

The Scientific Journal of Medical Scholar



The Scientific Journal of Medical Scholar

Volume 2020, Issue 1, January 2020

e-ISSN: 2833-3772

Contact emails: Info@realpub.org; Realpub044@gmail.com



e-ISSN: 2833-3772



Original Article

Renal Changes (Structural and Functional) in The High Fat Diet-Induced Obesity and The Effect of Food Restriction: An Experimental Study

Reda S. Taha¹, Ahmed S. Abdel Monsef², Mohamed E. Amer³, Medhat M. Darwish^{4*}

¹ Department of Anatomy, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.

² Department of Physiology, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.

³ Department of Histology, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.

⁴ Department of Biochemistry, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.

Article information

Submitted: September, 11th, 2019

Accepted: December, 28th, 2019

Published: January, 1st, 2020

DOI: 10.55675/sjms.v2020i1.37

Citation: Taha RS, Abdomonsef AS, Amer ME, Darwish MM. Renal Changes (Structural and Functional) in The High Fat Diet-Induced Obesity and The Effect of Food Restriction: An Experimental Study. SJMS 2020 January (1): 7- . DOI: 10.55675/sjms.v2020i1.37

ABSTRACT

Introduction and aim: Obesity is a worldwide epidemic and nearly affects every organ. However, the renal changes in obesity are not sufficiently addressed. Thus we aimed to investigate the effects of high-fat diet induced obesity on the kidney and explore the effect of caloric restriction on the renal changes associated with obesity.

Methodology: Thirty male albino rats, 160-180 g included and divided into three equal groups. The first is the control group (received nothing except normal diet). The second is the high fat diet-fed group, where rats fed on high fat diet for 12 weeks. The third group fed as the second one for 12 weeks followed by diet restriction for 6 weeks by feeding on normal chow diet. The following measurement were recorded: 1) Inital and final body weight, 2) serum value of different biochemical parameters (lipid profile, glucose, insulin, cytokines, inflammatory markers and renal function tests). Finally, kidney was extract, fixed and prepared for histopathological examination.

Results: The final weight significantly increased in the obese than the control and diet restriction groups (421.0±17.13 versus 279.50±11.17 and 333.0±13.33 g, successively). The total cholesterol, TG, LDL, vLDL, glucose, insulin, HOMA-IR, IL-6, leptin, resistin, TNF- α , CRP and Plasminogen activator inhibitor-1, creatinine, urea, protein in urine, uric acid were significantly higher in obese than control and diet-restriction groups. However, HDL and adiponectin were significantly reduced in obese than the control and diet restriction groups. The diet restriction significantly improved laboratory values, but it remains significantly different than the control group. The correlation between weight gain with other variables and renal structural changes confirmed the laboratory results.

Conclusion: Obesity is associated with functional and structural renal changes. The potential mechanisms involve inflammation, lipotoxicity and perhaps other unknown mechanisms. Weight reduction constitutes the most effective intervention to guard or treat obesity-associated chronic kidney disease.

Keywords: Obesity; Diet Restriction; Cytokines; Lipids.



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* Corresponding author

Email: meed7atdaarwish@gmail.com

INTRODUCTION

Over the last decades, there was a worldwide increase of obesity reaching an epidemic. In 2011, about 1.46 billion adults were overweight, 502 million adults were obese ⁽¹⁾. In industrialized countries, the obesity is considered a first order public health problem, that associated with a reduction in the overall life expectancy ⁽²⁾. Obesity-associated comorbid conditions included diabetes mellitus, cardiovascular disease, dyslipidemia, steatohepatitis, splenomegaly, chronic kidney diseases and certain types of cancer. In addition, 20.0%, 28% of all kidney cancers in males and females respectively, could be prevented by preservation of appropriate body weight. However, the pathogenic mechanism of obesity associated kidney cancers remains largely unrecognized ⁽³⁻⁵⁾.

Obesity is a complex condition with many pathophysiological mechanisms. It is often complicated by metabolic disorders, hypertension and cardiovascular diseases ⁽⁶⁾. However, renal effects of obesity, especially induction of new-onset renal disease did not well-recognized ^(7,8). Prior studies demonstrated that, kidney disease in obesity is stimulated by insulin resistance and truncal obesity ^(9,10), even in absence of clinical hypertension, diabetes mellitus or pre-existing renal disorders. Thus, obesity-associated metabolic syndrome may initiate renal destruction before the development of overt clinical hypertension and diabetes mellitus ^(11, 12). Moreover, central obesity is a major risk factor for the development diabetes and hypertension, which together account for about 70% of all cases of end-stage renal disease (ESRD) ⁽¹³⁾. However, a full understanding of the mechanisms involved in progressive renal disease is still unrecognized.

