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Does N-Acetylcysteine Alleviate Diabetic Cardiomyopathy in Diabetic Rats

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ABSTRACT

Diabetic cardiomyopathy, one of the complications of diabetes, is a major cause of heart failure. N-Acetylcysteine (NAC) is an agent with numerous biological effects. This study aimed to investigate the effects of NAC on diabetic cardiopathy in experimental diabetic rats induced with streptozotocin. Eighteen animals were divided into three groups (n=6). Rats in the control group received only water intragastrically. The diabetes (D) group received a single dose of 45 mg/kg STZ, and the D+NAC group received a single dose of 45 mg/kg STZ and 50 mg/kg/day NAC. At the end of the 28-day experiment, heart tissues taken from the animals were examined histologically using Hematoxylin and Eosin (H&E) and Masson Trichrome (MT) staining methods. In the diabetes group, myocardial apoptosis, myocardial fiber deterioration, and collagen accumulation were observed in microscopic examination of H&E and MT stains of the heart. However, NAC treatment significantly reduced these pathological changes. The findings of our study reveal that it may have a cardioprotective effect, reducing myocardial apoptosis and fibrosis in diabetic rats.

Keywords: Cardiomyopathy, Diabetes, Fibrosis, N-Acetylcysteine, Rat

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INTRODUCTION

Diabetes is a metabolic and chronic disease characterized by high blood sugar [1]. Affecting many individuals and increasing alarmingly, diabetes is estimated to affect 700 million people by 2045 [2]. Diabetes damages the heart and blood vessels, as it does many other tissues, leading to chronic heart disease. Myocardial infarction, a complication of diabetes, is approximately three times more common in diabetic patients [3]. The mechanism of diabetic cardiomyopathy is associated with oxidative stress, apoptosis, and inflammation. Oxidative stress occurring in hyperglycemia induces apoptosis and inflammation, leading to cardiocyte damage [4]. Furthermore, cardiac fibrosis, a complication of diabetic cardiomyopathy, contributes to the development of heart failure by causing cardiac cycle dysfunction [5].

N-acetyl cysteine (NAC) has many biological effects, as well as antioxidant and anti-inflammatory effects [6]. NAC protects tissues by scavenging free radicals, which increase in many pathological conditions [7]. Oxidative stress is thought to cause heart failure by inducing myocardial damage [8]. NAC has been reported to have a protective effect against cardiac damage by increasing the secretion of glutathione, an endogenous antioxidant that plays a vital role in cellular defense against oxidative stress [9]. NAC has also been reported to reduce the development of cardiac fibrosis, diastolic dysfunction, hypertrophic cardiomyopathy, and hypertrophic development in epicardial myocytes [10-12].

As understood from the literature, NAC administration has beneficial effects against cardiomyopathy occurring in various pathological conditions. However, the mechanism of action of NAC against cardiomyopathy in diabetic rats is not fully understood. This study aimed to investigate the protective effects of NAC against streptozotocin-induced cardiomyopathy in diabetic rats.

MATERIALS AND METHODS

Experimental Animals

Eighteen adult Wistar Albino male rats were used in the study. The rats were kept in polycarbonate rat cages at 21-24 °C (room temperature) with a 12-hour light/12-hour dark photoperiod and were fed with standard pellet rat food and tap water ad libitum.

Experimental Protocol

Animals were divided into 3 groups (n=6). For rats to be induced with diabetes, a single dose of 45 mg/kg STZ (sc-200719, Santa Cruz) was administered (IP) [13]. The groups are as follows: Control, D, D+NAC. Control group: Only water was administered intragastrically (IG) for 28 days. D group: A single dose of 45 mg/kg STZ was administered [13]. D+NAC group: 45 mg/kg single dose STZ (IP) and 50 mg/kg/day NAC (CAS: 616-91-1, Sigma Aldrich) by intragastrically (IG) for 28 days [14]. All protocols of this study were approved by Van Yuzuncu Yil University Animal Experiments Local Ethics Committee (Approval number: 2022/11-05). At the end of the experiment, rats were anaesthetised with 50 mg/kg Ketalar I.P. and 10 mg/kg Xylasine, and the thoracic region of the rats was opened, the heart was removed and placed in 10% formaldehyde for histological examination.

