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Comparison between the effects of Gum Arabic and Omega 3 Fatty Acids on The Plasma Level of Kidney Injury Molecule-1 and Kidney Functions in an Experimentally-Induced Model of Early Diabetic Nephropathy

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Abstract
Diabetic nephropathy (DN) is one of the most common devastating complication of diabetes mellitus. Several studies tried to find drugs that could hinder it or prevent it. The current study aims to compare between the effects of Gum Arabic and Omega-3 fatty acids administration on the plasma level of kidney injury molecule (KIM -1) and kidney functions in an experimentally induced model of early diabetic nephropathy in rats.
Methods: *Forty male albino rats were randomly assigned to four groups (n= 10 each): Group I (healthy control), group II (untreated diabetic control), group III (diabetic rats that received Gum arabic in a dose of 7.5 g/kg/day for 3 weeks) and group IV (diabetic rats that received Omega-3 fatty acids in a dose of 400 mg/kg/day for3 weeks after diagnosis of diabetes mellitus).*
Results: *Gum Arabic supplementation significantly decreased KIM-1, fasting blood glucose, proteinuria in the second and third week and improved creatinine clearance when compared to untreated diabetic rats. On the other hand, Omega-3 FA supplementation significantly decreased proteinuria in the second and third weeks compared to untreated diabetic group but it did not show significant effects on the other parameters.*
Conclusion: *GA is beneficial and may hinder the development of early diabetic nephropathy.*
Keywords: *Kidney injury molecule-1, Experimentally induced diabetes mellitus, Diabetic nephropathy, Kidney functions, Gum Arabic, Omega-3 fatty acids, Streptozotocin.*

Introduction

The prevalence of diabetes mellitus has been increasing in the last decades.(1) It is a group of metabolic derangements characterized by hyperglycemia resulting from defective insulin secretion, action, or both. The chronic hyperglycemia is associated with long-term damage of different organs as the kidneys, the eyes, the nerves, the heart, and blood vessels.(2) In fact, diabetic nephropathy has become the most common cause of end-stage renal disease worldwide.(3)

Medicinal foods are prescribed frequently even when their biologically active ingredients are still unknown, because of their safety, effectiveness, and availability.(4) One of these is Gum Arabic. It is a dietary polysaccharide extracted from either Acacia Senegal or A. seyal trees, which are cultivated in the Sudan as a cash crop in agro forestry systems.(5) GA is widely used in the pharmaceutical, cosmetic and food industries as a stabilizer and emulsifier. It is also used in the traditional treatment of patients with chronic kidney disease in some Middle Eastern

countries.[6] Another medicinal food that reported in literature is Omega-3 fatty acids (s). They are polyunsaturated fatty acids (PUFAs) derived from fish oil; the three types are α-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).(7)Epidemiological studies suggest that n-3 PUFA slow the progression of renal dysfunction, e.g., attenuate the decrease in creatinine clearance in healthy older people[8], lessen the risk of albuminuria in type 1 diabetic patients[9], and slow the progression of albuminuria in older patients with type 2 diabetes.[10]

Kidney injury molecule-1 (Kim-1) is a type I trans-membrane glycoprotein expressed on renal proximal tubule epithelial cells that undergo regeneration.[11] Many studies indicate that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis.[12] There are several characteristic features of KIM-1 that can be used as an ideal marker of kidney injury like the absence of KIM-1 expression in the normal kidney.[13] Several studies reflect the role of KIM-1 as a biomarker for diagnosis and prognosis of diabetic nephropathy among patients.[12,14,15]

Thus, diagnosis of diabetic nephropathy (DN) in an earlier stage is critical and helps to reduce morbidity and mortality.

Aim of the Study

The current study aims to compare between the effects of Gum Arabic and Omega-3 fatty acids administration on the plasma level of kidney injury molecule (KIM -1) and kidney functions in an experimentally induced model of early diabetic nephropathy in rats.

Material and Methods

After the approval of the Ethics Committee of the Faculty of Medicine, Alexandria University, this study was carried out on 40 male Albino rats weighing 200-250 g. Rats were maintained under standard conditions with free access to food and water. Type I DM was induced in thirty rats by a single intraperitoneal injection of Streptozotocin (STZ) (Sigma, Chemicals, St. Louis, MO) in a dose of 55 mg/kg, dissolved in sodium citrate buffer.[16] Only rats showing glucosuria > 50 mg/dl by strip (Medi-Test Combi 3A Strips; Germany), three days after injection of STZ were considered diabetic and were included in the study.[17] No hypoglycemic drugs were given to the rats during the study period. All animals were treated in accordance to the declaration of Helsinki for treating laboratory animals.