White adipose tissue (WAT) is now recognized to be an active endocrine organ, not just a fat storage organ. It produces many cytokines (e.g., leptin, adiponectin, interleukins, and angiotensin-II). These cytokines in normal balances regulate the appetite and food intake. Any disturbances (e.g., during obesity) leads to formation of a pro-inflammatory environment with development of insulin resistance. High levels of resistin a macrophage-secreted cytokine is associated with renal dysfunction ^(14,15).

Although the link between obesity and renal dysfunction has been established, the pathogenic mechanisms involved are still unclear. Different factors may play a role. Thus, in the current work, we aimed to study the effect of high-fat diet induced obesity on renal function and structure. In addition, the effect of caloric restriction on renal pathophysiological changes associated with obesity was addressed.

MATERIALS AND METHODS

Animals:

Thirty healthy adult male albino rats weighing 160-180 g were obtained from experimental animal house in Faculty of Veterinary Medicine of Cairo University. The animals were housed under hygienic conditions in plastic cages (5 rats per cage) in the research laboratory of physiology department, Faculty of Veterinary Medicine, Cairo University. Rats were kept on the standard laboratory diet with free access to food and water (ad libitum), kept at room temperature and were maintained on a 12 hr light/ 12 hr dark cycle. Two weeks were permitted before the study for acclimatization. Rats were

divided into equal three groups (each 10 rats). The first is the control group, where no active ingredients or high fat diets were used. The second is the high fat diet-fed group, where rats were fed on high fat diet for 12 weeks. The third group was the food restriction group, where rats were fed on high fat diet for 12 weeks (as the second group) followed by diet restriction for 6 weeks by feeding on normal chow diet. The normal chow diet consisted of (5% fat, 18 proteins and 77% carbohydrates). On the other side, the high fat diet group consisted of (58% fat, 18% protein, and 24% carbohydrates)

Drugs and chemicals:

Adiponectin (ADP) ELISA Kit: SUNRED Bio. Tech. (serial No. 201-11-0759) [SUNRED BIOLOGICAL TECHNOLOGY, Shanghai, CHINA]. IL-6 (Interleukin-6) ELISA Kit: AviBion (REF: IL06001) [Orgenium Laboratories, Tarom Applied Technologies Ltd.]. Resistin ELISA Kit: KOMA BIOTECH INC. (Catalog No.: K0331199) [Komabiotech, Seoul, Korea].

Glucose Monitor: Enzymatic colorimetric method, Elegance CT-X10 meters (Convergent Technologies, Germany). Kits for estimation of insulin: INS-EASIA, KAP1251 (BioSource Europe S.A.-Rue de l' Industrie, 8-B- 1400 Nivelles-Belgium). Cholesterol Enzymatic colorimetric kits [SPINREACT, S.A. ctra. Santa Coloma 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN] and spectrophotometer or colorimeter measuring at wavelength 505 nm were used. Triglycerides GPO – POD Enzymatic colorimetric kits [SPINREACT, S.A Ctra Coloma, 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN] and spectrophotometer or colorimeter measuring at wavelength 505 nm were used. TNF-alpha ELISA Kit: KOMA BIOTECH INC. (Catalog No.: K0331196) [KOMABIOTECH, Seoul, Korea]. Leptin (Rat) ELISA: DRG® Leptin ELISA (Catalog No.: EIA4607) [DRG International Inc., USA]. The HDL-C precipitating reagent kits [SPINREACT, S.A Ctra Coloma, 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN] and spectrophotometer or colorimeter measuring at wavelength 505 nm. Creatinine (Colorimetric) kit and Urea/BUN (Urease) kit [Vitro Scient, Inshas Industrial Zone, Belbis, Sharkia Egypt] for determination Creatinine in serum and urine. Glucose – Liquizyme GOD - PAP (Single Reagent) kits [Spectrum-The Creative Approach to Bioscience, Egyptian Company for Biotechnology (S.A.E) Obour city industrial area. block 20008 piece 19 A. Cairo. Egypt.] For determination of serum glucose. C-reactive protein (CRP) ELISA Kit: Sunred Bio. Tech. (serial No. 201-11-0054) [Sunred Biological Technology, Shanghai, CHINA]. Plasminogen activator inhibitor 1(PAI-1) ELISA Kit: Sunred Bio. Tech. (serial No. 201-11-0637) [Sunred Biological Technology, Shanghai, CHINA]. Uric acid (Uricase/Peroxidase) kits: BioSystems S.A. Quality System certified according to EN ISO 13485 and EN ISO 9001 standards Costa Brava, 30. 08030 Barcelona (Spain). Rat Urinary Protein Assay Kit Chondrex, Inc. 2607-151 place NE Redmond, WA 98052, USA.

