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Investigating the Relationship between Age-Related Cardiac Hypertrophy, Skeletal Muscle Strength, and the FNDC5 Protein as a Potential Regulator

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Abstract

Background: Aging-induced cardiac hypertrophy and reduced skeletal muscle strength contribute to increased disease risk and life burden in the elderly. FNDC5 acts as a protective muscle factor in both cardiac and skeletal muscle. This study aims to examine the relationship between cardiac FNDC5 and aging-related cardiac hypertrophy and decreased skeletal muscle strength. **Methods:** Male young C57BL/6 mice (5 months old, n = 6) and aged mice (21 months old, n = 6) were utilized in the study and housed in a specific pathogen-free (SPF) environment. Prior to the experiment, grip strength tests were performed on the mice, and heart tissues were collected for morphological analysis, including the assessment of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) and fibronectin type III-containing structural domain 5 (FNDC5) protein levels. Furthermore, myosin heavy chain II (MyHC II), skeletal muscle-specific transcription factor (MyoD), muscle RING-finger protein-1 (MuRF1), and FNDC5 levels were evaluated in the quadriceps muscle. The correlations between heart weight and FNDC5 expression levels, as well as skeletal muscle indices in the mice, were subsequently analyzed. **Result:** Aging leads to cardiac hypertrophy and reduced expression of PGC-1α and FNDC5 proteins. Concurrently, there is a decline in the strength of skeletal muscle, along with decreased expression of MyHC II and increased expression of MURF1 and MyoD. Correlation analysis demonstrated strong

positive associations between myocardial FNDC5 protein levels and limb grip strength, as well as MyHC II, and strong negative associations with MyoD and MuRF1. **Conclusion:** There may be a significant association between aging-induced cardiac hypertrophy and decreased skeletal muscle strength, with FNDC5 potentially playing a crucial role as a regulatory molecule facilitating communication between the heart and skeletal muscle.

Keywords

Aging, Heart Hypertrophy, Skeletal Muscle, FNDC5

1. Introduction

Cardiovascular disease (CVD) and skeletal muscle degeneration are emerging as significant global health issues due to the aging population [1] [2]. Research indicates that the aging heart undergoes various changes, including myocardial hypertrophy, abnormal electrical signals, systolic dysfunction, microcirculatory dysfunction, and heart failure [3]. Mechanisms such as oxidative stress, mitochondrial dysfunction, autophagy, and telomere damage play crucial roles in cardiac aging [4] [5]. Additionally, declining skeletal muscle function poses a significant health challenge for older individuals, resulting in decreased limb movement and overall quality of life [6]. There is a strong correlation between skeletal muscle and cardiovascular health. For example, according to clinical research, between 34% and 66% of heart failure patients have deteriorating muscular function [7]. Individuals with peripheral artery disease exhibit early age-related physiological changes, including inflammation, oxidative stress, mitochondrial dysfunction, and ischemia-reperfusion injury, which affect muscle performance [8]. Further research is necessary to fully understand the mechanisms underlying aging cardiac and skeletal muscle interaction.

Fibronectin type III-containing structural domain 5 (FNDC5) is a transmembrane protein primarily identified in muscle tissue [9]. FNDC5 serves as a transcriptional coactivator of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) [10]. Current studies demonstrate the role of FNDC5 in various tissues and underscore its importance in the field of health and disease. These changes significantly increase the risk of cardiovascular disease, leading to reduced cardiac function and stress tolerance. The expression of FNDC5/irisin is closely associated with the activation of the neuromodulatory pathway in the hippocampus, which is integral to memory and learning processes. In the mice model of Alzheimer's disease, FNDC5/irisin peripheral excessive expression has proven to significantly enhance the memory function, and it plays a key role in enhancing synapses and cognitive capabilities [11]. Furthermore, FNDC5/irisin is important in promoting bone health; its excessive expression is linked to enhanced bone cell function and bone formation, which can effectively mitigate the adverse effects associated with elevated glucose levels [12]. FNDC5/irisin also exhibits anti-

inflammatory properties, particularly in relation to the NLRP3 inflammasome, which helps suppress age-related cardiac dysfunction. This protective effect is mediated through the activation of AMP-activated protein kinase alpha (AMPKα), which may also aid in delaying the onset of dysfunction associated with aging [13]. Furthermore, administration of irisin has been demonstrated to attenuate the progression of conditions such as cardiac hypertrophy, heart failure, and myocardial infarction, suggesting potential protective effects on cardiovascular health [14]. Consequently, FNDC5/irisin has emerged as a promising therapeutic target for a range of diseases, including hypertension, atherosclerosis, and diabetes. In summary, while FNDC5/Irisin holds significant potential across various treatment areas, its precise mechanisms and efficacy require further elucidation. The complexity of interactions within different tissues and under varying conditions underscores the necessity for a comprehensive understanding of its pathways, which is vital for the advancement of targeted therapies. Research has shown that the overexpression of FNDC5 enhances cardiac function and skeletal muscle energy in aging animal models, whereas diminished levels of FNDC5 protein have been associated with age-related degenerative changes in both the heart and skeletal muscle. Consequently, investigating the relationship between aging cardiac and skeletal muscle is essential for alleviating the detrimental effects of aging.