Rats were randomly divided into four groups:

- Group I (Healthy control): 10 non-diabetic rats. Each of them received a single intraperitoneal injection of 0.01 mmol/L Sodium Citrate, pH =4.

- Group II (untreated diabetic): 10 diabetic rats were given oral saline daily, in a same volume as the drugs, starting the first dose on the same day of diagnosing diabetes.

- Group III (Gum Arabic treated group): 10 diabetic rats that received given Gum Arabic, by oral gavage, in a dose of 7.5 g/kg/day for 3 weeks[18], starting the first dose on the same day of diagnosing diabetes.

- Group IV (Omega-3 treated group): 10 diabetic rats that received omega -3 fatty acids, by oral gavage in a dose of 400 mg/kg daily for 3 weeks starting the first dose on the same day of diagnosing diabetes.[19]

The following parameters were weekly measured:

- Fasting blood glucose level (mg/dl) by glucose oxidase (GOD)-peroxidase (POD) method for assessment of diabetic state. (Diamond Diagnostic; Germany).[20]
- 24 hours total urinary protein concentration (mg/24 h) by Folin-Lowry colorimetric Method for assessment of diabetic nephropathy (Bio-diagnostic; Paterson, New Jersy, USA).[21]
- Serum urea level (mg/dl) by enzymatic method (Modified Berthelot reaction) for evaluation of renal function. (dp international; Tuscaloosa: USA).[22]
- Serum and urinary creatinine level (mg/dl) by a colorimetric kinetic method (Bio-diagnostic; Paterson, New Jersy, USA).[23] After measurements; creatinine clearance was

calculated using the following formula:[24] Creatinine clearance (ml/min) =(creatinine in urine(mg/dl)x volume of urine(ml/24hrs))/ (serum creatinine(mg/dl)x 1440)

- Plasma level of "kidney injury molecule-1" by ELISA technique, according to the manufacturer's instructions.(Biotech; Shanghai; China).[25]

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were:

- F-test (ANOVA): For normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pair wise comparisons
- ANOVA with repeated measures: For normally distributed quantitative variables, to compare between more than two periods or stages, and Post Hoc test (Bonferroni adjusted) for pair wise comparisons
- Kruskal Wallis test: For abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pair wise comparisons
- Friedman test: For abnormally distributed quantitative variables, to compare between more than two periods or stages and Post Hoc Test (Dunn's) for pair wise comparisons

Results

Intraperitoneal injection of Streptozotocin lead to development of hyperglycemia in group II, where fasting blood glucose level was significantly higher than group I at each point of the study. Treatment of rats having type I DM with Gum Acacia lead to significant reduction of blood glucose level as compared to untreated diabetic rats (263.29 ± 43.35, 260.71 ± 43.67 and 282.81 ± 64.41versus 389.85 ± 115.77, 369.16 ± 98.11 and 443.96 ± 127.59 mg/dl in untreated diabetic rats, p=0.027, p=0.015 and p=0.035 respectively), although it was higher than healthy rats (263.29 ± 43.35, 260.71 ± 43.67 and 282.81 ± 64.41versus 80.0 ± 7.02, 78.50 ± 5.58 and 77.90 ± 6.37mg/dl in healthy non diabetic rats, p=0.006, p=0.019 and p=0.004 respectively). On the other hand, treatment of rats with Omega-3 did not cause significant difference between it and untreated diabetic rats. In comparing between the two treated groups, the fasting blood glucose level was lower in the GA treated group with significant difference between GA treated group and Omega-3 treated group in the second week (260.71 ± 43.67 mg/dl versus 348.46 ± 78.07 mg/dl respectively, p= 0.047).(figure 1).

