British Journal of Medicine & Medical Research
20(6): 1-13, 2017; Article no.BJMMR.32349
ISSN: 2231-0614, NLM ID: 101570965

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Renal Insulin Sensitizing Effect of Exenatide in a High-fat Diet Obesity Rat Model

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2017/32349
Editor(s):
(1) E. Umit Bagriacik, Department of Immunology, Gazi University, Turkey.
Reviewers:
(1) Sembol Yildirmak, Giresun University Medical Faculty Medical Biochemistry, Giresun University Medical Faculty, Giresun, Turkey.
(2) Waleed Samy, Tanta College of Medicine, Tanta, Egypt.
Complete Peer review History: http://www.sciencedomain.org/review-history/18241

Original Research Article

Received 22nd February 2017
Accepted 10th March 2017
Published 17th March 2017

ABSTRACT

Insulin receptor (IR) is expressed throughout the nephron and is vital for the renal function. Renal complications may occur in insulin-resistant states. The aim of the present study was to find out the possible renoprotective effect of exenatide in rats fed a high-fat diet (HFD) and whether this therapeutic approach resulted in regulation of renal IR gene expression. Rats were fed HFD for 16 weeks and received exenatide (10 µg/kg, SC/d/ 4 weeks). The body weight, insulin resistance and lipid profile were measured. The renal function and histopathological changes were assessed. Also, IR gene expression was analyzed in the renal homogenate. HFD rats showed systemic alterations including obesity, insulin resistance, dyslipidemia and renal impairment. The renal injury was associated with down regulation of renal IR gene expression and minimal cytoplasmic reaction to insulin receptor immunohistochemical staining. The systemic and renal alterations induced by HFD were alleviated by exenatide with marked up regulation of renal IR gene expression. In conclusion, exenatide may be a novel therapeutic agent for renal damage induced by obesity. This renoprotective effect is partly produced by up-regulation of renal IR gene in addition to the control of body weight, insulin resistance and dyslipidemia.

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Keywords: Exenatide; high fat diet; insulin resistance; renal insulin resistance gene.

1. INTRODUCTION

The major adverse metabolic consequences of obesity are believed to be due to insulin resistance. The reduction in the sensitivity to the biological action of insulin affects not only glucose metabolism, but also all aspects of insulin action [1].

It has been established that insulin receptor (IR) is expressed throughout the nephron from the glomerulus to the collecting ducts which is vital for the renal function. Renal complications as albuminuric glomerular disease and hypertension may occur in insulin-resistant states [2].

The incidence between insulin resistance and kidney dysfunction in both non diabetic and diabetic subjects has been reported [3]. Elucidations of the precise mechanisms that are responsible for renal damage in insulin resistance enhance the design of therapeutic strategy against this renal injury. Obesity may cause atherogenic dyslipidaemia that initiates endothelial damage responsible for renal dysfunction. Also the overproduction of several adipocytokines and growth factors may lead to hemodynamic changes with focal segmental glomerulosclerosis and glomerulomegaly. Hyperglycaemia may increase the formation of advanced glycation end-products, activation of protein kinase C isoforms and, eventually, low-grade chronic inflammation. Hyperglycaemia also may increase the production of extracellular matrix by mesangial cells due to induction of transforming growth factor-β [4]. Hyperinsulinaemia may induce glomerular hyperfiltration, endothelial dysfunction and increase vascular permeability [5]. Impaired insulin sensitivity may contribute to renal damage via alteration of renal cellular metabolism and electrolyte composition, mesangial hyperplasia with renal hypertrophy, increase endothelial cell proliferation and deposition of lipid and hyaluronate in the renal matrix and inner medulla [6].

Exenatide is the synthetic form of exendin-4 and a long-acting mimetic of the incretin hormone glucagon-like peptide-1 (GLP-1). Exenatide is implicated in regulating food intake and inhibition of gastrointestinal motility. It also stimulates β-cell proliferation, glucose-dependent insulin response and suppresses glucagon secretion [7].

The aim of the present study was to find out the possible renoprotective effect of exenatide in rats fed a high-fat diet and whether this therapeutic approach resulted in regulation of renal IR gene expression.

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

Exenatide injection pen (BYETTA 250 µg/mL, Amylin Pharmaceuticals, Inc., San Diego).

HFD composition: Casein and sucrose were purchased from Diamond for high purity chemicals (Egypt). Cholesterol, sodium chloride, DL- methionine, vitamin and mineral mix were purchased from Sigma Chemical Co. (USA). Normal Powdered diet, Lard and Yeast powder were brought from Egyptian market.

2.2 Experimental Design

This study was carried on 40 Sprague–Dawley male rats weighing 160-170 g. They were maintained under standard conditions of temperature 22 ± 2°c with regular 12 h light/12 h dark cycle and allowed free access to standard laboratory food and water. All experimental procedures were performed in accordance with guidelines of the Institutional Animal Care and Use Committee of Mansoura University.

