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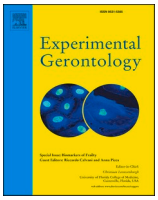

The effects of resveratrol and melatonin on biochemical and molecular parameters in diabetic old female rat hearts

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ABSTRACT

The roles of melatonin and resveratrol-enhanced activation of SIRT1 (silent information regulator 1), GLUT4 (glucose transporter type 4), and PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) in mediating the protective effects on the heart in aged female rats with streptozotocin-induced diabetes were investigated. 16-month-old 48 Wistar female rats were separated into 8 groups with equal numbers. Group 1: Control, Group 2: Resveratrol Control, Group 3: Melatonin Control, Group 4: Resveratrol and Melatonin Control, Group 5: Diabetes, Group 6: Diabetes Resveratrol, Group 7: Diabetes Melatonin, Group 8: Diabetes Resveratrol and Melatonin. A single dose of 40 mg/kg intraperitoneal streptozotocin was injected into the rats of Groups 5, 6, 7, and 8 to induce experimental diabetes. Blood glucose levels were measured from the tail veins of the animals six days after the injections, using a diagnostic glucose kit. Rats with a blood glucose levels ≥300 mg/dl were considered diabetic. 5 mg/kg/day of resveratrol (intraperitoneal) and melatonin (subcutaneous) were administered for four weeks. At the end of the applications, SIRT1, GLUT4, PGC-1α gene expression as well as MDA and GSH levels in the heart tissues were determined by the PCR method from heart tissue samples taken under general anesthesia.

The findings of our study show that suppressed antioxidant activity and decreased GLUT4, SIRT1, and PGC-1α gene expression in heart tissue can be reversed by the combination of resveratrol, melatonin, and resveratrol + melatonin in a diabetic aged female rat model. Resveratrol and melatonin supplementation may have a protective effect on cardiac functions in the diabetic aged female rat model.

1. Introduction

Diabetes mellitus (DM), a global health problem with high morbidity and mortality rates, is still posing a significant threat to human health (Tahara et al., 2013). It is estimated that approximately 380 million people worldwide have diabetes, and this figure will reach 439 million by 2030 (Nentwich and Ulbig, 2015). Among various events precipitating diabetes, the most important pathogenic factors are the generation of oxidative stress and tissue-specific inflammation (Akash et al., 2013; Movahed et al., 2013). Diabetes-related cardiovascular complications are the leading causes of mortality (Gili et al., 2013). Therefore, it is critical to identify an effective agent to avoid cardiovascular complications in patients with diabetes (Gili et al., 2013).

Along with its antioxidant capacity, favorable effects of resveratrol include regulation of ion channels and the activities and expression levels of proteins and enzymes associated with survival signals (Baur and Sinclair, 2006; Kwon et al., 2010). Studies on resveratrol have proved its promising effects on glucose metabolism (Pollack and Crandall, 2013). Resveratrol increases insulin-dependent glucose uptake in skeletal muscle, hepatocytes, and adipocytes with the activation of SIRT1 protein (Breen et al., 2008; Sun et al., 2007). In mice, resveratrol precipitates the activation of SIRT1 and its target, PGC-1α, which induces changes in the number and function of mitochondria (Lagouge et al., 2006). Resveratrol also provokes aggrandizement in SIRT1, PGC-

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1α, and mtDNA copy numbers and an improvement in high-fat diet-induced insulin resistance (Haohao et al., 2015). In terms of cardiovascular indicators, activation of SIRT1 with resveratrol in rats has been shown to improve cardiac contractility and left ventricular functions (Jian et al., 2012). Moreover, resveratrol-mediated SIRT1 activation in mice diminished plaque formation (Do et al., 2008). In another study, it was stated that the cardioprotective effects of exercise in the heart of aged rats were reinforced by resveratrol treatment, and this was acquired through the activation of SIRT1, which has inhibitory effects on FOXO3 (transcription factor) accumulation in the nucleus and inhibits cell death (Lin et al., 2014).