In the first week of the study, there was no statistical difference in urinary protein levels between the four studied groups (p= 0.067). Urine protein levels started to be significantly higher in the diabetic groups than the healthy control group from the second week. However urine protein levels in GA and Omega-3 groups were significantly higher than healthy control group, they were significantly lower than that of diabetic control group in the second and third weeks (4.13 ± 1.05 and 5.08 ± 1.92 mg/24 h in GA treated group and 4.04 ± 0.79 and 5.39 ± 1.77 mg/24 h in Omega-3 treated group versus 6.03 ± 2.31, 10.43 ± 2.75 mg/24 h in untreated diabetic control, p= 0.017, <0.001).(figure 2).

The serum urea levels were significantly higher in untreated diabetic than healthy control rats at each point of the study, with the highest significance detected in the third week (p <0.001). Gum Arabic lowered serum urea levels so there were no significant difference between it and healthy control rats. In addition, serum urea levels were also significantly lower than the untreated diabetic rats in the third week (58.38 ± 11.50 mg/dl in GA treated group versus 88.18 ± 23.52 mg/dl in diabetic control group, p=0.001). Serum urea levels were significantly higher in Omega-3 treated rats in the

first and third weeks, while it was non-significant in the second week as compared to the healthy control group. In comparing serum urea between Omega-3 treated group and diabetic control group, there was no significant difference along the three studied weeks. (figure 3).

The mean creatinine clearance in untreated diabetic rats significantly decreased below that of healthy control rats at each point of the study ($p < 0.001$). Creatinine clearance in GA treated rats was significantly higher than that of untreated diabetic control group along the three studied weeks (0.92 ± 0.28, 0.85 ± 0.40 and 1.04 ± 0.33 ml/min in GA treated group versus 0.60 ± 0.34, 0.45 ± 0.20 and 0.40 ± 0.18 ml/min , $p = 0.048$, 0.018 and 0.001 in the first, second and third week respectively) However, Gum Arabic- treated rats had a significantly higher creatinine clearance in the third week than omega3 treated rats (1.04 ± 0.33 ml/min versus 0.68 ± 0.33 ml/min respectively, $p= 0.043$). (figure 4).

KIM-1 levels in untreated diabetic rats were significantly higher than those of healthy control group in all the studied weeks ($p= 0.001$). KIM-1 levels in GA treated group were also significantly lower than those of untreated diabetic rats in all studied weeks (0.25 ± 0.23, 0.32 ± 0.19 and 0.44 ± 0.20 ng/ml versus 0.72 ± 0.54, 1.21 ± 0.58 and 1.69 ± 0.58ng/ml in untreated diabetic rats, $p = 0.045$, 0.003 and 0.001 respectively). However, Gum Arabic failed to lower KIM-1 levels to the normal non-diabetic levels, and were still significantly higher than those of healthy rats (0.25 ± 0.23, 0.32 ± 0.19 and 0.44 ± 0.20 ng/ml versus 0.06 ± 0.01, 0.06 ± 0.01and 0.06 ± 0.01ng/ml in healthy non diabetic rats, $p = 0.045$, 0.003 and 0.001 respectively). KIM-1 levels in Omega-3 treated group were also significantly higher in the first and third weeks, compared to the healthy control group, while no significant difference in the second week. Gum Arabic - treated rats had a significantly lower KIM-1 in the first and second weeks than omega3 treated rats (0.25 ± 0.23and 0.32 ± 0.19 ng/ml versus 0.63 ± 0.23 and 0.86 ± 0.27 ng/ml respectively, $p=0.014$, $p=0.018$). (figure 5).

Histopathological findings of kidney tissue sampling

Rats in the healthy control group and GA treated group showed normal kidney architecture and histology and complete absence of interstitial fibrosis (Figure 6, 7). While in diabetic control rats showed increased mesangial matrix with glomerulosclerosis and thickened glomerular basement membrane (figure 8). In rats treated with Omega 3; the study showed mild increased mesangial matrix and cellularity and mild thickening of the glomerular basement membrane (figure 9).

