THE EXERCISE INCREASE NUCLEAR FACTOR E2-RELATED FACTOR 2 (NRF2) ACTIVITY: A LITERATURE REVIEW

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Abstract: Aging is a progressive physiological change in organisms that lead to senescence. Aging is a multifactorial condition, and oxidative stress which is one of many predictors of aging plays a role in declining organs function, which results in accelerated aging. Nuclear Factor E-2 related factor 2 (NRF2) is known as antioxidants master regulator that plays a role in suppressing the damage caused by oxidative stress. NRF2 expression is influenced by many factors. This review was conducted to see the correlation between exercise and NRF2 expression to prevent aging. Sources of data obtained for this journal are through databases of scientific information sources such as Proquest, Pubmed, Mendeley, Elsevier, Google Scholar, and Google Search. We use a data collection strategy using keywords: oxidative stress, antioxidant regulators, mitohormesis, aerobic, skeletal muscle, nrf2, aging, exercise to find journals/articles to be reviewed, with a limit of 5 to 10 years of the latest articles. Exercise causes adaptive mitochondrial response (mitohormesis) which will improve mitochondria function via enhancing NRF2 activity. With increased mitochondrial function, organ damage can be prevented, and skeletal muscle performance will be improved, thus preventing the aging process. Besides, NRF2 deficiency is associated with an increase in free radicals that will affect organs and reduce the quality of life. This review summarizes the impact caused by NRF2 deficiency and exercise mechanisms in increasing NRF2 activity including the recommendation of type, duration and intensity to increase NRF2 and the best type of exercise for the elderly according to previous journals. The Limitation of this review is we used only research published last 10 years. The method limitation is a risk of bias.

Keywords: oxidative stress; antioxidant regulators; mitohormesis; aerobic; skeletal muscle

INTRODUCTION

Oxidative stress is well known as the major cause of aging. Oxidative stress is an imbalance condition between pro-oxidant and antioxidants which will cause both micro and macro damages to body components. Damages in DNA, cells, mitochondria, and impaired homeostasis of protein synthesis, result in increasing the risk of aging-related diseases.[1]

Nuclear factor erythroid 2-related factor 2 (NRF2) is a master antioxidant regulator which prevents cell senescence.[2] Several functions are obtained by NRF2 such as increasing the adaptive mechanism of mitochondria against oxidative stress (mitohormesis), glutathione synthesis, ROS and xenobiotics detoxification, heme metabolism, DNA repair, mitochondrial protection, NADPH production, and proteostasis (2). NRF2 deficiency causes mitochondrial damage, muscle atrophy, and increased fibrosis.[2–6] By increasing NRF2, oxidative stress can be prevented, and cell senescence can be inhibited.

Several kinds of literature showed NRF2 improvement through exercise. Exercise temporarily increases free radicals to induce adaptive responses to endogenous antioxidants that maintain a healthy body.[3,7,8] During exercise, NRF2 increases in peripheral blood circulation.[1] To obtain a better understanding of NRF-mechanisms and their relationship with aging and exercise, the authors composed this literature review.

METHOD

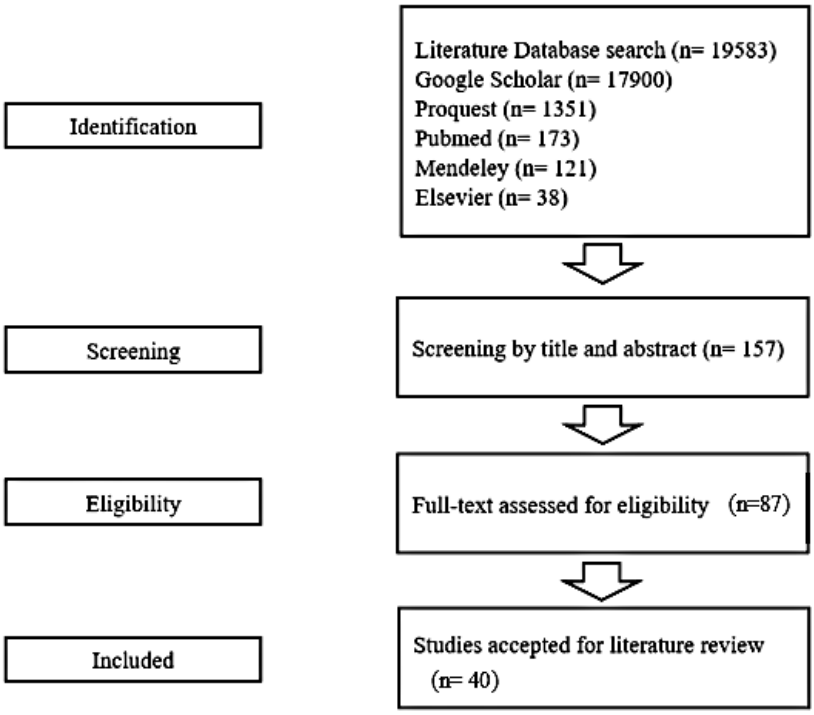
This paper is a literature review journal. Sources of data obtained for this journal are through databases of scientific information sources such as Proquest, Pubmed, Mendeley, Elsevier, Google Scholar, and Google Search. We use a data collection strategy using keywords: oxidative stress, antioxidant regulators, mitohormesis, aerobic, skeletal muscle, nrf2, aging, exercise to find journals/articles to be reviewed, with a limit of 5 to 10 years of the latest articles. Data collection

