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Role of sulfurous mineral water and sodium hydrosulfide as potent inhibitors of fibrosis in the heart of diabetic rats

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ABSTRACT

This study examined the downstream signaling whereby hyperglycemia may lead to myocardial fibrosis and apoptosis in the left ventricle of diabetic rats. The effects of sulfurous mineral water or sodium hydrosulfide (NaHS) as possible modulators were also examined. Sulfurous mineral water (as drinking water) and NaHS (14 μmol/kg/day, IP) were administered for 7 week to rats with streptozotocin (STZ)-induced diabetes. Hyperglycemia, overproduction of glycated hemoglobin (HbA1C) and serum decline in insulin, C-peptide and insulin like growth factor-I (IGF-I) were observed in diabetic rats. Up-regulation of gene expressions of nuclear factor (NF-κB), profibrogenic growth factor such as transforming growth factor-β1 (TGF-β1), matrix metalloproteniase-2 (MMP-2), procollagen-1 and Fas ligand (Fas-L) were observed in the left ventricle of diabetic rats. A linear positive correlation between TGF-β1 and MMP-2 was also detected in diabetic group. An increase in hydroxyproline level and a disturbance in oxidative balance were detected in heart of diabetic rats. Sulfurous mineral water and NaHS treatment possibly, by improving cardiac GSH level, counteracted the enhanced expression of NF-κB, the profibrogenic and apoptotic parameters. Histopathological examination was in accordance with the biochemical and molecular findings of this study. We suggest a novel therapeutic approach of sulfurous mineral water and exogenous supplementation of H_2S in diabetic cardiomyopathy.

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Introduction

The incidence of cardiovascular disease (CVD)[1] is approximately twice as high in patients with type 2 diabetes as in age matched non-diabetic controls [1]. Diabetic cardiomyopathy is a commonly used description of the complex changes in the myocardium characterized by myocyte loss and myocardial fibrosis in patients with diabetes in the absence of significant coronary atherosclerosis and hypertension [2]. The pathophysiology of diabetic cardiomyopathy is multifactorial, and an important role has been attributed to persistent hyperglycemia [3]. This condition induces oxidative stress and activates a number of secondary messenger pathways, leading to cardiac fibrosis and cell death [4].

Transforming growth factor-β1 (TGF-β1) is a profibrotic cytokine that stimulates the production of extracellular matrix (ECM) proteins in a number of different organ systems. In the heart, TGF-β1 induces the differentiation of cardiac fibroblasts to more active connective tissue cells known as myofibroblasts [5]. Petrov et al. [6] found that myofibroblasts can produce up to twice as much collagen as their fibroblast precursors. TGF-β1 is also involved in raising the production of cellular adhesion molecules, which are thought to increase myofibroblast survival and activity [7]. In fibrosis, the excess production of extracellular matrix proteins alters the structure, architecture and shape of the heart. Such changes have marked effects on ventricular contractility, valvular functioning and electrical conduction. In particular, TGF-β1 has been implicated in the pathogenesis of each of these three facets of cardiac functioning [8].

Until very recently, the extracellular matrix was considered to be a static network of proteins. However, research now indicates that this network is constantly changing in both structure and composition. Proteolytic enzymes, such as matrix metalloproteinases

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[1] *Abbreviations used:* APDC, ammonium pyrrolidinedithiocarbamate; Ang II, angiotensin II; CRP, C-reactive protein; CVD, cardiovascular disease; CBS, cystathionine-β-synthetase; CSE, cystathionine-γ-synthase; ECM, extracellular matrix; HbA1C, glycated hemoglobin; GSSG, oxidized glutathione; GSH, reduced glutathione; HF, heart failure; IkB, inhibitory-kB; IGF-I, insulin like growth factor-I; MMP-2, matrix metalloproteniase-2; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NF-κB, nuclear factor kappa-kB; PMN, polymorphonuclear leukocytes; PARP, poly(ADP-ribose) polymerase; PrSH, protein thiols; RAGE, receptor for advanced glycation end products; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF-β1, transforming growth factor-β1; NaHS, sodium hydrosulfide; STZ, streptozotocin; TIMP-2, tissue inhibitor matrix metalloproteniase-2; VSMCs, vascular smooth muscle cells.

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(MMPs), play an integral role in promoting change and remodeling. One of the hallmarks of diabetic cardiomyopathy is the extracellular matrix remodeling leading to the increased fibrosis of myocardium. The amount of extracellular collagen is determined by the balance between synthesis and degradation, which is mediated by MMPs and their tissue inhibitors (TIMPs). MMP activities increase in the failing myocardium of patients and animal models of myocardial remodeling and heart failure (HF). Collagen synthesis and the derangement of MMP regulation are considered to be critical factors for diabetic cardiac dysfunction [9,10]. MMP activity is significantly increased in diabetic rat tissues and in the endothelial cell cultures exposed to high levels of glucose [10]. The enhanced collagen synthesis and MMP activity are related to reactive oxygen species (ROS) formation, because if ROS formation is blocked, the enhanced expression of MMP by high levels of glucose can be prevented [11].