Methodology

For all rats, the following measurements were done and documented: 1) Initial and final body weight, 2) blood sampling for measurement of different biochemical parameters (lipid profile, glucose, insulin, cytokines and inflammatory markers, and renal function tests).

Blood sampling: The blood samples were drawn from the sinus orbitus vein (orbital venous plexus) after an overnight fast. The total amount of blood

per rat reached up to 10 ml and was placed in a test tube, permitted to clot for 2 hours at room temperature before centrifuging for 10 minutes at 5000 rpm. The separated serum was stored at -20°C until the time of analysis, and repeated freezing was avoided. All biochemical analyses were performed according to methods described by the kits manufacturers.

Histopathology tissue sampling:

After collection of blood samples, the rats were decapitated, kidneys were immediately extracted, rinsed with ice-cold normal saline (4°C), blotted and dried with filter paper then tissue portions from kidneys were kept in 10% buffered formalin- saline at 4°C for at least one week (primary fixation). The specimens were then dehydrated with a series of ascending grades of ethanol from 75 to 100%. Tissues were placed thereafter in xylol and embedded in paraffin wax. Cross sections of about 1-2 μm thickness of the kidneys were processed on slides and stained with Hematoxylin and eosin (H&E) stain to study general microscopic characters (by the light microscopy at magnification powers [200x and 400x] ⁽¹⁶⁾. Urine collection: Collect urine for 24 hours by metabolic cages. Measure the urine volume and centrifuge to remove insoluble materials. Keep the supernatant in a refrigerator for short-term storage and -20°C for long-term storage ⁽¹⁷⁾.

Data analysis:

The collected data were fed to personal computer excel sheet, then transferred to the statistical package of social sciences (SPSS) version 16 (SPSS Inc., Chicago, USA). Mean and standard deviations were used as statistical measures of continuous normally distributed variables. Means were compared by one-way analysis of variance (ANOVA) test with the post hoc least significant differences (LSD) for comparison between two groups. Spearman's correlation coefficient was calculated between weight gain and other studied variables. It was positive (proportional) or negative (inverse) and ranged between 0 and 1. The correlation is absent if $r = 0$, mild ($r < 0.3$), moderate (0.3 to 0.7), powerful ($r > 0.7$) and complete if $r = 1$. P value < 0.05 was considered statistically significant.

RESULTS

At the beginning of experiment, there was no significant difference between the control, obese and diet-restriction groups regarding body weight. However, the final weight significantly increased in the obese than the control and diet restriction group (421.0 ± 17.13 versus 279.50 ± 11.17 and 333.0 ± 13.33 g, successively). The weight in the diet restriction group significantly reduced than obese, but still significantly higher than the control group. In

addition, total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol and very low density lipoprotein cholesterol, were significantly higher, while high density lipoproteins were significantly lower among obese than the control and diet restriction groups. The diet restriction significantly improved the dyslipidemic state. However, it remains high than the control group (Table 1).

The glucose levels, insulin and HOMA-IR (a marker of insulin resistance) were significantly increased in obese than the control and diet restriction group. Diet restriction in obese rats lead to significant reduction but not return to normal values as in the control group (Table 2).

In the current work, adiponectin significantly reduced in the obese than the control and diet restriction group (4.00 ± 0.74 vs 6.36 ± 0.34 and 5.41 ± 0.42 ng/dl, respectively). However, IL-6, leptin, resistin, tumor necrosis factor- α , C-reactive protein and Plasminogen activator inhibitor-1 were significantly increased among obese than the control and diet restriction groups. In addition, values in diet restriction still significantly higher than the control group (Table 3).

Regarding renal function, it was significantly impaired in obese than normal and diet restriction (e.g., serum creatinine, urea, protein in urine were significantly increased while glomerular filtration rate was significantly reduced in obese than control and diet restriction groups). In addition, serum uric acid was significantly increased in obese (1.14 ± 0.10 mg/dl) than control (0.53 ± 0.07 mg/dl) and diet restriction (0.83 ± 0.07 mg/dl) (Table 4).

The weight gain (g) significantly and negatively correlated with HDLc, adiponectin and glomerular filtration rate. Otherwise, it significantly and positively (proportional) correlated with other variables (e.g., TC, TG, LDLc, glucose, insulin, HOMA-IR, IL6, leptin, resistin, TNF- α , CRP, PAI-1, creatinine, urea, serum uric acid, and protein in urine) (Table 5).