The energy metabolism of cardiac and skeletal muscle exhibits significant similarities. Consequently, the potential mechanisms facilitating communication between cardiac and skeletal muscle during physiological or pathological processes remain uncertain. Our study examined the expression of FNDC5 in these tissues and explored potential correlations to uncover any connections between the aging heart and skeletal muscle.

2. Materials and Methods

2.1. Experimental Protocols

2.1.1. Animals

Male young C57BL/6 mice (3 months old, n = 6) and aged mice (19 months old, n = 6) were purchased from Tianqin Biotechnology Company (Changsha, China). All mice were housed in an SPF environment. Under the conditions of 24˚C ± 1˚C and relative humidity of 50% - 60%, 3 to 4 mice were raised in each cage, with a light/dark cycle of 12:12 hours, and fed with standard feed and water. Muscle strength was tested 12 hours before execution after eight weeks of regular feeding. Approval for all animal procedures was granted by the Institutional Animal Care and Use Committee at Youjiang Medical University for Nationalities (Approval number: 2022100801).

2.1.2. Grip Strength

Grip strength was performed as described previously [15]. Utilizing a commercial Grip Strength Meter, the maximum muscular force was determined (Sansbio, China). In this experiment, when the forelimbs of the mice grasped the lever of the grip strength meter, the experimenter horizontally pulled back the tail of the

mice until their forelimbs were detached from the lever, at which point the maximum value was recorded as the forelimb grip strength. Following the assessment of forelimb grip strength, all mice were permitted to rest for 15 minutes. Subsequently, when the mice grasped the grid, the experimenter again pulled the mice's tail horizontally backward until the limbs were detached from the grid, recording the maximum value as the limb grip strength. The highest value obtained was noted as the final grip strength. This procedure was repeated three times for each mouse, and the average value was calculated to determine the final grip strength.

2.1.3. Immunofluorescence

Formalin-fixed paraffin-embedded cardiac slices were stained after mouse cardiac tissue was fixed in 10% formalin in PBS. Wheat germ agglutinin (L4895, Sigma) was applied to tissue slices and left overnight at 4˚C to stain them. Goat anti-mouse secondary antibody (Alexa Fluor® 488 conjugate, Thermo Fisher) was applied to the signal and allowed to sit at room temperature for one hour. Using a Leica laser scanning confocal microscope, pictures were captured. Using Image J software (NIH Image), three randomly chosen fields of vision from each sample were quantitatively assessed.

2.1.4. Protein Expression Analysis

PGC1α, NT-PGC1α, and FNDC5 levels were assessed in myocardial tissue, while MyHC II, MyoD, MuRF1, and FNDC5 proteins were measured in quadriceps femoris muscle. Samples were ground in PMSF (Solarbio, China) with a high dose of RIPA buffer (ABExBIO, USA) and protein phosphatase inhibitors (Solarbio, China). Protein concentration was determined using a bicinchoninic acid (Beyotime, China) assay. Proteins were separated using 10% SDS-PAGE and moved onto a PVDF membrane (Innobilon, USA). The membranes were blocked over 2 hours by introducing either 5% skimmed milk or 5% BSA into a three-phase buffered saline solution (pH 7.4) with 0.1% Tween 20. Then incubated with NT-PGC-1α/PGC-1α (clone D-5, 1:1000 dilution, ThermoFisher), FNDC5 (1:1000 dilution, ThermoFisher), MyHC II (clone MY-32, 1:1000 dilution, Sigma), MyoD (clone 5.8A, 1:1000 dilution, ThermoFisher), MuRF1 (clone C-11, 1:1000 dilution, Santa Cruz), primary antibodies at 4 ˚C overnight, then incubated with horseradish peroxidase-conjugated secondary antibody for 1 hour at room temperature and developed with ECL blotting substrate (ABclonal, China). All antibodies were diluted using Antibody Diluent (Beyotime, Chian). Western blot images were analyzed using Image J software (public software). Protein levels were normalized to the internal control β-actin, α-actin or GAPDH.

