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Adriamycin-induced cardiomyopathy can serve as a model for diabetic cardiomyopathy – a hypothesis

Kaviyarasi Renu[1], V.G. Abilash[1], P.B. Tirupathi Pichiah[2], Thabassum Akthar Syeda[1], Sankarganesh Arunachalam[3*]

[1]*School of Biosciences and Technology, VIT University, Vellore, Tamil Nadu 632014, India*

[2]*Department of Animal Science, School of Life Sciences, Bharathidasan University, Tiruchirappalli, Tamil Nadu 620024, India*

[3]*Department of Biotechnology, Kalasalingam University, Krishnankoil 626126, Tamil Nadu, India*

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ABSTRACT

Diabetic cardiomyopathy is one of the life threatening complications of diabetes. A number of animal models are being used for studying diabetic cardiomyopathy. In laboratory animal models, induction of cardiomyopathy happens in two stages: first being the induction of diabetic condition and the second being the induction of cardiomyopathy by prolonging diabetic condition. It takes a longer time to develop diabetes with the limited success rate for development of cardiomyopathy. Adriamycin is an effective anti-cancer drug limited by its major side-effect cardiomyopathy. A number of features of Adriamycin treatment mimics diabetes. We postulate that Adriamycin-induced cardiomyopathy might be used as a model system to study diabetic cardiomyopathy in rodents since a number of features of both the cardiomyopathies overlap. Left ventricular hypertrophy, systolic and diastolic dysfunction, myofibrillar loss, and fibrosis are hallmarks of both of the cardiomyopathies. At the molecular level, calcium signaling, endoplasmic reticulum stress, advance glycation endproduct activation, mitochondrial dysfunction, inflammation, lipotoxicity and oxidative stress are similar in both the cardiomyopathies. The signature profile of both the cardiomyopathies shares commonalities. In conclusion, we suggest that Adriamycin induced cardiomyopathic animal model can be used for studying diabetic cardiomyopathy and would save time for researchers working on cardiomyopathy developed in rodent using the traditional method.

1. Introduction

Diabetes is one of the alarming diseases in the developing and developed world. It affects a number of organ systems including kidneys, liver, eyes, reproductive system, heart *etc.* Diabetic cardiomyopathy is one of the leading causes of death compared to other complications of diabetes [1]. The incidence of diabetic heart failure is correlated with increase in age, blood pressure, weight and cholesterol levels [2]. It is characterized by a series of alterations in structure and functions of the heart, without a coronary artery disease and hypertension, ultimately leading to heart failure. Pathophysiology includes left ventricular hypertrophy, systolic and diastolic dysfunctions [3].

Adriamycin is an anthracycline class of anti-cancer drug. In a rodent model, the drug induces a variety of symptoms which coincide with type II diabetes [4]. One of the major side effects of the drug is cardiomyopathy [5]. Since cardiomyopathy being a complication of diabetes, we compared both the cardiomyopathies (*i.e.*, Diabetic cardiomyopathy and Adriamycin-induced cardiomyopathy). Surprisingly, we observed striking commonalities between both. In the current article, we discuss similarities between both the cardiomyopathies and therefore we postulate that Adriamycin cardiomyopathy could serve as a model system to study diabetic cardiomyopathy. Adriamycin induced cardiomyopathy has several advantages over the currently used model systems to study diabetic cardiomyopathy.

*Corresponding author: Sankarganesh Arunachalam, Department of Biotechnology, Kalasalingam University, Anand Nagar, Krishnankoil, 626126, Tamilnadu, India.
E-mail: sankarganesh@gmail.com (S. Arunachalam).

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2. Diabetic cardiomyopathy

Diabetic cardiomyopathy is characterized by changes in cardiac functions such as systolic and diastolic dysfunction, left ventricular hypertrophy, fibrosis [3], increased left ventricular mass [6] *etc.* At the cellular level, there is a profound change in expression of NFκB [7], increased level of cardiac troponin 1 levels are prominent [8]. Mitochondrial dysfunction [3] and myofibrillar disarray [8] are also observed in diabetic cardiomyopathy.