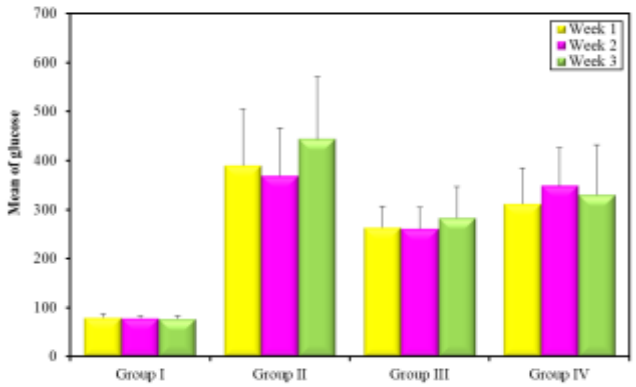

Fig. 1 Fasting blood glucose in mg/dl in the different studied groups

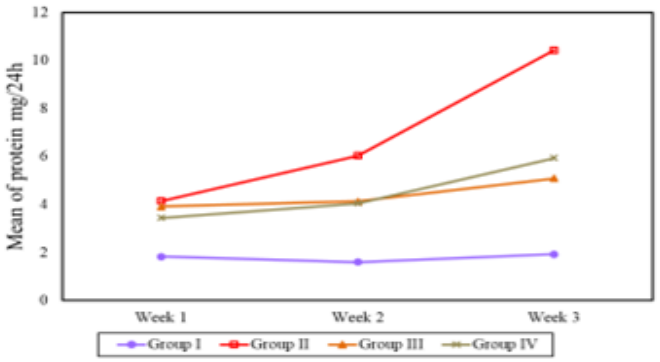

Fig. 2 Proteinuria in mg/dl in the different studied groups

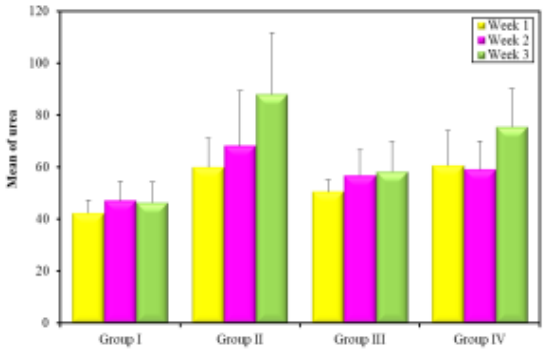

Fig. 3 Serum urea in mg/dl in the different studied groups

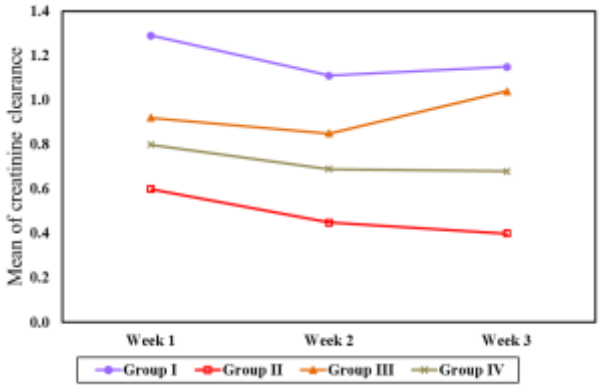

Fig. 4 Creatinine clearance in ml/min in the different studied groups

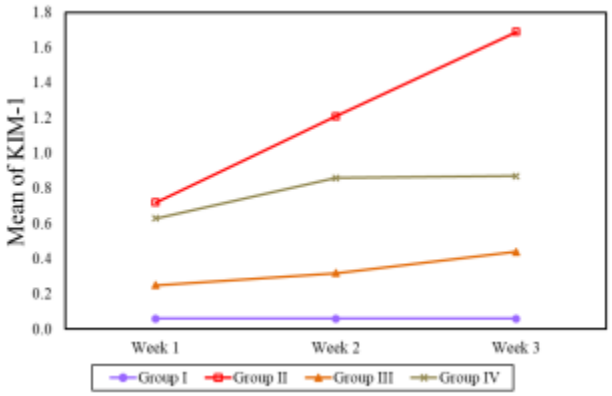

Fig. 5 Plasma level of KIM-1 in ng/ml in the different studied groups

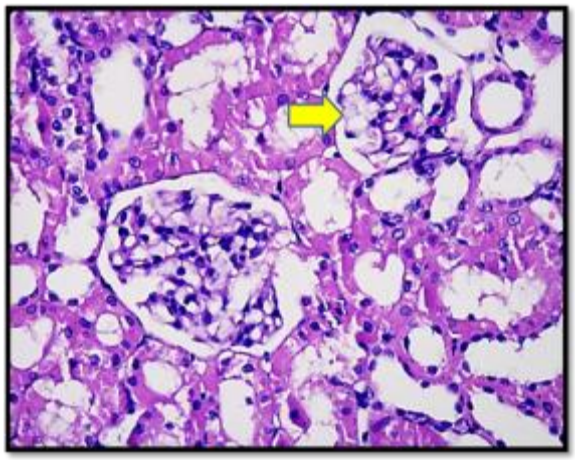

Fig. 6 Histopathology of renal tissue of healthy control rats: normal renal tissue showing normal thickness of the glomerular basement membrane (arrow) and normal glomerular cellularity (H&E x400)

