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Cardiac effects of cigarette tobacco smoking in rat model of diabetes

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ABSTRACT

Aims: Tobacco smoking is considered a global health issue, contributing to increased risk of cardiovascular disease (CVD) and diabetes (DM). We aimed to assess effects of cigarette smoking on cardiac inflammation, oxidative stress and fibrosis in rat model of streptozotocin (STZ)-induced diabetes.

Main methods: Adults Wistar rats were assigned into control (fresh air, intraperitoneal injection (i.p) of citrate buffer), cigarette smoking (1 h daily for 4 weeks, i.p citrate buffer), DM (35 STZ mg/kg single i.p, fresh air), and DM + Smoking groups for 4 weeks. Cardiac biomarkers of oxidative stress, inflammation, and fibrosis were evaluated.

Key findings: STZ-induced diabetes as documented by the persistent increase in blood glucose. Relative to control, a significant decrease in body weight was observed in diabetic groups paralleled with increased heart to body weight ratio and systolic blood pressure in all groups. Levels of total nitrite, thiobarbituric acid substances, endothelin −1, interleukin-6 and myeloperoxidase were increased in the DM, Smoking and DM + Smoking groups without changes in C-reactive protein. Cardiac levels of GSH were increased in Smoking groups whereas activities of catalase and superoxide dismutase increased in DM, Smoking and DM + Smoking groups. DM but not smoking increased cardiac fibrosis with a parallel increase in transforming growth factor beta. Cardiac levels of matrix metalloproteinase-2 were elevated in Smoking groups and decreased in DM.

Significance: Exposure to cigarette smoke may increase risk of CVD in DM by increased cardiac oxidative stress and inflammation. Smoking was associated with increased oxidant enzymes and metalloproteinase-2 probably to prevent cardiac fibrosis.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder that is associated with several complications. Cardiovascular disease (CVD), as one of these complications, is considered the leading cause of morbidity and mortality among diabetics [1]. Tobacco smoking is considered a global health issue, contributing to increased risk of CVD and DM. The progression of cardiovascular diseases is accelerated by smoking [2]. Several factors contribute to the development of CVDs during diabetes. These factors include oxidative stress, inflammation and remodeling. Metabolic changes associated with hyperglycemia [3] and metabolites produced by cigarette smoking [4] increase the production of reactive oxygen (ROS) and nitrogen species (RNS) contributing to oxidative damage and remodeling. Oxidative stress is associated with the onset of CVD and heart failure (HF) [5]. In a model of DM, we have documented increased cardiac levels of nitrite, nitrotyrosine and lipid peroxides [6,7]. Smoking also promotes myocardial oxidative stress, characterized by increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and lipid peroxides, and decreased antioxidant enzymes [4]. Oxidative stress causes sustained inflammation and fibrosis [8] contributing to CVD and other disease processes. High inflammatory states are noticed to be associated with diabetes [9] and smoking [10]. Smoking promotes significant increase in aortic expression of interleukin (IL)-1β, tumor necrosis factor alpha (TNFα) and fibronectin contributing to cardiac hypertrophy [10]. Diabetes is associated with marked cardiac structural changes [11,12]. In streptozotocin-induced diabetes model, endothelin 1 (ET-1) stimulates fibroblast proliferation and cardiac fibrosis [12]. However, the effects of cigarette smoking on diabetic hearts have not been characterized yet.

The aim of this study was to evaluate the impact of cigarette smoking on cardiac inflammation, oxidative stress, and fibrosis in rat model of diabetes.

2. Material and methods

2.1. Animals

Male Wistar rats (weight = 250–300 g) were housed at room

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Table 1
Characteristics of study groups.

	Control	Smoking	DM	DM + Smoking	p value
Body WT (g)	306.3 ± 10.39	290.0 ± 5.78	234.7 ± =10.25*	228.8 ± 9.82*,$	< 0.0001
Heart WT (mg)	951.4 ± 33.61	1004.0 ± 35.50#	797.1 ± 41.17	823.1 ± 35.55$	0.0016
Heart WT/BWT (mg/g)	3.120 ± 0.079	3.454 ± 0.083	3.411 ± 0.122	3.632 ± 0.117*	0.0064
Glucose	161.9 ± 6.919	129.4 ± 4.433#	662.4 ± 34.42*	593.0 ± 44.72*,$	< 0.0001
HbA1c (%)	5.388 ± 0.164	5.153 ± 0.157	6.213 ± 0.195	6.975 ± 0.296*,$	0.0006
Total cholesterol	72.79 ± 1.939	71.86 ± 2.431#	81.50 ± 1.525	72.72 ± 2.516#	0.0132
LDL	32.25 ± 1.701	30.95 ± 2.472	39.45 ± 2.100	31.68 ± 2.039	0.0270
HDL	31.50 ± 1.500	31.50 ± 1.585	34.27 ± 1.278	32.67 ± 1.647	0.5610
Triglyceride	48.77 ± 4.349	52.00 ± 3.451	53.81 ± 6.185	50.13 ± 5.082	0.8723
Systolic Bp	116.90 ± 0.417	123.30 ± 0.338*,#	118.80 ± 0.317*	124.10 ± 0.445*,#	< 0.0001
Diastolic Bp	65.50 ± 0.374	72.00 ± 1.038*	69.21 ± 0.792	75.73 ± 2.144*	< 0.0001

Data are presented as mean ± sem. DM: diabetes, WT: weight, BWT: body weight, HbA1c: glycated hemoglobin, LDL: low density lipoprotein, HDL: high density lipoprotein, Bp: blood pressure. Unit for serum glucose and lipids is mg/dl. Unit for Bp is mm Hg, and beat/min for heart rate. Number is 14–18 rats each group.