includes inclusion and exclusion criteria, selection of articles, and an assessment of the quality of articles relevant to the topic.

Inclusion criteria: authors enter reputable journals or articles with a range of 2012 to 2022 related to nrf2, exercise, and aging. The author uses a minimum of 40 journals or articles in this literature review. Exclusion criteria: the authors decided not to include journals or articles in quartiles 3 and 4 in the literature review.

The approach we use in analyzing the data is by describing the existing data and finding a correlation between the data.

Figure 1. Diagram of Literature Review Process of The Study Selection



RESULTS

Table 1. Deficiency of NRF2 and its impact on Aging and Health

Authors	Purpose	Method	Results
Yu Kitaoka, Yuki Tamura, Kenya Takahashi, Kohei Takeda, Tohru Takemasa, Hideo Hatta (2019).[9]	To determine the effect of decreased NRF2 on mitochondrial dysfunction and muscle atrophy in skeletal muscle.	An experimental study with subjects aged - mice (22 months) with decreased NRF2 (knockout mouse), young mice (4 months), and age-matched/ WT mice (aged 22 months) which were given euthanasia and examined muscle mass, sarcopenia index, expression antioxidant	It was found that the total muscle mass of knockout mice was lower than young and WT mice. There was a decrease in NRF2 expression in knockout (KO) mouse muscle cells, but mRNA expression was not affected. On examination of mitochondrial function, it was found

		genes, oxidative stress, and mitochondrial function.	that oxidative stress increased in the mitochondrial fraction examined from knockout mice, mitochondrial respiration decreased with age, while higher ROS production was found in knockout rats. .
Seungha Hyeon, Hyojung Lee, Yoohee Yang, Woojin Jeong (2013). [10]	Investigate the effect of NRF2 deficiency in differentiation osteoclasts (OC), resorption bone, and transduction RANKL - induced signaling using derived OC precursors from NRF2 *knockout mice*.	Male C57BL/6 J mice were divided into 2 groups, NRF2 knockout mice (NRF2 -/-) and NRF2 +/+ mice as wild-type controls. Bone marrow-derived macrophages (BMM) were prepared as OC cell precursors from the femur and tibia of 4 to 8 weeks old male mice.	NRF2 negatively regulates RANKL-induced OC differentiation, inhibits actin ring formation and bone resorption, and controls OC differentiation via ROS. NRF2 deficiency causes oxidative stress which may be due to defects in the production of antioxidant enzymes and GSH (glutathione). There is increased MAPK (mitogen-activated protein kinase) activation in RANKL-induced NRF2 deficiency.
Fearo Hayashi, Takashi Kudo, Ryo Fujita, Shinichiro Fujita, Hirona Tsubouchi, Sayaka Fuseya, Riku Suzuki, Michito Hamada, Risa Okada, Masafumi Muratani, Dai Shiba, Takafumi Suzuki, Eiji Warabi, Masayuki Yamamoto, Satoru Takahashi (2021).[11]	To find out the role of NRF2 deficiency on fiber type transition in soleus muscle during flight.	Twelve mice were housed for 31 days. Histological analysis and immunohistochemistry of soleus muscle were frozen with liquid nitrogen and cut using a cryostat.	NRF2 deficiency increases the metabolic expression of glycolysis. NRF2 deficiency enhances the transition from slow fibers of oxidative metabolism to fast fibers of glycolysis metabolism in soleus muscle during microgravity conditions.