Physiological effects of melatonin include detoxification of free radicals, regulation of immune functions, protection of nerve cells, anticancer effects, and improvement of cardiovascular functions, reproduction, and fetal development (Samanta, 2020). Cell protective and anti-inflammatory properties of melatonin are considered to comprise the dynamic effects of the SIRT1 pathway (Lim et al., 2012). Melatonin exerts affirmative effects associated with the potentiation of mitochondrial biogenesis via the SIRT1-dependent PGC-1α pathway in cadmium-induced hepatotoxicity. Melatonin has also been demonstrated to have a cardioprotective effect against myocardial ischemia-reperfusion injury by abating oxidative stress damage through receptor-dependent SIRT1 signal activation (Yu et al., 2014). The first findings regarding this affirmative connection between sirtuins and melatonin were obtained in SAMP8 mice with accelerated senescence and it was shown that melatonin increased SIRT1 (Gutierrez-Cuesta et al., 2008). In this study, it has been suggested that melatonin controls certain genes and regulates the circadian rhythm via SIRT1, and this may be the mechanism of the link between melatonin and aging and susceptibility to cancer. The authors also stated that the effect of melatonin in cellular pathways is regulated by SIRT1 (Hardeland, 2013; Tajes et al., 2009). Melatonin has a robust potential as a treatment option notwithstanding its faint and infrequent toxicity profile (Reiter et al., 1996). Possible synergistic effects of melatonin and resveratrol were examined in numerous studies which exhibited similar salutary features. Nevertheless, resveratrol and melatonin possibly affect different targets and change different pathways in glucose and lipid metabolism (Majumdar et al., 2014).

Planned from this perspective, our study intended to investigate the therapeutic effects of resveratrol and melatonin supplementation on SIRT1, PGC-1α, GLUT4 and oxidative stress parameters in the heart tissue of aged female rats with streptozotocin (STZ) induced diabetes.

2. Material and methods

2.1. Experimental animals and groups

16-month-old female Wistar rats with an initial weight of 350–400 g were used in all experiments, and only female rats were preferred to minimize physiological variations. This study protocol was approved by the Experimental Animals Ethics Committee of Selcuk University Experimental Medicine Research and Application Center with the decision number 2018-34 on 12.09.2018.

48 rats in total were randomly allocated into 8 groups with an equal number of animals. Control Group (Con) ($n = 6$): The animals in this group were fed with standard rat provender. Resveratrol Control Group (Con + Res) (n = 6): The animals in this group fed with standard rat chow were additionally given resveratrol (5 mg/kg/day) for 4 weeks (i.p.). Melatonin Control Group (Con + Mel) ($n = 6$): The animals in this group fed with standard rat provender were additionally given subcutaneous melatonin (5 mg/kg/day) for 4 weeks. Resveratrol and Melatonin Control Group (Con + Res + Mel) ($n = 6$): The animals in this group were administered i.p. resveratrol (5 mg/kg/day) and subcutaneous melatonin (5 mg/kg/day) for 4 weeks in addition to the standard rat feed. Diabetes Group (DM) ($n = 6$): The animals in this group, whose diabetes was induced by intraperitoneal administration of a single dose of streptozotocin (STZ) (40 mg/kg), were fed with standard rat chow. Diabetes Resveratrol Group (DM + Res) ($n = 6$): Following a single dose of STZ (40 mg/kg) injection, resveratrol (5 mg/kg/day) was given i.p. for 4 weeks starting from the end of the seventh day, in addition to the standard rat provender Diabetes Melatonin Group (DM + Mel) ($n = 6$): Following a single dose of STZ (40 mg/kg) injection, melatonin (5 mg/kg/day) was administered to the diabetic rats subcutaneously for 4 weeks starting from the end of the seventh day, in addition to the standard rat provender. Diabetes Resveratrol and Melatonin Group (DM + Res + Mel) ($n = 6$): Following a single dose of STZ (40 mg/kg) injection, subcutaneous melatonin (5 mg/kg/day) and intraperitoneal resveratrol (5 mg/kg/day) were administered to the diabetic rats for 4 weeks starting from the end of the seventh day, additional to the standard rat provender.

All animals were kept at the standard room temperature (21 ± 1 °C) and the humidity, with 12/12 light/dark cycles, throughout the injections. Housing was organized as 3 animals per cage and food and water were supplied ad libitum. The animals were adjusted to be at the same age according to their birth time, considering the experimental time difference between the first and last animals.