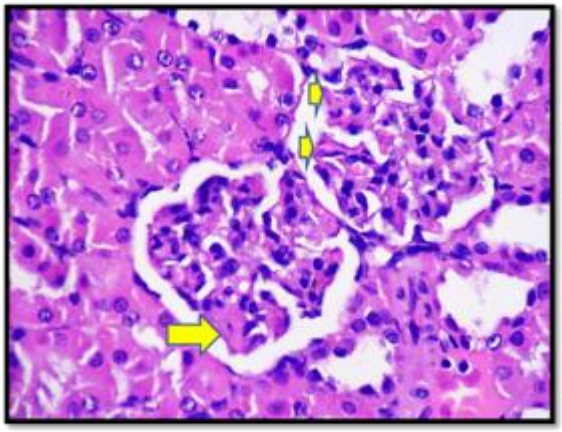

Fig. 7 Histopathology of renal tissue of untreated diabetic rats showing increased mesangial matrix with glomerulosclerosis (arrow) and thickened glomerular basement membrane (arrow heads) (H&E x400)

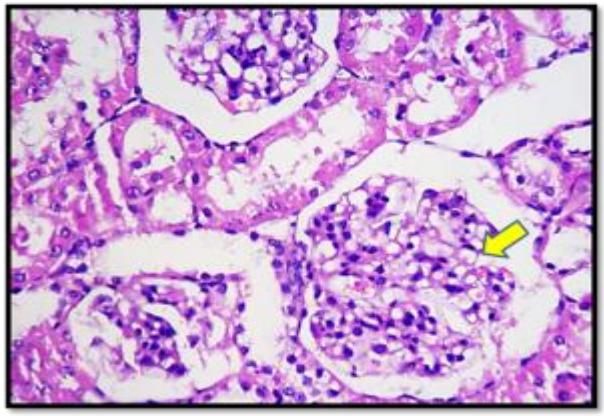

Fig. 8 Histopathology of renal tissue of Gum A treated rats showing average mesangial matrix and normal thickness of the glomerular basement membranes (arrow) (H&E x400)

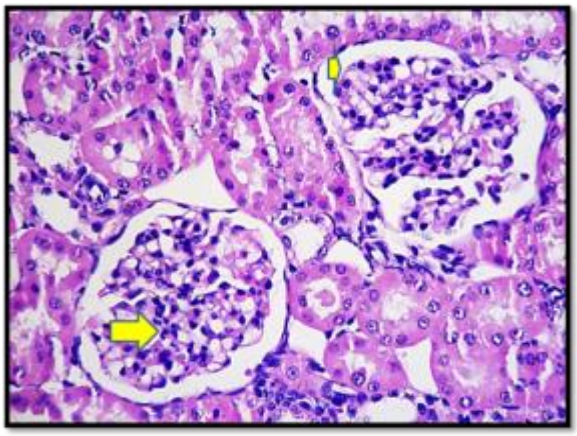

Fig. 9 Histopathology of renal tissueof Omega-3 treated rats showing mild increased mesangial matrix and cellularity (arrow) and mild thickening of the glomerular basement membrane (arrow head) (H&E x400)

Discussion

Diabetes Mellitus (DM) is one of the most common metabolic disorders worldwide and its prevalence has been increasing.[1] Morbidity and premature mortality in diabetes mellitus relate mostly to the development of late complications affecting multiple organ systems. Uncontrolled high blood glucose level is a major factor leading to diabetic complications as diabetic nephropathy. Diabetic nephropathy, has become the most common aetiology of end-stage renal disease (ESRD) worldwide.[3] Therefore, studies suggest that proper control of blood glucose is the most important factor in managing diabetes and its related end-organ damage.[26]

In the present study, fasting blood glucose level was significantly higher in the untreated diabetic group than in the healthy control group. This was expected due to the cytotoxic effect of Streptozotocin on ß-cells of islands of Langherhans with liberation of free radicals and toxic amount of nitric oxide which cause cellular necrosis.