Rats were divided into two main groups (20 rats for each group); Lean and HFD groups. Lean group was fed normal chow diet; the remaining rats received high fat diet (HFD) for 16 weeks to establish diet-induced obesity [8]. The formula of the HFD provides 17% energy as carbohydrates, 25% as protein, and 60% as fat as a percentage of total kcal/g (Table 1). The standard rodent normal chow diet was prepared by thoroughly mixing cornstarch, powdered rat feed, sodium chloride salt mixture and water while the cornstarch was replaced with lard, casein, cholesterol, vitamin and minerals to form the high fat diet. The dietary ingredients were homogenized in distilled water at 60°C and the homogenate was used to prepare the pellets. Diets were given fresh each day as dry pellets. 16 weeks after daily receiving the normal or high fat diet, rats of both groups were weighted and were subdivided equally into 2 groups with the final results of the following four groups (10 rats

each): Group-I: Non-treated control lean rats received saline (1 ml). Group-II: control lean rats treated with exenatide (10 µg/kg body weight) [9]. Group-III: Non-treated HFD rats received saline (1 ml). Group-IV: HFD rats treated with exenatide (10µg/kg body weight). The saline or exenatide was administered once daily for another four weeks by subcutaneous injection. All rats were monitored daily for food, water intake. The body weight was measured every week. The mean arterial pressure (MAP) of all rats were measured every week via non invasive method of rats tail cuff plethysmography using LE 5001 pressure meter (LETICA Scientific Instruments, Barcelona, Spain).

At the end of the experimental period, the rats were housed in metabolic cages for 24 h to collect urine samples. Urine volumes were measured and samples were centrifuged at 3000× *g* for 10 min and stored at −80°C. Then rats were fasting overnight, weighed and sacrificed by an overdose of anesthesia on the next day. The blood of each rat was collected by direct cardiac puncture and allowed to clot and centrifuged at 4000 rpm for 15 minutes. The serum samples were separated and stored at −20°C for subsequent biochemical assay. Laparotomy was done to dissect the visceral fat (epididymal, visceral suprarenal and retroperitoneal) and both kidneys. The right kidney is immediately immersed in liquid nitrogen and stored at -80°C for quantitative real time-polymerase chain reaction (RT-PCR) analysis of IR gene. The left kidney was fixed with 10% neutral buffered formalin for 24 hr at 4°C for histopathological examination.

Adiposity index: Adiposity index was determined by the sum of epididymal, visceral and retroperitoneal fat weights divided by body weight × 100, and expressed as adiposity percentage [10].

Biochemical analyses: Serum cholesterol, triglycerides and HDL-cholesterol were measured using spectrophotometric assay kits (SPINREACT, SPAIN). Low-density lipoprotein cholesterol (LDL cholesterol) concentration was calculated according to Friedewald equation LDL cholesterol = Total cholesterol - HDL Cholesterol - (Triglycerides / 5) [11].

Fasting serum glucose was measured by glucose kits (BioMed-Glucose L.S, Eng Chem for lab technology, Hannover, Germany). Rat serum insulin concentration was determined by ELISA using a commercially available kit (My BioSource, Inc., California, USA). Homeostasis model of assessment of insulin resistance (HOMA-IR) can be calculated from the following equation =fasting glucose (mg/dl) x fasting insulin (µIU/ml) divided on 405 [12].

The serum and urine creatinine was determined using creatinine-colorimetric kit (Diamond diagnostic, USA). Creatinine clearance rate (Ccr) was calculated using the following formula and expressed as mL/min [13]. Ccr (mL/min/kg body weight) = [urinary creatinine (mg/dL) ×24 hr urine volume (mL)] / [serum creatinine (mg/dL) × 1440 (min)]

Quantitative real time- PCR: Total RNA was isolated from kidney using RNeasy Mini kit (Qiagen, Valencia, CA, USA). RNA concentrations and integrity were determined using RNA 6000 Nano Assay Kit and the Bioanalyzer 2100 according to the manufacturer's instructions. mRNA levels were assessed by real-time quantitative RT-PCR. All PCR reactions were performed in a total volume of 25 µl and included the following components: cDNA derived from 25 ng of total RNA, 400 nM of each primer (Table 2), RNase-free water, and 12.5 µl of SYBR Green PCR Master Mix (ABI), an optimized buffer system containing AmpliTaq Gold DNA polymerase and dNTPs. All PCR reactions were performed in duplicate and cycling parameters were as follows: after an initial denaturation step for 10 min at 95°C, 40 subsequent cycles were performed in which samples were denatured for 15 s at 95°C followed by primer annealing and elongation at 60°C for 1 min. The relative quantities of mRNA were normalized by 18S rRNA content.

