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ORIGINAL ARTICLE

The Effect of Aerobic Exercise and Chromium Picolinate Supplementation on Expression of Cardiac Injury-Related Genes in Elderly Diabetic Rats

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ABSTRACT

Background: An area of concern for older adult patients with diabetes is the diabetic cardiomyopathy which develops due to oxidative stress, inflammation, and metabolic disorders. It is quite clear that current therapies do not sufficiently address the multifactorial problems; therefore, we studied the combined effects of aerobic exercise (AE) and *Chromium picolinate* (CrPic) supplementation on cardiac injury related genes.

Methods: Fifty male Wistar rats (22 months) were enrolled in groups of healthy control (G1), diabetic control (G2), and three intervention groups (G3-G5: AE+CrPic, AE only, CrPic only, respectively). Diabetes was induced through streptozotocin (STZ), while; all rats underwent 10 weeks of AE (treadmill training) and/or CrPic (1 mg/kg/day). The expression of cardiac genes was measured by qRT-PCR.

Results: G2 presented an increased TNFR1 expression (p<0.0001 vs. G1), decreased levels of VEGF (p<0.0001), VEGFA (p=0.01) and CD147 (p=0.005). AE+CrPic demonstrated the greatest reduction in TNFR1 expression in G3 (p=0.002 vs. G2) and outperforming of G4 and G5 monotherapies (p=0.01 and p=0.005, respectively). AE significantly restored VEGF level near to normalization (p=0.004 vs. G2), and further enhancement by CrPic (1.8-fold increase, p<0.0001). CD147 was significantly upregulated in G3 (p=0.01 vs. G2). MCT1 showed negligible baseline expression; but an elevation trend was noticed in G3 (p=0.07).

Conclusion: Combining AE and CrPic may work simultaneously to reduce the effects of diabetic cardiomyopathy by lessening inflammation (TNFR1), restoring angiogenesis (VEGF and VEGFA), as well as increasing metabolic flexibility (CD147).

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Introduction

More than 500 million adults suffer from the metabolic disorder of diabetes mellitus, and 25% of people of 65 years and older were shown to have the disease (1). The condition has several complications including cardiomyopathy, which has now emerged as one of the frontrunners in diabetes complications and is well recognized as a significant health issue; because of its considerable frequency and bleak outlook (2). Hyperglycemia stimulates inflammation by activating the pro-inflammatory signaling pathway, developing the apoptotic caspase-3 and lipids Tumor Necrosis Factor alpha (TNF-α) driven gaps that coronary arteries spawn the outgrowth of constricting scar tissue from the heart's mega fibroblasts and remodeling of expanded ventricular fibrotic hardening (3). In addition, hyperglycemia suppresses reparative angiogenesis by inhibiting Vascular Endothelial Growth Factor (VEGF) and its isoform, the Vascular Endothelial Growth Factor A (VEGFA) which that are critical for the survival of endothelial cells and maintenance of the capillary bed through microvascular caliper reduction which further aggravates myocardial hypoxia and advances substrate development for incisional damage (4).

Diabetes concurrently affects and causes the main hallmark of heart abnormalities, which include severe and rigid echocardiographic flexibility, a passive inotropic response, decreased lactate transporter Monocarboxylate Transporter 1 (MCT 1) shuttling, decreased complex-directional Cluster of Differentiation 147 (CD147)-driven extracellular matrix remodeling activity, and dysregulation of the glycoprotein matrix metalloproteinase activator which acts as a strong weakening force (5). These conditions synergize to accelerate myocardial remodeling that render the elderly diabetic heart being vulnerable to irreversible damages (5). Despite advances in pharmacological management of the injuries, current therapies for diabetic cardiomyopathy remain insufficient, particularly in elderly populations where age-related factors in tissue repair decrease and exacerbate cardiac vulnerability (6). These underestimated opportunities highlight the need for a multi-faced approach to be designed in remedy of metabolic and inflammatory dysregulations, simultaneously. In this regard, aerobic exercise serves as an effective non-invasive remedy as it not only improves insulin sensitivity but also hyperactive inflammatory pathways and restores VEGF-dependent angiogenic capillary growth in the heart muscle of diabetics (7).