Histopathology: Sections from the control group showed normal renal architecture (normal renal glomeruli surrounded by normal renal tubules) (Figure 1). However, sections from the high fat group showed hydropic degenerations with obliterated lumina of the renal tubules. In addition, some tubules showed atrophy of the epithelial lining (Figure 2), and renal glomeruli were surrounded by heavy aggregates of mononuclear cell infiltrates (Figure 3). In diet restriction group, renal vascular tissues obtained a thick walled vascular spaces surrounded by an increased amount of the interstitial tissues and aggregates of inflammatory cells (Figure 4). However, renal tubules and glomeruli showed atrophic changes with increased interstitial tissue and per-renal fat (Figure 5).

Table (1): Comparison between groups regarding body weight and lipid profile

	Control		Obese		Diet restriction		F	P
	Mean	SD	Mean	SD	Mean	SD		
Initial weight (g)	167.40	6.00	168.40	5.70	169.10	4.23	0.253	0.778
Final weight (g)	279.50	11.17	421.00*	17.13	330.00**	13.33	258.9	<0.001 [§]
Weight change (g)	112.10	14.73	252.60	18.77	160.90	13.25	204.92	<0.001 [§]
TC (mg/dl)	67.69	3.64	182.20*	11.85	111.60**	16.77	230.2	<0.001 [§]
TG (mg/dl)	89.10	6.31	144.70*	13.39	98.30**	33.91	19.4	<0.001 [§]
HDLc (mg/dl)	34.00	2.71	26.10*	1.73	30.00**	1.76	34.8	<0.001 [§]
LDLc (mg/dl)	17.10	1.79	126.90*	10.99	60.00**	15.97	242.4	<0.001 [§]
VLDLc (mg/dl)	18.00	1.33	29.30*	2.67	21.20**	2.49	67.4	<0.001 [§]

Table (2): Comparison between groups regarding glucose, insulin and HOMA-IR

	Control		Obese		Diet restriction		F	p
	Mean	SD	Mean	SD	Mean	SD		
Glucose (mg/dl)	84.30	4.81	217.50*	16.55	115.90**	14.06	293.6	<0.001 ⁵
Insulin (μU/ml)	24.40	1.71	46.00*	3.59	34.30**	3.23	133.4	<0.001 ⁵
HOMA-IR	5.15	0.38	25.16*	3.51	9.59**	1.23	237.6	<0.001 ⁵

Table (3): Comparison between groups regarding cytokines and inflammatory markers

	Control		Obese		Diet restriction		F	p
	Mean	SD	Mean	SD	Mean	SD		
Adiponectin (ng/dl)	6.36	0.34	4.00*	0.74	5.41**	0.42	49.8	<0.001 ⁵
IL-6 (pg/ml)	7.87	2.14	22.12*	3.59	13.65**	1.98	72.0	<0.001 ⁵
Leptin (ng/ml)	3.33	0.56	9.87*	1.92	6.01**	1.26	57.9	<0.001 ⁵
Resistin (ng/ml)	8.49	1.06	22.94*	1.99	12.40**	2.01	183.8	<0.001 ⁵
TNF-α (ng/ml)	45.90	1.79	59.70*	2.26	50.60**	2.27	109.4	<0.001 ⁵
CRP (mg/L)	0.04	0.02	0.16*	0.04	0.08**	0.01	65.6	<0.001 ⁵
PAI-1 (ng/ml)	4.27	0.89	18.67*	2.47	11.30**	1.87	149.8	<0.001 ⁵

Table (4): Comparison between groups regarding

	Control		Obese		Diet restriction		F	P
	Mean	SD	Mean	SD	Mean	SD		
Creatinine (mg/dl)	0.79	0.12	1.89*	0.19	1.35**	0.10	148.9	<0.001 ⁵
Urea (mg/dl)	24.40	4.22	40.90*	4.91	33.20**	1.87	45.0	<0.001 ⁵
Uric Acid (mg/dl)	0.53	0.07	1.14*	0.10	0.83**	0.07	148.3	<0.001 ⁵
Protein in urine (mg/24H)	51.42	8.31	305.10*	48.27	125.40**	8.72	206.2	<0.001 ⁵
GFR (ml/24h)	7.31	1.01	3.72*	0.32	5.02**	0.34	80.5	<0.001 ⁵

Table (5): Correlation between the weight gain (final minus initial) and other parameters