Hyperglycemia-derived advanced glycated end products (AGEs) acting either directly or through interacting with their receptors were reported to activate several critical molecular pathways, most notably the activation of redox transcription factors nuclear factor-κB (NF-κB). NF-κB is a ubiquitous inducible transcription factor that activates a number of genes known to play roles in various cardiovascular disease states [12,13]. Moreover, low level of insulin like growth factor-I (IGF-I) often associated with diabetes, has been linked to increased cardiovascular disease incidence [14]. IGF-I also acts as an anti-apoptosis factor of multiple cell types, and its anti-apoptotic effects occur through engagement with IGF-I receptor (IGF-IR) that thought to activate an intracellular signal transduction pathway that may modulate the mitochondrial and cytochrome *c* pathway [15–17]. Apoptotic cell death associated with oxidative stress in multiple organs of diabetes mellitus has been documented [18,19]. Several in vivo studies also demonstrated the induction of myocardial cell apoptosis in experimental diabetic rats [20], mice [21], and diabetic patients [22]. It is reported that oxidative DNA damage caused by hyperglycemia activates poly(-ADP-ribose) polymerase (PARP) activity [23] and up-regulates p53 and angiotensin II (Ang II) system [24] to initiate myocardial cell death under diabetic conditions.

Sulfur (S) is an interesting non-metallic element representing about 0.25% of our total body weight [25,26]. As a part of the amino acids methionine, cysteine and taurine, S performs a number of functions in enzyme reactions and protein synthesis. It is necessary for the formation of collagen, keratin, and taurine. S is part of other important body chemicals such as insulin, IGF-I, TGF-β1 and glutathione (GSH). For all these reasons, sulfurous mineral water employed in thermal medicine, containing S in the format of sulfate (SO_4^{2-} > 200 mg/L) and/or hydrogen sulfide (H_2S > 1 mg/L), has a long history of use in the treatment of various clinical conditions, from dermatological, muscle/skeletal disorders to aging and age-related degenerative diseases [27–29]. Caraglia et al. [30] evidenced the antioxidant effect of mud therapy in mice with osteoarthritis showing a significant decrease in the production of endogenous nitric oxide (NO) [31]. Together with mud and bath therapies, therapies involving the drinking of water containing S (hydropinic treatments) is also employed in thermal medicine, especially for their action on gastroenteric and hepatic functions.

Despite its long-standing reputation as a foul smelling and toxic gas that is associated with the decay of biological matter, hydrogen sulfide (H_2S) has emerged as an important regulator of cardiovascular and nervous systems. H_2S promotes a number of cellular signals that regulate metabolism, cardiac function and cell survival. H_2S has been shown to exhibit potent vasodilator activity both in vitro and in vivo most probably by opening vascular smooth muscle K_{ATP} channels. Of the two enzymes, cystathionine-γ-synthase (CSE) and cystathionine-β-synthase (CBS), which utilize L-cysteine as substrate to form H_2S, CSE is believed to be the key enzyme, which forms H_2S in the cardiovascular system [32] (Supplementary Fig. S1). There appear to be several options for H_2S therapy in cardiovascular disease including H_2S gas, H_2S donors or releasing compounds, and H_2S pro-drugs that activate H_2S-generating enzymes to increase circulating and tissue levels of H_2S [33]. Brancaleone et al. [34] demonstrated the decline of vascular reactivity, plasma H_2S level, and vascular H_2S production progressively as the severity of diabetes increases over time in a diabetic mouse model.

The present study aimed to investigate the effects of sulfurous mineral water and sodium hydrosulfide (NaHS), the main active ingredient of sulfurous mineral water on cardiac fibrosis of streptozotocin (STZ)—diabetic rats. To our knowledge, this is the first in vivo study that investigates the effect of oral intake of sulfurous mineral water on cardiac fibrosis in a diabetic rat model.

Materials and methods

Drugs and chemicals

Streptozotocin and hydroxyproline were purchased from Sigma Chemicals Company, St. Louis, MO, USA. All other chemicals used were of the highest purity and analytical grade.

Experimental design

Forty-two male Wistar rats weighing 200–220 g were used in this study. Animal care was supervised and approved by the Local Ethical Committee. Animals had free access to rat chow and water throughout the study. Diabetes was induced by a single intraperitoneal injection of STZ, 50 mg/kg body weight, freshly prepared in 0.1 M citrate buffer, pH 4.5 [35]. A normal control group (n = 7) was injected with the appropriate volume of the citrate buffer. During the first 24 h of diabetes induction, STZ-treated rats were allowed to drink 5% glucose solution to overcome drug-induced hypoglycemia [36]. Four days later a blood sample was collected from the tail bleeding and hyperglycemia was confirmed by a blood glucose level ⩾ 300 mg/dl. Glucose was measured using an analyzer (Roche Diagnostic Accu-Check test strips, Germany).

Diabetic rats were randomly divided into three groups (n = 7 rats in each group). The first group was the untreated-diabetic group. The second group was supplied daily with sulfurous mineral water from the Thermal Center of Helwan (Helwan Kabritage, Helwan Province; south of Cairo, Egypt), which has a sulfuric degree of 8.4 mg/L, as reported in Table 1 instead of their drinking water [37]. The rats in the third group were intraperitoneally injected

Table 1
Physico-chemical characteristics of the sulfurous mineral water of Helwan Kabritage.

Parameter	Unit	Result
pH	—	6.69
Conductivity	μS/Cm	6590
Fixed residue (at 180 °C)	mg/L	6480
Sulfuric degree	mg/L	8.4
CO_2	mg/L	80
Ca^{2+}	mg/L	403
Mg^{2+}	mg/L	49
Na^{+}	mg/L	1300
K^{+}	mg/L	2
HCO_3^{-}	mg/L	180
F^{-}	mg/L	1.5
Cl^{-}	mg/L	1560
NO_2^{-}	mg/L	<0.01
SO_4^{2-}	mg/L	844
NO_3^{-}	mg/L	0.04
Iron	mg/L	0.006

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