In addition, *Chromium picolinate* as a trace chromium mineral exerts insulin-sensitizing activity and free radical scavenging action which can reduce hyperglycemic oxidative damages (7, 8). Importantly, aerobic exercise can enhance reparative angiogenesis and Tumor Necrosis Factor Receptor 1 (TNFR1) overexpression; while *C. picolinate* (CrPic) can strengthen the insulin receptor signaling to induce the redox homeostasis (8). Regardless of these combined benefits, the coexistence of aging and diabetes on a molecular level was illustrated to provide a new frontier in research (9). This research examined the impact of aerobic exercise (AE) and supplementation of CrPic on diabetes and specifically in diabetic cardiomyopathy of elderly rats. CrPic was selected based on its merits in increasing insulin sensitivity and reducing blood glucose that makes it an effective intervention for diabetes (10).

Elderly rats were selected to portray the age-related metabolic and physiological changes which exacerbate the complications of diabetes due to the rising incidence of diabetes among older people (11). This study has also addressed the critical knowledge gap by investigating the effect of AE and CrPic on cardiac injury-related genes (TNFR1, VEGF, VEGFA, CD147, MCT1) in elderly diabetic rats. We hypothesized that this dual intervention would provide a superior cardiac protection when compared to monotherapies. They synergistically attenuate diabetic cardiomyopathy through coordinated suppression of inflammatory cascades and restoration of angiogenic and metabolic resilience in a senescent myocardial tissue.

Materials and Methods

Elderly male Wistar rats aged 22 months (a long period in lifespan of these animals) by following the ARRIVE guidelines for animal studies were enrolled (Table 1) (12). An intraperitoneal injection of 110 mg/kg of nicotinamide was used to induce diabetes. A second intraperitoneal injection of 55 mg/kg of streptozotocin (STZ) in a 0.01 M citrate buffer with a pH of 4.5 after a period of fifteen minutes was made again. Using a glucometer (Accu-Check, Germany), the fasting blood glucose (FBS) level was measured one week after the induction. The rats were randomized into five groups of ten animals including a control group of healthy elderly rats, AE plus CrPic supplementation in diabetic rats, AE only in diabetic rats, and CrPic supplementation only in diabetic rats (Table 2). All animals were housed in regular laboratory circumstances with a 12-hour light/dark cycle, a controlled temperature of 24±1°C, and a humidity level of 55±5%. They were also given unlimited access to standard pellet food and water. Under registration number of IR.IAU.SARI.REC.1403.001, the Sari Azad University Ethics Committee established moral guidelines for the use and care of animals to be adhered to.

Table 1: Body weight and blood glucose levels of rats before and after induction of diabetes.

Group	Body weight (g), before	Body weight (g), after	Blood glucose (mg/dL), before	Blood glucose (mg/dL), after
Group 1 (Healthy control)	208	203	99	201
Group 2 (Diabetic control)	206	202	101	185
Group 3 (Aerobic exercise+*Chromium picolinate*)	201	206	97	184
Group 4 (Aerobic exercise only)	213	201	96	196
Group 5 (*Chromium picolinate* only)	204	202	92	192

The values are averages for each group.

Table 2: Experimental groups and mortality rate in different groups of elderly diabetic rats.

Group	Initial rats (n)	Remaining rats (n)	Mortality (n)
Group 1 (Healthy control)	10	10	0
Group 2 (Diabetic control)	10	7	3
Group 3 (Aerobic exercise+*Chromium picolinate*)	10	8	2
Group 4 (Aerobic exercise only)	10	7	3
Group 5 (*Chromium picolinate* only)	10	8	2

Each group consisted of 10 rats, and the number of rats remaining at the end of the study is provided along with the number of rats that died. The final analysis was conducted using 7 rats from each group due to mortality rates.

