | | | | | | | |
| DBP_2 | | | | | | **-0.392**** | 0.01 | | | | | | | | | |
| DBP_3 | | | | | | | **0.336*** | 0 | | | | | | | | |
| LDL-C_1 | | | **-0.347*** | 0.03 | | | | | | | | | | | | |
| TC_1 | | | **-0.388*** | 0.01 | | | | | | | | | | | | |
| TG_2 | | | **-0.394*** | 0 | **0.418*** | 0 | | | **0.390*** | 0.033 | | | | | **-0.477**** | 0 |

R: correlation coefficient; *statistically significant at P value ≤0.05.

**Table 5: Correlations between plasma biomarkers and clinical parameters in CKD controls**

| Parameters/CKD plasma molecular biomarkers | Nesfatin-1 | | Zinc alpha 2-glycoprtein | | Ghrelin | | Kisspeptin | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *P value* | *r* | *P value* | *r* | *P value* | *r* | *P value* |
| SBP_3 | **0.375*** | **0.019** | **0.322*** | **0.045** | | | | |
| TC_2 | | | | | | | **0.392*** | **0.039** |
| TG_1 | | **-0.339*** | **0.035** | | | | | |
| TG_2 | | **-0.124** | **0.529** | **0.445*** | **0.018** | | | |

r: correlation coefficient; *statistically significant at P value ≤0.05

would lower blood pressure. The recommended daily dosage of Arabic gum powder is two table spoons, dissolved in a cup of water, taken once in the morning and once in the evening. We conducted Alshelleh et al.[7] study that examined the impact of Arabic gum on various clinical indicators in patients with CKD, particularly those with diabetes.[7] Apparently Arabic gum showed a promising effect on lowering serum creatinine and eGFR in CKD patients with diabetes. Despite of small sample size and difficulty encountered consequently to prove causality; it seemingly opened our mind to study the effect of this widely used CAM supplement in our region on biomarkers implicated in the pathogenesis and progression of CKD. Invariably proven effects of Arabic gum on decreasing CKD-linked oxidative stress and inflammation may potentially improve the prognosis of patients with ischemic cardiac disease. [8d,e,f, 77a-e] These findings were substantiated by Arabic gum decreasing levels of TGFB1.[78a-e] Purposefully in signifying newer plasma and urine biomarkers for better diagnosis and management of CKD;[79a-e] the comparisons of selected plasma markers between 2 CKD groups (GA consumers vs. non-consumers) could convey its promising effect on CKD clinical parameters and kidney disease progression as in eGFR, lipid profile uric acid levels, blood sugar, hemoglobin levels, body fat, BMI and inflammatory markers.[8a-m, 77a-e, 80a-c]

The problematic limitations of albuminuria and eGFR in predicting the course of DKD were described in depth by Swaminathan et al.[81] Additionally the complex pathophysiology of DKD and the identification of critical biomarkers can lead to more focused and efficient diabetes treatment based on prognosticating progression stages. This lessens the burden of DKD and ESRD by effectively extending the diagnostic window to identify individuals with varying stages of DKD progression. [80a-c] Together the study's results show that combining a variety of complementary biomarkers can improve kidney pathology detection accuracy and provide insight into the molecular mechanisms behind chronic kidney disease (CKD) as well as the relevant therapies. This essentially offers clinicians and clinical researchers a tremendously beneficial way to target high-risk individuals with CKD beside preventing the onset and progression of CKD as a goal for clinical trial researchers and physicians involved in therapy and preventive care.[4,81]Aside from the potential use of exosomes, microRNAs, and microvesicles as CKD and DKD diagnostic tools, [80a-c] precision medicine's use of artificial intelligence (AI) can unquestionably improve the diagnosis and prognosis of microvascular problems.[82] Stopping the onset and progression of CKD is a goal for clinical trial researchers and physicians who are involved in therapy and preventive care.[3,81a-d] Besides, microRNAs, microvesicles and exosomes as future CKD and DKD diagnostic tools; [80a-c]artificial intelligence (AI) implication in precision medicine can definitively facilitate the improvement of diagnosis/prognosis of microvascular complications.[82]