2.2. Experimental applications

2.2.1. Experimental diabetic method

A single dose of 40 mg/kg streptozotocin (STZ) “Sigma S-0130” was injected intraperitoneally to induce diabetes experimentally. 6 days after injections, blood glucose levels were measured from the tail veins of the animals using a diagnostic glucose kit. Rats with blood glucose levels of 300 mg/dl and above were considered as diabetic.

2.2.2. Resveratrol application

Resveratrol (R5010-Sigma) applications were performed intraperitoneally for four weeks at a daily dose of 5 mg per kg bodyweight of the experimental animal.

2.2.3. Melatonin administration

Commercially available melatonin (Sigma M-5250) was applied by injecting subcutaneously to the rats at 10:00 am at a daily dose of 5 mg per kg bodyweight of the experimental animal, and melatonin administration was carried out at the same time of the day for 4 weeks.

2.2.4. Sample collection

Heart tissues of the animals were gathered under general anesthesia for lipid peroxidation measurement and RT-PCR analysis at the end of 4 weeks of experimental applications.

2.3. Biochemical analysis

2.3.1. Determination of tissue malondialdehyde levels

Heart tissue malondialdehyde (MDA) levels were measured by using the Mihara and Uchiyama method with the SPECTROstar (BMG Labtech, Germany) device. The results were defined as nmol/g tissue.

2.3.2. Tissue glutathione analysis

Heart tissue glutathione (GSH) levels were measured by applying the Ellmann method with the SPECTROstar (BMG Labtech, Germany) device and data are presented as mg/g tissue.

2.4. RNA extraction and real-time quantitative PCR analysis

2.4.1. mRNA isolation

Total RNA was isolated from heart tissue (50 mg) using the nucleozol Macherey Nagel brand RNA Isolation Kit (Germany) according to the manufacturer's instructions. The amount of RNA was measured using a Merinton brand SMA1000 model spectrophotometer (CHINA). Furthermore, the usability of RNAs was determined by running on a 1 %

agarose gel and seeing specific 18S and 28S bands.

2.4.2. Real-time quantitative PCR analysis

1 μg of RNA per sample was reverse transcribed using the Biorad (California, USA) cDNA synthesis kit to generate cDNA. The cDNA mix was containing 1 μg RNA, 4 μl cDNA master buffer, 1 μl Reverse transcriptase enzyme, with a total volume of 20 μl. The resulting cDNA was used for quantitative real-time PCR amplification of the targeted gene (SIRT1, PGC-1α, and GLUT4) and reference gene (β-actin) using Biorad Real-Time PCR Detection Systems (California, USA). Primer sets used for expression analysis of target genes at the mRNA level are shown in Table 1. These determined primers were obtained by synthesizing them in the manufacturing company (Sentegen).

2.5. Statistical analysis

Statistical tests were performed using the GraphPad Prism-8 program. One-way ANOVA was used to compare the means of the data of the groups in a single direction. Moreover, the Tukey post hoc test was used to determine the difference between assorted groups. Differences at the $p < 0.05$ level were considered significant.

3. Results

3.1. Findings of biochemical studies

MDA and GSH levels of the experimental groups are given in Table 2 as mean ± standard error. Diabetes provoked a significant increase in the heart tissue MDA level ($p < 0.05$) and the highest MDA level was observed in the diabetes group. When the DM + Res, DM + Mel, and DM + Res + Mel groups of the treatment groups were compared with the DM group, a significant decrease was observed, while each treatment group brought these values suppressed by diabetes closer to the control group values ($p < 0.05$) (Table 2). When the heart tissue GSH levels were compared with the control group, a significant decrease was obtained in the diabetes group ($p < 0.05$). Furthermore, the lowest GSH level was observed in the diabetes group. It was realized that the control values were reached when DM + Res, DM + Mel, and DM + Res + Mel groups were compared with the control group ($p < 0.05$) (Table 2). Heart tissue MDA and GSH levels of the other groups were not different from each other ($p > 0.05$) (Table 2).

3.2. Findings of molecular studies

3.2.1. Findings of SIRT1 expression values

A significant decrease in the cardiac tissue SIRT1 expression values of the group DM was noted when compared with group Con. These values, which were reduced by diabetes, improved to the control values in the treatment groups ($p < 0.05$). The cardiac tissue SIRT1 expression values of the other groups were not different from each other ($p > 0.05$) (Table 3).

