Effect of L-Carnitine on Endothelial Dysfunction markers in Diabetic-Irradiated rats.

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Abstract
Dimethylarginine (ADMA), endothelin-1 (ET-1) and total nitrate/nitrite (NO(x)) are mediators of endothelial dysfunction and involved in the pathogenesis of cardiovascular diseases. Diabetes and γ-irradiation (IRR) exposure are associated with the development of various cardiovascular diseases. Oxidative stress plays a major role in the pathogenesis of diabetes mellitus leading to various complications including endothelial dysfunction. The present study was designed to evaluate the effect of L-carnitine (L-car) on ADMA, endothelin-1 and NO(x) in diabetic-γ-irradiated (STZ-IRR)rat and evaluate the anti-hyperglycemic properties of L-carnitine on streptozotocin (STZ)-induced diabetes. Serum lipid profiles, glucose level, ADMA, ET-1 and NO(x) were determined. The cellular changes were estimated using malondialdehyde (MDA) as indicies of lipid peroxidation, the antioxidants superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and reduced glutathione (GSH) and NO(x). Circulatory lipid profiles, ADMA, endothelin-1 and cardiac MDA were increased significantly, whereas the level of serum NO(x) and cardiac GSH and antioxidant enzymes were significantly decreased in IRR (5 Gy), STZ and STZ-IRR rats. Treatment with L-carnitine (200 mg/kg, i.p., every other day) for 28 days, resulted in a significant decrease in the levels of blood glucose and lipid profiles along with a significant decrease in the levels of serum ADMA, endothelin-1 and cardiac MDA. The cardiac antioxidant enzymes and GSH were increased significantly along with the serum NO(x). In conclusion, ADMA, endothelin-1 and NO(x) were implicated in endothelial dysfunction of rats exposed to STZ and/or gamma-radiation. L-carnitine offers promising radioprotective and antidiabetic effects that may be mainly attributed to its potent antioxidant.

Key Words: Asymmetric dimethylarginine, endothelin-1, nitric oxide, streptozotocin, ionizing radiation, L-carnitine.

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1. Introduction
Diabetes and cancer are common diseases with tremendous effect on health worldwide, and diagnosed within the same individual more frequently than would be expected [1]. Treatments vary considerably, depending on the type of cancer and its progression. The most two common types of treatment are radiotherapy and chemotherapy. Radiation-induced heart disease is a potentially life-threatening side effect of radiotherapy of thoracic and chest wall tumors [2]. Nevertheless, normal tissue radiation toxicity remains the most important dose limiting factor in radiotherapy. Ionizing radiation-induced injury involves the generation of reactive oxygen species, which show high reactivity to a variety of cellular macromolecules, including DNA, lipids, and proteins [3]. Diabetes mellitus is a global health problem due to its serious complications [4]. Metabolic abnormalities found in diabetes such as hyperinsulinaemia, hyperglycaemia, and dyslipidaemia along with oxidative stress were shown to contribute to endothelial dysfunction [5]. Oxidative stress mediated by hyperglycemia-induced generation of free radicals, contributes to the development and progression of diabetes and related complications [6]. Endothelial dysfunction, defined as an imbalance of endothelial-derived vasoconstrictor and vasodilator substances, is involved in the pathogenesis of both macro and microvascular complications in diabetes [7]. Previous studies have reported endothelial dysfunction in both human [8] and animal subjects [9] exposed to ionizing radiation. Endothelial dysfunction due to reduced synthesis and/or bioavailability of nitric oxide has been found associated with almost all cardiovascular risk factors and in diabetes mellitus [10]. Nitric oxide is synthesized from L-arginine via the action of nitric oxide synthase, which is known to be blocked by endogenous L-arginine analogues such as asymmetric dimethylarginine (ADMA), a well-known endogenous nitric oxide synthase inhibitor found in plasma.
and various types of tissues [11]. One important feature of endothelial dysfunction is an increased production of the potent vasoconstrictor and proinflammatory peptide endothelin (ET-1). Circulating ADMA and endothelin-1 levels has been shown to be a marker of endothelial dysfunction in humans and have been assessed in a variety of systemic cardiovascular diseases, renal failure and diabetes [12].