Table 2. Exercise Induces NRF2 Expression

Authors	Purpose	Methods	Results
Linjia Wang, Simin Yang, Lu Yan, Hao Wei, Jianxiong Wang, Siwang Yu, Ah-Ng Tony Kong, Ying Zhang	To investigate the hypoxia precondition (HP) effect on NRF2 activity and exercise capacity	Male rats NRF2 -/- (knock-out) dan NRF2 +/+ (wild type) were divided in 4 groups: WT-no HP (WT without	HP significantly increased exercise capacity and protein HIF-1 level after exercise in the WT group but

(2019).[12]		given Hp preconditioning), WT-HP (WT with HP preconditioning), KO-no HP (KO without HP preconditioning), and KO-HP (KO with HP preconditioning), HP (hypoxia precondition) group was given hypoxia exposure for 48 hours (11,2% oxygen) before undergo treadmill training.	showed no effect in the KO group. HP significantly increased NRF2 expression after exercise in the WT-HP group compared to the WT-no HP group. Exercise can increase the level of HIF-1 and NRF2 expression to reduce stress oxidative.
Yunyi Zou, Zhanglin Chen, Chenchen Sun, Dong Yang, Zuoqiong Zhou, Xiyang Peng, Lan Zheng and Changfa Tang (2021).[13]	To investigate the role of exercise in liver function of high-fat diet-fed zebrafish.	Zebrafish are divided into 3 groups: normal diet (ND), high-fat diet (HFD), and high-fed diet + exercise/swimming (HEX). NRF2 and liver function were analyzed after the trial	Swimming successfully protects the liver of the zebrafish from oxidative stress. It is found HEX group showed lower ROS levels than the HFD group. In addition, it is reported the P-AKT and NRF2 expression is lower in the HFD group compared to another group, SUGGESTING that swimming can suppress the degradation of p-AKT and NRF2. Antioxidant genes such as NRF2ho-1, nqo1, and CAT is significantly lower in the HFD group than in the HEX group.
Renata alves Camila Liyoko Suehiro, Flavia Garcia de Oliveira, Eliete Dalla Corte Frantz Renata, Frauches de Medeiros Rodolfo Paula Vieira, Milton de Arruda Martins, Chin Jia Lin, Antonio Claudio Lucas da Nobrega, Alessandra Choqueta de Toledo-Arruda (2019).[14]	To investigate the exercise's impact on modulation of NRF2/KEAP1 and cardiac function in chronic fructose consumption models	C57BL/6 41 mice were divided into groups; Fructose group, Exercise (treadmill exercise at moderate intensity) group, and Fructose + Exercise groups, and the assessment was analyzed after 12 weeks of trial	Left ventricle hypertrophy was found in the fructose group. The fructose group also showed a higher level of cholesterol and triglyceride but lower in fructose+exercise groups suggesting that exercise can reduce cardiac hypertrophy and serum cholesterol. The cardiac NRF2/Keap1mRNA and protein expression ratio also decreased in the Fructose group, but exercise improve these proteins expression

DISCUSSION

a. NRF2 as master of the antioxidant regulator and the Impact of Its deficiency

NRF2 is the main regulator of many antioxidant genes.[2] Besides, NRF2 plays a role as a regulator of muscle mass.[5]

In homeostatic conditions, NRF2 is present in the inactive phase and will naturally degrade through -mediated proteasome-ubiquitin pathway Kelch-like ECH-associated protein 1 (Keap1). Keap1 is a cysteine-rich protein that can be oxidized through interaction with ROS. As compensation, Keap1 will release NRF2 resulting in translocation of NRF2 to the core for binding with a specific DNA sequence, antioxidant response element (ARE). These mechanisms activate a group of associated genes with antioxidant and detox response.[15,16]

NRF2 maintains redox balance and stimulates antioxidant activity such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), heme oxygenase-1 (HO-1), glutathione reductase, thioredoxin reductase, ferritin, and NAD(P)H: quinone oxidoreductase 1 (NQO1).[3]

A decrease in NRF2 affected age is possibly related to enhancement ROS production in muscles, depletion of glutathione, and enhancement damage oxidative on protein, DNA, and good lipids in man nor mice.[17,18]