## CONCLUSION

Interestingly in CKD cases on GA modality, ghrelin had substantial inverse correlations with dialysis duration, FBS and uric acid in CKD cases. Pronounced proportional associations of sCr levels were found with ghrelin, hsCRP and resistin in the same pool of cases. eGFR disproportionally correlated with cases' hsCRP and resistin. In GA-naïve-CKD controls; sCr related proportionally and significantly with asymmetric dimethylarginine (ADMA) and Zinc alpha 2-glycoprtein. It is noteworthy that urinary adiponectin is being considered as a novel diagnostic marker for chronic kidney disease (CKD) and could potentially be utilized as a non-invasive urine test. Furthermore, there is a strong association between Interleukins (ILs) 1, 6, and 18, proinflammatory tumor necrosis factor-α (TNF-α), and diabetic kidney disease (DKD).[83a,b] In patients with type 2 diabetes (T2D), it was observed that serum TNFRs had a more significant relationship with albuminuria and eGFR compared to urine TNFRs.[84a-c] In addition, the development of a simple panel test could facilitate the frequent use of various biomarkers in clinical settings with relevant translational importance and evidence. Multiple studies have consistently demonstrated that compared to traditional clinical factors alone, a multimarker score significantly improves the accuracy of prognostic predictions and the classification of acute kidney injury and CKD.[85] Markers indicating damage to the endothelial cells in the renal glomeruli and tubules could be considered for inclusion in larger interventional research studies. The variability of each biomarker between individuals may be increased by using random urine samples, and it may be necessary to verify the findings using either a 24-hour urine collection or first morning void urine samples. Using multiple biomarkers could aid in the development of new approaches for preventing and treating conditions, as well as in assessing the risk of developing these conditions. Additionally, the use of multiple biomarkers could be beneficial in predicting mortality in individuals with heart failure, diabetes mellitus, sickle cell anemia, and atrial fibrillation.[4,86] Overall, more extensive prospective longitudinal studies are needed to confirm our results.

**Limitations**

Initially, the main constraints are the small sample of patients from a single centre and the small number of biomarkers. Furthermore, the assays utilizing enzyme-linked immunosorbents for the single-point assessment of marker plasma levels are still awaiting prospective validation in a limited group concerning their individual urine levels and possible associations with eGFR [84-86] or albuminuria.[87]Promising noninvasive indicators of renal failure include urinary proteins. Regarding this framework, the clinical efficacy of urinary adiponectin as a novel CKD diagnostic index could reduce patient burden by acting as a non-invasive urine test alone.

## AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. All authors contributed equally towards rationale conceptualization, experimental design, data collection and analyses, manuscript write up, and proofreading.All authors read and approved the final manuscript

## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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## ABBREVIATIONS

ADMA: asymmetrical dimethylarginine;

AIP: atherogenecity index of plasma;

BMI: body mass index;

BUN: blood urea nitrogen;

CAR: hsCRP/albumin ratio;

CKD: chronic kidney disease;

CRP: C-reactive protein;

CVD: cardiovascular disease;

DKD: diabetic kidney disease;

eGFR: estimated glomerular filtration rate;

ESR: erythrocyte sedimentation rate;

ESRD: end stage renal disease;

FPG: fasting plasma glucose;

GA gum Arabica;

GFR: glomerular filtration rate;

HbA1c: glycated hemoglobin;

KIM-1: kidney injury molecule-1;

MPV: mean platelet volume;

NGAL: neutrophil gelatinase-associated lipocalin;

NO: nitric oxide;

NOX4/ROS/ERK: NADPH Oxidase 4/ reactive oxygen species/ extracellular signal-regulated protein kinase.

OGTT: oral glucose tolerance test;

PDW: platelet distribution width;

PLCR: platelet/large cell ratio;

ROS: reactive oxygen species;

SCr: serum creatinine;

SDMA: symmetric dimethylarginine;

SCN: sickle cell nephropathies;

T2D: type 2 diabetes;

TGF β1: Transforming growth factor beta1;

UACR: urine albumin-to-creatinine ratio;

VEGF: vascular endothelial growth factor;