L-carnitine (β-hydroxy-γ-N-trimethylammonium butyric acid) is quaternary ammonium compound biosynthesized from amino acids lysine and methionine [13]. L-carnitine plays an essential role in the transport of long-chain fatty acids from the cytosol to the mitochondrial matrix as acylcarnitine esters where β-oxidation takes place [14]. L-carnitine has a protective effect on lipid peroxidation by reducing the formation of hydrogen peroxide [15]. It is also improve antioxidant status in rats and showed free radical scavenging activity and prevents the accumulation of free fatty acids and their toxic intermediates, thus preventing their harmful effects on mitochondrial and cell membranes [16]. Therefore, the present study was designed to study the effect of L-carnitine on ADMA, endothelin-1 and nitric oxide as oxidative stress markers in diabetic-irradiated rats.

2. Materials and Methods

2.1. Animals

Male adult Wistar albino rats weighing 120–150 g were obtained from the Egyptian Organization for Biological Products and Vaccines (VACSERA, Giza, Egypt). Animals were kept under standard conditions and were allowed free access to a standard requirement diet and water ad. Libitum. Animals were kept under a controlled lighting condition (light: dark, 13 h: 11 h), 25±2°C, relative humidity 50%. Animals were acclimatized to laboratory conditions before the test. The animals’ treatment protocol has been approved by the animal care committee of the National Centre for Radiation Research and Technology (NCRRT), Cairo, Egypt, following the guidelines of National Institutes of Health (NIH).

2.2. Chemicals

L-carnitine and streptozotocin were purchased from Sigma Chemical Co., St. Louis, USA. All other chemicals and solvents used were of the highest purity grade available.

2.3. Irradiation:

Whole-body γ-irradiation was performed at the National Centre for Radiation Research and Technology (NCRRT), Cairo, Egypt, using an AECL 137Cs Gamma Cell-40 biological irradiator. Animals were irradiated at an acute single dose level of 5 Gy delivered at a dose rate of 0.012 Gy/s.

2.4. Experimental design:

2.4.1. Induction and assessment of diabetes:

A single dose of 65 mg/kg streptozotocin (STZ) prepared in citrate buffer (pH 4.5, 0.1M) was injected intraperitoneally to induce diabetes. The age-matched control rats received an equal volume of citrate buffer and used along with diabetic animals. Diabetes was confirmed after 72 h of STZ injection, the blood samples were collected through caudal vein and blood glucose levels were estimated by diagnostic kit method. Rats receiving STZ were given 10% sucrose water in the first 48 hrs after injection to prevent hypoglycemia. The rats having blood glucose levels more than 300 mg/dl were selected and used for the present study.

2.4.2. Treatment schedule:

Forty eight male albino rats weighing about 150-180 g were divided randomly into 8 groups (6 animals each). Group I (Control): rats were injected with 0.5 mL of 0.1 mol/L citrate buffer, pH 4.5. 3 days later; rats were injected with normal saline (0.5 mL, i.p.) every other day for 28 days. Group II (L-car): rats were injected with 0.5 mL of 0.1 mol/L citrate buffer, pH 4.5. 3 days later; rats were injected intraperitoneally with L-carnitine (200 mg/kg body weight, every other day for 28 days). Group III (STZ): rats were made diabetic by a single intraperitoneal injection of STZ (65 mg/kg body weight) dissolved in 0.1 M citrate buffer, 3 days later, rats were injected with normal saline (0.5 mL, i.p.) every other day for 28 days. Group IV (IRR): Rats were received the same dose as in group I and on day 28 rats was submitted to a single dose of whole-body gamma irradiation (5 Gy). Group V: (STZ + IRR): rats were made diabetic as in group III, 3 days later, rats were injected with normal saline (0.5 mL, i.p.) every other day for 28 days, on day 28 rats were submitted to a single dose of whole-body gamma irradiation (5 Gy). Group VI (STZ + L-car): rats were made diabetic as in group III, 3 days later, rats were injected with L-car (200 mg/kg body weight, every other day for 28 days). Group VII (L-car + IRR): rats were injected with 0.5 mL of 0.1 mol/L citrate buffer, pH 4.5, 3 days later; rats were injected intraperitoneally with L-carnitine (200 mg/kg body weight, every other day for 28 days), one hour after the last dose, rats were irradiated (5 Gy). Group VIII (STZ + L-car+ IRR): rats were made diabetic as in group III, 3 days later, rats were injected with L-car (200 mg/kg body weight, every other day for 28 days), one hour after the last dose, rats were irradiated (5 Gy).