Rats recruited in the research with defined blood glucose level of more than 200 mg/dL were considered to be afflicted by diabetes. The doses of 0.5-3 mg/kg/day of CrPic were typically considered safe; while the doses above 3-5 mg/kg/day were described to cause toxicity to liver, kidneys and lead to disruption in glucose metabolism. To verify that all groups got the same treatment, rats in the supplementation group were orally given 1 mg/kg/day of CrPic (21st century brand) by gavage for 10 weeks, whereas the control groups received 1 mL of distilled water. Two hours after the final training session, all animals were sacrificed by intraperitoneal injection of xylazine (20%) and ketamine (80%). Then, sample heart tissues were collected, blood clots were cleaned with cold saline and finally, tissues were snap-frozen in liquid nitrogen and stored at -70°C until additional molecular diagnostic procedures were carried out.

Over the course of ten weeks and five sessions per week, AE was performed on a five-lane animal treadmill (Tehran, Iran). Every training session was a 5-minute warm-up plan at a speed of 16 meters per minute as a major running phase with gradually increasing intensity, and then another 5-minute cool-down at a speed of 16 meters per minute with a steady reduction in speed. There were three separate phases in the training program. To get used to treadmill activity, rats ran for 10 to 15 minutes at a pace of 10 meters per minute during the familiarization phase (weeks 1-2). During the overload phase (weeks 2-5), the animals ran for 20-25 minutes at a speed of 20 meters per minute, followed by 30-35 minutes at a speed of 22 meters per minute, 40-45 minutes at a speed of 24 meters per minute, and finally for 50-55 minutes at a speed of 26 meters per minute. The running duration and speed were gradually increased. To sustain exercise intensity and adaptability during the stability period (weeks 8-10), the rats ran continuously for 60 minutes at a steady pace of 27 meters per minute.

Following the manufacturer's instructions, total RNA was isolated from cardiac tissues using the RNA extraction kit (Favorgene, Iran). A Synergy spectrophotometer (BioTek) was utilized to measure absorbance ratios at 260/280 nm and 230/260 nm in order to determine the content and purity of RNA. Using 1% agarose gel electrophoresis, the integrity of the RNA was verified. Then, by employing the cDNA synthesis kit (Yekta Tajhiz Azma, Iran), cDNA was created from 2 µg of total RNA. Random hexamer and oligo (dT) primers were added to the reaction mixture, which was incubated for 60 minutes at 42°C before being heat-inactivated for five minutes at 70°C. By use of Oligo7 and SnapGene software, gene-specific primers were created for TNFR1, VEGF, VEGFA, CD147, MCT1, and the housekeeping gene β-actin. The Primer-BLAST tool (NCBI) was applied to confirm the primer specificity, and Metabion (Germany) that produced the primers. Utilizing a Rotor-Gene 6000 System (Corbett Research, USA) and SYBR Green Master Mix (Yekta Tajhiz Azma, Iran), quantitative real-time PCR (qRT-PCR) was carried out. Totally, 10 minutes of initial denaturation at 95°C was carried out and then followed by 40 cycles of denaturation (95°C, 15 seconds), annealing (60°C, 20 seconds), and extension (72°C, 20 seconds) under thermal cycling conditions. Analysis of the melting curve (60-95°C) verified the specificity of the amplification. Every reaction was carried out twice.

Table 3: Cardiac gene expression findings.

Gene	G1	G2	G3	G4	G5
TNFR1	Low	High	Significantly decreased	Decreased	Decreased
VEGF	Normal	Reduced	Significantly increased	Increased	Mildly increased
VEGFA	Normal	Reduced	Increased	Mildly increased	Not Significant
CD147	Normal	Reduced	Increased	Mildly increased	Borderline increase
MCT1	Negligible	Negligible	Trend to increase	Negligible	Negligible

G1: Healthy control, G2: Diabetic control, G3: Diabetic+Aerobic exercise+*Chromium picolinate*, G4: Diabetic+Aerobic exercise, G5: Diabetic+*Chromium picolinate*. Cluster of Differentiation 147 (CD147), Monocarboxylate Transporter 1 (MCT 1), Tumor Necrosis Factor alpha (TNF-α), Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial Growth Factor A (VEGFA), Tumor Necrosis Factor Receptor 1 (TNFR1).