3. Adriamycin-induced cardiomyopathy (AiC)

The ultrastructural changes in cardiomyocytes during AiC include swelling of mitochondria [9], cytoplasmic vacuolization [9], loss of myofibril [9], changes in lysosomal number [10], chromatin decondensation [11], reduction in contractile force [11], shrinkage of nucleoli, disruption of cytoskeleton, and disruption of mitochondrial network [12]. Some of the crucial genes involved in myocardial functions such as desmin, troponin-I, troponin-C, α-actin, α-tropomyosin, myosin light and heavy chains gets deregulated [13,14], leading to the changes in the physiology and metabolic function of heart such as left ventricular dysfunction, systolic and diastolic dysfunction, increased left ventricular thickness [15–17].

4. Comparison diabetic cardiomyopathy *vs*. Adriamycin induced cardiomyopathy

4.1. Similarities in circulatory profile of diabetic cardiomyopathy and Adriamycin cardiomyopathy

During diabetic cardiomyopathy there is elevated glycemic level, lipidemic level [3] and pro-inflammatory cytokines [18]. Correspondingly, the notable changes found in circulation in doxorubicin treated condition would cause hyperglycemia, hyperlipidemia [4] and elevated pro inflammatory cytokines level includes IL-1 and TNF-α [19].

4.2. Similarities between diabetic cardiomyopathy and Adriamycin cardiomyopathy at molecular level

In both type 1 and type 2 diabetes condition, endoplasmic reticulum stress is one of the factors leading to apoptosis of cardiomyocytes, ultimately resulting in cardiomyopathy. Elevated levels of unfolded protein response (UPR) signaling proteins such as glucose regulated protein and caspase12, act as a biomarker for endoplasmic reticulum stress, have been observed in diabetic cardiomyopathy [20,21]. Similarly, there is also an elevated level of UPR signaling protein as well as caspase 12 in AiC [22].

The altered expression of micro RNA is found in both diabetes and doxorubicin cardiomyopathies. In diabetic cardiomyopathy, following miRNAs have been found to be elevated which includes miR-1, miR-133, miR-206, miR-320, miR-21, miR-223, miR-141, miR-195, miR-199a-3p, miR-700, miR-142-3p, miR-24, miR-21, miR-221, miR-499-3p, miR-208a, miR-705 and decreased level of miR-195, miR-199a-3p, miR-700, miR-142-3p, miR-24, miR-21, miR-221, miR-499-3p, miR-208a and miR-705 [23,24]. Under doxorubicin treatment, the upregulation of miR-146a, miR-367, miR-215, miR-216b, miR-208b, miR-34c cause apoptosis in cardiomyocytes, further it leads to form cardiomyopathy [25,26].

Epigenetic modifications are found in both the histone 3 and CpG island in diabetic cardiomyopathy, whereas in case of doxorubicin cardiomyopathy, there is no evidence of epigenetic modification. Autophagy and mitophagy are commonly observed in diabetic cardiomyopathy. Mitochondria are the power house of the cell. It has the capability to produce more reactive oxygen species during diabetic cardiomyopathy which would lead to mitochondrial damage further is cleared by autophagy. Some of the atg genes are altered in both diabetic and doxorubicin-induced cardiomyopathy conditions [27,28].

In both cases of cardiomyopathies, oxidative stress is one of the contributing factors of the pathophysiology. Nicotinamide adenine dinucleotide phosphate oxidase, xanthine oxidase and some of the enzymes of electron transport chain in mitochondria are increased during both the cases of cardiomyopathies [29,30]. Advance glycation endproduct (AGE) enhances nicotinamide adenine dinucleotide phosphate oxidase through a series of events. In both the cases of cardiomyopathies elevated the level of AGE has been observed [31,32]. Apparently, reactive oxygen species induced by hyperlipidemia and dyslipidemia, plays the crucial role in the development of both the cardiomyopathies [3,4]. Thus, reactive oxygen species leads to enhanced cell death. The outcome of oxidative stress is fibrosis, hypertrophy, apoptosis, alterations in calcium homeostasis, endothelial dysfunction, accumulation of extracellular matrix, and lipotoxicity [5,33].