Histological examination protocol

5 µm-thick sections were taken from paraffin blocks by a microtome. To evaluate possible pathological changes in the heart, slides were stained with Hematoxylin & Eosin (H&E), and to evaluate cardiac fibrosis, slides were stained with Masson trichrome (MT). The stained slides were examined under a light microscope (Olympus, BX53, Japan) to evaluate pathological changes in the heart [15-16]. According to the histopathological findings observed in the tissue, it was evaluated as normal (-), low (+), moderate (++), and intense (+++).

RESULTS

Heart tissues from the control group had normal histological architecture. Compared to the control group, myocardiocytes in the D group exhibited apoptosis, disruption of myocardial fiber structure, and collagen accumulation in the extracellular space. However, these pathological changes were reduced with NAC treatment (**Figure 1 and Table 1**).

Table 1. Histopathological evaluation score of rat heart tissues

Groups	Apoptotic cells	Disruption of myocardial fiber structure	Collagen accumulation
Control	-	-	-
D	++	+	++
D+NAC	+	-	+

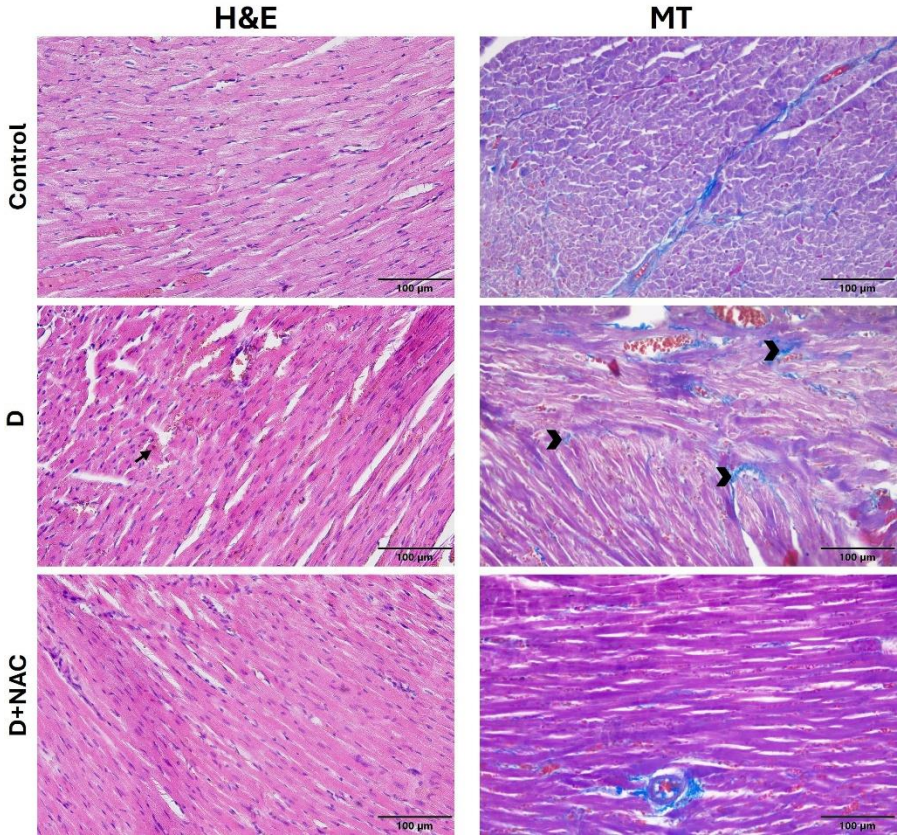

Figure 1. Microscopic images of the heart using H&E and MT staining. Arrow: apoptotic cell, arrowhead: collagen deposition.