Renal histopathological and immuno-histochemical study: The fixed kidney tissues in 10% formalin were processed routinely for paraffin embedding and 4 mm sections were prepared, stained with haematoxylin & eosin (H&E), periodic acid-Schiff (PAS) and Masson Trichroma (M.T) to be examined under light microscopy. Sections were incubated with a rabbit Anti-Insulin Receptor Beta Polyclonal Antibody, Unconjugated (bs-0290R, Bioss Inc. Woburn, Massachusetts, USA) at 1:200 concentration according to manufacturer instructions. Power-stain 1.0 poly HRP DAB Kit (Genemed Biotechnologies, Inc. South San Francisco, USA) was used as detection kit.

2.3 Statistical Analysis

Statistical analysis was performed using The Statistical Package for Social Science (SPSS) program version 13. Data of biochemical parameters were presented as mean ± standard error of means (SEM). Differences among groups within the experiment were analyzed by the one-way ANOVA analysis of data followed by post hoc test of Tukey HSD. A *P* value of <0.05 value was considered significant.

3. RESULTS

3.1 Food Intake, Body Weight and Adiposity Index

Rats received HFD for 16 weeks showed significant increase in the mean values of body weight, food intake, and adiposity index as compared to the lean rats. Treatment of either lean or HFD rats with exenatide 10µg/kg/d for 4 weeks caused significant decrease in the food intake, body weight and adiposity index in comparison to the non-treated lean or HFD rats, respectively (Table 3 and Fig. 1).

3.2 Mean Arterial Blood Pressure (MAP)

HFD Rats showed significant increase in the MAP as compared to the lean rats. Treatment of HFD rats with exenatide 10µg/kg/d for 4 weeks caused significant decrease in the MAP in comparison to the non-treated HFD rats (Table 3).

3.3 The Fasting Serum Glucose, Insulin and HOMA-IR Index

The fasting glucose, insulin and HOMA-IR index mean levels were significantly increased in the sera of HFD rats in comparison to those of lean rats. Treatment of HFD rats with exenatide led to significant decrease in the mean glucose, insulin levels and HOMA-IR index as compared to the non-treated HFD rats with a non-significant change from those of the lean rats (Table 4).

Table 1. Composition of Normal chow diet and HFD diet

Ingredients	Normal chow diet (g/kg)	High fat diet (g/kg)
Corn starch	438	97
Sucrose	100	125
Casein	200	250
Soybean oil	30	67
Lard	0	310
Cholesterol	0	10
Vitamin mix	10	14
DL-methionine	3	3
Yeast powder	1	1
Sodium chloride	1	1
Mineral mix	35	47

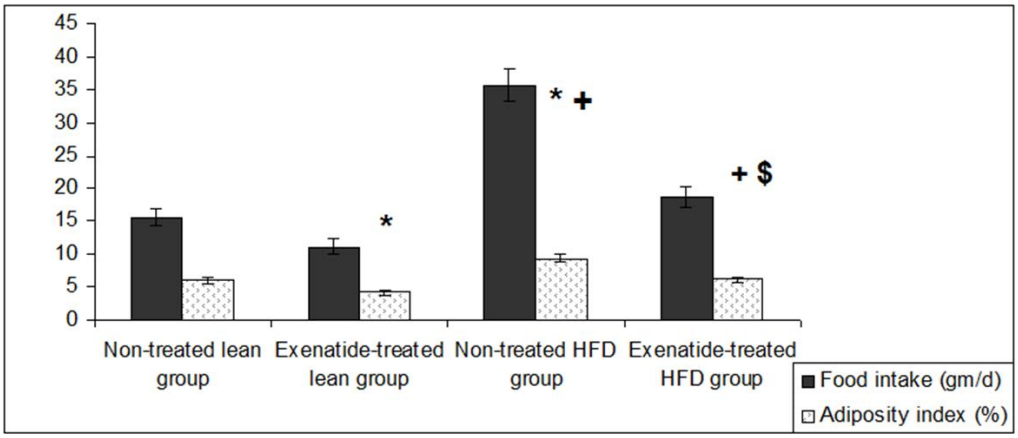

Fig. 1. Effect of exenatide (10µg/kg/d for 4 weeks sc) on the food intake and adiposity index in HFD rats

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means of 10 rats ± SEM
**Indicates significant change from non-treated lean group values at p < 0.05*
+ Indicates significant change from exenatide-treated lean group at p < 0.05.
$ Indicates significant change from non-treated HFD group at p < 0.05

Table 2. Primers sets used in qRT-PCR (Biosearch technologies, CA, USA)

Name	Sequence	Reference Sequence	Product Length
GAPDH Forward	5`-CCATCAACGACCCCTTCATT-3`	NM 017008.4	194
GAPDH Reverse	5`-CACGACATACTCAGCACCAGC-3`		
IR Forward	5'CAAAAGCACAATCAGAGTGAGTATGAC3'	NM 017071	222
IR Reverse	5'-ACCACGTTGTGCAGGTAATCC-3'		