Gene expression analysis was done quantitatively with the 2-ΔΔCt method. For ΔCt computation, the β-actin housekeeping gene was subtracted from the target gene, and subsequently ΔΔCt values were computed to determine changes in gene expression among different experimental groups. For each analysis performed, GraphPad Prism version 6, SPSS software (version 22, Chicago, IL, USA) and Microsoft Excel were utilized. Data were displayed as mean value and standard deviation (SD) of the samples. Statistical significance between the different groups was assessed using one-way ANOVA and then followed with Tukey's post hoc test, or other statistical tests as indicated, accepting a *p* value less than 0.05 to be significant.

Results

The analysis of the impact of the effect of CrPic together with AE on cardiac-specific biomarkers of elderly STZ-induced diabetic rats was demonstrated in Table 3 and Figure 1. Diabetic rats exhibited expression of the cardiac TNFR1 gene significantly in comparison to non-diabetic healthy control group ($p<0.0001$) indicating an elevated inflammatory signaling in

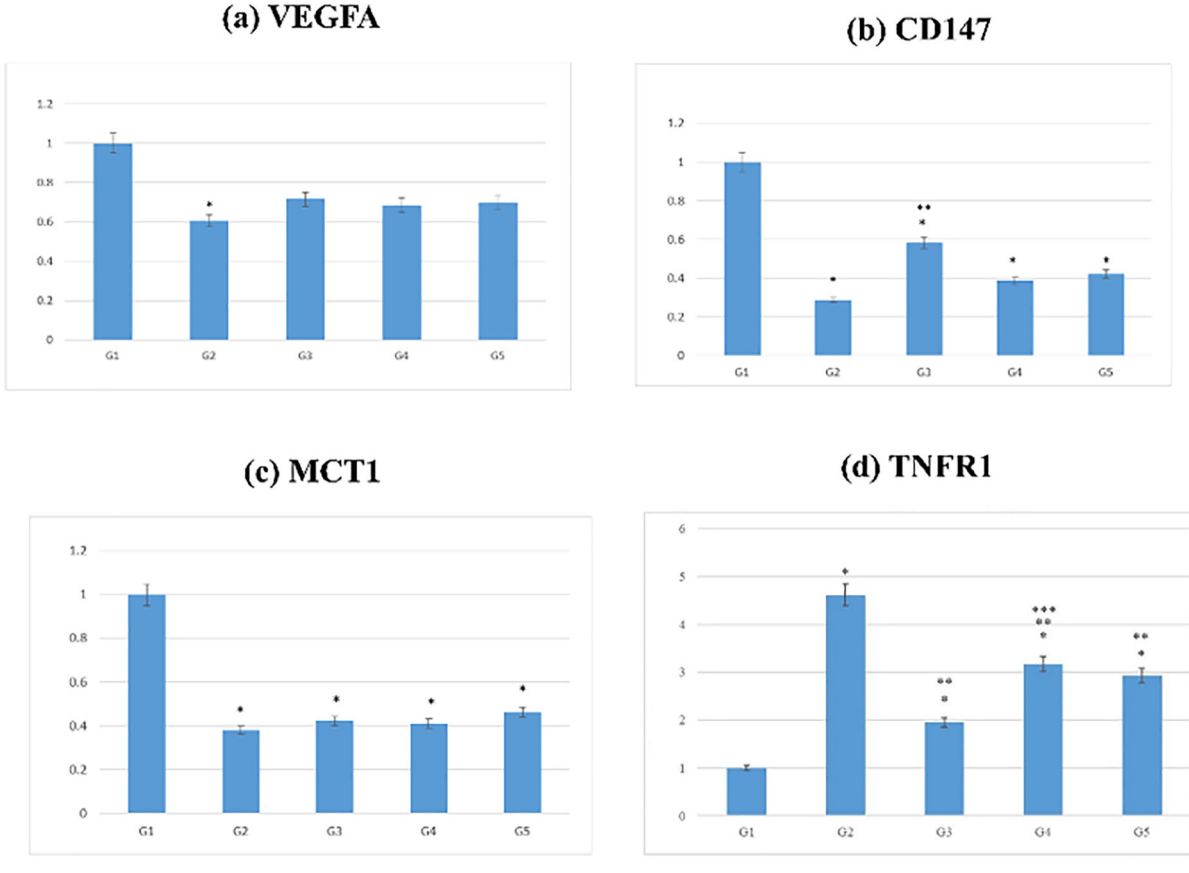

Figure 1: Gene expression levels of VEGFA, CD147, MCT1, and TNFR1 in elderly diabetic rats (G1: Healthy control, G2: Diabetic control, G3: Diabetic+Aerobic exercise+*Chromium picolinate*, G4: Diabetic+Aerobic exercise, G5: Diabetic+*Chromium picolinate*). Cluster of Differentiation 147 (CD147), Monocarboxylate Transporter 1 (MCT 1), Tumor Necrosis Factor alpha (TNF-α), Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial Growth Factor A (VEGFA), Tumor Necrosis Factor Receptor 1 (TNFR1).

the pathophysiology of diabetic cardiomyopathy. AE and/or CrPic supplementation could significantly reduce this impact. AE alone when compared to diabetic rats (p=0.01) and CrPic alone in comparison to diabetic rats (p=0.03) could significantly decrease TNFR1 expression. The combined impact of CrPic and AE was noteworthy (p=0.005 vs. G5; p=0.01 vs. G4). The diabetic rats (G2) had substantially less cardiac production of VEGF and VEGFA as critical mediators of angiogenesis and vascular repair (p<0.0001 and