DISCUSSION

The current study aimed to investigate the protective effects of NAC against cardiotoxicity in experimental diabetic rats. Our study findings demonstrated that NAC treatment reduced cardiac fibrosis, apoptosis, and structural deterioration in myocardiocytes in diabetic rats. Previous studies have reported that hyperglycemia in diabetes induces oxidative stress, leading to cardiac damage [17]. Oxidative stress has been proposed as a common pathway linking the mechanisms involved in the development of many diabetic complications. Increased ROS induce apoptosis in both endothelial cells and cardiocytes, leading to cardiac dysfunction and cardiac fibrosis [18].

Cardiac fibrosis, characterised by matrix accumulation in the extracellular space, causes both systolic and diastolic cardiac dysfunction in many cardiac pathophysiological conditions. For normal heart function, collagen synthesis and degradation must be in balance. When this balance is disrupted, increased collagen accumulation in the extracellular space leads to ventricular hypertrophy [19].

In various pathological conditions, myocardial fibroblasts accumulate in the myocardial interstitium and synthesise

extracellular matrix (ECM) proteins, causing cardiac fibrosis [20]. Previous studies have frequently detected the presence of myocardial fibrosis (scarring) in diabetic patients using imaging methods, even in the absence of myocardial infarction (MI) [21]. Similarly, in experimental animal models, diabetes-induced induction of profibrotic genes and cardiac hypertrophy have been reported to be closely associated with cardiac fibrosis [22,23]. Cardiac fibrosis is associated with many pathological mechanisms. Jia et al. [24], in a study investigating the role of the TRPV4 channel in cardiac fibrosis in diabetic animals, demonstrated that TRPV4 may cause cardiac fibrosis via the TGF-β1/Smad3 signaling pathway.

In myocardial fibrosis, myocardial stiffness increases with the deterioration of microvascular and cardiac structures. This contributes to cardiac failure by reducing cardiac stroke volume. In previous studies, various therapeutic agents have been used to prevent diabetic myocardial fibrosis. It has been reported that dapagliflozin can prevent myocardial fibrosis by inhibiting endothelial-to-mesenchymal transition and fibroblast activation, which play an essential role in fibroblast proliferation [25]. Zhao et al. [26] demonstrated that liraglutide can improve cardiac fibrosis by reducing P4hα-1 expression, which is associated with fibrosis, in streptozotocin-induced diabetic cardiomyopathy. Similarly, ibuprofen has been suggested to reduce cardiac fibrosis by inhibiting the ACE/AngII/AT1-R pathway in diabetic rats [27]. Additionally, the antifibrotic effects of NAC have been proven in an experimental hypertrophic cardiomyopathy model in mice [28]. Consistent with the literature, our study examined cardiac tissues microscopically using H&E and MT staining in streptozotocin-induced diabetic rats. Apoptosis was observed in myocardiocytes, and an increase in the density of MT staining, a collagen staining method, was observed in the interstitial space of the diabetic rats. However, NAC administration was observed to reduce these pathological changes in cardiac tissue significantly.

CONCLUSION

In conclusion, this study reveals that NAC treatment may have a cardioprotective effect by reducing myocardial fibrosis and apoptosis associated with cardiomyopathy. However, additional studies are needed to understand the mechanism of action of NAC in diabetic cardiomyopathy fully.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflicts of Interest

There is no conflict of interest for the publication of this article.

Disclosure

The authors have reported no conflicts of interest in preparing and publishing this article.

Ethics committee approval

This study was approved by Van Yuzuncu Yil University Animal Experiments Local Ethics Committee (Approval number: 2022/11-05).

