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ORIGINAL ARTICLE

Biotin amelioration of nephrotoxicity in streptozotocin-induced diabetic mice

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Abstract The current study was carried out to investigate the protective role of biotin in kidney injury and oxidative stress in diabetic mice type 1. Male Swiss albino mice were randomly divided into 3 groups. Control group received saline. Diabetes type 1 was induced in second and third groups by intraperitoneal injection of streptozotocin as a single dose (150 mg/kg). Second group remained as the untreated diabetic group and the third group received 15 mg/kg daily oral dose of biotin for 12 successive days. Biochemical results showed significant elevation in blood glucose and urea levels in both diabetic groups. Also, there is an increase in glomerular areas and decrease in glomerular cellularity in both diabetic groups. Histopathological results showed severe alterations in the untreated diabetic group represented by distorted glomeruli, inflammatory cells, and giant macrophages. In addition, there was an intense immune-reaction response toward acrolein indicator of oxidative damage. Upon biotin administration of diabetic mice, the above mentioned histopathological changes were reduced and also acroline reaction of oxidative damage was diminished. Our findings prove that biotin has a protective role against streptozotocin-induced oxidative damage in kidneys of laboratory mice.

1. Introduction

Diabetes mellitus is the most common metabolic disorder. It is characterized by hyperglycemia that results from an absolute or relative insulin deficiency and is associated with long-term complications affecting the eyes, kidneys, heart and nerves (Gispen and Biessels, 2000). Diabetes mellitus is classified into two types, insulin dependent diabetes mellitus (IDDM, type 1) and non-insulin-dependent diabetes mellitus (NIDDM, type 2). Type I diabetes is an autoimmune disease characterized by a local inflammatory reaction in and around islets that is

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followed by selective destruction of insulin-secreting β-cells. Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion (Foulis, 1987; Arora et al., 2009). The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al., 2003). In spite of the introduction of hypoglycemic drugs, diabetes and related complications continue to be a major medical problem (Nammi et al., 2003). The chronic hyperglycemia was found to increase the production of free radicals that is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (Mohamed et al., 1999; Baynes, 1991).

Diabetic nephropathy is a major cause of end-stage renal failure worldwide, with a prevalence expected to double over the next decade (Locatelli et al., 2003). Type 2 diabetes accounts for 90% of patients with diabetic nephropathy. Despite conventional therapies of glycemic and BP control, many patients still have evidence of renal damage (Svensson et al., 2003). Kidney macrophage accumulation is known to play a role in non-diabetic renal injury and the mechanisms of macrophage accrual are well-established in these diseases (Nikolic-Paterson and Atkins, 2001). However, diabetic nephropathy is not generally considered to be an inflammatory disease. This view is currently changing because recent studies of human biopsy samples and animal models have established kidney macrophage accumulation as a characteristic of diabetic nephropathy (Sassy-Prigent et al., 2000; Chow et al., 2004). Renal macrophage accumulation correlates with the severity of glomerular and tubulointerstitial injury in experimental diabetic nephropathy and non-diabetic models of renal disease (Yang et al., 1998; Lan et al., 1991).

Biotin (Vitamin H) is part of the B complex group of vitamins. All B vitamins help the body to convert food (carbohydrates) into fuel (glucose), which is used to produce energy. These B vitamins, often referred to as B complex vitamins, also help the body metabolize fats and protein. B complex vitamins are needed for healthy skin, hair, eyes, and liver. The body needs biotin to metabolize carbohydrates, fats, and amino acids (the building blocks of protein). Like all B vitamins, it is a water-soluble vitamin, meaning the body does not store it. However, bacteria in the intestine can make biotin. It is also available in small amounts in a number of foods. Biotin is also important for normal embryonic growth, making it a critical nutrient during pregnancy (Said, 2002; Báez-Saldaña et al., 2004; Mock et al., 2002; Fiume, 2001).

The aim of the current work is to investigate whether biotin can reduce diabetic nephropathy in type 1 diabetic mice and hence can be advised for diabetic patients to keep kidneys safe from injury or not.

2. Material and methods

2.1. Animals and experimental design

Thirty male Swiss albino mice (25 ± 3 g) were randomly divided into three groups, ten mice per each group. Mice were housed in polypropylene cages inside a well-ventilated room at 22 ± 1 °C and 12-h periods of light and dark, with free access to clean water and commercial mice food. All mice were fasted for 20 h before experimental induction of diabetes. The first group received cold citrate buffer (pH 4.5) and served as control. Experimental diabetes was induced in the second and third groups via intraperitoneal injection of a single dose of 150 mg/kg streptozotocin (Sigma Chemicals Co., St. Louis, MO, USA) dissolved in cold 0.01 M citrate buffer, pH 4.5. The experiments were approved by state authorities and followed Saudi Arabian rules for animal protection. The induced diabetes was confirmed via colorimetric detection of blood glucose levels after three days of STZ injection in blood collected from tails of study animals. After three days of induction of diabetes, animals within the third group received a daily dose of biotin (15 mg/kg) orally for twelve successive days. At the end of experimental period, animals were sacrificed.