Treatment of rats with GA lead to significant decrease of fasting blood glucose levels as compared to untreated diabetic rats but it did not return back to normal levels. This effect of GA may be due to its power to inhibit intestinal glucose absorption via interaction with membrane sodium-glucose linked transporter (SGLT1). A previous study also found that GA significantly blunted the increase in body weight, fasting plasma glucose and fasting insulin concentration during intake of a high fibre diet.[27] Similar results were reported by Musa H. et al.[4] who studied a model of diabetes established by intraperitoneal injection of Streptozotocin (STZ) in rats. They found that after 30 days, GA significantly decreased serum glucose level compared with untreated diabetic group. This hypoglycemic effect is of great therapeutic importance as prolonged elevated blood glucose levels (i.e. poorly controlled diabetes) is considered the major underlying mechanism causing diabetic nephropathy and chronic kidney disease

Contradictory results were reported by Naser et al, [28] who studied Akita mice, which spontaneously develop insulin deficiency and hyperglycemia. The researchers found that GA shows a tendency to slightly decrease the plasma glucose concentration, without reaching statistical significance. However, the treatment significantly reduced the urinary glucose excretion.

Omega-3 fatty acids supplementation failed to lower the fasting blood glucose compared to untreated diabetic rats. Similar results were obtained by a meta-analysis study that included 20 randomized clinical trials on the effects of Omega-3 fatty acid supplementation on glucose control and lipid levels in type 2 diabetic patients.[29] Contradictory to the previous results, Garman J. et al.[30] reported that canola oil supplementation, (which is rich in Omega-3 FAs) reduced blood glucose levels in rats with diabetic renal disease. In addition, Lee S. et al.[31] found that elevated blood glucose levels seemed to be lowered by Omega-3 FA supplementation in comparison to olive oil in diabetic patients. Similarly, Han E. et al,[9] documented that fasting and postprandial blood glucose levels were significantly decreased after Omega -3 FAs supplementation and suggested that improved hyperglycemia may contribute to renal function maintenance.

Early DN is clinically diagnosed by the leakage of albumin in urine.[32] This pathological change is caused by disturbed glomerular filtration barrier including endothelial cell injury, loss of podocytes, thickening of the glomerular basement membrane and expansion of the mesangium. These changes are due to oxidative stress, activation of renin angiotensin system and mostly accumulation of advanced glycation end products, leading to protein damage. The continuous persistent leakage of these proteins into urine results in overt DN.[33] i.e., proteinuria reflects glomerular dysfunction and it is usually used as a marker of glomerular damage.[34]

In the present study, untreated diabetic rats showed higher urinary protein excretion that was significantly higher in the second and third weeks when compared with values from healthy control rats. Histopathological study of renal tissues of these rats showed increased mesangial matrix with

glomerulosclerosis and thickened glomerular basement membrane. These findings are consistent with previous studies of STZ-induced diabetes in rats that demonstrated the presence of glomerular and mesangial cell changes in STZ-induced DN as early as day 3. These changes increased progressively throughout short term diabetes (up to 3 months) as well as long term diabetes (exceeding 8 months).[4,35,36,37]

Although urinary protein levels in GA and Omega-3 treated groups were significantly higher than healthy control group, proteinuria started to be significantly lower than of untreated diabetic rats at the end of the second week. It continued to be significantly lower in the third week. However, the development and progression of proteinuria were slower and non-significant in GA treated rats in comparison to those treated with Omega-3 FAs. Previous studies are in agreement with these results. In fact, Nasir O. et al,[28] and Musa H. et al,[4] reported that the proteinuria was significantly decreased by GA treatment .This is beneficial as decreased proteinuria is expected to delay the progression of renal disease.

Moreover, in the current work, histopathological examination of kidneys of GA treated rats showed average mesangial matrix and glomerular basement membranes in contrast to the pathological changes observed in the untreated diabetic group. Similar improvement was reported by Musa H. et al,[4] where diabetic rats that received gum arabic had less tubulointerstitial collagen compared to untreated diabetic rats. Ali B. et al,[38] also reported that GA significantly lowered the extensive signs of inflammation and fibrosis in kidneys of the adenine-induced chronic renal failure in rats. Garman J. et al.[30] even stated that the renal changes reported in the untreated diabetic rats were completely absent in the diabetic rats treated with Omega-3 rich diet.