	Final weight	
	r	p
TC (mg/dl)	0.916**	<0.001
TG (mg/dl)	0.669**	<0.001
HDLc (mg/dl)	-0.803**	<0.001
LDLc (mg/dl)	0.919**	<0.001
VLDLc (mg/dl)	0.840**	<0.001
Glucose (mg/dl)	0.954**	<0.001
Insulin (μU/ml)	0.918**	<0.001
HOMA-IR	0.944**	<0.001
Adiponectin (ng/dl)	-0.841**	<0.001
IL-6 (pg/ml)	0.922**	<0.001
Leptin (ng/ml)	0.865**	<0.001
Resistin (ng/ml)	0.949**	<0.001
TNF-α (ng/ml)	0.914**	<0.001
CRP (mg/L)	0.873**	<0.001
PAI-1 (ng/ml)	0.939**	<0.001
Creatinine (mg/dl)	0.939**	<0.001
Urea (mg/dl)	0.842**	<0.001
Uric Acid (mg/dl)	0.894**	<0.001
Protein in urine (mg/24H)	0.945**	<0.001
GFR (ml/24h)	-0.849**	<0.001

** Correlation is significant at the 0.01 level (2-tailed).

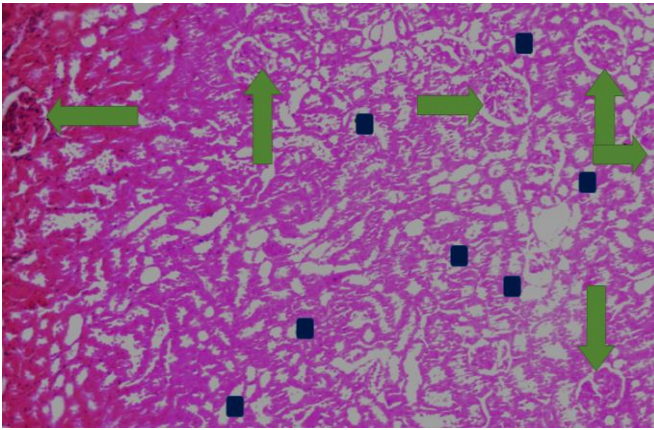


Figure (1): Photomicrograph of normal renal tissue showing normal renal glomeruli (green Arrow) surrounded by normal renal tubules (square) (H&E X200) [Control group].

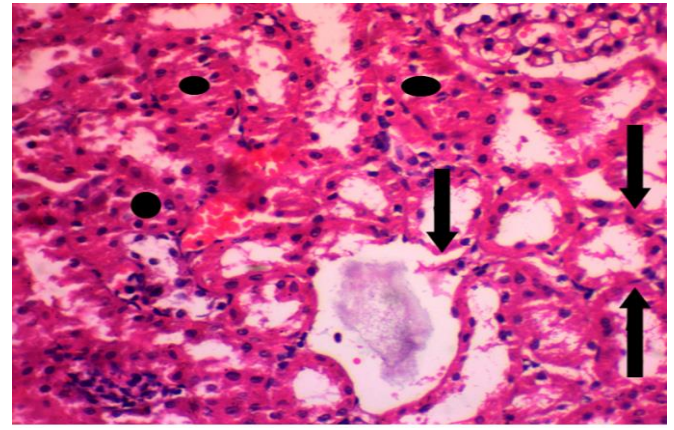


Figure (2): Photomicrograph of renal tissue showing hydropic degeneration with obliterated lumina (circle) in some tubules and atrophy of the epithelial lining in other tubules (arrow) (H&E X400) [High fat diet group].

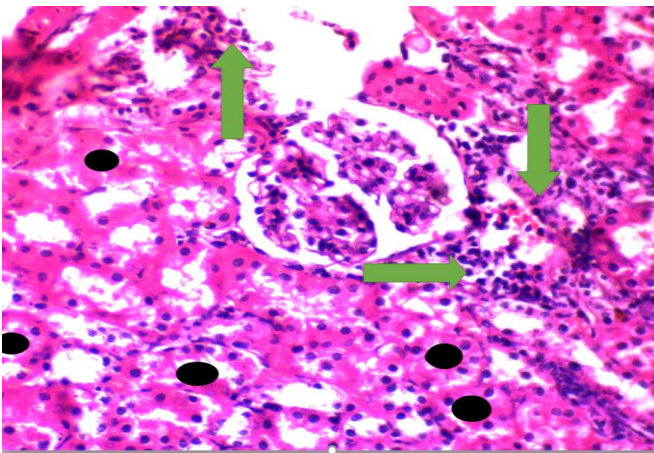


Figure (3): Photomicrograph of renal tissue showing hydropic degeneration of the renal tubules (Circle) and a renal glomerulus in the center surrounded by heavy aggregates of mononuclear cell infiltrate (Arrow) (H&E X400) [High fat diet group].