2.2. Kidney index

Each mouse was weighed individually; and both kidneys were weighed. Finally, the kidney index was calculated by dividing the kidney weight by the body weight and then multiplying by 100 and the results were statistically analyzed by SPSS.

2.3. Biochemical analysis

Blood was collected from the heart of animals into heparinized tubes and plasma was separated by cold centrifugation. Plasma was assayed for levels of glucose, urea and creatinine using commercially available kits (Biomerieux, Marcy l'Etoil, France).

2.4. Histological examination and renal injury

Pieces of kidney were freshly prepared, fixed in 10% neutral buffered formalin, and then embedded in paraffin. Sections were cut and stained with hematoxylin and eosin.

The stained tissue sections were scanned for renal tissue abnormalities. Glomerular cellularity was determined by counting the number of nuclei in 20 hilar glomerular tuft cross-sections per animal. The glomerular tuft areas were measured with Motic 200 image analyzer (Hong Kong, China).

2.5. Immunohistochemical localization of acrolein (ABC method)

Paraffin embedded kidney sections were deparaffinized in xylene and rehydrated in descending grades of alcohol and finally distilled water. Sections then were heated in citrate buffer (pH 6) within microwave for 5 min. After that sections were washed with PBS buffer for 5 min and incubated in peroxidase blocking solution for 10 min. Sections were incubated overnight at 4 °C in diluted primary antibody (anti-acrolein) (mouse monoclonal antibody ab48501) then incubated in biotinylated goat anti-mouse (ab128976) as secondary antibody for 30 min, followed by incubation in avidin–biotin complex for 30 min, then incubated in DAB (ab64238) as chromogenic substrate for ten minutes. The stained sections were counter stained with Mayer's hematoxylin, and dehydrated within ascending grades of alcohol and cleared with two changes of xylene, mounted with cover slip based on DPX mountant. All reagents were purchased from Abcam

company (Cambridge, UK). Kidney sections were examined under microscope for brown immunoreactivity color and photos at magnification of 200×.

2.6. Statistical analysis

One-way ANOVA was carried out, and the statistical comparisons among the groups were performed with Duncan's test using a statistical package program (SPSS version 17.0). All P values are two-tailed and $P < 0.05$ was considered as significant for all statistical analysis in this study.

3. Results

3.1. Kidney index

Statistical analysis of kidney indices for comparison between control, non treated diabetic treated diabetic with biotin mice groups registered 0.62 in the control group, 0.78 and 0.61 in non treated and treated diabetic groups, respectively (Table 1) that showed a significant increase in the nontreated diabetic group compared to the control group, a significant decrease in the treated diabetic group compared to the non-treated group and no difference in kidney index value between treated diabetic and control groups.

3.2. Renal injury

Glomerular areas of the experimental groups were measured that showed an increase in glomerular areas in diabetic groups when compared with the control group, control group registered (2.9 μm^3), whereas, untreated diabetic and treated diabetic glomerular areas registered (3.3 and 4.3 μm^3) respectively (Table 1) that considered a significant increase ($P < 0.05$) between control and diabetic groups, but there was an insignificant increase between untreated and treated diabetic groups. Glomerular cellularity showed a significant decrease in diabetic groups when compared with the control group ($P < 0.05$) that registered (64, 24 and 26 cells/gcs) for control, untreated diabetic and treated diabetic with biotin, respectively (Table 1) that showed an insignificant difference between untreated and treated diabetic groups.

Table 1 Biotin induced changes in kidney index, glomerular area and glomerular cellularity of STZ-induced diabetes in mice.

Group	Kidney index (%)	Glomerular area (μm^3)	Glomerular cellularity (cells/gcs)
Non-diabetic (−Biotin)	0.62 ± 0.12	2.9 ± 0.723	64 ± 8.7
Diabetic (−Biotin)	0.78 ± 0.2[a]	3.3 ± 0.285	24 ± 2.3[a]
Diabetic (+Biotin)	0.61 ± 0.15[b]	4.3 ± 0.357	26 ± 1.8[a]

Values are means ± SD.
[a] Significant against non-diabetic (−Biotin) group at $P \leqslant 0.05$.
[b] Significant against diabetic (−Biotin) group at $P \leqslant 0.05$.