Referee Evaluation Process

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REFERENCES

1. Tian H, Xiong Y, Zhang Y, Leng Y, Tao J, Li L, et al. Activation of NRF2/FPN1 pathway attenuates myocardial ischemia–reperfusion injury in diabetic rats by regulating iron homeostasis and ferroptosis. Cell Stress and Chaperones. 2022;27(2):149-164. https://doi.org/10.1007/s12192-022-01257-1
2. HeatherLC,1Hafstad AD, Halade GV, Harmancey R, Mellor KM, Mishra PK et al. Guidelines on models of diabetic heart disease. Am J Physiol Heart Circ Physiol. 2022;323(3):176–200. https://doi.org/10.1152/ajpheart.00058.2022
3. Laddha AP, Kulkarni YA. Daidzein mitigates myocardial injury in streptozotocin-induced diabetes in rats. Life Sciences. 2021;284(1):119664. https://doi.org/10.1016/j.lfs.2021.119664
4. Abdulwahab DA, El-Missiry MA, Shabana S, Othman AI, Amer ME. Melatonin protects the heart and pancreas by improving glucose homeostasis, oxidative stress, inflammation and apoptosis in T2DM-induced rats. Heliyon. 2021;7(3):3e06474. https://doi.org/10.1016/j.heliyon.2021.e06474
5. Youssef ME, El-Azab MF, Abdel-Dayem MA, Yahya G, Alanazi IS, Saber S. Electrocardiographic and histopathological characterizations of diabetic cardiomyopathy in rats. Environmental Science and Pollution Research. 2022;29:25723–25732. https://doi.org/10.1007/s11356-021-17831-6
6. Abdel-Wahab WM, Moussa FI. Neuroprotective effect of N-acetylcysteine against cisplatin-induced toxicity in rat brain by modulation of oxidative stress and inflammation. Drug Design, Development and Therapy. 2019;13:1155-1162. https://doi.org/10.2147/DDDT.S191240
7. Ali T, Mushtaq I, Maryam S, Farhan A, Saba K, Jan MI et al. Interplay of Nsingle bond acetyl cysteine and melatonin in regulating oxidative stress-induced cardiac hypertrophic factors and microRNAs. Archives of Biochemistry and Biophysics. 2019;661:56-65. https://doi.org/10.1016/j.abb.2018.11.007