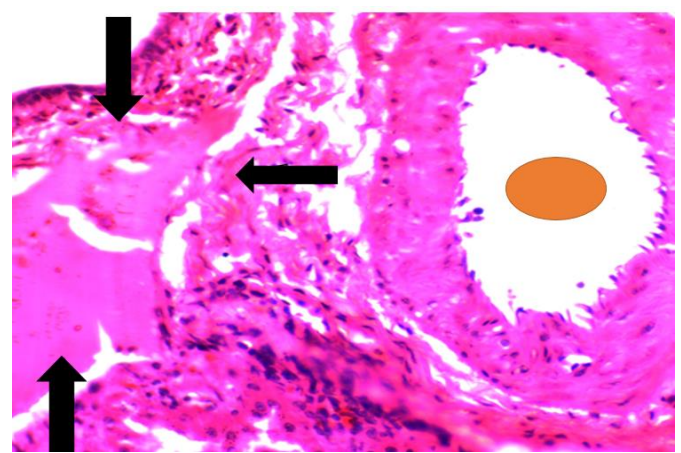
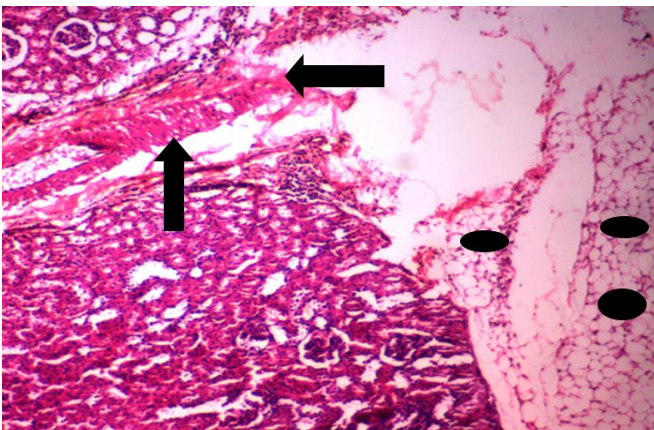


Figure (4): Photomicrograph of renal tissue showing thick walled vascular space (Yellow circle) surrounded by increased amount of the interstitial tissue (black arrow) and aggregate of inflammatory cells (H&E X400) [Diet restriction group].



Picture (5): Photomicrograph of renal tissue showing atrophy of renal tubules and glomeruli with increased amount of interstitial tissue (arrow) and increased per-renal fat (circle) (H&E X200) [Diet restriction group].

DISCUSSION

The results of the present study revealed that high fat diet was associated with marked increase of body weight, with significant dyslipidemia, insulin resistance, cytokines and inflammatory markers with significant deterioration of renal function. Food restriction was associated with improvement of all studied variables. However, it did not return to

normal values, indicating persistent renal affection. The biochemical results were confirmed by the histopathological changes. These results are in line with previous studies⁽¹⁸⁻²⁰⁾. Results of the current work are also in line with the study of Field et al.⁽²¹⁾ who reported a significant association between higher body mass index (indicating obesity) and the increased risk of type-2 diabetes, cardiovascular disease and renal dysfunction.

An interesting study by Ryu *et al.* (22) indicated that, the mere weight gain is associated with the increased risk of chronic kidney disease, even if not reach the margin of obesity.

Kopple and Feroze (23) also confirmed the link between obesity from one side and dyslipidemia and increased fasting glucose level from the other side indicating associated metabolic derangements associated with obesity or overweight.

The central obesity directly affects the renal function by increased adipose tissues, that completely encircles the kidney and infiltrates the medullary sinuses with subsequent compression and increased intrarenal pressure (9).

Obesity also leads to marked histological changes of the renal medulla leading to medullary compression and impaired natriuresis. The thin loops of Henle were compressed by increased extracellular matrix inside the low-compliant renal capsule. The net result is the reduction of blood flow and increased tubular reabsorption. This mechanism confirmed in the study of Naumnik and Mysliwiec (24) who reported a significant increase in the renal interstitial fluid pressure in obese animals.

The current increase in serum glucose in obese animals, which was associated with increased insulin resistance (indicating type-2 diabetes mellitus) goes in line with the study of Darkhal *et al.* (25).

This was attributed to reduced hepatic and muscular glucose uptake, leading to hyperlipidemia due increased mobilization of the fat and resistance to anti-lipolytic actions of the insulin. This impaired action of insulin is associated with lipids oversupply with increased availability of lipids and increased lipid storage in insulin targeted tissues (mainly muscles and liver) or increased free fatty acids and triglycerides. In other turn, free fatty acids and dyslipidemia exert a harmful effect on insulin uptake by the liver and insulin resistance not confined to adipocytes but extends to skeletal muscles (26).