p=0.01, respectively) when compared to the G1 control rats. After undergoing AE (G4), VEGF expression increased to almost normal values (p=0.004 vs. G2) and increased further in the combined AE and diabetic rats (G3); that illustrated a 1.8-fold increase over G2 (p<0.0001). The same was true in G3 and G4, when VEGFA expression recovered (p=0.02 vs. G2 and p=0.03 vs. G2, respectively). The supplementation of CrPic alone did not achieve any statistical significance (p=0.08 vs. G2).

CD147 as a glycoprotein involved in metabolism and stress response showed a reduced cardiac expression in the diabetic group (p=0.005 vs. G1). Unlike the independent effects of AE (G4; p=0.01 vs. G2) and CrPic supplementation alone (G5; p=0.06 vs. G2), AE and CrPic combination could greatly amplify CD147 expression. Related to the role of cardiac tissue in a diabetic state, cardiac expression of MCT1 as a lactate transporter had considerable importance regarding metabolic flexibility. It was absent in all groups; however, it is still vital that MCT1 expression to show some increase in G3 (p=0.07 vs. G2), and demonstrate an exercise-induced metabolic shift. Taken together, AE in conjunction with CrPic supplementation reversed diabetes dysregulated cardiac biomarkers. The interventions could enhance the stress-responsive pathways (CD147), suppressed inflammatory pathways (TNFR1), and restore the angiogenic potential (VEGF/VEGFA) that underscore their efficacy to mitigate the impact of diabetic cardiomyopathy in older patients. Our research revealed that combination of AE plus CrPic could provide more therapeutic benefits than CrPic alone or AE alone. Notably, AE+CrPic had the highest glucose control and improvement for inflammatory markers and vascular repair. Looking at individual results, AE was shown to have greater benefits than CrPic for reducing inflammatory markers such as TNFR1, and improving metabolic flexibility (CD147). Conversely, CrPic displayed stronger results than AE for blood glucose control. But in this case, using both strategies yielded the best overall results, which indicated that AE and CrPic worked synergistically.