3.2.2. Findings of PGC-1α expression values

The mean values of heart tissue PGC-1α expression were significantly decreased in group DM compared to group Con ($p < 0.05$). However, the mean values of the DM + Res, DM + Mel, and DM + Res + Mel groups decreased with diabetes and reached the control values after treatment ($p < 0.05$). There was no significant difference between the mean values of the other groups ($p > 0.05$) (Table 4).

Table 1
Primer sets of target genes.

PGC-1α F	CGGGATGGCAACTTCAGTAA
PGC-1α R	CCCAAGGGTAGCTCAGTTTATC
SIRT1 F	CATAGGTTAGGTGGCGAGTATG
SIRT1 R	GTTGGTGGCAACTCTGATAAATG
GLUT4 F	CACTGGTCCTTGCTGTATTCT
GLUT4 R	GCTCTGTTCAATCACTTTCTGTG
Actin Beta F	TGTGACGTTGACATCCGTAAAG
Actin Beta R	GGCAGTAATCTCCTTCTGCATC

Table 2
MDA (nmol/g tissue) - GSH (mg/g tissue) values of heart tissues of all experimental groups.

Groups ($N = 6$)	MDA (nmol/g tissue)	GSH (mg/g tissue)
Con	82.92 ± 2.97^{b}	474.2 ± 42.2^{a}
Con + Res	83.99 ± 4.15^{b}	459.4 ± 29.3^{a}
Con + Mel	81.74 ± 3.16^{b}	454.1 ± 22.1^{a}
Con + Res + Mel	84.03 ± 2.28^{b}	448.1 ± 38.5^{a}
DM	110.60 ± 1.70^{a}	51.6 ± 9.9^{b}
DM + Res	95.04 ± 1.32^{b}	434.7 ± 31.8^{a}
DM + Mel	95.06 ± 5.01^{b}	447.9 ± 29.6^{a}
DM + Res + Mel	80.25 ± 4.62^{b}	458.6 ± 17.9^{a}

MDA (nmol/g tissue) and GSH (mg/g tissue) values of heart tissues are presented as mean ± standard error. a, b: The difference between the means between groups with different letters in the same column is significant (a > b) ($p < 0.05$).

Table 3
SIRT1 expression values of heart tissues of all experimental groups.

Groups ($N = 6$)	SIRT1 gene activation ($2^{-\Delta CT}$)
Con	0.122 ± 0.018^{a}
Con + Res	0.042 ± 0.024^{a}
Con + Mel	0.068 ± 0.030^{a}
Con + Res + Mel	0.095 ± 0.037^{a}
DM	0.004 ± 0.001^{b}
DM + Res	0.134 ± 0.043^{a}
DM + Mel	0.073 ± 0.002^{a}
DM + Res + Mel	0.024 ± 0.002^{a}

SIRT1 expression values of heart tissues are shown as mean ± standard error. a, b: The difference between the means between groups with different letters in the same column is significant ($p < 0.05$).

3.2.3. Findings of GLUT4 expression values

The mean values of the heart tissue GLUT4 expression decreased significantly in group DM compared to group Con ($p < 0.05$). In the DM + Res, DM + Mel, and DM + Res + Mel groups, a significant increase was observed when compared to the group DM, and it was realized to approach the control values when compared with the group Con. Heart tissue GLUT4 expression values of the other groups were not different from each other ($p > 0.05$) (Table 5).

4. Discussion

4.1. Discussing MDA values

In our study, the highest MDA values in the heart tissue of old female rats were obtained in the diabetes group. The increased MDA levels we obtained in the heart tissue of diabetic rats can be supposed as a result of

Table 4
PGC-1α expression values of heart tissues of all experimental groups.