8. Munzel T, Gori T, Keaney Jr JF, Maack C, Daiber A: Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications. Eur Heart J. 2015;36:2555-2564. https://doi.org/10.1093/eurheartj/ehv305
9. Reyes DRA, Gomes MJ, Rosa CM, Pagan LU, Damatto FC, Damatto RL. et al. N-Acetylcysteine Influence on Oxidative Stress and Cardiac Remodeling in Rats During Transition from Compensated Left Ventricular Hypertrophy to Heart Failure. Cell Physiol Biochem. 2017;44:2310-2321. https://doi.org/10.1159/000486115
10. Foltz WU, Wagner M, Rudakova E, Volk T. N-acetylcysteine prevents electrical remodeling and attenuates cellular hypertrophy in epicardial myocytes of rats with ascending aortic stenosis. Basic Res Cardiol. 2012;107:290. https://doi.org/10.1007/s00395-012-0290-4
11. Wilder T, Ryba DM, Wieczorek DF, Wolska BM, Solaro RJ. N-acetylcysteine reverses diastolic dysfunction and hypertrophy in familial hypertrophic cardiomyopathy. Am J Physiol Heart Circ Physiol. 2015;309(10):1720-1730. https://doi.org/10.1152/ajpheart.00339.2015
12. Giam B, Chu PY, Kuruppu S, Smith AI, Horlock D, Kiriazis H, et al. N-acetylcysteine attenuates the development of cardiac fibrosis and remodeling in a mouse model of heart failure. Physiol Rep. 2016;4(7):e12757. https://doi.org/10.14814/phy2.12757
13. Dey P, Kundu A, Le HE, Kar B, Vishal V, Dash S, et al. Molineria recurvata Ameliorates Streptozotocin-Induced Diabetic Nephropathy through Antioxidant and Anti-Inflammatory Pathways. Molecules. 2022;27(15):4985. https://doi.org/10.3390/molecules27154985
14. Costa M, Bernardi J, Fiuza T, Costa L, Brandão R, Pereira ME. N-acetylcysteine protects memory decline induced by streptozotocin in mice. Chemico-Biological Interactions. 2016;253:10-17. https://doi.org/10.1016/j.cbi.2016.04.026
15. Dogan Z, Annac E, Cetin S, Uludag O. Investigation of the effects of Sugammadex and Rocuronium on rat lung tissue. Neuro-Cell Mol Res. 2024;1(1):14-20. https://doi.org/10.5281/zenodo.11652915
16. Keleş ÖF, Demir A, Çiçek HA, Yıldızhan Y, Çelik İ. The effect Eremurus spectabilis M. Bieb. on diethylnitrosamine-induced neurotoxicity in hippocampus (cornu ammonis) of rat. Neuro-Cell Mol Res. 2024;1(3):53-59. https://doi.org/10.5281/zenodo.14543899
17. Dludla PV, Nkambule BB, Dias SC, Johnson R. Cardioprotective potential of N-acetyl cysteine against hyperglycaemia-induced oxidative damage: a protocol for a systematic review. Systematic Reviews. 2017;6:96. https://doi.org/10.1186/s13643-017-0493-8
18. Liu C, Lu ZZ, Shen MZ, Xing CY, Ma J, Duan YY, et al. N-Acetyl Cysteine improves the diabetic cardiac function: possible role of fibrosis inhibition. BMC Cardiovascular Disorders. 2015;15:84. https://doi.org/10.1186/s12872-015-0076-3
19. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fibrosis. Cell Mol Life Sci. 2014;71(4):549-74. https://doi.org/10.1007/s00018-013-1349-6
20. Cheng Y, Wang Y, Yin R, Xu Y, Zhang L, Zhang Y, et al. Central role of cardiac fibroblasts in myocardial fibrosis of diabetic cardiomyopathy. Front. Endocrinol. 2023;14:1162754. https://doi.org/10.3389/fendo.2023.1162754
21. Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular mechanisms and therapeutic opportunities. Journal of Molecular and Cellular Cardiology. 2016;90:84-93. https://doi.org/10.1016/j.yjmcc.2015.12.011
22. Huynh K, McMullen JR, Julius TL, Tan JW, Love JE, Cemerlang N, et al. Cardiac-specific IGF-1 receptor transgenic expression protects against cardiac fibrosis and diastolic dysfunction in a mouse model of diabetic cardiomyopathy. Diabetes. 2010;59(6):1512–1520. https://doi.org/10.2337/db09-1456
23. Hao PP, Yang JM, Zhang MX, Zhang K, Chen YG, Zhang C, et al. Angiotensin-(1–7) treatment mitigates right ventricular fibrosis as a distinctive feature of diabetic cardiomyopathy. Am J Physiol Heart Circ Physiol. 2015;308:1007–1019. https://doi.org/10.1152/ajpheart.00563.2014
24. Jia X, Xiao C, Sheng D, Yang M, Cheng Q, WuJ, et al. TRPV4 Mediates Cardiac Fibrosis via the TGF-β1/Smad3 Signaling Pathway in Diabetic Rats. Cardiovascular Toxicology. 2020;20:492–499 https://doi.org/10.1007/s12012-020-09572-8
25. Tian J, Zhang M, Suo M, Liu D, Wang X, Liu M, et al. Dapagliflozin alleviates cardiac fibrosis through suppressing EndMT and fibroblast activation via AMPKα/TGF-β/Smad signalling in type 2 diabetic rats. J Cell Mol Med. 2021;25(16):7642–7659. https://doi.org/10.1111/jcmm.16601
26. Zhao T, Chen H, Xu F, Wang J, Liu Y, Xing X, et al. Liraglutide alleviates cardiac fibrosis through inhibiting P4hα-1 expression in STZ-induced diabetic cardiomyopathy. Acta Biochim Biophys Sin. 2019;51(3):293–300. https://doi.org/10.1093/abbs/gmy177
27. Qiao W, Wang C, Chen B, Zhang F, Liu Y, Lu Q et al. Ibuprofen Attenuates Cardiac Fibrosis in Streptozotocin-Induced Diabetic Rats. Cardiology. 2015;131(2):97–106. https://doi.org/10.1159/000375362
28. Marian AJ, Senthil V, Chen SN, Lombard R. Antifibrotic Effects of AntioxidantN-Acetylcysteine in a Mouse Modelof Human Hypertrophic Cardiomyopathy Mutation. JACC. 2006;47(4):827-834. https://doi.org/10.1016/j.jacc.2005.10.041