In type 1 and type 2 diabetes, there is a reduction in glucose uptake, glycolysis and pyruvate oxidation [34]. Therefore, heart switches to enhanced fatty acid metabolism to meet its energy demands [35]. Adipose derived fatty acids serve as the substrate during this metabolic shift [36]. It is almost the same series of events during Adriamycin treatment [37,38]. The circulatory profile during both diabetic and Adriamycin cardiomyopathies exactly overlap. Triglyceride, long-chain fatty acid, cholesterol and transporters of lipids such as low density lipoprotein and very low-density lipoprotein are elevated during both the conditions [39,40]. In both the cases, lipotoxicity is observed in cardiomyocytes along with ceramide accumulation [41,42].

Expression of intracellular cell adhesion molecule-1 such as interleukin-1β and interleukin-6 are increased in both the cases of cardiomyopathies [43,44]. Interestingly, proinflammatory transcription factor NF-κB is elevated [45,46] with elevated macrophage infiltration in both the cases [19,47].

5. Rodent models of diabetic cardiomyopathy

There are several rodent models being used to investigate diabetic cardiomyopathy. Beta cell over-expression of calmodulin [48], non-obese diabetic [49], BB rat [50], streptozocin [51], alloxan [8], Akita [52], ob/ob mice [43], db/db mice [53], Otsuka Long-Evans Tokushima Fatty rat [54], Zucker fatty/Zucker diabetic fatty rats [55], Goto-Kakizaki rats [56] are among the frequently used models.

Developing diabetic cardiomyopathy involves two stages: (1) inducing diabetes (2) developing cardiomyopathy. Diabetic cardiomyopathy using Streptozocin follows the same rule. Similarly, Akita diabetic mice model also takes 5–6 weeks to develop hyperglycemia [57]. Ob/ob mice also take as high as 15 weeks just to develop hyperglycemic condition [53]. Further, it would take a few more weeks to develop cardiomyopathy. The db/db mice take at least 8 weeks to develop the diabetic condition and would,

therefore, take further time to show the signs of cardiomyopathy [53]. In the Western diet-induced diabetic model it takes 20 weeks to develop cardiac dysfunction [58]. In Otsuka Long-Evans Tokushima Fatty rats it takes 18 weeks to induce hyperglycemia [54]. The Bio Breeding rats take 60–120 days to induce diabetes. WBN/Kob rat takes 21 weeks of age to induce glucose intolerance and glucosuria [59]. Zucker diabetic fatty rat model takes 6–8 weeks to induce diabetes in males and 9 to 11 for females [60,61]. The disruption of islets and fibrosis is found in six-month-old ESS-rat [62,63]. In Bureau of Home Economics rats, to induce diabetic conditions like hyperglycemia and hyperinsulinemia, it takes 50 days of age and the diabetic condition occurs only at maturity level [54]. Non-obese diabetic mice take 100–200 days to induce diabetic condition [64]. Sand rat forms diabetes in 2–3 months [65]. In summary, all the diabetic rodent models take longer period of time to develop the diabetic condition and further prolongation may induce cardiomyopathy.

Therefore, Adriamycin would be a better alternative to the aforementioned cardiomyopathic models. Most importantly at 4th week of Adriamycin administration, there is a pronounced incidence of cardiomyopathy [66].

6. Conclusion

Diabetic cardiomyopathy is one of the life threatening complications associated with diabetes. Even though a number of animal models for diabetic cardiomyopathy are available, each one of them has its own limitations. Previously we reported that doxorubicin treatment mimics type 2 diabetic condition. Literature survey reveals striking similarities in the key hallmarks of diabetic cardiomyopathy and Adriamycin induced cardiomyopathy. The circulatory profile in both the cases is marked with hyperlipidemia with prominent elevation in fatty acid levels. Inflammatory cytokines are elevated in both the cases which seem to have important roles in the progression of both the types of cardiomyopathies. At the organ level, literature survey reveals left ventricular dysfunction as a result of left ventricular hypertrophy, which is a significant feature of both the cardiomyopathies. Cardiac relaxation is hampered in both the cases. At molecular mechanistic level also there are quite a lot of similarities such as endoplasmic reticulum stress, impaired calcium signaling, Renin angiotensin aldosterone system activation, lipotoxicity. Therefore, we hypothesize that doxorubicin in rodents might also be used for studying the complications of diabetic cardiomyopathy. Relatively, there are a number of advantages in using doxorubicin such as rapid induction of cardiomyopathy and cost effectiveness. The simple and effective model would enable a number of research groups to explore the disease and therefore, a better understanding of the complication which would speed up the process of identifying better treatment strategies.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