In fact, diabetes mellitus and hypertension raise the intraglomerular pressure, which leads to podocyte and tubular injury resulting in albuminuria. If left untreated, this leads to persistent inflammation, mesangial cell activation, and glomerulosclerosis, which result in a decline in glomerular filtration rate (GFR). Animal models suggest that the Omega-3fatty acid supplementation prevents the development of diabetic kidney disease.[30] In addition, fish oil supplementation also lowers inflammation and vascular stiffness with an improvement in blood pressure.[39]

Long chain omega-3-PUFA modulate inflammatory pathways by competing with the enzymatic metabolism of omega- 6 PUFA (arachidonic acid), which is converted to pro-inflammatory eicosanoids such as prostaglandins, thromboxane, and leukotrienes. Eicosapentaenoic acid is metabolized to the prostaglandins (PGE3), thromboxanes (TXA3), and leukotrienes (LTB5), which exert anti-inflammatory and anti-coagulant effects.[40] In addition to anti-inflammatory properties, omega-3 PUFAs possess several other potentially beneficial properties, including anti-lipidemic, anti-hypertensive, and anti-coagulant actions, and they have recently been demonstrated to modulate gastrointestinal microorganisms.[41] Furthermore, in animal studies, supplementation with omega-3 PUFA improved insulin sensitization, potentially via increased levels of adiponectin, an emerging protective risk factor, reduced inflammation and thus decelerate the occurrence of proteinuria.[42,43]

Similar results were reported by other studies as Han E. et al,[9] who found that Omega 3 FA supplementation in diabetic patients with hypertriglyceridemia shows benefits of reducing albuminuria and maintaining renal function. The effects are dependent on the daily dose of Omega 3FA. Also, in a meta-analysis of trials done by Miller E et al.[44] in patients with diabetic nephropathy, lupus, or IgA nephropathy have suggested a greater reduction in urinary protein excretion after omega-3 PUFA supplementation with median follow-up 9 months.

Serum urea level measurement is widely used in monitoring kidney functions especially in diabetic patients when microalbuminuria has been confirmed.[45] In this study, serum urea level in untreated diabetic rats was significantly increased in the third week compared to that of the healthy

control rats. This increase was expected due to the injurious effect of hyperglycemia on renal functions.

Serum urea level was significantly lower in GA treated rats than in untreated diabetic rats in the third week. This is highly suggestive that prolonged use of GA may contribute to further decrease in serum urea level. Similarly, Nasir O. et al,[28] found that serum urea concentration and fractional urea excretion decreased in akita +/– mice after starting treatment with GA. It also increased the release of ADH. On the other hand, Omega-3 FAs supplementation showed no beneficial effect on serum urea levels as it progressively increased along the three studied weeks. Serum urea level of Omega-3 treated rats was significantly higher than in both healthy control and GA treated groups.

The laboratory test most commonly used to asses kidney functions is the glomerular filtration rate (GFR). In clinical practice and animal experiments, the GFR is estimated by methods and/or equations which rely on measuring urinary creatinine, serum creatinine and 24h urine flow.[46] Yearly estimation of serum creatinine and eGFR should be done in all diabetic patients to monitor possible decline in renal functions.[47]

In the current study, treatment of diabetic rats with GA lead to improvement of kidney functions as demonstrated by a higher creatinine clearance (which reflects the GFR) than that of untreated diabetic rats along the three studied weeks . In fact, the creatinine clearance returned to normal levels of healthy control group. On the other hand, Omega-3 failed to raise creatinine clearance to normal levels although it succeeded in improving it as compared to untreated diabetic group. This potential renoprotective effect of GA is multifactorial. It may be due to decreased blood glucose level, and a possible antioxidant action of the gum. It has been also hypothesized that gum Arabic induced a modest nephroprotective in gentamicin (GM)-induced nephrotoxicity, probably through its oral sorbent action. Others claimed that the nephroprotective action of gum Arabic in GM-treated rats is due to a possible antioxidant action of the gum, although others could not confirm this antioxidant action.[48] In addition, formation of short-chain fatty acids such as butyrate, which are produced during GA degradation by intestinal bacteria, which have been shown to increase glomerular filtration rate and renal blood flow.[49] Although Nasir O. et al,[50] reported that GA supplementation to healthy mice significantly increased their creatinine clearance, they failed to prove this effect in diabetic rats.[28] In previous studies, Ali B. et al.[51] and Suleimani Y. et al.[52] studied the effect of GA on blood pressure in rats with adenine-induced chronic renal failure, reported that treatment with GA significantly minimize the decrease in creatinine clearance caused by adenine.