Table 3. Effect of exenatide (10 µg/kg/d for 4 weeks sc) on the body weight and MAP in HFD rats

Treatment	Non-treated lean group	Exenatide-treated lean group	Non-treated HFD group	Exenatide-treated HFD group
Body weight (gm)	215.7 ± 20.3	175.5 ±12.7 *	396.6 ± 35.4 *+	252.2 ± 25.7 +$
MAP (mmHg)	106.6 ±8.9	111.7 ±8.2	154.7 ±31.6*+	132.5 ±10.3* +$

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means of 10 rats ± SEM
**Indicates significant change from non-treated lean group values at p < 0.05*
+ Indicates significant change from exenatide-treated lean group at p < 0.05.
$ Indicates significant change from non-treated HFD group at p < 0.05

Table 4. Effect of exenatide (10 µg/kg/d for 4 weeks sc) on the fasting serum glucose, insulin and HOMA-IR index in HFD rats

Treatment	Non-treated lean group	Exenatide-treated lean group	Non-treated HFD group	Exenatide-treated HFD group
serum fasting glucose (mg/dl)	106.4 ± 10.1	108.3 ±10.2	186.4 ± 16.5 *+	113.5 ± 12.6 $
Serum insulin (µIU/ml)	33.4 ±3.1	34.8 ±3.3	74.6 ±6.9 *+	40.5 ±4.4 $
HOMA-IR index (%)	8.7 ±0.7	9.3 ±0.8	34.3 ±3.1*+	10.7 ±1.1 $

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means of 10 rats ± SEM
**Indicates significant change from non-treated lean group values at p < 0.05*
+ Indicates significant change from exenatide-treated lean group at p < 0.05.
$ Indicates significant change from non-treated HFD group at p < 0.05

3.4 The Lipid Profile

HFD rats showed significant increase in the mean values of serum total cholesterol, triglyceride and LDL cholesterol and significant decrease in the mean level of serum HDL cholesterol as compared to the lean rats. Treatment of HFD rats with exenatide led to significant decrease in the mean total cholesterol, triglyceride and LDL cholesterol and significant increase in the mean HDL cholesterol as compared to the non-treated HFD rats (Fig. 2).

3.5 The Creatinine Clearance

The creatinine clearance was significantly decreased in the HFD rats in comparison to lean rats. Treatment of HFD rats with exenatide led to significant increase in the creatinine clearance as compared to the non-treated HFD rats (Fig. 3).

3.6 Quantitative RT-PCR of Renal IR Gene Expression

HFD rats showed significant decrease in renal IR gene expression in comparison to the lean rats.

Treatment of HFD rats with exenatide led to significant up-regulation of the renal IR gene expression as compared to the non-treated HFD rats up to a non-significant level from that of lean rats (Fig. 4).

3.7 Renal Histopathological and Immuno-histochemical Results

Light microscopic examination of renal tissue of the healthy control rats presented a normal architecture with normal reaction to insulin receptor immunohistochemical staining. Renal tissue of HFD rats stained with H&E showed fat globules deposition (steatosis) in the cytoplasm of renal tubules (Fig. 5). PAS stain showed mild increase the in mesangial matrix (Fig. 6) while Masson Trichroma stain showed no evidence of any glomerular or interstitial fibrosis (Fig. 7). Immunohistochemical examination of renal tissue of HFD rats showed decrease of cytoplasmic reaction to insulin receptor β immuno-histochemical staining in renal tubular and glomerular cells compared with the reaction of control tissue (Fig. 8). Administration of exenatide 10 µg/kg/d for 4 weeks reversed these changes to near-normal control.

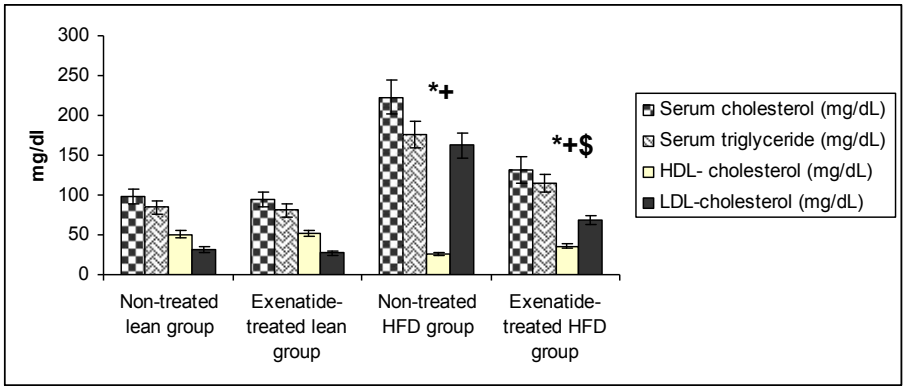

Fig. 2. Effect of exenatide (10µg/kg/d for 4 weeks sc) on the serum lipid profile in HFD rats

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means of 10 rats ± SEM

**Indicates significant change from non-treated lean group values at p < 0.05*

+ Indicates significant change from exenatide-treated lean group at p < 0.05.