3.3. Biochemical analysis

Biochemical analysis of blood sera collected from the three experimental groups showed normal glucose level in the control group (104 gm/d1) (Table 2) and a significant increase of blood glucose level ($P < 0.05$) in untreated and treated diabetic groups (333 and 294 gm/d1) respectively, there was a slight decrease in glucose levels between untreated diabetic and treated diabetic with biotin groups that considered an insignificant decrease. Blood urea nitrogen (BUN) showed a significant increase ($P < 0.05$) between the control group that registered normal BUN level (20 mg/dl) and untreated and treated diabetic groups that registered (36 and 30 mg/dl), respectively (Table 1), an insignificant decrease in BUN levels was registered between untreated and treated diabetic groups. Diabetic groups (0.6, 0.4 and 0.4), respectively (Table 2) represented an insignificant difference among the three experimental groups.

3.4. Histological and immunohistochemical results

Kidney sections of control mice showed normal histology of cortex and medulla, cortex section (Fig. S1A) showed normal glomerulus in Bowman's capsule surrounded by clear area called capsular space, macula densa appeared near vascular pole of the glomerulus surrounded by many sections of proximal and distal convoluted tubules. Control kidney section showed a negative response to anti-acrolein immunohistochemistry reaction with no brownish immunoprecipitate (Fig. S1B).

Histological examination of kidney of diabetic mice showed severe histopathological alterations as: distorted glomeruli surrounded by aggregations of neutrophilic inflammatory cells, giant rounded macrophages among inflammatory cells, increasing of myofibroblast cells, and degeneration of both distal and proximal convoluted tubule cells. Other evidences of histopathological damage by diabetes include the increase in the capsular space around glomeruli due to diminishing of glomerular size itself, darkly stained lymphocytes appeared forming lymphocytic infiltration and scattered lymphocytes and neutrophils inflammatory cells among tubules besides accumulation of myofibroblast cells. Dilatation in kidney blood vessels with erythrocytic congestion surrounded by leukocytic infiltration was also seen (Fig. 1A and B). Diabetes induced moderate to intense acrolein immune-reactivity in

Table 2 Biotin induced changes in glucose, blood urea nitrogen and creatinine in blood of STZ-induced diabetic mice.

	Blood glucose (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)
Non-diabetic (−Biotin)	104 ± 36	20 ± 4	0.6 ± 0.2
Diabetic (−Biotin)	333 ± 46[a]	36 ± 1[a]	0.4 ± 0
Diabetic (+Biotin)	294 ± 97	30 ± 3[a,b]	0.4 ± 0.03

Values are means ± SD.
[a] Significant against non-diabetic (−Biotin) group at $P \leqslant 0.05$.
[b] Significant against diabetic (−Biotin) group at $P \leqslant 0.05$.