Groups ($N = 6$)	PGC-1α gene activation ($2^{-\Delta CT}$)
Con	1.500 ± 0.133^{a}
Con + Res	2.144 ± 0.500^{a}
Con + Mel	1.496 ± 0.145^{a}
Con + Res + Mel	1.637 ± 0.040^{a}
DM	0.057 ± 0.021^{b}
DM + Res	1.765 ± 0.399^{a}
DM + Mel	1.505 ± 0.126^{a}
DM + Res + Mel	1.603 ± 0.135^{a}

PGC-1α expression values of heart tissues are shown as mean ± standard error. a, b, c: The difference between the means between groups with different letters in the same column is significant ($p < 0.05$).

Table 5
GLUT4 expression values of heart tissues of all experimental groups.

Groups ($N = 6$)	GLUT4 gene activation ($2^{-\Delta CT}$)
Con	0.055 ± 0.009^{a}
Con + Res	0.049 ± 0.005^{a}
Con + Mel	0.058 ± 0.014^{a}
Con + Res + Mel	0.053 ± 0.015^{a}
DM	0.0009 ± 0.003^{b}
DM + Res	0.055 ± 0.015^{a}
DM + Mel	0.055 ± 0.004^{a}
DM + Res + Mel	0.056 ± 0.006^{a}

GLUT4 expression values of heart tissues are shown as mean ± standard error. a, b, c: The difference between the means between groups with different letters in the same column is significant ($p < 0.05$).

experimental diabetes. The findings of researchers reported that oxidative stress increases in the heart tissue in diabetes (Ghyasi et al., 2019; Petrie et al., 2018; Wang et al., 2018; Zabihi et al., 2018; Zhang et al., 2016) have been strongly compatible with the findings of our study. Previous studies have reported that resveratrol attenuates diabetes-induced cardiovascular system disorders through different endogenous signaling pathways, including oxidative stress/antioxidant defense system and glucose/insulin metabolism (Guo et al., 2014; Xu et al., 2019). Defined as a natural antioxidant, resveratrol has been shown to prevent oxidative damage by directly scavenging hydroxyl (•OH) and superoxide ($O2^{\bullet -}$) radicals. This direct free-radical-scavenging effect indicates that resveratrol can suppress lipid peroxidation (Ahangarpour et al., 2019; Bonnefont-Rousselot, 2016). In our study, the increased MDA levels in the heart tissue of diabetic rats were significantly suppressed by resveratrol supplementation and decreased to the values of healthy controls. This finding is coherent with the impression that resveratrol can suppress lipid peroxidation by directly scavenging hydroxyl and superoxide radicals.

Our findings have revealed that the increased MDA levels in the heart tissue of diabetic rats were also suppressed by melatonin supplementation. Oxidative stress, posing an important role in the induction of various complications of diseases such as diabetes, is effectively weakened by the antioxidant activity of melatonin (Mok et al., 2019; Pourhanifeh et al., 2020). Moreover, this hormone neutralizes ROS and protects beta cells of the pancreas with its low antioxidant content (Pourhanifeh et al., 2020). Therefore, melatonin is considered a suitable candidate for the prevention and treatment of diabetic complications. Amin et al. (2015) reported that melatonin, as an effective antioxidant, reduces the oxidative damage in the heart tissue caused by diabetes, improves the antioxidative status, and reduces the lipid peroxidation level in the heart tissue to almost control values (Amin et al., 2015). Our findings, that the increased MDA levels in the heart tissue of diabetic rats were significantly suppressed by melatonin support, parallel the findings of the previous reports that showed both free radical scavenging effect (Mok et al., 2019; Pourhanifeh et al., 2020) and the cardioprotective effect (Pourhanifeh et al., 2020) of melatonin hormone in diabetes.

No previous study has evaluated resveratrol and melatonin combination in the prevention of oxidative stress in the cardiac tissue of diabetic rats so far. Our study presents that the increased MDA values in diabetes were suppressed by the combined administration of resveratrol and melatonin. However, combined supplementation of resveratrol and melatonin did not elicit a stronger effect in the treatment of oxidative damage when compared to the administration of resveratrol or melatonin separately.