$ Indicates significant change from non-treated HFD group at p < 0.05

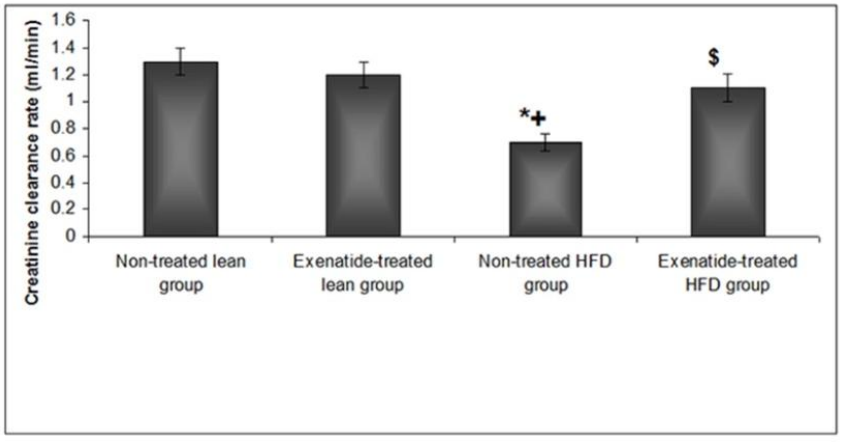

Fig. 3. Effect of exenatide (10µg/kg/d for 4 weeks sc) on the creatinine clearance in HFD rats

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means of 10 rats ± SEM

**Indicates significant change from non-treated lean group values at p < 0.05*

+ Indicates significant change from exenatide-treated lean group at p < 0.05.

$ Indicates significant change from non-treated HFD group at p < 0.05

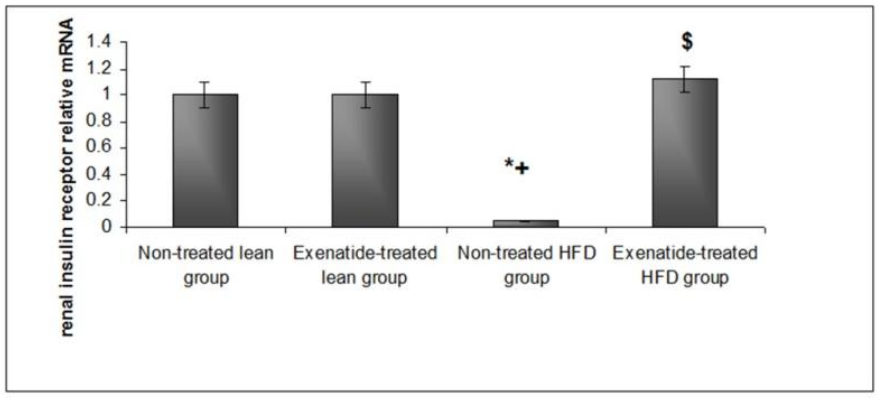

Fig. 4. Effect of exenatide (10µg/kg/d for 4 weeks sc) on the renal insulin receptor gene expression in HFD rats

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means of 10 rats ± SEM

**Indicates significant change from non-treated lean group values at p < 0.05*

+ Indicates significant change from exenatide-treated lean group at p < 0.05.

$ Indicates significant change from non-treated HFD group at p < 0.05

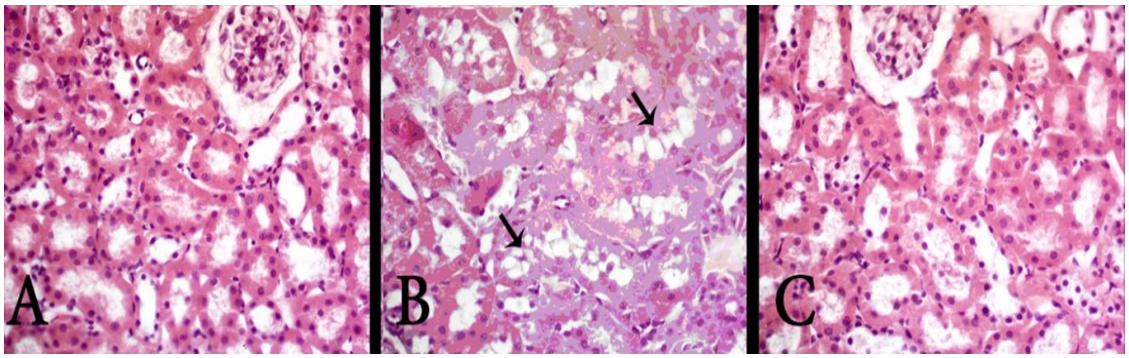

Fig. 5. Photo-microphotograp of renal tissue of control lean groups (A) showing normal glomeruli and tubules, non-treated HFD group (B) showing cytoplasmic fat globules (arrow) in the renal tubules and exenatide-treated HFD group (C) showing intact glomeruli and tubules with little fat vacuoles (H&E stain, 400x)