2.2. Statistical Analysis

Mean ± SEM data from every trial were presented and analyzed with GraphPad Prism (GraphPad Software, Inc., USA). Differences among groups were evaluated using one-way ANOVA and t-test. Any p-value below 0.05 ($p < 0.05$) was deemed statistically significant.

3. Results

3.1. Cardiac Hypertrophy in Elderly Mice Closely Linked to Reduced Muscle Strength

To investigate the relationship between cardiac alterations and changes in muscle strength in aging mice, we examined body weight, heart weight, and muscle strength. Our results showed that the old mice had a heavier body weight as well as heart weight when compared to the young mice (Figure 1A & Figure 1B). In terms of grip strength, we observed a significant reduction in the relative limb grip index, relative forelimb grasp index, and suspension time index in old mice compared to the young mice (Figures 1C-E). Additionally, we conducted correlation analyses between heart weight and the relative limb grip index, relative forelimb grasp index, and suspension time index. We found that heart weight was significantly and negatively correlated with relative forelimb grasp index ($p = 0.0055 < 0.01$, $r = -0.6413$, Figure 1F) and relative limb grip index ($p = 0.0288 < 0.05$, $r = -0.5294$, Figure 1G). However, we observed that heart weight was significantly and negatively correlated with the suspension time index ($p = 0.0767$, $r = -0.4706$,