4.2. Discussing GSH values

Inflammation, and particularly oxidative stress, plays an important role in the pathogenesis of diabetic cardiomyopathy, and this represents an attractive target for tackling this disease (Li et al., 2019). Therefore, it is reasonable to propose that the approach to combating both inflammation and oxidative damage can effectively prevent the progression of diabetic cardiomyopathy and emphasize the importance of endogenous and exogenous molecules that enable the activation of the antioxidant system. In our study, diabetic aged female rats had the lowest heart GSH values among all groups. It has already been proven in many studies that there is suppression of antioxidant activity in diabetic rats (Li et al., 2019; Ma et al., 2018; Shen et al., 2004). Correspondingly, the suppressed GSH values we obtained in the heart tissue of diabetic aged female rats can be considered a finding that supports this hypothesis.

In our study, antioxidant activity suppressed by diabetes in elderly female rats was increased with resveratrol supplementation. In other words, resveratrol supplementation brought the decreased GSH levels in diabetes to control values. Regarding the central role of oxidative stress and proinflammatory cytokines in the pathogenesis of diabetes, a great deal of research in recent years has focused on the role of resveratrol in the prevention or treatment of diabetes complications (Öztürk et al., 2017). Accordingly, it has been shown that short-term treatment (2–8 weeks) with resveratrol produces beneficial antidiabetic effects and prevents oxidant damage, especially by strengthening the antioxidant system suppressed in diabetes (Sharma et al., 2011). In our study, resveratrol supplementation provided activation of the antioxidant system, which had been suppressed by diabetes, consistent with the findings of the aforementioned previous studies.

Melatonin is a highly effective internal antioxidant that regulates glutathione synthesis as well as stimulates antioxidant enzymes including glutathione peroxidase and glutathione reductase (Reiter et al., 2016). These indirect antioxidant functions of melatonin place this molecule, even more potent, as a key endogenous factor in limiting free radical damage (Reiter et al., 2016; Tordjman et al., 2017). Similar to resveratrol administration, melatonin supplementation resulted in an increase in suppressed GSH values in the diabetic elderly female rat model of our study. The GSH activation we obtained with the support of melatonin is in parallel with the reports of Reiter et al., who reported that melatonin is a highly effective internal antioxidant that regulates glutathione synthesis (Reiter et al., 2016).

The fact that they exhibit synergistic effects in phytomedicine studies suggests that the combination of resveratrol and melatonin may have a stronger antioxidant effect (Kwon et al., 2011; Lee et al., 2018). The combination of resveratrol and melatonin intensified the antioxidant activity suppressed in the heart tissue in diabetes and brought GSH values to healthy control levels. However, the combination of resveratrol and melatonin did not display a more potent effect than administrating separately. In other words, we didn't obtain a finding similar to the reports in phytomedicine studies, which are claimed to have a synergistic effect (Kwon et al., 2011; Lee et al., 2018). Therefore, we argue that the resveratrol-melatonin combination does not show a synergistic effect on increasing antioxidant activity in a diabetic aged female rat model.

4.3. Discussion of SIRT1 expression values

In our study, the lowest SIRT1 expression values in heart tissue were obtained in the diabetes group. This result was consistent with a previous report by Waldman et al. (2018) that presented decreased SIRT1 expression in heart tissues of diabetic rats (Waldman et al., 2018). Similarly, it has been revealed that myocardial SIRT1 expression and activity are decreased in mice with STZ-induced diabetes (Tao et al., 2018). The decreased SIRT1 expression we obtained in the diabetic aged rat heart in our study is compatible with the reports presented above, as well as many other studies (Fourny et al., 2019; Qu et al., 2017; Ying et al., 2019).

Due to the potent effect of SIRT1 on diabetes, many studies have been designed to observe the effects of resveratrol as an activator of SIRT1 in experimental diabetes models (Riba et al., 2017; Sharma et al., 2011). In our study, resveratrol supplementation to diabetic rats

significantly increased SIRT1 expression compared to diabetic controls, reaching healthy control values. Sulaiman et al. (2010) reported that enzymatic activity of cardiac SIRT1 is decreased in chronic diabetes (Sulaiman et al., 2010). They concluded that the cardiac protective effects of resveratrol supplementation were associated with its ability to activate SIRT1 expression (Sulaiman et al., 2010). Similarly, it has been shown that decreased SIRT1 expression in the heart tissue of rats with diabetes was prevented by resveratrol supplementation (Bagul et al., 2015b). The increased cardiac SIRT1 expression obtained with resveratrol supplementation in diabetic rats in our study is consistent with the findings of the aforementioned reports.