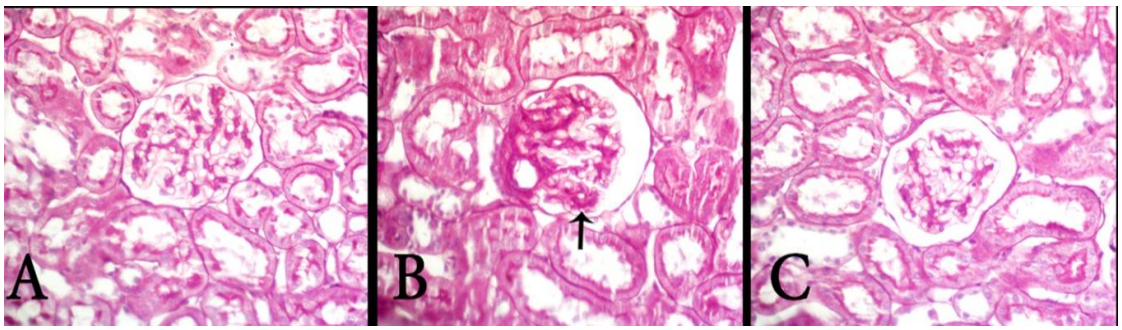

Fig. 6. Photo-microphotograp of renal tissue of control lean groups (A) showing normal glomeruli, non-treated HFD group (B) showing mild increase in mesangial matrix (arrow) and exenatide-treated HFD group (C) showing normal appearance of the glomeruli (PAS stain, 400x)

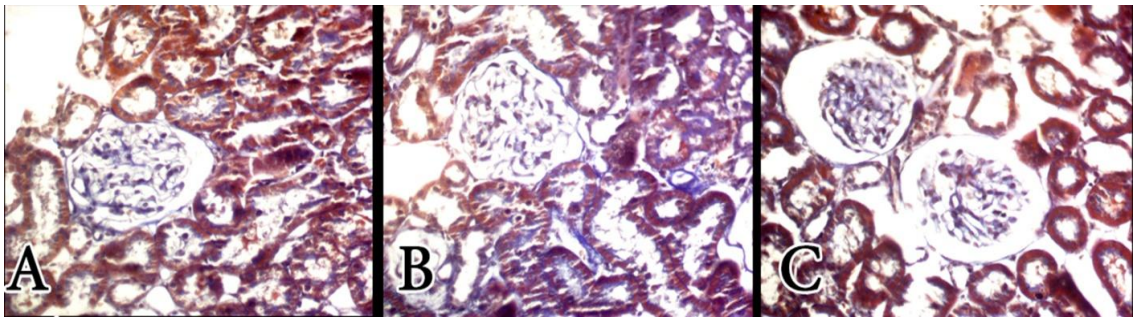

Fig. 7. Photo-microphotograp of renal tissue of control lean groups (A), non-treated HFD group (B) and exenatide-treated HFD group (C) showing no evidence of glomerular or interstitial fibrosis (Masson Trichroma stain, 400x)

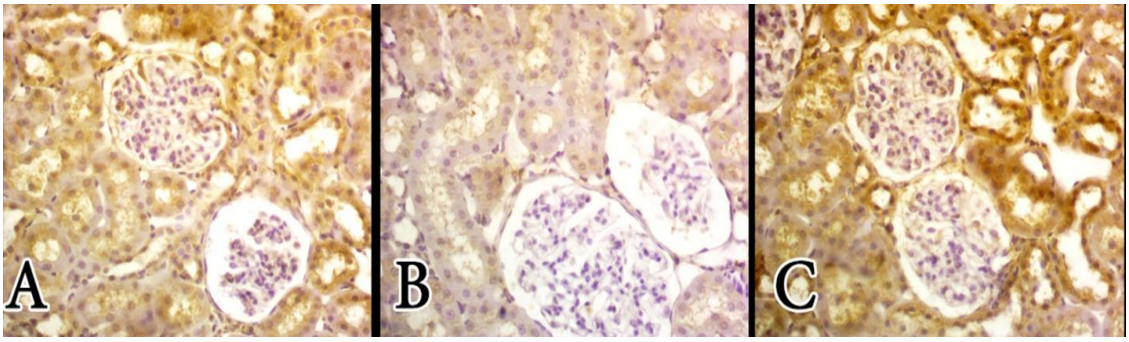

Fig. 8. Photo-microphotograp of immunohistochemical staining of insulin receptor B of renal tissue of control lean groups (A) showing strong diffuse cytoplasmic reaction, non-treated HFD group (B) showing mild diffuse cytoplasmic reaction and exenatide-treated HFD group (C) showing strong diffuse cytoplasmic reaction (400x)