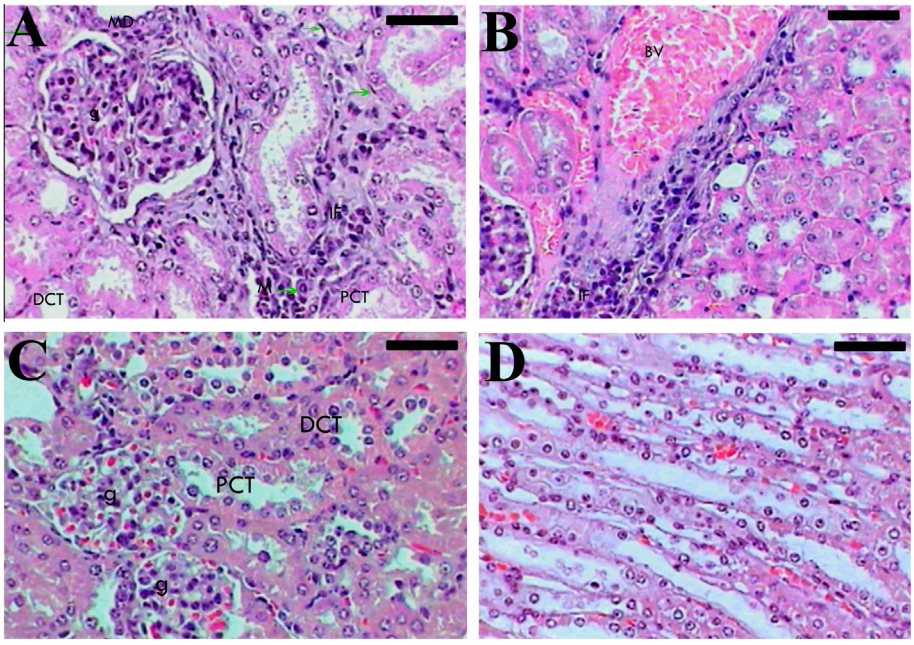

Figure 1 Histopathological alterations in renal tissue of STZ-induced diabetic mice. G: distorted glomeruli, IF: leukocytic inflammation, Mand arrow: giant macrophage (A), BV: congested blood vessels (B). Renal tissue of STZ-induced diabetic mice and treated with biotin. Sections show improved glomeruli in cortex and more or less healthy cubical cells of convoluted tubules and with healthy medullary rays (C and D). Sections are stained with hematoxylin and eosin. Scale bar = 50 μm.

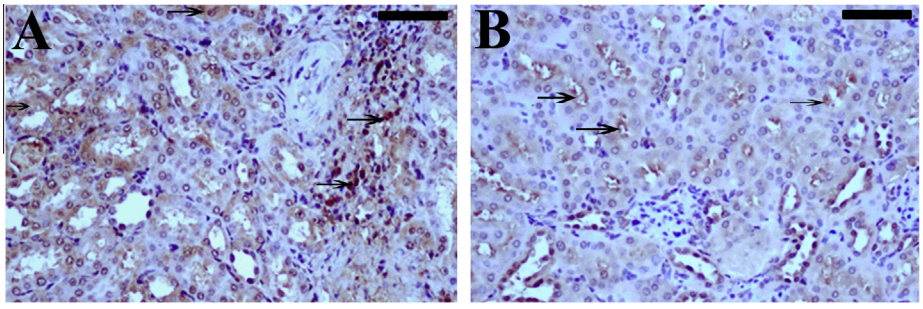

Figure 2 Renal tissue of STZ-induced diabetic mice with intense acrolein reddish brown precipitate of avidin–biotin complex in glomeruli and tubules (arrows) (A). Renal tissue of STZ-induced diabetic mice and treated with biotin showing slight brown precipitate of acrolein in convoluted tubules (arrows) (B). Sections are stained with ABC immunostain. Scale bar = 50 μm.

the glomeruli and tubular epithelial cells manifested by dark reddish brown precipitate (Fig. 2A).

Kidney sections of diabetic mice treated with 15 mg/kg of biotin showed less pathological changes compared with diabetic group. There was an improvement within glomeruli with high cellularity appeared in the cortex tissue and most of distal and proximal tubules showed healthy cubical cells with abundant nuclei (Fig. 1C). Medulla section showed wide dilated collecting tubules with abundant nuclei, some of tubular cells showed degenerated cytoplasm and other showed apoptotic nuclei (Fig. 2B). Treatment with biotin for diabetes mice reduced acrolein expression in kidneys represented by pale reddish brown precipitate (Fig. 2B).

4. Discussion

In the current work, diabetes was induced in laboratory mice via intraperitoneal injection of (150 mg/kg/bw) streptozotocin. STZ is considered to be toxic to insulin producing beta cells within pancreas, and thus it is widely used to induce experimental diabetes in laboratory animals (Casey et al., 2004; Gojo et al., 2007).

Our data showed that STZ-induced diabetic mice showed a significant increase in blood urea and glucose levels, and kidney index between control and diabetic groups, and with insignificant changes in serum creatinine and glomerular areas. Upon biotin administration to diabetic mice, both kidney index and blood urea nitrogen were significantly decreased, and there were no significant changes in blood glucose, glomerular cellularity and serum creatinine in comparison with untreated diabetic mice.

Biotin is the cofactor for many enzymes in the body. Physiologically, biotin is playing a key role in the metabolism of carbohydrates, lipids, proteins and nucleic acid. It plays an irreplaceable role in maintaining metabolic dynamic equilibrium (Pacheco-Alvarez et al., 2002). Pharmacologically, biotin

can reduce type I diabetes blood sugar levels, improve the experimental rats glucose tolerance and insulin resistance (Fernandez-Mejia, 2005). Biotin regulates blood glucose levels in both hypo- and hyperglycemia. Biotin treatment lower postprandial glucose levels, improved glucose tolerance and enhanced endogenous insulin sensitivity (Reddi et al., 1988). In addition, biotin enhances insulin biosynthesis and hence protects β-cell dysfunction induced by glucotoxicity or lipotoxicity (Yoshikawa et al., 2002).