[1] Control/CFD, Prevention. *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States*. 2010. Available from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.
[2] American Diabetes Association. Standards of medical care in diabetes-2017 abridged for primary care providers. *Clin Diabetes* 2017; **35**(1): 5-26.
[3] Williams LJ, Nye BG, Wende AR. Diabetes-related cardiac dysfunction. *Endocrinol Metab* 2017; **32**(2): 171-9.
[4] Arunachalam S, Tirupathi P, Achiraman S. Doxorubicin treatment inhibits PPARγ and may induce lipotoxicity by mimicking a type 2 diabetes-like condition in rodent models. *FEBS Lett* 2013; **587**(2): 105-10.
[5] Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. *J Mol Cell Cardiol* 2012; **52**(6): 1213-25.
[6] Kozakova M, Morizzo C, Fraser AG, Palombo C. Impact of glycemic control on aortic stiffness, left ventricular mass and diastolic longitudinal function in type 2 diabetes mellitus. *Cardiovasc Diabetol* 2017; **16**(1): 78.
[7] Aragno M, Mastrocola R, Medana C, Catalano MG, Vercellinatto I, Danni O, et al. Oxidative stress-dependent impairment of cardiac-specific transcription factors in experimental diabetes. *Endocrinology* 2006; **147**(12): 5967-74.
[8] Lorenzo-Almorós A, Tuñón J, Orejas M, Cortés M, Egido J, Lorenzo Ó. Diagnostic approaches for diabetic cardiomyopathy. *Cardiovasc Diabetol* 2017; **16**(1): 28.
[9] Singal P, Li T, Kumar D, Danelisen I, Iliskovic N. Adriamycin-induced heart failure: mechanisms and modulation. *Mol Cell Biochem* 2000; **207**(1–2): 77-86.
[10] Koleini N, Kardami E. Autophagy and mitophagy in the context of doxorubicin-induced cardiotoxicity. *Oncotarget* 2017; **8**(28): 46663.
[11] Arola OJ, Saraste A, Pulkki K, Kallajoki M, Parvinen M, Voipio-Pulkki LM. Acute doxorubicin cardiotoxicity involves cardiomyocyte apoptosis. *Cancer Res* 2000; **60**(7): 1789-92.
[12] Sardão VA, Oliveira PJ, Holy J, Oliveira CR, Wallace KB. Morphological alterations induced by doxorubicin on H9c2 myoblasts: nuclear, mitochondrial, and cytoskeletal targets. *Cell Biol Toxicol* 2009; **25**(3): 227-43.
[13] Gewirtz D. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. *Biochem Pharmacol* 1999; **57**(7): 727-41.
[14] Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy: from the cardiotoxic mechanisms to management. *Prog Cardiovasc Dis* 2007; **49**(5): 330-52.
[15] Cappetta D, Esposito G, Coppini R, Piegari E, Russo R, Ciuffreda LP, et al. Effects of ranolazine in a model of doxorubicin-induced left ventricle diastolic dysfunction. *Br J Pharmacol* 2017. https://doi.org/10.1111/bph.13791.
[16] Clements I, Davis BJ, Wiseman G. Systolic and diastolic cardiac dysfunction early after the initiation of doxorubicin therapy: significance of gender and concurrent mediastinal radiation. *Nucl Med Commun* 2002; **23**(6): 521-7.
[17] Christiansen S, Perez-Bouza A, Schälte G, Hilgers RD, Autschbach R. Selective left ventricular adriamycin-induced cardiomyopathy in the pig. *J Heart Lung Transpl* 2008; **27**(1): 86-92.
[18] Tuttle HA, Davis-Gorman G, Goldman S, Copeland JG, McDonagh PF. Proinflammatory cytokines are increased in type 2 diabetic women with cardiovascular disease. *J Diabetes Complicat* 2004; **18**(6): 343-51.
[19] Wang L, Chen Q, Qi H, Wang CM, Wang C, Zhang J, et al. Doxorubicin-induced systemic inflammation is driven by upregulation of toll-like receptor TLR4 and endotoxin leakage. *Cancer Res* 2016; **76**(22): 6631-42.
[20] Lakshmanan AP, Harima M, Suzuki K, Soetikno V, Nagata M, Nakamura T, et al. The hyperglycemia stimulated myocardial