Discussion

The important role of exercise in health status has been emphasized before (13). Our study showed that the combined treatment of AE and CrPic supplementation could refrain the progression of diabetic cardiomyopathy in elderly diabetic rats via inflammatory, angiogenic, and metabolic pathways. Our results indicated that this dual intervention provided additional cardioprotective effects, at least in part, through decreased cardiac TNFR1 expression, a prominent inflammatory and apoptotic marker induced by hyperglycemia (14), when compared to monotherapies. While AE treatment restored VEGF and VEGFA, albeit partially, the addition of CrPic increased this synergistic effect and resulted in a nearly normal-expression (15). Strikingly, the combination group presented considerable elevation in CD147 level as a glycoprotein associated with metabolism and remodeling of the extracellular matrix (16) indicating a better stress response in the aging heart tissue. MCT1 expression did not substantially differ across groups, but AE+CrPic demonstrated a modest increase that suggests an exercise-related finding, though potentially constrained, metabolic adaptation and due to reliance on fatty acid oxidation in a diabetic state (17).

These findings highlight the treatment prospects of AE together with CrPic in mitigating the multimorbidity of aging and diabetes, even monotherapies alone with AE or CrPic were less effective due to redox balance and repairing processes which were age-related (18). Our findings offer three key takeaways as first, the most notable decrease of TNFR1 expression came from the combined AE+CrPic intervention had the highest impact that surpasses the results of each intervention alone indicating a synergistic collaboration. The AE and CrPic combination is probably a synergistic intervention because of the complementary way of action. Because CrPic functions as a chromium insulin receptor signaling augmentor and ROS scavenger, AE has also been documented to improve insulin sensitivity and anti-inflammatory responses (19). Regarding both actions, the combined measures can simultaneously diminish inflammatory responses such as TNFR1, recover altered angiogenic pathways like VEGF, and restore metabolic flexibility CD147 within the diabetic heart's tissues (19). This synergy appears to stem from the fact that AE augments endothelial function and vasorelaxation via nitric oxide production which positively rends the expression of VEGF; while CrPic enhances insulin sensitivity and supports more glucose uptake and less oxidative stress (20).

All these effects work together to improve the management of the dysregulated diabetes cardiomyopathy changes, where both chronic inflammation and metabolic dysregulation are tackled simultaneously (21). The supporting outcomes by lowering inflammation and restoring body vascular repair systems together with active fuel movement can aid to a better result in diabetic elderly rats (18, 21). This supports TNFR1 to be a mediator of diabetic cardiomyopathy by NF-κB stimulation and insulin resistance (22). The probable explanation is that AE reduces adipose tissue, TNF-α level and oxidative stress and when coupled with CrPic, as an insulin-sensitizing and reactive oxygen species (ROS) scavenging activity can blunt the driver pathways signaling TNFR1 (23). Second, the marked impact of AE alone to restore the expression of VEGF/VEGFA to baseline has been capped by coronary capillaries that are proportional to the amount of cardiac muscle which have a critical role. It was even more pronounced with the addition of CrPic; potentially due to greater insulin receptor signaling and increased eNOS creating shear stress which in turn can positively regulate the VEGF transcription (24).

Third, the combination group of AE together with CrPic illustrated a marked increase in secretion of CD147 glycoprotein which is crucial for lactate transport through MCT1 and the induction of matrix metalloproteinases (25). Conversely, MCT1 expression revealed a slight upward trend which was not statistically significant that is in line with its restricted role at baseline in diabetic hearts. However, the findings related to CD147 indicated better extracellular matrix control and metabolic ability. All these results highlight the potential of combinatory therapy to reduce inflammation and restore angiogenic balance, in addition to driving adaptive metabolic changes, while managing the complex pathophysiological connections of diabetic cardiomyopathy in older patients (26, 27). The enhanced effectiveness of AE+CrPic when compared to monotherapies of AE or CrPic alone, emphasizes the greater need for multi-modal therapy in older patients, where age-related reductions in antioxidant defense and tissue repair require multi-targeted approach (28).