All rats were fasted overnight. Twenty-four hours after the last dose of specific treatment, and animals were sacrificed by decapitation after exposure to ether in a dessicator kept in a well-functioning hood. Blood samples were obtained by heart puncture and serum samples were separated by centrifugation (Sorvall TC centrifuge, Hamburg, Germany) at 750g at room temperature for 10 min. Samples were stored at −80°C until assayed. Serum were used for determination of glucose, total cholesterol (TC), Triglycerides (TG), High density lipoprotein-cholesterol (HDL-C), Low density lipoproteins-cholesterol (LDL-C), total nitrate/nitrite (NO(x)), endothelin-1 (ET-1) and asymmetric dimethylarginine (ADMA).

Hearts were quickly excised, washed with saline, blotted with a piece of filter paper and homogenized in ice-cold 0.15MTris-KCl buffer (pH 7.4) to yield a 20% (w/v) homogenate using a Branson sonifier (250, VWR Scientific, Danbury, CT, USA). The homogenates were used for the determination of malondialdehyde (MDA) level, glutathione peroxidase (GSHPx) and superoxide dismutase (SOD) activities, total glutathione (GSH) content, and total nitrate/nitrite (NO(x)). The homogenates were centrifuged at 800 g for 5 min at 4°C to separate the nuclear debris. The supernatant so obtained was centrifuged...
(Eppendorf AG, centrifuge 5804R, Hamburg, Germany) at 15000 g for 30 min at 4 ºC to get the post mitochondrial supernatant which was used to assay superoxide dismutase (SOD) activity.

2.5. Biochemical studies:
Serum glucose, triglycerides, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and total cholesterol were determined according to the methods described by Barham and Trinder[17], Fossati and Prencipe [18], Friedwald et al. [19], Demacker et al.[20] and Richmond [21], respectively. ADMA was estimated using a standard enzyme linked immunosorbent assay (ELISA) method according to the manufacturer’s instructions (Immundiagnostik AG, Stubenwald-Allee, Bensheim). Endothelin-1 measurements were accomplished by indirect ELISA method according to the manufacturer’s instructions (R and D system, USA). Total nitrate/nitrite (NO(x)) was measured as stable end product, nitrite, according to the method of Miranda et al. [22]. In cardiac tissue homogenates Malondialdehyde (MDA) and reduced glutathione (GSH) levels were determined spectrophotometrically using the method of Buege and Aust [23] and Ellman [24], respectively. Total nitrate/nitrite (NO(x)) was measured as stable end product, nitrite, according to the method of Miranda et al. [22]. Glutathione peroxidase (GSHPx) and superoxide dismutase (SOD) activities were determined in cardiac homogenate according to the methods of Lawrence and Burk [25] and Minami and Yoshikawa [26] respectively.

2.6. Statistical analysis:
Results were expressed as mean± SEM. The intergroup variation was measured by one way analysis of variance (ANOVA) followed by Tukey’s Multiple comparison test. Statistical significance was considered at p < 0.05.

3. Results:
STZ, IRR and STZ-IRR rats had significantly increased serum levels of glucose, cholesterol, triglycerides and LDL-C and decreased levels of HDL-C as compared to control group. The most pronounced effect was for the combined group. Administration of L-car induced no significant change in glucose and lipid profiles as compared to control group. The administration of L-car to STZ and IRR resulted in significant recovery in blood glucose levels, reduced cholesterol, triglyceride and LDL-C levels, and increased HDL-C levels, compared to IRR and STZ groups. Administration of L-car in the combined group (STZ+L-car+ IRR) induced significant decrease in glucose level, triglycerides, total cholesterol, LDL-C and significant increase in HDL-C level as compared to STZ and IRR groups (Table 1).

Figure 1: Effect of L-carnitine (L-car), streptozotocin (STZ), irradiation (IRR) (5 Gy) and their combination on [A] serum asymmetric dimethylarginine (ADMA), [B] serum endothelin-1 (ET-1) and [C] serum total nitrate/nitrite (NO(x)). abc and d indicate significant change from control, STZ, IRR (5 Gy) and STZ+IRR respectively at p≤ 0.05 using ANOVA followed by Tukey-Kramer as a post ANOVA test.