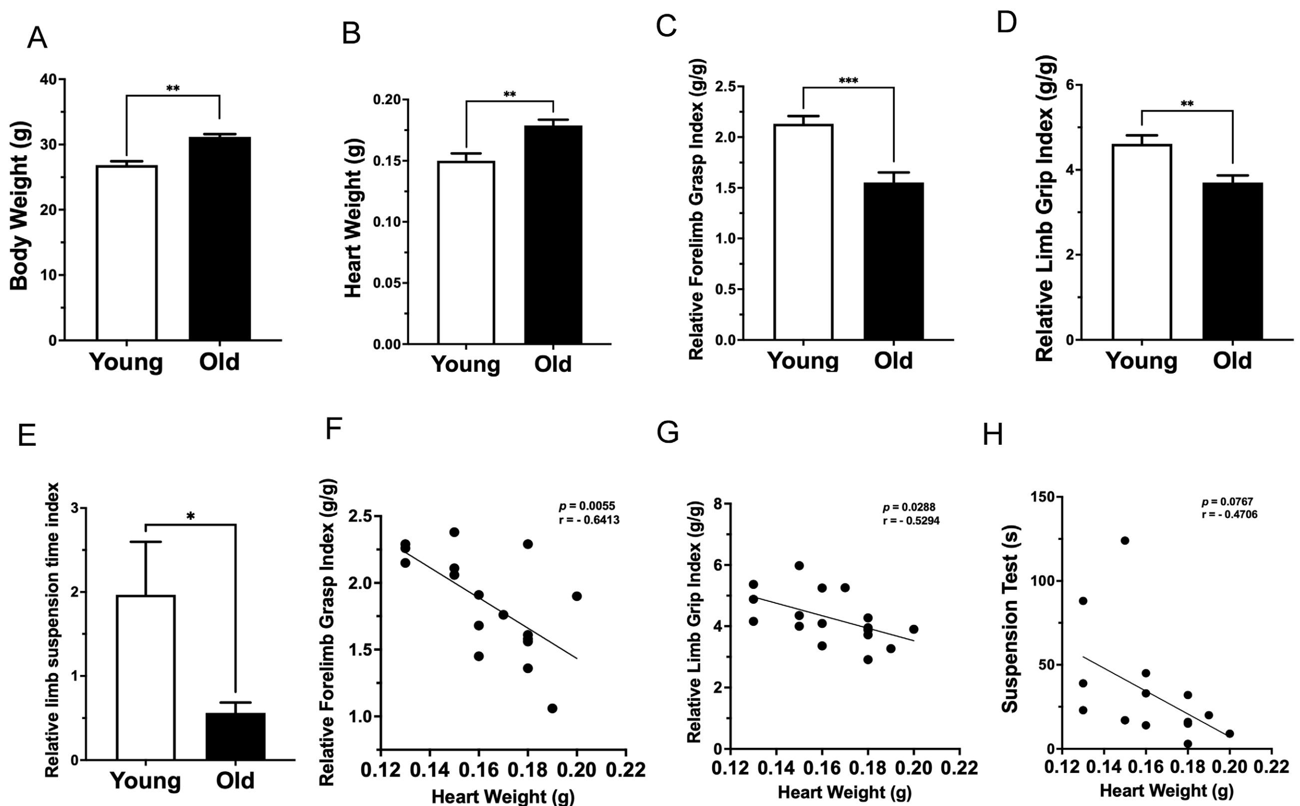

Figure 1. Cardiac hypertrophy in elderly mice is closely linked to reduced muscle strength. A & B. Quantitative data of body and heart weight. Data are presented as mean ± SEM. **$p < 0.01$ vs Young group. C & D. Quantitative data of relative limb grip index and relative forelimb grasp index. Data are presented as mean ± SEM. **$p < 0.01$, ***$p < 0.001$ vs Young group. E. Quantitative data of relative limb suspension time index. Data are presented as mean ± SEM. *$p < 0.05$ vs Young group. F. Correlation analysis of heart weight with relative forelimb grasp index ($p = 0.0055 < 0.01$, $r = -0.6413$). G. Correlation analysis of heart weight with relative limb grip index ($p = 0.0288 < 0.05$, $r = -0.5294$). H. Correlation analysis of heart weight with suspension time ($p = 0.0767$, $r = -0.4706$).

Figure 1H). These data illustrate hypertrophic changes in the hearts of old mice and a decrease in muscle strength and tolerance, with some negative correlation between the two.

3.2. Increased Cross-Section of Cardiomyocytes in Old Mice

Increased cardiomyocyte cross-section is a significant marker of cardiac hypertrophy; therefore, we conducted WGA immunofluorescence on cross-sectional sections of the heart for observation. Our results indicated that older mice exhibit a lower number of cardiomyocytes along with a larger cross-sectional area of these cells compared to younger mice (Figure 2A & Figure 2B). These data suggest that cardiomyocytes in mice increase in size with age.

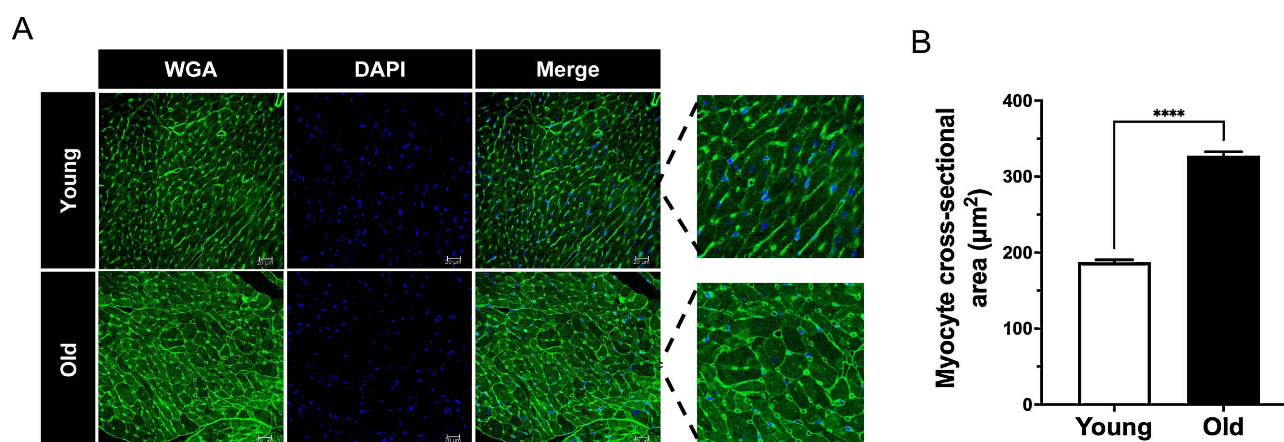

Figure 2. Increased cross-section of cardiomyocytes in old mice. A. WGA staining was used to show the cross-sectional area of cardiomyocytes and DAPI was used to show the nuclei. B. Quantitative analysis of myocyte cross-sectional area (n = 6/group). Data are presented as mean ± SEM. ****$p < 0.0001$ vs. Young.

3.3. Decreased Protein Expression of Myocardial PGC-1α/FNDC5 Pathway in Old Mice

PGC-1α/FNDC5 is intricately linked to energy metabolism in the heart. Therefore, we investigated the expression levels of PGC-1α/FNDC5 pathway proteins in the myocardium. The results indicate a reduction in PGC-1α expression in the myocardium of old mice compared to young mice (Figure 3A & Figure 3B). NT-PGC-1α also plays a very important role in energy metabolism as the terminally sheared form of PGC-1α. Similarly, we observed a significant decrease in NT-PGC-1α in the myocardium of old mice compared with young mice (Figure 3A, C). In addition, FNDC5 protein expression levels were significantly decreased in old mice compared with young mice (Figure 3A, Figure 3D). These data illustrate that PGC-1α/FNDC5 pathway protein expression declines with age and may affect cardiac energy metabolism.