4. DISCUSSION

In the current study, feeding rats on HFD induced major systemic alterations including obesity, hyperglycemia, hyperinsulinemia, insulin resistance and dyslipidemia. Additionally, HFD rats showed alteration of the renal function detected by low creatinine clearance and microvesicular steatosis with increase in the mesangial matrix. This renal damage was associated with low cytoplasmic reaction to insulin receptor β immunohistochemical staining and down regulation of renal IR gene expression. The systemic alterations and renal injuries induced by HFD were prevented by exenatide with marked up regulation of renal IR gene expression.

Consistent with our results, HFD has been shown to produce rapid weight gain, hyperglycemia, hypertriglyceridemia hyper-cholesterolemia and compensatory hyper-insulinemia in rodents [8]. Also, Roza et al. [14] concluded that HFD-fed rats showed rise in arterial blood pressure and peripheral glucose intolerance. This may be due to the consumption of energy dense diet rich in saturated fat, its deposition in various body fat pads, decreased energy expenditure, and high rate of lipogenesis and triglycerides accumulation in liver [15]. Fruchart et al. [16] had reported that lipids in adipose tissue are largely derived from circulating triglycerides especially during high-cholesterol diet feeding.

Early in the development of insulin resistance in obesity, blood glucose concentration can generally be maintained in a normal range due to an enhanced glucose-sensing pathway and increased insulin output [17]. However, hyperglycemia occurs in obesity despite of hyperinsulinemia. Steil et al. [18] recorded that insulin-resistant states in obesity or diabetes are often associated with a decrease in the binding of insulin to IR and/or a decrease in insulin-stimulated activation of IR. It has been proposed that increased visceral adipose tissue impairs insulin sensitivity through promoting the secretion

of free fatty acids and adipocyte-derived inflammatory cytokines such as tumor necrosis factor-α or Interleukin-6 [19]. According to many studies, fatty acid incubation of insulin sensitive cells, particularly saturated fatty acids, increase intracellular fatty acid metabolites such as diacylglycerol, fatty acyl-Coenzyme A and ceramides. These fatty acid metabolites decreased phosphorylation level of proteins involved in insulin signaling [20].

In the present study, HFD led to deterioration of the renal function in the form of decrease creatinine clearance and microvesicular steatosis with enlargement of mesangial matrix. These results are in accordance with Sharma et al. [21] who found hydropic change in proximal convoluted tubules and more widening of matrix in a model of diabetic insulin resistance rats. The local alteration of lipid metabolism in the kidney may play an important role in the pathogenesis of the renal injury in metabolic syndrome [22]. Feeding a HFD to mice induced altered imbalance between renal lipogenesis and lipolysis that caused renal injuries [23]. Systemic lipid overload “lipotoxicity,” can induce systemic inflammation and oxidative stress leading to glomerulosclerosis, interstitial fibrosis, and albuminuria [24].

Although a growing evidence that the increased renal lipogenesis plays a role in the pathogenesis of renal injury [25], the precise mechanisms for renal lipid accumulation have not been fully determined. Therefore, we tried to clarify the role of renal IR in lipogenesis in HFD rats in the present study. Down-regulation of IR mRNA expression and attenuation of the cytoplasmic reaction to the insulin receptor β immuno-histochemical staining in HFD rats were clearly detected suggesting the crucial role of IR in the pathogenesis of renal damage. This observation was previously noted by Hale and Coward [26] who found that IR is down-regulated in the kidneys of systemic insulin resistance models and concluded that IR is important for renal function in the glomeruli and tubules. When signalling is diminished as in insulin-resistant states, it may be responsible for a number of renal complications including albuminuric glomerular disease and hypertension [2]. It has been shown that kidney expresses IR isoform B which is the isoform found in the classically insulin-responsive, glucose-regulating, tissues of fat, liver and skeletal muscle. So that insulin is involved in a number of homoeostatic physiological responses throughout the kidney [27]. Mima et al. [28] found that the glomerulus is more prone to developing insulin resistance in diabetes and obesity. The IR is important for podocyte function, which are unique cells found on the urinary side of the glomelular filteration barrier to maintain its integrity [29]. Loss of podocyte results in features resembling diabetic nephropathy [30]. Insulin resistant podocytes showed lipid accumulation and exhibited an inflammatory state with increase oxidative stress that ended in apoptosis [31]. However Hale and Coward [26] suggested that hyperstimulation of the insulin signalling axis and not loss of insulin sensitivity in the kidney may occur early in insulin resistance that may also have a detrimental effect. A consequence of increased insulin signalling in the podocyte is increased translocation of the glucose transporter GLUT4 and GLUT1 to the plasma membrane of this cell, allowing more glucose to passively diffuse into the cell producing glucose toxicity responsible for cellular dysfunction in the setting of diabetes [32]. An evidence that overexpression of GLUTs in the mesangial cell is detrimental to the glomerular function [33]. In addition to glomeruli, the IR is expressed throughout the renal tubule [34]. It has been speculated that in diabetic nephropathy, hyperinsulinaemic state promotes sodium reabsorption from the renal tubules and contributes to hypertension [35].