Serum ADMA and endothelin-1 level was markedly increased in STZ and/or IRR groups with a concomitant decrease in serum NO(X) as compared to the control group. Administration of L-car prior to IRR or to STZ groups, resulted in a significant decrease in serum endothelin-1 and ADMA levels and a significant increase in NO(X) level as compared to the IRR and STZ groups (P < 0.001, Fig. 1A, 1B&1C). Administration of L-car in the combination group
Table (1): Effect of irradiation (5 Gy) (IRR), L-carnitine (L-car) and their combination on the levels of glucose, triglycerides, total cholesterol, high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) in diabetic (STZ) rat serum.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
<th>Total Cholesterol (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>84.3±0.5</td>
<td>79.5±0.5</td>
<td>84.3±0.9</td>
<td>40.3±0.4</td>
<td>39.6±0.8</td>
</tr>
<tr>
<td>L-car</td>
<td>86.9±0.5</td>
<td>78.1±0.7</td>
<td>82.6±1.7</td>
<td>41.3±0.6</td>
<td>37.2±0.9</td>
</tr>
<tr>
<td>STZ</td>
<td>213.0±1.0a</td>
<td>124.9±0.9b</td>
<td>149.2±1.8c</td>
<td>17.6±0.5a</td>
<td>102.2±1.9b</td>
</tr>
<tr>
<td>IRR</td>
<td>146.7±0.4b</td>
<td>110.5±0.6b</td>
<td>117.4±1.2c</td>
<td>19.2±0.2a</td>
<td>71.9±1.7b</td>
</tr>
<tr>
<td>STZ+IRR</td>
<td>246.3±0.9abc</td>
<td>169.0±3.0abc</td>
<td>195.4±2.7abc</td>
<td>14.2±0.9abc</td>
<td>138.7±4.6abc</td>
</tr>
<tr>
<td>STZ+L-car</td>
<td>88.5±0.8abc,abd</td>
<td>82.3±0.5bced</td>
<td>91.3±1.4bced</td>
<td>39.1±1.1bced</td>
<td>43.1±1.1bced</td>
</tr>
<tr>
<td>L-car+IRR</td>
<td>85.1±1.0abc,abd</td>
<td>78.8±0.4bced</td>
<td>85.4±1.1bced</td>
<td>41.3±1.0bced</td>
<td>39.4±0.8bced</td>
</tr>
<tr>
<td>STZ+L-car+IRR</td>
<td>113.0±0.9abc,bed</td>
<td>84.8±1.9bced</td>
<td>91.6±1.5bced</td>
<td>38.4±1.0bced</td>
<td>42.7±1.4bced</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S.E., n= 6. *a,b,c* and *d* indicate significant change from control, STZ, IRR (5 Gy) and STZ+IRR respectively at p≤ 0.05 using ANOVA followed by Tukey-Kramer as a post ANOVA test.

Figure [2]: Effect of L-carnitine (L-car), streptozotocin (STZ), irradiation (IRR) (5Gy) and their combination on [A] reduced glutathione (GSH) content, [B], superoxide dismutase (SOD) activity, [C] malondialdehyde level and [D] glutathione peroxidase (GSHPx) activity in cardiac tissues

*abc* and *d* indicate significant change from control, STZ, IRR (5 Gy) and STZ+IRR respectively at p≤ 0.05 using ANOVA followed by Tukey-Kramer as a post ANOVA test.

(STZ+L-car+IRR) induced significant decrease in ADMA and endothelin-1 levels as compared to STZ and/or IRR groups (Fig. 1A &B). Treatment with L-car resulted in a complete reversal of STZ and/or IRR-induced decrease in serum NO(x) level to the control value (Fig. 1C). The effect of STZ, IRR, L-carnitine and their combination on the oxidative, nitrosative stress biomarkers GSH, SOD, GSHPx, NO(x) and indices of lipid peroxidation (MDA) in cardiac tissues are shown in Fig. 4,5,6,7 &8. The STZ-induced diabetes resulted in significant increase in MDA and NO(x) (96.8% and 144.6%) respectively, and a significant decrease in GSH, GSHPx and SOD (58.3%, 57% and 53.5%) respectively compared to the control group. In addition, gamma irradiation (5 Gy) induced significant increase in MDA and NO(x) (68.5% and 108.2%) respectively, and a significant decrease in GSH, GSHPx and SOD (56.3%, 50.1% and 44.3%) respectively compared to the control group. There is no significant change in oxidative, nitrosative stress biomarkers and index of lipid peroxidation observed with L-carnitine supplementation alone. Irradiation of STZ group resulted in significant decrease in the activities of SOD and GSHPx
and in the content of GSH (54.2%, 60.1% & 63.4 %) respectively and significant increase in MDA and NO(x) levels (117.4% and 191.6%) respectively, in cardiac tissues as compared to control group. Administration of L-car to STZ group induced significant increase in the activities of SOD and GSHPx activities and GSH content (105.5%,103.4% & 92.1%) respectively, and significant decrease in MDA and NO(x) levels (48.9% & 48.1%) respectively, as compared to STZ group (Fig. 2A, 2B, 2C, 2D&2). Pre-administration of L-car to irradiated rats resulted in a significant increase in the activities of SOD and GSHPx and GSH content (80.9 %, 119.5%, and 118.8 %) respectively, as compared with irradiated group, and significant decrease in MDA and NO(x) levels (43.5% and 45.6% ) respectively as compared to irradiated group (P<0.01). Administration of L-car in combination groups induced significant change as compared to STZ and/or IRR group.