The likely reason for suppression of TNFR1 in AE+CrPic group is due to the decreases in adipose-derived TNF-α and oxidative stress caused by AE which impinge the activation of NF-κB pathway. Meanwhile, CrPic enhances insulin sensitivity and function as a direct ROS scavenging property, thus breaking the self-sustaining circuit of TNFR1-mediated apoptosis (29). This is exacerbated by the synergistic effect of AE on endothelial function and shear stress-induced nitric oxide release, and redox balance modulation by CrPic that safeguards the cardiomyocyte cell death (28, 30). Restoration of VEGF/VEGFA, which counteracts diabetes-associated angiogenesis is suggested to result from hemodynamic force of activated eNOS-dependent VEGF transcription and enhanced insulin receptor signaling by CrPic; thereby, it can provide greater endothelial cell survival and capillary proliferation (31). The novel observation of CD147 upregulation in this elderly diabetic rat model can be explained by AE as the origin of such phenomena along with CrPic mitigation of hyperglycemic glycation can prevent CD147 participation in lactate transport and preservation of metabolic flexibility (31, 32). It underscores the diabetic heart's preferential reliance on fatty acid oxidation due to MCT1's baseline expression, shifts the lactate efflux and depicts an exercise-induced increase in MCT1 suggesting some degree of metabolic adjustment (33).

These integrated mechanisms are reveal how AE and CrPic together have a dual impact to mitigate diabetes related cardiac injury in elderly patients. In addition, the modulation of biological markers of TNFR1, VEGF/VEGFA and CD147 as previously mentioned suggests the possibility of more precise therapeutic regimens focused on elderly diabetics with complex and intermingling metabolic-inflammatory comorbidities (34). AE+CrPic could also enhance therapeutic angiogenesis; suppress inflammatory processes and improve lactate shuttling with evolving strategies to mitigate the effect of accelerated aging on cardiac function. It focuses on multitargeted intervention approaches to treat the added complexities of age-related cardiac genes reduction (34). This not only adds to the current arsenal of drugs such as Sodium-glucose cotransporter-2 inhibitors (SGLT2s), but also has the potential to fill the existing management voids by intervening at the primary molecular level through mechanisms that facilitate cardiac injury upstream pathways unaddressed by glucose-limited therapies (34, 35).

Although these findings are novel contributions, some gaps must be noted. The use of an STZ-induced rodent model for preclinical testing is missing the chronicity and the comorbidities like hypertension which are essential to human diabetic cardiomyopathy, which restricts its clinical translation (36). As for MCT1 mRNA trends, they remain unexplored for proteomic validation, which is needed to confirm functional protein expression and its associated metabolism (36). Although the 10-week intervention period is likely to capture some molecular alterations, it may underestimate chronic adaptations, especially in older models with reduced

adaptability (36). The omission of female rats is also a limitation because of generalizability, as sex-specific hormonal and metabolic determinants may impact the therapeutic efficacy (37). Applying the elderly with diabetes as a target population, functional cardiac assessment (e.g. echocardiography) would provide important insights into the relationship between molecular modifications and clinical impacts (38). It remains to be noticed if AE+CrPic administration is longer that can increase the metabolic flexibility, or if it hastens the decline of age-related cardiac functions (38). From a mechanistic standpoint, combinations of SGLT2 inhibitors may enhance cardioprotective outcomes (39). Epigenetic studies have focused on methylation of TNFR1/VEGF/CD147 to elucidate the regulatory frameworks of those genes. Addressing age-related impairments in tissue repair through the addition of senolytic agents within this framework can paradoxically rejuvenate the diabetic myocardium (40). These steps will refine our understanding of multimodal interventions in the complex interplay of aging and diabetes.

Conclusion

This study revealed that AE in conjunction with CrPic can affect an improvement in diabetic cardiomyopathy in elderly rats via TNFR1 inflammatory inhibition, restoration of the VEGF/VEGFA angiogenesis, and an increase in CD147 metabolic flexibility. These findings can support the use of multi-faceted, non-invasive approaches in addition to current treatments as clinical trials to confirm the practical application of these theories to older patients.

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Authors' Contribution

The conceptualization, methodology design, data collection, experimental procedures, data analysis, and original draft writing were all performed by the first author (SB). Final editing and revision of the manuscript were carried out in consultation with the academic supervisor (HM) and advisor (SR).

Conflict of Interest

None declared.

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