3.4. Aging Affects Myogenic and Atrophic Proteins of Skeletal Muscle

We next examined the expression levels of myogenesis in myasthenia gravis-related

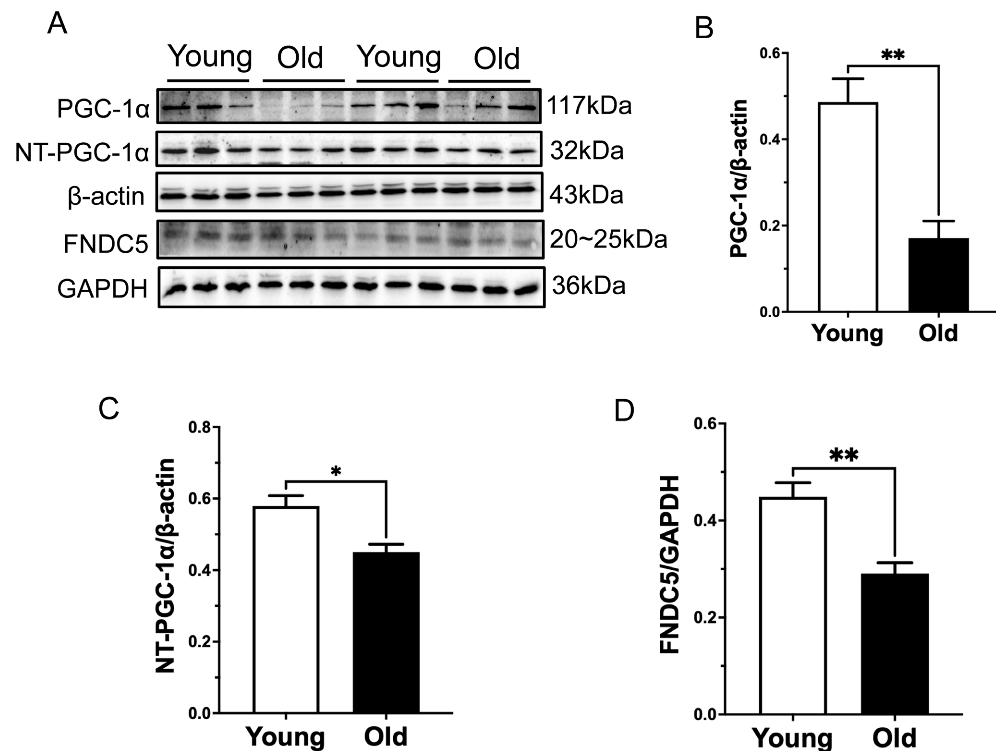

Figure 3. Decreased protein expression of PGC-1α/FNDC5 pathway in myocardial old mice. A. Western blot detecting PGC-1α, NT-PGC-1α and FNDC5 protein levels. B. Quantitative data of A showed the ratio of PGC-1α protein expression protein level. Data are presented as mean ± SEM. $^{**}p < 0.01$ vs. Young group. C. Quantitative data of A showed the ratio of NT-PGC-1α protein expression protein level. Data are presented as mean ± SEM. $^{*}p < 0.05$ vs. Young group. D. Quantitative data of A showed the ratio of FNDC5 protein expression protein level. Data are presented as mean ± SEM. $^{**}p < 0.01$ vs. Young group.

proteins in the quadriceps muscle. Our results showed that in the quadriceps muscle of old mice, the expression of the myogenesis-related protein MyHC II was significantly decreased compared to young mice (Figure 4A, Figure 4B), but interestingly, the expression of MyoD protein in the quadriceps muscle of old mice was significantly increased compared to young mice(Figure 4A, Figure 4C). Additionally, we observed that the expression levels of MuRF1 were higher in older mice than in younger mice. Furthermore, FNDC5 protein expression was found to be increased in the quadriceps muscle of older mice compared with younger mice (Figure 4A, Figure 4D).

3.5. Myocardial FNDC5 Expression Correlates Significantly with Muscle-Related Indices

We used myocardial FNDC5 protein expression levels to correlate with relative limb grip index, MyHC II, MyoD, and MuRF1, respectively. The results showed that myocardial FNDC5 protein expression showed a significant positive correlation with relative limb grip index ($p = 0.0438 < 0.05$, $r = 0.7024$, Figure 5A), a significant positive correlation with MyHC II protein ($p = 0.0113 < 0.05$, $r = 8679$, Figure 5B), and a significant negative correlation with MyOD protein expression