4. Discussion

Oxidative stress is thought to play a major role in the etiology of a wide variety of diseases including diabetes and cancer [1]. In the present study, the STZ-induced diabetic rats showed significant increase in blood glucose levels, total cholesterol, triglyceride, LDL-Cholesterol, VLDL-Cholesterol and significant decrease of HDL-Cholesterol in STZ-induced diabetic rats compared to control rats. This was consistent with early reports [27, 28]. Diabetes mellitus is a complex metabolic disease caused by impairment of insulin signaling, pathways, and the defect usually results from pancreatic β-cell deficiency and/or a deficiency of insulin [4]. Mathe [29] reported that hypercholesterolemia in STZ-induced diabetic rat’s results from increased intestinal absorption and synthesis of cholesterol. The levels of acute and chronic hyperglycemia correlate strongly with the level of LDL cholesterol oxidation [30]. Oxidative stress could be due to the ability of glucose overload to generate excessive reactive oxygen species, which initiate a chain reaction leading to the formation of oxidized lipoproteins as oxidized LDL [31]. Oxidative stress and the generation of reactive oxygen species have been implicated as putative mediators of injury in myocardial infarction [32]. In diabetes, protein glycation and glucose auto-oxidation may generate free radicals, which in turn catalyze lipid peroxidation and cause pronounced increase in Thioharbituric acid reactive substances in hyperlipidemic patients with diabetes [30].

In the present study, IRR induced a significant increase in serum levels of glucose, cholesterol, triglycerides and LDL and decreased levels of HDL compared to control group. Mansour [33] reported that whole body exposure to gamma radiation induces hyperlipidemia. Increased level of serum cholesterol fractions was probably due to its release from tissues, destruction of cell membranes and increase rate of cholesterol biosynthesis in the liver and other tissues. Lipoprotein modifications that appeared following radiation exposure may result from an induced inflammatory state and may further contribute to vascular damage[33].

Treatment with L-carnitine ameliorated the levels of glucose and lipid profiles as compared to the diabetic and/or irradiated group. These observations support the antioxidant and lipid-lowering role of L-carnitine, which is most likely due to stabilization of various membranes, including the mitochondria [34]. Furthermore, the possible mechanism by which L-carnitine mediated its antidiabetic effect could be by potentiation of pancreatic secretions of insulin from existing β-cells of islets[28]. L-carnitine supplementation is effective at improving insulin-stimulated glucose utilization, in reversing abnormalities of fuel metabolism associated with type2 diabetes and decreasing in total cholesterol and triglyceride concentrations [35]. Administration of L-carnitine may shift the metabolic bias of the liver away from esterification and synthesis of triglycerides toward the formation of acetylcaritines. This could decrease synthesis of triglycerides and VLDL cholesterol and likely increase mitochondrial β-oxidation of fatty acids [36].

In the present study, the STZ-induced diabetic rats and/or γ-irradiated rats showed significant increase in serum ADMA and endothelin-1 in concomitant with significant decrease in NO(x) level. In agreement with our results, previous studies have reported that, the elevated ADMA and endothelin-1 levels and the decreased NO(x) level were present in patients with types 1 and 2 diabetes [12, 37], as well as experimental diabetes [38] and is usually associated with micro/macrovacular diabetic complications, and may predict cardiovascular events in diabetes mellitus [12]. In addition, increased plasma levels of endothelin-1 have been demonstrated in states of myocardial ischemia and heart failure in human [39] and in the response of endothelial cells to ionizing radiation [40] and it could be used as a biomarker for irradiation of endothelial tissues. Radiation-induced endothelial dysfunction is associated with nitric oxide impairment [41] and up-regulation of endothelin-1 [2]. The reduction of NO(x) levels might be due to both decreased production and increased consumption, with possible endothelial dysfunction and vascular impairment [41]. Furthermore, endothelin-1 may contribute to the development of endothelial dysfunction, and consequently insulin resistance, by increasing the production of ROS, mainly superoxide anion, in the vasculature. Reactive oxygen species can react with NO.
forming peroxynitrite, and thus decrease the bioavailability of NO resulting in endothelial dysfunction [42]. On the other hand, Gurdol et al. [43] reported that, diabetic patients have significantly low circulating nitric oxide (NO) levels because the stimulatory action of insulin on NO synthesis is absent. Increases in endothelin-1 are well known to interact negatively with the NOS pathway and, together with elevations in ADMA, could represent a potent vasoconstrictor combination that sets the stage for progression of vascular disease and its complications [44]. ADMA is metabolized by dimethylarginine dimethylaminohydrolase (DDAH) to L-citrulline and dimethylamine. Lin et al. [45] found that hyperglycemia elevates ADMA by impairing DDAH activity in vascular smooth muscle and the endothelium. The effect is probably mediated by oxidative stress [46]. Elevated levels of ADMA inhibit nitric oxide synthesis and therefore impair endothelial function [11].