In the present study, weight loss was observed in HFD rats treated with exenatide, consistent with the appetite reducing effects of glucagon like peptide (GLP-1) analogues. Fasting blood glucose, insulin, and HOMA-IR were significantly decreased together with improvement of dyslipidemia and hypertension. Consistent with the current results, Mack et al. [9] showed that systemic exenatide reduced body weight gain, fat mass, food consumption patterns, plasma cholesterol, triglycerides and insulin resistance in high-fat-fed rodents. Also, Laugero et al. [36] demonstrated the antihypertensive effect of exenatide in a rat model of the metabolic syndrome.

One mechanism produced by exenatide administration to decrease both body weight and food intake behavior is through modulation of neuronal transmission in the central nervous system (CNS) via GLP-1 containing neurons in the nucleus of the tractus solitarius which projects into thalamic and hypothalamic regions implicated in the control of food intake [37]. Another possibility is that circulating GLP-1

directly reaches accessible receptors located in blood brain barrier-free areas (area postrema and subfornical organ) that in turn relay to brain nuclei involved in nutrient homeostasis. It is also likely that gastric emptying mediated by GLP-1 increases the sensation of fullness and leads to the termination of meal ingestion, there by participating in the regulation of food intake [37,38]. GLP-1 analogues may regulate total fat weight by increasing brown adipose tissue thermogenesis [39]. The decrease in the total fat weight may be due to decrease fat pad mass by reduced formation of new adipocyte from precursor cells (adipocyte differentiation) or decreased adipocyte size due to fat storage (adipocyte hypertrophy) [40]. GLP-1 can also regulate serum triglycerides and cholesterol levels by numerous mechanisms. Acute or long term treatment with either GLP-1 or its stable analogs reduced fasting and postprandial lipids in healthy as well as diabetic patients. GLP-1R signaling reduces hepatic VLDL-TG production. Also it modulates the key enzymes of lipid metabolism in liver to reduce TG content. Additionally GLP-1 impairs β-oxidation and de novo lipogenesis in the hepatocyte and lastly modulates reverse cholesterol transport [41].

It was previously demonstrated that exenatide acts in the endocrine pancreas by maintaining optimal β-cell mass and function by increasing the β-cell gene expression [42]. Exenatide can exert its secretagogue effect on insulin release by activating GLP-1receptor (GLP-1R) in the β-cells. GLP-1R regulates pancreatic β-cell differentiation to extend its lifespan via cAMP and phosphatidylinositol-3-kinase /protein kinase B-dependent system leading to an increase in the β-cell mass [43]. So, exenatide can affect the release of insulin in response to hyperglycaemia with the result of concomitant reduction in both blood glucose and insulin release [44]. Also, GLP-1 reduces glucagon secretion from pancreatic α-cells, probably through inhibitory binding effect of GLP-1 to its receptors expressed in pancreatic α-cell [45].

In the current study exenatide improved the renal function and reversed the renal pathological changes induced by HFD to near normal. These changes were accompanied by up-regulation of renal IR mRNA expression and marked cytoplasmic reaction to the insulin receptor immunohistochemical staining. This renoprotective effect was previously noted by Lotfy et al. [46] who reported that exenatide treatment could protect the diabetic rats from kidney dysfunction. Several mechanisms might be responsible for the protective effects of exenatide against renal injury in diabetes. Deji et al. [47] suggested that the control of body weight and dyslipidemia in metabolic syndrome is an important therapeutic target to prevent the development of renal lipid metabolism imbalance and chronic kidney disease. Also, exenatide might reduce apoptosis and oxidative stress in diabetic rats [48]. Our explanation for this renal protection induced by exenatide is through up-regulation of renal IR gene expression which was not previously reported to the best of our knowledge.

5. CONCLUSION

In conclusion, the results obtained in the present study suggested that exenatide exerted a renoprotective effect in rats fed a HFD. This effect is partly produced by up-regulation of renal IR gene in addition to the control of body weight, insulin resistance and dyslipidemia. So exenatide may be a novel therapeutic agent for obesity induced renal damage clinically.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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