Melatonin is also known as the heart-protective hormone. It activates a wide range of molecules in cardiomyocytes, including acting through SIRT1. SIRT1 plays a role in the cardioprotective effects of melatonin, which exerts its beneficial effects by reducing oxidative stress and alleviating diabetes-induced cardiac dysfunction (Favero et al., 2020). Melatonin has been shown to reduce myocardial ischemia-reperfusion injury in both non-diabetic and diabetic animals through SIRT1 activation (Yu et al., 2015; Yu et al., 2014). In our study, melatonin supplementation increased SIRT1 expression in heart tissue, which was significantly reduced in a diabetic aged female rat model, to control values. This result, which we obtained with melatonin supplementation in our study, is also in line with the studies reporting that SIRT1 plays a critical role in the cardioprotective effects of melatonin.

The results of the reports presented above indicate that both resveratrol and melatonin activate sirtuins such as SIRT1. However, there is little study on how the co-administration of resveratrol and melatonin affects SIRT1 proteins in the cardiac tissue of diabetic animals. Previously decreased cardiac SIRT1 expression in diabetic rats supplemented with resveratrol and melatonin combination increased to the levels of healthy control rats. However, the combination of resveratrol and melatonin did not differ from the results obtained with separate administrations of resveratrol and melatonin. The combination of resveratrol and melatonin does not produce an additional increase in cardiac SIRT1 expression, as in others.

4.4. Discussing GLUT4 expression values

Expression and membrane translocation of GLUT4 are decreased in cardiac muscle of animals with both type 1 and type 2 diabetes (Hou et al., 2019). A similar finding of decreased GLUT4 expression in cardiomyocytes was also demonstrated in cell culture studies (Bowman et al., 2019). In our study, GLUT4 expression in the cardiac tissues of the diabetic group was lower than in all other study groups. The decreased cardiac GLUT4 expression we obtained in diabetic rats can be considered an expected result when compared with the findings of the above reports.

Studies on rats with STZ-induced diabetes presented that the expression of the insulin-dependent glucose transporter GLUT4 increased after resveratrol intake (Vallianou et al., 2013; Yonamine et al., 2017). Proving that resveratrol increases GLUT4 expression in diabetic rats has also revealed the idea that resveratrol can be used in the treatment of diabetes (Wong and Howe, 2018; Yonamine et al., 2017). In this study, decreased GLUT4 expression in the heart tissue of diabetic rats reached the level of healthy control animals with resveratrol supplementation. This finding strongly supports the findings of researchers suggesting that resveratrol can be used in the treatment of diabetes.

Studies investigating the relationship between melatonin and GLUT4 expression have exhibited that melatonin modulates GLUT4 expression in cell culture medium (Maria et al., 2018). Melatonin supplementation has been demonstrated to increase GLUT4 expression back to normal levels in pinealectomized rats and therefore, pinealectomy-induced insulin resistance is preventable. It has also been reported that decreased GLUT4 expression in pinealectomized rats reaches normal levels with melatonin supplementation, and pinealectomy-induced insulin resistance is preventable (Zanquetta et al., 2003). Correspondingly, decreased GLUT4 expression in cardiac tissue of rats with hyperthyroidism was improved with melatonin supplementation, proving a robust relationship between melatonin and cardiac GLUT4 expression (Ghosh et al., 2007). Although the relationship between melatonin and GLUT 4 expression has been reported in many studies, reports propounding the effects of melatonin supplementation on GLUT4 expression in the cardiac tissue of diabetic rats are scarce. In this study, melatonin supplementation reversed decreased GLUT4 expression in the heart tissue of diabetic rats. This is the first study to investigate and report that melatonin supplementation increases cardiac GLUT4 expression in a diabetic aged female rat model.

Our findings imply that decreased GLUT4 expression in cardiac tissue of diabetic rats can be treated with the administration of both resveratrol and melatonin. Furthermore, we obtained the same results with the combination of resveratrol and melatonin. The combined administration of resveratrol and melatonin increased the decreased GLUT4 expression in the heart tissue of diabetic rats to the level of healthy control animals. However, the outcome of co-administration did not differ from the results obtained with separate administrations of resveratrol and melatonin.