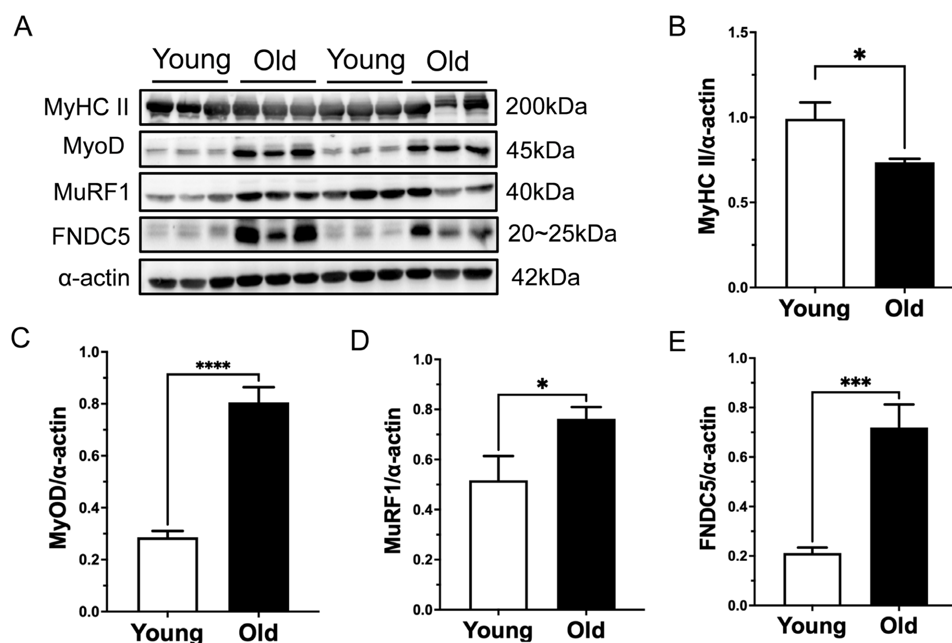

Figure 4. Aging affects myogenic and atrophic proteins of skeletal muscle. A. Western blot detecting MyHC II, MyoD, MuRF1 and FNDC5 protein levels. B. Quantitative data of A showed the ratio of MyHC II protein expression protein level. Data are presented as mean ± SEM. *p < 0.05 vs. Young group. C. Quantitative data of A showed the ratio of MyoD protein expression protein level. Data are presented as mean ± SEM. ****p < 0.0001 vs. Young group. D. Quantitative data of A showed the ratio of MuRF1 protein expression protein level. Data are presented as mean ± SEM. *p < 0.05 vs. Young group. E. Quantitative data of A showed the ratio of FNDC5 protein expression protein level. Data are presented as mean ± SEM. ***p < 0.001 vs. Young group.

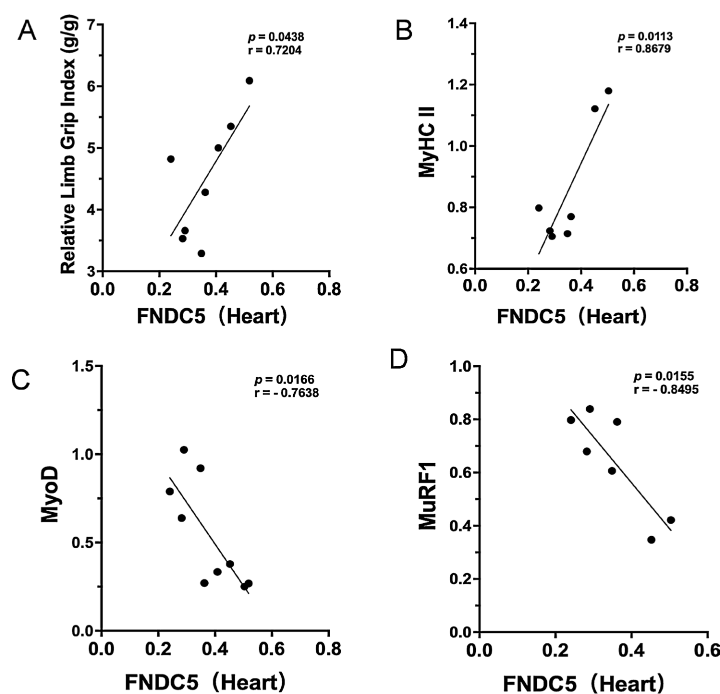

Figure 5. Myocardial FNDC5 expression correlates significantly with muscle-related indices. A. Correlation analysis of myocardial FNDC5 protein expression with relative limb grip index (p = 0.00438 < 0.05, r = 0.7204). B. Correlation analysis of myocardial FNDC5 protein expression with MyHC II (p = 0.0113 < 0.05, r = −0.8679). C. Correlation analysis of myocardial FNDC5 protein expression with MyoD (p = 0.0166 < 0.05, r = −0.7638). D. Correlation analysis of myocardial FNDC5 protein expression with MuRF1 (p = 0.0155 < 0.05, r = −0.8495).