endoplasmic reticulum (ER) stress contributes to diabetic cardiomyopathy in the transgenic non-obese type 2 diabetic rats: a differential role of unfolded protein response (UPR) signaling proteins. *Int J Biochem Cell Biol* 2013; **45**(2): 438-47.
[21] Yang Q, Gao H, Dong R, Wu YQ. Sequential changes of endoplasmic reticulum stress and apoptosis in myocardial fibrosis of diabetes mellitus-induced rats. *Mol Med Rep* 2016; **13**(6): 5037-44.
[22] Wang XY, Yang CT, Zheng DD, Mo LQ, Lan AP, Yang ZL, et al. Hydrogen sulfide protects H9c2 cells against doxorubicin-induced cardiotoxicity through inhibition of endoplasmic reticulum stress. *Mol Cell Biochem* 2012; **363**(1–2): 419-26.
[23] Zhou Q, Lv D, Chen P, Xu T, Fu S, Li J, et al. MicroRNAs in diabetic cardiomyopathy and clinical perspectives. *Front Genet* 2014; **5**: 185.
[24] Shantikumar S, Caporali A, Emanueli C. Role of microRNAs in diabetes and its cardiovascular complications. *Cardiovasc Res* 2012; **93**(4): 583-93.
[25] Vacchi-Suzzi C, Bauer Y, Berridge BR, Bongiovanni S, Gerrish K, Hamadeh HK, et al. Perturbation of microRNAs in rat heart during chronic doxorubicin treatment. *PLoS One* 2012; **7**(7): e40395.
[26] Roca-Alonso L, Pellegrino L, Castellano L, Stebbing J. Breast cancer treatment and adverse cardiac events: what are the molecular mechanisms? *Cardiology* 2012; **122**(4): 253-9.
[27] Smuder AJ, Kavazis AN, Min K, Powers SK. Doxorubicin-induced markers of myocardial autophagic signaling in sedentary and exercise trained animals. *J Appl Physiol* 2013; **115**(2): 176-85.
[28] Ouyang C, You J, Xie Z. The interplay between autophagy and apoptosis in the diabetic heart. *J Mol Cell Cardiol* 2014; **71**: 71-80.
[29] McLaughlin D, Zhao Y, O'Neill KM, Edgar KS, Dunne PD, Kearney AM, et al. Signalling mechanisms underlying doxorubicin and Nox2 NADPH oxidase-induced cardiomyopathy: involvement of mitofusin-2. *Br J Pharmacol* 2017. https://doi.org/10.1111/bph.13773.
[30] González DR, Treuer AV, Novoa U. Nitroso-redox crosstalk in diabetic cardiomyopathy. *Free Radic Dis InTech* 2016. https://doi.org/10.5772/63668.
[31] Suchal K, Malik S, Khan SI, Malhotra RK, Goyal SN, Bhatia J, et al. Protective effect of mangiferin on myocardial ischemia-reperfusion injury in streptozotocin-induced diabetic rats: role of AGE-RAGE/MAPK pathways. *Sci Rep* 2017; **7**: 42027. https://doi.org/10.1038/srep42027.
[32] Moriyama T, Kemi M, Okumura C, Yoshihara K, Horie T. Involvement of advanced glycation end-products, pentosidine and N ε-(carboxymethyl) lysine, in doxorubicin-induced cardiomyopathy in rats. *Toxicology* 2010; **268**(1): 89-97.
[33] Watanabe K, Thandavarayan RA, Harima M, Sari FR, Gurusamy N, Veeraveedu PT, et al. Role of differential signaling pathways and oxidative stress in diabetic cardiomyopathy. *Curr Cardiol Rev* 2010; **6**(4): 280-90.
[34] Brahma MK, Pepin ME, Wende AR. My sweetheart is broken: role of glucose in diabetic cardiomyopathy. *Diabetes Metab J* 2017; **41**(1): 1-9.
[35] An D, Rodrigues B. Role of changes in cardiac metabolism in development of diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2006; **291**(4): H1489-506.
[36] Kim MS, Wang Y, Rodrigues B. Lipoprotein lipase mediated fatty acid delivery and its impact in diabetic cardiomyopathy. *Biochim Biophys Acta* 2012; **1821**(5): 800-8.
[37] Tokarska-Schlattner M, Zaugg M, Zuppinger C, Wallimann T, Schlattner U. New insights into doxorubicin-induced cardiotoxicity: the critical role of cellular energetics. *J Mol Cell Cardiol* 2006; **41**(3): 389-405.
[38] Arunachalam S, Kim SY, Kim MS, Yi HK, Yun BS, Lee DY, et al. Adriamycin inhibits adipogenesis through the modulation of PPARγ and restoration of adriamycin-mediated inhibition of adipogenesis by PPARγ over-expression. *Toxicol Mech Methods* 2012; **22**(7): 540-6.
[39] Hong YM, Kim HS, Yoon HR. Serum lipid and fatty acid profiles in adriamycin-treated rats after administration of L-carnitine. *Pediatr Res* 2002; **51**(2): 249-55.