ZAG: zinc-α2-glycoprotein

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| **Table 1S:** Demographic parameters and medical history of study participants and their comparison between the groups (N=93) at visit 1 | | | | | |
|---|---|---|---|---|---|
| **Characteristic** | | **Total (**N=93) | **Cases** (N=45) | **Controls** (N=48) | **p-value** |
| **Age,** mean (SD) | | 68.12 (10.01) | 68.49 (10.52) | 67.77 (9.60) | 0.731* |
| **BMI,** mean (SD) | | 31.22 (5.78) | 32.43 (6.50) | 30.05 (4.76) | **0.048*** |
| **Sex,** N (%)@ | **Male** | 56 (60.2%) | 26 (57.8%) | 30 (62.2%) | 0.676** |
| | **Female** | 37 (39.8%) | 19 (42.2%) | 18 (37.5%) | |
| **CKD stage,** N (%) | Stage 2 | 12 (12.9%) | 6 (13.3%) | 6 (12.5%) | 0.912*** |
| | Stage 3a | 19 (20.4%) | 9 (20.0%) | 10 (20.8%) | |
| | Stage 3b | 18 (19.4%) | 7 (15.6%) | 11 (22.9%) | |
| | Stage 4 | 35 (37.6%) | 18 (40.0%) | 17 (35.4%) | |
| | Stage 5 | 9 (9.7%) | 5 (11.1%) | 4 (8.3%) | |
| **CKD duration,** years, mean (SD) | | 6.94 (7.76) | 6.49 (8.86) | 7.37 (6.66) | 0.590* |
| **Presence of diabetes mellitus,** N (%) | | 51 (54.8%) | 24 (53.3%) | 27 (56.3%) | 0.836** |
| **Diabetes mellitus duration,** years, mean (SD) | | 17.14 (8.86) | 16.77 (8.85) | 17.48 (9.01) | 0.777* |
| **Presence of diabetic neuropathy,** N (%) | | 24 (25.8%) | 12(26.7%) | 12(25.0%) | 1.00** |
| **Diabetic neuropathy duration,** years, mean (SD) | | 5.84 (5.13) | 7.13 (5.55) | 5.20 (5.10) | 0.533* |
| **Presence of hypertension,** N (%) | | 86 (92.5%) | 42 (93.3%) | 44 (91.7%) | 1.00** |
| **Hypertension duration,** years, mean (SD) | | 13.49 (9.20) | 13.69 (9.65) | 13.30 (8.85) | 0.847* |
| **Presence of dyslipidemia,** N (%) | | 57 (64.8%) | 29 (70.7%) | 28 (59.6%) | 0.371** |
| **Dyslipidemia duration,** years, mean (SD) | | 8.71 (6.41) | 9.00 (7.50) | 8.44 (5.33) | 0.773* |
| **Presence of coronary artery disease,** N (%) | | 37 (39.8%) | 16 (35.6%) | 21 (43.8%) | 0.526** |
| **Coronary artery disease duration,** years, mean (SD) | | 6.08 (4.97) | 5.08 (3.63) | 6.67 (5.63) | 0.340* |
| **Presence of heart failure,** N (%) | | 7 (7.5%) | 4 (8.9%) | 3 (6.3%) | 0.709** |
| **Heart failure duration,** years, mean (SD) | | 8.33 (1.53) | 8 | 8.50 (2.12) | 0.879* |
| **Presence of thyroid/parathyroid disease,** N (%) | | 14 (15.1%) | 8 (17.8%) | 6 (12.5%) | 0.568** |
| **Thyroid/parathyroid disease duration,** years, mean (SD) | | 5.74 (4.63) | 6.67 (4.97) | 4.81 (4.51) | 0.512* |

*by independent-sample t-test; **by Fisher's exact test; ***by Chi-square test
@within the group
CKD: chronic kidney disease; SD: standard deviation

| **Table 2S:** Urinary protein and urine glucose results at visit 1 | | | | | |
|---|---|---|---|---|---|
| **Results** | | **Total** (N=91), N (%) | **Cases** (N=44), N (%) | **Controls** (N=47), N (%) | **P-value*** |
| **Total Protein** | Nil | 26 (28.6%) | 14 (31.8%) | 12 (25.5%) | 0.058 |
| | 1 | 18 (19.8%) | 6 (13.6%) | 12 (25.5%) | |
| | 2 | 14 (15.4%) | 3 (6.8%) | 11 (23.4%) | |
| | 3 | 20 (22.0%) | 13 (29.5%) | 7 (14.9%) | |
| | 4 | 13 (14.3%) | 8 (18.2%) | 5 (10.6%) | |
| **Urine Glucose** | Nil | 68 (74.7%) | 30 (68.2%) | 38 (80.9%) | 0.488 |
| | 1 | 13 (14.3%) | 9 (20.5%) | 4 (8.5% | |
| | 2 | 3 (3.3%) | 2 (4.5%) | 1 (2.1%) | |
| | 3 | 3 (3.3%) | 1 (2.3%) | 2 (4.3%) | |
| | 4 | 4 (4.4%) | 2 (4.5%) | 2 (4.3%) | |

*By Chi-square test

**Table 3S:** Comparison of eGFR, SBP, DBP and SCr and their respective changes between the study groups at different assessment time points