($p = 0.0166 < 0.05$, $r = -0.7638$, Figure 5C), and a significant negative correlation with MuRF1 ($p = 0.0155 < 0.05$, $r = -0.8495$, Figure 5D).

4. Discussion

This study investigated potential connections between cardiac and skeletal muscle in elderly mice. The results revealed that older mice exhibited heart enlargement, decreased levels of PGC-1α/FNDC5 pathway proteins, reduced skeletal muscle strength, and changes in the expression of muscle-associated factor proteins. Additionally, there was a significant correlation between FNDC5 protein expression in cardiac muscle and measures related to skeletal muscle.

Aging has been shown to impact both the heart and skeletal muscle, leading to changes in structure and function. Research indicates that aging can lead to increased peripheral vascular resistance, resulting in higher blood pressure, and the heart may undergo hypertrophy due to prolonged high loads [16]. Ventricular hypertrophy associated with aging is characterized by cardiomyocyte hypertrophy and myocardial fibrosis rather than cardiomyocyte proliferation [17]. Our findings align with previous studies, as we observed cardiac hypertrophy and larger cardiomyocyte cross-sections in old mice. Furthermore, age-related changes in skeletal muscle function and structure are often marked by a decline in skeletal muscle strength [18]. We examined muscle strength in older mice and found that grip strength and muscular endurance, however, were significantly reduced. Additionally, skeletal muscle degeneration is closely linked to CVD. Individuals with heart failure may experience compromised myocardial function, leading to inadequate blood supply to the muscles and subsequent declines in muscular function [19]. Chronic inflammation can further exacerbate muscle deterioration by disrupting protein function and signaling pathways [20]. Inflammatory factors can also impact the myocardium, contributing to fibrosis and apoptosis, ultimately affecting cardiac structure and function [21].

The skeletal muscle-specific transcription factor MyoD controls the expression of myosin heavy chain (MyHC) isoforms, including MyHC I, MyHC IIa, MyHC IIb, and MyHC IIx genes, which are associated with impaired muscle regeneration and repair in aging [22]. MyHC is crucial for muscle cell development and the formation of different muscle fiber types. Recent studies suggest that changes in type II muscle fibers are more pronounced than in type I fibers during the aging process [23]. MyoD governs multiple factors involved in skeletal muscle formation and repair [24]. MuRF, an E3 ligase, plays a role in regulating muscle protein degradation. Aging skeletal muscle experiences increased protein breakdown due to declining muscle function, leading to decreased MyoD expression and increased MuRF1 expression [25] [26]. Consistent with prior findings, aging skeletal muscle exhibits reduced MYHC II expression alongside increased MURF1 expression. Interestingly, MyoD protein expression is elevated, potentially linked to the hypoxic environment in aged skeletal muscle. The reduction in capillary density within skeletal muscle impedes efficient blood flow and nutrient delivery [27]. Diminished blood supply is correlated with endothelial dysfunction, which hampers blood vessel dilation due to age-

related oxidative stress and inflammation, leading to decreased oxygen and nutrient diffusion to muscle fibers [28]. Recent studies have demonstrated that under hypoxic conditions, hypoxia-inducible factor-α promotes early differentiation but does not influence myoblast proliferation. Furthermore, hypoxia enhances the late differentiation of myoblasts independently of HIF-α [29]. Additional research is necessary to clarify the specific mechanisms involved.