As regards Omega-3, Garman J. et al.[30] studied the effect of two types of Omega-3 fatty acid rich diets on diabetic nephropathy in humans and rats and did not identify any changes in creatinine clearance among any of their treatment groups. Also, in a randomized controlled clinical trial performed by Soleimani A. et al.[53] on 60 patients with DN; there was no significant difference in creatinine clearance between the patients who received placebo and Omega-3 FA.

KIM-1 is a type I trans membrane protein that is not detected in normal kidneys but was up regulated in renal proximal tubules after injury.[12] It has proved to be an indicator of kidney injury in the rat, outperforming serum creatinine as a predictor of histopathological changes in the proximal tubules.[54]

Plasma levels of KIM-1 in untreated diabetic rats started to increase significantly than those of healthy group I rats as early as the end of the first week. This indicated that there was a tubular injury caused by hyperglycaemic state induced by STZ. Up to date, only a limited number of studies have investigated the association of tubular markers such as KIM-1 with the severity of chronic kidney disease in DN. Nauta et al.[55] reported that increased urinary KIM-1 correlated with diabetes.

KIM-1 levels were elevated in the first week even before the occurrence of albuminuria in the second week. This classifies KIM -1 as an early indicator of

renal injury. KIM-1 is an indicator of kidney injury in the rat, outperforming BUN and serum creatinine as predictors of histopathological changes in the proximal tubule.[54] This trans-membrane glycoprotein is expressed on renal proximal tubule epithelial cells undergoing regeneration after toxic or ischemic injury.[11] i.e., Kidney injury molecule-1 (KIM-1) is believed to play a role in tubulo-interstitial damage.(56) Tubular KIM-1 expression was also observed in human renal biopsies after ischemic or toxic acute tubular necrosis and in tubular cells adjacent to renal carcinoma cells. [57-59] These studies specifically reported KIM-1 expression in dedifferentiated tubular epithelium, which suggests a role for KIM-1 in tubular fibrosis.

Our results coincide with those of a recent study that reported elevated KIM-1 levels in diabetic patients with normo-albuminuria[55], indicating that renal tubular damage may be involved in early stages of the development of diabetic nephropathy.

Plasma levels of KIM-1 in the GA treated group started to decrease significantly below than those of untreated diabetic rats as early as the end of the first week. Though it increased at the end of the second and third week, it continued to be significantly lower than that of untreated diabetic rats in all the studied weeks. Nevertheless, H and E staining of renal tissues showed normal kidney architecture and histology, with absence of interstitial fibrosis.

These findings reinforce the protective properties of Gum Arabic, previously suggested by other researchers that demonstrated that acacia gum (AG) treatment was effective in ameliorating several biochemical and histopathological indices, and motor and behavioral changes in adenine-induced CRF.[60,61] It is to be noted that in patients with CRF in the Sudan, claim that Gum Arabic intake was able to decrease urea and creatinine plasma concentrations and reduced the need for dialysis from 3 to 2 times per week.[62]

Omega 3 failed to lower the plasma levels of KIM-1 compared to that of untreated diabetic rats in the 3 studied groups. It continued to be significantly higher than that of healthy rats in all the studied weeks.

Conclusion

From the previous findings, we conclude that KIM-1 is an early indicator of kidney injury in diabetic rats, that increases in plasma even before the appearance of proteinuria and elevation of serum creatinine.

Treatment of diabetic rats with Gum Arabic is rather more beneficial than with omega 3 FA as GA decreases glucose absorption, fasting blood glucose levels, KIM -1 levels, elevates the creatinine clearance to near normal levels and prevents and/or hinder development of histopathological changes pathognomonic of diabetic nephropathy, better than omega 3 FA.

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