Consistent with previous studies [47, 48], the present study showed that endothelial profile levels were ameliorated by the administration of L-carnitine. Alvarez et al. [49] and Chen et al. [50] reported that, L-carnitine improved endothelial responses by decreasing reactive oxygen species production and lower ADMA concentrations and increasing nitric oxide availability, thus ameliorating endothelial dysfunction.

In this study, significant increase in the levels of MDA and NO(x) and significant decrease in the activities of SOD and GSHPx and GSH content were observed in diabetic, γ-irradiated and diabetic-γ-irradiated rats. The decrease in antioxidant enzymes might be due to radiation-induced production of free radicals, which in turn can impair the antioxidant defense mechanism, leading to an increased membrane lipid peroxidation. The decreased level of GSH in γ-irradiated mice may be due to their utilization by the enhanced production of reactive oxygen species [51]. Glutathione peroxidase (GSHPx) plays an important role in the defense mechanisms of mammals against damage by catalyzing the reduction of H$_2$O$_2$ and hydroperoxides into water and alcohols respectively, consuming GSH as the hydrogen donor and its depletion leads to GSHPx inactivation [52]. The significant decrease in cardiac GSHPx activity of irradiated rats could be attributed to its inactivation by lipid peroxidation byproducts [53].

Ibuki and Goto [54] have shown that the increase of NO(x) production in irradiated macrophages contributed to tumoricidal activity, with the activation mechanisms differing between high-dose and low-dose irradiation. High-dose irradiation activates macrophages directly, whereas low-dose irradiation acts indirectly through interaction with neighboring cells and the paracrine induction of cytokines. Nitrosative stress occurs when the generation of reactive nitrogen species in a biological system exceeds its ability to neutralize them. In agreement with our results, previous studies [4, 55 & 56] have reported that, gamma irradiation significantly decreased the activities of SOD and GSHPx and GSH level and significantly increased MDA and NO(X) levels in cardiac tissues. In the present study, increased levels of MDA and NO(x) and decrease in the activity of SOD, GSHPx, and GSH content were noticed in cardiac tissues of STZ-induced diabetic rats. The results are in agreement with the study of Wang et al. [57]. Increased lipid peroxidation suggests an increase in reactive oxygen species, which could be due to increased glucose concentrations [58]. Many studies have shown that diabetes mellitus is associated with increased formation of free radicals and decreased antioxidant potential, leading to oxidative damage of cell components [57, 59]. In this study, administration of L-carnitine induced significant increase in the SOD activity and GSH content and significantly decreased the level of MDA and NO(x) in rat cardiac tissues. This might be due to its active role in the transport of fatty acids for energy production, thereby lowering the availability of lipids for peroxidation. L-carnitine protected cardiac cells against oxidative stress, by decreasing the levels of toxic acyl-CoA derivatives and regulating carbohydrate metabolism [60]. Moreover, it has been reported that L-carnitine suppressed hydroxyl radical production in the Fenton system, probably by chelating the iron required for the generation of hydroxyl radicals [Mister et al., 2002]. Thus, the reduction in lipid peroxidation in the present study might be due to the iron-chelating property of L-carnitine. This hypothesis is consistent with the previous study which has demonstrated that L-carnitine showed a strong antioxidant activity against irradiation-induced lipid peroxidation and has free radical scavenging effects [Mansour, 2006].

5. Conclusion

This prospective study suggests that alteration of serum ADMA, endothelin-1 and NO(x) as were implicated in cardiovascular toxicity in diabetic-irradiated rats. L-carnitine has a cardioprotective effect which is attributed to stimulating the antioxidant capacity of cardiac tissues.

6. References


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