PGC-1α and its splice variant NT-PGC-1α are crucial regulators of oxidative metabolism, playing significant roles in mitochondrial biogenesis and fatty acid oxidation [30]. FNDC5, a muscle-derived factor regulated by PGC-1α, is currently recognized for its involvement in the regulation of mitochondrial biogenesis and its contribution to enhancing mitochondrial quality. A central hypothesis regarding FNDC5's role in metabolism posits that the extracellular domain of FNDC5 is cleaved to produce soluble irisin, which then circulates and targets various tissues. Irisin has demonstrated therapeutic effects across a range of cardiovascular diseases, alleviating diabetic cardiomyopathy by activating αV/β5-AKT integrin signaling and reducing oxidative/nitrosative stress [31]. Additionally, it prevents vascular calcification by promoting autophagy and inhibiting pyroptosis in vascular smooth muscle cells (VSMCs) via NLRP3 [32]. Furthermore, studies indicate that the injection of irisin into aging C57 mice can enhance FNDC5 expression and improve age-related cardiac dysfunction through the activation of AMPKα [13]. We have observed the decline in the expression of FNDC5 in aging mice, which may be attributed to the important role played by FNDC5 in mitochondrial integrity. It participates in mitochondrial organisms and regulation through PGC-1α and other channels. The reduction of FNDC5 in the aging heart may damage the mitochondrial function, resulting in a decrease in ATP and the level of active oxygen [33]. In skeletal muscle, FNDC5/Irisin exerts a protective effect against age-related skeletal muscle diseases. Numerous studies have confirmed that exercise-induced expression of FNDC5/Irisin enhances the functionality of aging skeletal muscle and promotes the browning of white fat [34]. Conversely, FNDC5 expression increased in the quadriceps muscle of aged mice, which may be attributed to differences in muscle fiber type. Research indicates that type I slow-twitch fibers generally become more stable with age, whereas type II fast-twitch fibers tend to degenerate over time [35]. Slow-twitch muscle fibers are abundant in mitochondria and rely on oxidative phosphorylation for ATP production [36] [37]. This relative shift in fiber type is often associated with a decline in motor function and muscle strength. As we age, slow-twitch muscle fibers remain relatively stable while fast-twitch muscle fibers diminish. This transition may represent an adaptive response to compensate for the loss of fast-twitch muscle fibers [38]. Additionally, slow-twitch muscle fibers primarily depend on aerobic glycolysis for metabolism, and FNDC5 is involved in this process, potentially leading to an increase in FNDC5 expression [39]. Furthermore, irisin secretion is influenced by N-glycosylation. Impaired irisin secretion due to the blockage of N-glycosylation may be linked to the instability of FNDC5 and defective signal peptide cleavage [40].

The disintegration of integrin metalloproteinase (ADAM-10) also plays a role in the cleavage of FNDC5 [41], and these factors may disrupt the normal cleavage of FNDC5, resulting in its accumulation in the quadriceps muscle. We speculate that the normal cracking of FNDC5 is hindered in the quadriceps of aging mouse stocks, reducing the generation of Irisin in the cycle, affecting the muscle fiber distribution and function of the muscle, and ultimately led to the reduction of muscle strength. However, more evidence is required in future research.

Cardiac muscle and skeletal muscle are two vital muscle tissues in the body that play important roles in physiological functions and are closely intertwined in pathological conditions [42]-[44]. Despite the current lack of research on the specific connection between the heart and skeletal muscle, this study aimed to investigate whether FNDC5, a muscle factor, contributes to a potential "crosstalk" between these two types of muscle. While our findings revealed varying trends in FNDC5 protein expression in old mice's cardiac and skeletal muscle, these differences could be attributed to distinct functional and metabolic mechanisms inherent to each type of muscle [45] [46]. Nonetheless, we identified strong correlations between cardiac FNDC5 protein expression and parameters such as relative limb grip strength index, Myhc II, MyoD, and MuRF1 protein expression. This observation suggests a potential relationship between cardiac FNDC5 expression and metabolic processes in skeletal muscle, although further research is needed to elucidate the underlying mechanism.

5. Conclusion

FNDC5 may be associated with aging-induced cardiac hypertrophy and decreased skeletal muscle strength, potentially facilitating communication between the heart and skeletal muscle.

6. Limitation

In this study, we realize that there are still some aspects worth further improvement. First of all, although we have preliminarily discussed the role of FNDC5 in aging myocardial and skeletal muscles, it has not yet made a more comprehensive assessment of myocardial function, which may affect the in-depth analysis of heart health changes to a certain extent. At present, the conclusion of FNDC5 as a signal transmission between myocardial and skeletal muscles is mainly dependent on correlation data. It still needs to be verified by further mechanism experiments. In the future, we plan to combine more cardiac functional evaluation, quantitative muscle quality analysis and mechanism verification experiments in subsequent research, in order to richer and improve the current research results.

Authors' Contributions

SL: Conceptualization, funding acquisition, and resources; TF, ZF, YL, XZ, YL, SM, JW, XF, BL and LH: Performed experiments; TF and ZF: Formal analysis; TF: Writing—original draft; SL and JW: Writing—review and editing.

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Compliance with Ethical Standard

All animal experiments were performed according to guidelines approved by the Institutional Animal Care and Use Committee of Youjiang Medical University for Nationalities (Approval number: 2022100801).

Availability of Data and Materials

The data used in this study are available from the corresponding authors on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

Cardiovascular Disease (CVD); Fibronectin Type III-Containing Structural Domain 5 (FNDC5); Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α (PGC-1α); Fibronectin Type III-Myosin Heavy Chain II (MyHC II); Skeletal Muscle-Specific Transcription Factor (MyoD); Muscle RING-Finger Protein-1 (MuRF1); A Disintegrin and Metalloproteinase 10 (ADAM-10).