[40] Iliskovic N, Singal PK. Lipid lowering: an important factor in preventing adriamycin-induced heart failure. *Am J Pathol* 1997; **150**(2): 727.
[41] Chong CR, Clarke K, Levelt E. Metabolic remodelling in diabetic cardiomyopathy. *Cardiovasc Res* 2017; **113**(4): 422-30.
[42] Andrieu-abadie N, JaffrÉzou JP, Hatem S, Laurent G, Levade T, Mercadier JJ. L-carnitine prevents doxorubicin-induced apoptosis of cardiac myocytes: role of inhibition of ceramide generation. *FASEB J* 1999; **13**(12): 1501-10.
[43] Mishra PK, Ying W, Nandi SS, Bandyopadhyay GK, Patel KK, Mahata SK. Diabetic cardiomyopathy: an immunometabolic perspective. *Front Endocrinol (Lausanne)* 2017. https://doi.org/10.3389/fendo.2017.00072.
[44] Guo RM, Xu WM, Lin JC, Mo LQ, Hua XX, Chen PX, et al. Activation of the p38 MAPK/NF-κB pathway contributes to doxorubicin-induced inflammation and cytotoxicity in H9c2 cardiac cells. *Mol Med Rep* 2013; **8**(2): 603-8.
[45] Mantawy EM, Esmat A, El-Bakly WM, ElDin RAS, El-Demerdash E. Mechanistic clues to the protective effect of chrysin against doxorubicin-induced cardiomyopathy: plausible roles of p53, MAPK and AKT pathways. *Sci Rep* 2017; **7**(1): 4795.
[46] Gilca GE, Stefanescu G, Badulescu O, Tanase DM, Bararu I, Ciocoiu M. Diabetic cardiomyopathy: current approach and potential diagnostic and therapeutic targets. *J Diabetes Res* 2017; **2017**(2017): 1310265. https://doi.org/10.1155/2017/1310265.
[47] Guido MC, Marques AF, Tavares ER, Tavares de Melo MD, Salemi V, Maranhão RC. The effects of diabetes induction on the rat heart: differences in oxidative stress, inflammatory cells, and fibrosis between subendocardial and interstitial myocardial areas. *Oxid Med Cell Longev* 2017; **2017**(2017): 5343972. https://doi.org/10.1155/2017/5343972.
[48] Xu Z, Tong Q, Zhang Z, Wang S, Zheng Y, Liu Q, et al. Inhibition of HDAC3 prevents diabetic cardiomyopathy in OVE26 mice via epigenetic regulation of DUSP5-ERK1/2 pathway. *Clin Sci* 2017; **131**(15): 1841-57.
[49] Pacher P, Liaudet L, Soriano FG, Mabley JG, Szabó É Szabó C. The role of poly (ADP-ribose) polymerase activation in the development of myocardial and endothelial dysfunction in diabetes. *Diabetes* 2002; **51**(2): 514-21.
[50] Mullen Y. Development of the nonobese diabetic mouse and contribution of animal models for understanding type 1 diabetes. *Pancreas* 2017; **46**(4): 455.
[51] Zhang Y, Wang J-H, Zhang Y-Y, Wang YZ, Wang J, Zhao Y, et al. Deletion of interleukin-6 alleviated interstitial fibrosis in streptozotocin-induced diabetic cardiomyopathy of mice through affecting TGFβ1 and miR-29 pathways. *Sci Rep* 2016; **6**: 23010.
[52] Fuentes-Antras J, Picatoste B, Gomez-Hernandez A, Egido J, Tunon J, Lorenzo O. Updating experimental models of diabetic cardiomyopathy. *J Diabetes Res* 2015; **2015**: 656795. https://doi.org/10.1155/2015/656795.
[53] Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology* 2005; **146**(12): 5341-9.
[54] Kumar S, Singh R, Vasudeva N, Sharma S. Acute and chronic animal models for the evaluation of anti-diabetic agents. *Cardiovasc Diabetol* 2012; **11**(9): 1-13.
[55] Seino S. A novel rat model of type 2 diabetes: the Zucker fatty diabetes mellitus ZFDM rat. *Exp Diabetes Res* 2013; **2013**: 103731. https://doi.org/10.1155/2013/103731.
[56] Sárközy M, Szűcs G, Fekete V, Pipicz M, Éder K, Gáspár R, et al. Transcriptomic alterations in the heart of non-obese type 2 diabetic Goto-Kakizaki rats. *Cardiovasc Diabetol* 2016; **15**(1): 110.
[57] Bugger H, Boudina S, Hu XX, Tuinei J, Zaha VG, Theobald HA, et al. Type 1 diabetic akita mouse hearts are insulin sensitive but manifest structurally abnormal mitochondria that remain coupled despite increased uncoupling protein 3. *Diabetes* 2008; **57**(11): 2924-32.
[58] Kim JK, Kim HJ, Park SY, Cederberg A, Westergren R, Nilsson D, et al. Adipocyte-specific overexpression of FOXC2 prevents diet-