* $p < 0.05$ vs. control.

\# $p < 0.05$ vs. DM.

$ $p < 0.05$ vs. smoking.

temperature with a 12 h dark/light photoperiods, and free access to food and water. All procedures were performed in accordance with the guidelines of Animal Care and Use Committee (The Institutional Animal Care and Use Committee Guidebook, 2ndedition of 2002 [13]) at Jordan University of Science and Technology (JUST).

2.2. Experimental design

Rats were randomly assigned into 4 groups (14–18 animals in each group):

(1) Non-diabetic control rats exposed to fresh air (control): rats received a single dose of intraperitoneal citrate buffer (10 mmol/) and were exposed to fresh air.
(2) Non-diabetic rats exposed to cigarette smoke (Smoking): rats received a single dose of intraperitoneal citrate buffer (10 mmol/l) and were exposed to cigarette smoke for 1 h daily for 4 weeks (6 days/week).
(3) Diabetic rats (DM)/fresh air: rats received a single dose of intraperitoneal streptozotocin (35 STZ mg/kg, Sigma-Aldrich Corp, St. Louis, MO, USA) dissolved in citrate buffer (10 mmol/l) and were exposed to fresh air.
(4) Diabetic rats exposed to cigarette smoke (DM + Smoking): rats received intraperitoneal STZ (35 mg/kg) dissolved in citrate buffer (10 mmol/l) and were exposed to cigarette smoke.

Diabetic rats were kept in 10% sucrose solution added in drinking water for 24 h after STZ injection to avoid hypoglycemia. Diabetes was established by elevated glucose levels that are ≥300 mg/dl in addition to presence of polydipsia and polyuria [14]. Blood glucose levels and body weight were measured at baseline before any experimental procedure and throughout the study [14]. Blood pressure was measured at baseline and at the end of the study using the tail-cuff plethysmography (computerized tail-cuff plethysmography blood pressure system, IITC Life Science, Woodland Hills, CA, USA) as previously prescribed [14,15].

2.3. Cigarette smoke exposure system

A cigarettes smoke whole body animal exposure chamber was used for this study as previously described from our laboratory [16]. The exposure chamber (38 × 25 × 25 cm, L × W × H) was made from transparent polycarbonate, and had a removable ceiling fitted with flow ports for the smoke inlet, fresh air inlet, and excess flow outlet. A 3 cm fan was suspended from the lid to ensure that the chamber contents were well mixed during each exposure session. Fresh air was continuously pumped into the chamber, resulting in an air change rate of approximately 1.5 changes per hour. Cigarettes smoke exposed animals were placed in the chamber and were exposed to side stream cigarette smoke by hanging a smoldering cigarette in the upper middle half of the chamber [16]. The cigarettes were regular (Gold) Marlboro™ (Philip Morris, USA) purchased in Irbid, Jordan. For each exposure session (1 h), approximately 6 cigarettes were consumed [16]. We based the daily exposure period (60 min/day) on the published literature for cigarette smoke [17].

2.4. Blood collection

After 4 weeks, fresh blood samples were collected and centrifuged at 5000 rpm for 10 min in gel-treated red topped tubes to prepare serum, and in EDTA lavender tubes to prepare plasma samples. Blood glucose and lipids levels were measured immediately using standard colorimetric techniques as previously described [14,15]. Blood levels of glycated hemoglobin percentage (HbA1c%) were measured using a chromatographic-spectrophotometric-ion exchange kit (Biosystems, Barcelona, Spain).

2.5. Molecular analysis of cardiac biomarkers

After 4 weeks of exposure to cigarette smoke/fresh air, rats were sacrificed by decapitation. Hearts were removed, weighed and homogenized in a cold phosphate buffer saline mixed with protease inhibitors (Sigma, St. Louis, MO, USA, catalog number: S8830). Cardiac homogenates were centrifuged at 15,000× rpm for 15 min at 4 °C and the lysates were collected for measurements of biomarkers. Samples aliquots were kept at −80 °C until analysis.

Cardiac total nitrite was determined using total nitric oxide and nitrate/nitrite parameter assay kit (R&D Systems, MA, USA). Levels of thiobarbituric acid reactive substances (TBARS) were measured by TBARS assay kit (R&D Systems, MA, USA). The activity of superoxide dismutase (SOD) and total glutathione levels were measured by standard colorimetric assays (Sigma-Aldrich Corp, St. Louis, MO, USA). Cardiac activity of catalase was determined by catalase assay kit (Cayman Chemical, MI, USA) Cardiac C reactive protein (CRP) and myeloperoxidase (MPO) contents were measured by ELISA kits (Rat CRP and MPO ELISA kits, MyBioSource, Inc. CA, USA). Cardiac levels of endothelin-1 (ET-1), platelet derived growth factor, transforming growth factor-beta (TGF-β1) and matrix metalloproteinase-2 (MMP-2) were determined by specific ELISA assays (Quantikine ELISA, R&D Systems, MA, USA). Cardiac level of interleukin-6 (IL-6) was determined by ELISA assay (Invitrogen, Thermo Fisher SCIENTIFIC, Vienna, Austria).

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