| Parameter | Cases | | | Controls | | | p-value |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | |
| **eGFR/CKD-EPI** | 45 | 34.02 | 17.72 | 48 | 37.01 | 16.76 | 0.406* |
| **ESR** | 27 | 55.2 | 28.7 | 24 | 52.2 | 33.7 | 0.731* |
| **CRP** | 25 | 20.4 | 36 | 27 | 22.9 | 28.4 | 0.787* |
| **HbA1c** | 45 | 6.62 | 1.36 | 45 | 7.08 | 1.67 | 0.158* |
| **FPG** | 45 | 129.6 | 64.5 | 47 | 140.1 | 73.1 | 0.470* |
| **SCr1** | 44 | 2.1691 | 0.9801 | 48 | 1.9306 | 0.9103 | 0.231* |
| **SCr2** | 45 | 2.2169 | 1.0718 | 48 | 2.0469 | 0.9052 | 0.412* |
| **ΔSCr2-SCr1** | **44** | **0.0223** | **0.3412** | **48** | **0.1163** | **0.2876** | **0.155$** |
| **SCr3** | 38 | 2.3037 | 1.3334 | 45 | 2.1636 | 1.0298 | 0.599* |
| **ΔSCr3-SCr2** | **38** | **0.887** | **0.397** | **45** | **0.8** | **0.303** | **0.912$** |
| **ΔSCr3-SCr1** | **37** | **0.1157** | **0.5346** | **45** | **0.1958** | **0.2868** | **0.416$** |
| **SBP1** | 42 | 145.52 | 16.793 | 39 | 137.64 | 19.45 | 0.055* |
| **SBP2** | 44 | 144.55 | 15.992 | 45 | 136.11 | 19.49 | **0.028*** |
| **ΔSBP2-SBP1** | 42 | -0.67 | 17.75 | 36 | -1.67 | 3.03 | **0.807$** |
| **SBP3** | 44 | 143.02 | 16.97 | 43 | 134.09 | 17.81 | **0.019*** |
| **ΔSBP3-SBP2** | 44 | -1.52 | 19.42 | 43 | -3.16 | 15.18 | 0.663$ |
| **ΔSBP3-SBP1** | 42 | -2.45 | 19.58 | 35 | -4.31 | 17.25 | 0.658$ |
| **DBP1** | 42 | 78.48 | 12.12 | 39 | 77.51 | 12.94 | 0.731* |
| **DBP2** | 44 | 80.48 | 12.498 | 45 | 74.64 | 12.85 | **0.033*** |
| **ΔDBP2-DBP1** | 42 | 2.38 | 11.84 | 36 | -2.83 | 9.3 | **0.036$** |
| **DBP3** | 44 | 78.98 | 10.29 | 43 | 73.79 | 10.86 | **0.025*** |
| **ΔDBP3-DBP2** | 44 | -1.5 | 12.29 | 43 | -0.79 | 10.12 | 0.769$ |
| **ΔDBP3-DBP1** | 42 | 0.76 | 12.18 | 35 | -3.23 | 11.73 | 0.148$ |
| **UA1** | 41 | 7.3 | 1.5 | 46 | 9.2 | 15.6 | 0.447* |
| **UA2** | 41 | 6.8 | 1.6 | 38 | 6.6 | 1.4 | 0.592* |
| **ΔUA2-UA1** | 38 | -5 | 1.7 | 36 | -3.1 | 17.8 | 0.390$ |
| **HDL1** | 40 | 41.7 | 13.3 | 42 | 40.3 | 9.2 | 0.570* |
| **HDL2** | 30 | 42.2 | 12.2 | 31 | 43.1 | 12.5 | 0.770* |
| **ΔHDL2-HDL1** | 26 | 4 | 9.17 | 29 | 3.9 | 8.5 | 0.966$ |
| **LDL1** | 40 | 93.4 | 33.8 | 42 | 106.6 | 37.4 | 0.098* |
| **LDL2** | 30 | 103.1 | 32.2 | 31 | 109 | 46 | 0.569* |
| **ΔLDL2-LDL1** | 26 | 3.7 | 33.3 | 29 | 6.2 | 39.1 | 0.852$ |
| **TC1** | 40 | 150.8 | 38.3 | 42 | 168 | 44.4 | 0.065* |
| **TC2** | 30 | 165.3 | 36.3 | 31 | 166 | 52.4 | 0.954* |
| **ΔTC2-TC1** | 26 | 8.3 | 34.4 | 29 | -2 | 47.4 | 0.359$ |
| **TG1** | 40 | 166.4 | 80.2 | 42 | 164.8 | 63.6 | 0.920* |
| **TG2** | 30 | 189.2 | 78.1 | 31 | 176.5 | 70.2 | 0.507* |
| **ΔTG2-TG1** | 26 | -4 | 69.7 | 29 | -3.5 | 57.5 | 0.979$ |

*by independent sample t-test; $by paired-sample t-test;
Δ: changes between respective visits; SrCr: serum creatinine;
Numbers 1, 2 and 3 indicate visits 1, 2 and 3, respectively
CRP: C-reactive protein; DBP: diastolic blood pressure; eGFR/CKD-EPI: Estimated Glomerular Filtration Rate, Chronic Kidney Disease Epidemiology Collaboration creatinine equation; ESR: erythrocyte sedimentation rate; FPG: fasting plasma glucose; HbA1C: glycated hemoglobin; LDL: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SrCr: serum creatinine; TC: total cholesterol; TG: triglycerides; UA: uric acid