The FFA elevation in plasma leads to an inappropriate homeostasis of glucose production and hepatic utilization (impaired glucose tolerance). Reduced hepatic clearance of insulin leads to increased (systemic) insulin and down regulates insulin receptors. In the initial phases of this process, the pancreas can compensate the changes by maintaining a state of hyperinsulinemia with prevention of gross decompensation of glucose tolerance. With further increasing of plasma concentrations of FFAs, the insulin resistant individual cannot continue to maintain this state of compensatory hyperinsulinemia, and hyperglycemia dominates (27).

Insulin resistance is a key risk promoting chronic kidney disease (13). In the kidney, insulin promotes its effects by binding and activating two insulin receptors, which activate molecular signaling pathways to promote glucose uptake, cell growth, or nitric oxide production (28).

In obesity, abnormal modulations of insulin receptors and signaling have been shown. These changes were associated with an increased level of many cytokines and inflammatory mediators like TNF- α , angiotensin-II, endothelin, free fatty acids (FFAs), oxidative stress, and amino acids (29, 30).

In addition, the lipid accumulation occurs in the kidney after a high-

fat caloric exposure, leading to insulin resistance associated with impairment of tubular cell structure and inflammation as well as the fibrosis (13). The rapid expansion of adipose tissue leads to an abnormal production of proinflammatory cytokines that initiate a state of low-grade inflammation (31).

The current study revealed a significant increase in some adipocytokines and inflammatory indicators such as Leptin, resistin, TNF- α , IL-6, CRP while there was a significant reduction in others. These findings are in line with the previous study of Jung and Choi (32), who reported that, the expansion of the adipose tissue is associated with significant increase of bioactive substances which trigger a state of low grade inflammation and interfere with biological processes in different organs with ill-defined mechanisms. However, the dysregulated production or secretion of these cytokines caused by excess adipose tissue and adipose tissue dysfunction contribute to the development of obesity-related metabolic changes via alteration of glucose and lipid homeostasis as well as inflammatory response. In addition, inflammation can modify the size, composition and function of HDLs, leading to the impairment of reverse cholesterol transport and changes in apolipoproteins, cholesterol metabolism-related enzymes and anti-oxidant capacity.

Several cytokines also stimulate lipolysis in adipocytes and decrease the clearance of triglyceride rich particles. IL-6 and TNF- α enhanced lipolysis and suppressed activity of lipoprotein lipase, a key regulatory enzyme in the catabolism and clearance of triglyceride-rich lipoproteins (33).

The significant increase in the serum TNF- α in the current work agree with a previous study stated that TNF- α was originally recognized as an inducer of hypertriglyceridemia. Levels of plasma TNF- α are higher in hypolipidemic patients compared with healthy controls and are positively correlated with concentrations of triglyceride (32).

The present study showed a significant decrease in serum levels of adiponectin in obese than control or diet restriction rats. This is in accordance with a previous study demonstrating that adiponectin has beneficial effects on lipid metabolism and also plays a role as a cardiovascular protective agent. Levels of plasma adiponectin have been found to be negatively correlated with triglycerides and positively correlated with HDL cholesterol. Adiponectin stimulates fatty acid oxidation and glucose utilization through activation of adenosine monophosphate-activated protein kinase (AMPK) in the liver and skeletal muscle, which has been associated with many of the positive effects of adiponectin on lipoprotein metabolism as well as insulin sensitivity. Adiponectin also induces activation of lipoprotein lipase (LPL), thereby enhancing VLDL clearance and reducing plasma triglyceride levels (34).

The reduction of adiponectin is also associated with reduced insulin sensitivity and lead to initiation and promotion of the proinflammatory process in the kidney (35).

On the other side, the increased leptin levels in the current research are in line with Jung and Choi (32) who reported significant increase of leptins in obese rats, which involved in the regulation of energy production and utilization and inhibits appetite and food intake, while at the same time increased energy expenditure. In addition, the circulating leptin levels

and its expression in adipose tissues are increased in response to pro-inflammatory cytokines and endotoxin lipopolysaccharide. Accordingly, the interactions between leptin and inflammation are bidirectional^(36, 37).

Resistin is also an adipocyte specific secreted cytokine, and it stimulates both inflammation and insulin resistance. Levels of circulating resistin were found to be significant increase in obese rats. A lack of resistin protects mice from diet-induced hyperglycemia⁽³⁸⁾. High serum resistin levels have been associated with kidney dysfunction, including reduced GFR and increased albuminuria. Thus, resistin may have a direct deleterious effect on the glomeruli⁽¹⁵⁾.