Previous studies proved that, diabetes mellitus type I induces hypertrophic changes within kidneys (Yamamoto et al., 2001; Romero et al., 2013). In addition, morphometric analysis of kidney sections revealed that STZ-induced diabetic mice had an increase in glomerular areas and hypercellularity (Wada et al., 2001; Chow et al., 2004; Spencer et al., 2004; Kiran et al., 2012). The present study agreed with previous studies that untreated and treated diabetic mice groups showed an increase in glomerular area due to expansion of glomerular cells, distortion and dilatation in Bowman's capsules which lead to an increase in capsular space, but the present study revealed that early stage of nephrotoxicity in diabetes mice STZ-induced showed hypocellularity due to degeneration of glomerular cells.

The present study showed marked pathological changes in untreated STZ-induced diabetic kidney mice as manifested by distorted and dilated glomeruli with expanded matrix and degenerated cells, giant multinucleated macrophages, aggregations of neutrophils, lymphocytic infiltration, accumulation of myofibroblast like cells and degeneration of tubular cells. Approximately 30% of insulin-dependent diabetes mellitus patients suffer from diabetic nephropathy which is considered to be a life-threatening complication of diabetes mellitus (Bojestig et al., 1994; Krolewski et al., 1996). Our results are in agreement with many previous studies that proved these induced pathological alterations (Zafar et al., 2009; Wada et al., 2001; Chow et al., 2005) whereas treated diabetic mice with biotin showed less pathological alterations compared with the untreated diabetic group manifested by more or less healthy tubules and improved glomeruli.

Examination of kidney sections incubated with anti-acrolein antibodies showed an intense immunoreactivity against acrolein in renal tissues which indicates the strong oxidative damage in kidneys of STZ-induced diabetic mice. Upon treatment of diabetic mice with biotin, the immunoreactivity against acroline was strongly reduced indicating that biotin reduced oxidative stress in diabetic kidney mice.

Diabetes is usually associated with a status of oxidative stress represented as decreased GSH levels and increased lipid peroxidation products (Seghrouchni et al., 2002). STZ injection causes inflammatory cell infiltration within the pancreas followed by the onset of insulin deficiency, and activates protein kinase-C, poly (ADP-ribose) polymerase and NAD(P)H oxidase, with consequent generation of ROS and advanced glycation end products resulting in renal damage and nephropathy (Kolb and Kroneke, 1993; Like and Rossini, 1976; Szabo, 2005; Arora et al., 2009).

There is increasing evidence that aldehydes generated endogenously during lipid peroxidation contribute to the pathophysiologic effects associated with oxidative stress in cells and tissues. A number of reactive lipid aldehydes, such as 4-hydroxy-2-alkenals and malondialdehyde, have been implicated as causative agents in cytotoxic processes initiated by the exposure of biologic systems to oxidizing agents. Recently, acrolein (CH_2═CH─CHO), a ubiquitous pollutant in the environment, was identified as a product of lipid peroxidation reactions. The identification of acrolein as an endogenous lipid-derived product suggests an examination of the possible role of this aldehyde as a mediator of oxidative damage in a variety of human diseases (Uchida, 1999). Lipid peroxidation is implicated in the pathogenesis of numerous diseases; including atherosclerosis, diabetes, cancer, and rheumatoid arthritis, as well as in drug-associated toxicity, post is chemic reoxygenation injury, and aging. Lipid peroxidation proceeds by a free-radical chain reaction mechanism and yields lipid hydroperoxides as major initial reaction products. Subsequently, decomposition of lipid hydroperoxides generates a number of degradation products that lead to a wide variety of damaging actions (Esterbauer et al., 1991). The present study reported that kidneys of untreated diabetic mice showed intense acrolein gene expression immunoreactivity as a product of lipid peroxidase that leads to oxidative stress whereas, kidneys of diabetic mice treated with biotin showed slight acrolein immunoreactivity indicating that biotin reduced oxidative stress in diabetic kidney mice.

Although its beneficial effects are largely known, there are no available data in the literature regarding the protective role of biotin against organ induced cytotoxicity or its antioxidant properties. It was found that biotin levels positively correlate with antioxidant levels as reduced glutathione, glutathione peroxidase, catalase and superoxide dismutase (Al-Qudah and Ismail, 2012). Low serum biotin levels initiate a series of biochemical events that lead potentially to the release of harmful lipid peroxidation by-products. In addition, biotin plays an important role in the regulation of chromatin structures, gene expression, and DNA repair (Gravel and Narang, 2005; Hassan and Zempleni, 2006) that may investigate the obtained data of low immunoreactivity against acrolein in renal tissues after biotin treatment of STZ-induced diabetic mice.

In conclusion, biotin is found to reduce STZ-induced diabetic associated renal tissue alterations and oxidative damage.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sjbs.2015.03.003.

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