induced increases in intramuscular fatty acyl CoA and insulin resistance. *Diabetes* 2005; **54**(6): 1657-63.

[59] Yagihashi S, Wada R, Kamijo M, Nagai K. Peripheral neuropathy in the WBN/Kob rat with chronic pancreatitis and spontaneous diabetes. *Lab Investig* 1993; **68**(3): 296-307.

[60] Peterson RG, Shaw WN, Neel MA, Little LA, Eichberg J. Zucker diabetic fatty rat as a model for non-insulin-dependent diabetes mellitus. *ILAR J* 1990; **32**(3): 16-9.

[61] Lee Y, Hirose H, Ohneda M, Johnson J, McGarry JD, Unger RH. Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proc Natl Acad Sci U S A* 1994; **91**(23): 10878-82.

[62] Tarrés M, Martínez S, Liborio M, Rabasa S. Diabetes mellitus en una línea endocrinada de rata. *Mendeliana* 1981; **5**: 39-48.

[63] Dumm CLG, Semino MC, Gagliardino JJ. Sequential morphological changes in pancreatic islets of spontaneously diabetic rats. *Pancreas* 1990; **5**(5): 533-9.

[64] Baeder W, Sredy J, Sehgal S, Chang J, Adams L. Rapamycin prevents the onset of insulin-dependent diabetes mellitus (IDDM) in NOD mice. *Clin Exp Immunol* 1992; **89**(2): 174-8.

[65] Strasser H. A breeding program for spontaneously diabetic experimental animals: *Psammomys obesus* (sand rat) and *Acomys cahirinus* (spiny mouse). *Lab Anim Care* 1968; **18**(3): 328.

[66] Kang Y, Wang W, Zhao H, Qiao Z, Shen X, He B. Assessment of subclinical doxorubicin-induced cardiotoxicity in a rat model by speckle-tracking imaging. *Arq Bras Cardiol* 2017; **109**(2): 132-9.