4.5. Discussion of PGC-1α expression values

The available evidence has revealed a possible role of reduced PGC-1α activity, the transcriptional coactivator PGC-1α in mitochondrial biosynthesis, which is associated with multiple glycolytic metabolisms in the heart (Hu et al., 2016; Ping et al., 2015). Decreased cardiac PGC-1α expression in leptin-resistant obese mice characterized by type 2 diabetes was reported to return to normal levels in parallel with the increase in SIRT1 with caloric restriction (Waldman et al., 2018). In conclusion, the findings presented above highlight the critical role of decreased PGC-1α expression in impaired cardiac function in diabetes. In the current study, we also found reduced PGC-1α expression in the heart tissue of aged female rats with diabetes. This result is consistent with the findings of the above investigators who reported decreased PGC-1α values in diabetic heart tissue.

Increasing evidence has shown that diabetes impairs cardiac mitochondrial function and contributes to diabetic cardiomyopathy (Bombicino et al., 2016). Therefore, prevention of cardiac oxidative stress and mitochondrial dysfunction in diabetic patients can improve cardiac function and reduce hypertrophy (Bagul et al., 2015a). Correspondingly, it was investigated whether resveratrol alleviates cardiac dysfunction in diabetes by improving mitochondrial function via SIRT1-mediated PGC-1α deacetylation in diabetic rats (Fang et al., 2018). In that study, researchers have depicted that resveratrol supplementation leads to a protective effect during diabetic cardiac dysfunction via the SIRT1/PGC-1α pathway (Fang et al., 2018). Available data on resveratrol support these notions. Considered a natural SIRT1 stimulant, resveratrol improves mitochondrial function by activating both SIRT1 and PGC-1α via SIRT1. Resveratrol supplementation also augments insulin sensitivity in Type 2 diabetes by activating SIRT1/PGC-1α. Correspondingly, resveratrol-induced increment in SIRT1/PGC-1α expression reveals a beneficial and protective effect in diabetes (Bheereddy et al., 2021; Repossi et al., 2020). These results are critical in asserting that the SIRT1/PGC-1α pathway may also be a therapeutic target for the treatment of diabetic cardiomyopathy. In our study, decreased cardiac tissue PGC-1α expression in diabetes reached healthy control values with resveratrol support. This finding strongly parallels reports that resveratrol activates the SIRT1/PGC-1α pathway.

Melatonin regulates the regulation of PGC-1α in conjunction with various molecules such as SIRT1 (Lee et al., 2020). The results of our current study propounded that decreased PGC-1α expression in the diabetic rat heart reaches the values of healthy control animals with melatonin supplementation. Melatonin supplementation attenuated the development of diabetes-induced cardiac dysfunction in STZ-induced diabetic mice via the SIRT1/PGC-1α pathway (Ding et al., 2018). This

report by Ding et al. (2018) constitutes an important proof of the melatonin-induced PGC-1α expression boost in diabetic rat hearts (Ding et al., 2018).

In our study, the combination of melatonin and resveratrol compensated for the diminished PGC-1α expression in the diabetic rat heart to control values. However, the combination of melatonin and resveratrol did not potentiate the effect when compared with supplementation of both resveratrol and melatonin separately. Consequently, it is possible to claim that the melatonin-resveratrol combination did not produce a synergistic effect on PGC-1α expression in diabetic rat hearts.

The findings of our study present that the suppressed antioxidant activity, decreased GLUT4, SIRT1 and PGC-1α gene expression in the heart tissue of diabetic aged female rat model can be restored with resveratrol, melatonin, and resveratrol + melatonin combination. Hence, resveratrol and melatonin supplementation may have a protective effect on cardiac functions in the diabetic elderly female rat model.

The most important limitation of the present study is that it was performed on female rats.

Conflict of interest

The authors declare that they have no potential conflicts of interest to disclose.

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CRediT authorship contribution statement

NAU, OU, EGM made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; SO, RM and AKB drafted the work or revised it critically for important intellectual content, approved the version to be published. The authors declare that all data were generated in-house and that no paper mill was used.

Research data policy and data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Compliance with ethical standards

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Experimental Animals Ethics Board of Selcuk University's Experimental Medicine Research and Application Center (2018-34). This research was performed on the animals (rat).

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