PAI-1 is significantly increased in obese than normal or diet restricted groups in the current research. These increased levels are associated with several chronic inflammatory states that are associated with chronic kidney disease, and it may contribute to the pathogenesis of the accelerated vascular disease in this patient population. Increased PAI-1 levels correlate with level of proteinuria rather than with degree of proliferation⁽³⁹⁾. PAI-1 is increased and localized to mesangial lesions at early time points, suggesting a possible role of PAI-1 in cell migration⁽⁴⁰⁾.

The current research revealed a significant increase in the serum levels of CRP in obese rats. This result is in agreement with that of previous studies⁽⁴¹⁾. Many studies have shown associations between increased CRP and increased risk for cardiovascular disease, diabetes, and multiple components of metabolic syndrome, including obesity, insulin resistance and dyslipidemia. The chronic inflammatory state could be recognized by slight increase of CRP⁽⁴²⁻⁴³⁾.

The increased levels of CRP initiates a state of pro-inflammation, pro-oxidant and pro-coagulation by increasing the activity of macrophages⁽⁴⁴⁾.

As expected, there was significant increase of total cholesterol, LDL, vLDL and triglycerides with significant reduction of HDL in high fat induced obesity than controls and restricted fat diet groups. These results are well-known hallmarks of obesity in the previous studies. Obesity associated dyslipidemia is a risk factor for cardiovascular diseases, cerebrovascular accidents and respiratory problems. This dyslipidemia is due to increased hepatic synthesis of triglycerides from lipolysis of increased fatty tissues⁽⁴⁵⁾.

Structural changes in the kidney secondary to obesity is important due to increased pressure exerted by the fat deposits around the kidneys and increased abdominal pressure of central obesity. Moreover, the hyperfiltration observed in obesity lead to progressive glomerular loss and loss of renal function and increased arterial pressure^(30, 46).

As in the present study demonstrated, previous studies showed that HFD-induced obesity was associated with renal damage and deterioration of renal function as evidenced by the presence of a significant increase in serum levels of urea, creatinine, uric acid, together with obvious proteinuria and a significant reduction in creatinine clearance. In addition, renal histopathological examination showed that obesity was associated with glomerular hypertrophy, vacuolar degeneration in renal tubules, and increased glomerular extracellular matrix accumulation^(47, 48). The results of the current work are in line with that of Hamidian *et al.*⁽⁴⁹⁾ and Amin

et al.⁽⁵⁰⁾ who reported that, there was a significant increase in serum urea and creatinine levels in obese than controls. This could be attributed to the metabolic derangements (e.g., hyperlipidemia, oxidative stress and NO inactivation by reactive oxygen species leading to reduction in NO bioavailability and renal dysfunction with significant elevation of serum urea and creatinine levels.

Obesity is acknowledged as a significant independent risk factor for kidney impairment. This may be explained by the renal intracellular lipid accumulation⁽⁵¹⁾.

In addition, metabolic disorders in obesity associated with high blood pressure, poor glycemic control and dyslipidemia were considering risk factor for susceptibility of chronic renal disease. Glomerular hypertension and endothelial dysfunction were regarded as common mechanisms by which rennin-angiotensin system produces CRD⁽⁵⁰⁾.

HFD induces alteration of renal lipid metabolism by an imbalance between lipogenesis and lipolysis in the kidney, as well as systemic metabolic abnormalities and subsequent renal lipid accumulation leading to renal injury⁽⁵²⁾.

In addition, HFD resulted in hyperinsulinemia, activation of the renin-angiotensin system, glomerular hyperfiltration and structural changes in the kidney that may be the precursors of more severe glomerular injury associated with prolonged obesity⁽⁵³⁾.

The present study showed that caloric restriction in obese rats resulted in improvement of renal structure and function.

These findings are in line with Chagnac *et al.*⁽⁵⁴⁾ who demonstrated that caloric restriction was associated with weight loss and improvement of renal function, GFR and filtration fraction. This improvement was associated with a significant reduction of albuminuria. In addition, they showed that weight loss was followed by independent improvement of both glucose tolerance and renal filtration which were impaired in obesity. The reversal of the changes of adipocyte derived cytokines and the amelioration of oxidative stress might be the mechanisms by which weight loss improved renal function and proteinuria in diabetic nephropathy with obesity.

In conclusion, obesity is an independent risk factor for chronic kidney disease. The potential mechanisms involve inflammation, lipotoxicity; hemodynamic effects and perhaps other unknown mechanisms. Weight reduction and treatment of associated metabolic complications constitute the most effective interventions to prevent obesity-associated chronic kidney disease.

Financial and non-financial activities and relationships of interest

None

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Volume 2020, Issue 1, January 2020

e-ISSN: 2833-3772

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e-ISSN: 2833-3772