NRF2 deficiency causes osteoclast differentiation, bone resorption, and MAPK (mitogen-activated protein kinase) activation induced by RANKL (receptor activator of NF-κB ligand), due to higher levels of oxidative stress and aberrant production of antioxidant enzymes.[10,19] Moreover, it may cause decreases in mitochondrial function and biogenesis that are responsible for defects in antioxidant gene expression resulting in increased oxidative stress that promotes osteoclast formation and function.[3,20]

NRF2 deficiency results in the conversion of slow fibers to fast fibers through glycolysis metabolism under microgravity conditions. NRF2 deficiency is associated with muscle atrophy and decreased skeletal muscle performance.[2,5]

A study by oh using an animal model showed the deficiency of NRF2 decreases the metabolism of antioxidant enzymes and causes a greater effect on skeletal muscle of old animals than in young animals. It is found an increase in ROS and 4-HNE (hydroxynonenal) levels across the muscle of aged mice by NRF2 knock out.[19]

b. Exercise induces NRF2 activity

Exercise potentially causes oxidative stress by increasing the accumulation of Reactive Oxygen Species (ROS). During exercise, muscle consumes more energy which increases energy demand and causes a 10-20 fold increase in oxygen consumption. These mechanisms result in promote ROS generation in muscle fiber. It was reported that the main resource of ROS formation is found in active skeletal muscle and has been associated with (1) oxidant damage in tissues, (2) accelerated muscle fatigue, and, (3) biochemical signaling activation pathway.[21,22]

Although the theory of exercise-induced ROS has been accepted, several studies report the role of exercise in increasing NRF2 activity; the main regulator of antioxidant genes and protective indicator of aging, thereby suppressing ROS formation.[23] An experimental study involving young man (age 20+/- 3 years) showed an increase in mRNA NRF2, NRF1, and TFAM expression ($p<0.05$) in skeletal muscle both in acute (30 minutes of continuous cycling/END and supramaximal interval exercise/TABATA in 4 minutes) and chronic exercise (TABATA in 4 weeks). Based on theory, an increase in NRF2 expression is associated with the increases in ROS and nitric oxide production induced by exercise. Both substances play a role in the Keap1 mechanism to release NRF2, thus activating the NRF2 pathway as an antioxidant inducer. Moreover, the activation of NRF2 could be independently controlled by Keap1 through several intracellular kinase pathways in a specific condition such as stress or activity.[19]

Another study investigates whether exercise (aerobic exercise) affects specific disease improvement. C57BL/6 mice with lung damage induced by water pipe smoke (WPS) were given aerobic exercise (40 minutes/day, 5days/week). Exercised mice with lung damage had lower Nf-kB expression and higher NRF2 expression compared to non-exercised mice. It was supported by histology investigation which showed less quantity of neutrophils, lymphocytes, and plasma cells in exercised mice. This study proved the role of exercise in inflammation, oxidative stress, and DNA damage via Nf-Kb Inhibition and NRF2 activation.[20,24] Study demonstrated by Zou et al (2021) showed the improvement in NRF2 expression in the liver of zebrafish with high fat diet after exercise (swimming). Another finding by Alves et al (2019) showed the reduction in cholesterol serum and improvement in cardiac hypertrophy after exposure to exercise in mice with chronic fructose consumption. These studies showed the role of exercise in many diseases improvement by the modulation of NRF2 expression.[13,14]

Moreover, Wang et al (2016) compared the activity of NRF2 in 0, 90, 120, and 150 minutes of exercise. This study showed that 90, 120, and 150 min of exercise increased NRF2 activity as well as

downstream target transcription in skeletal muscle compared to the sedentary group with no exercise.[25]Another study by Li et al (2015) using C57BL/6J mice demonstrated nuclear NRF2/ARE binding activity in skeletal muscle. Exercise for 6 hours showed a significant increase in NRF2/ARE binding activity compared to one-hour exercise. It is also reported that Keap1, a cysteine-rich protein oxidized by interaction with ROS was increased in the cytosol after 6 h of exercise, proving that duration affects the separation of the NRF2/Keap1 bond in the cytosol. In addition, several antioxidants including Superoxide dismutase (SOD), Hemooxygenase 1 (Ho1), Glutamylcysteine ligase catalytic (GCLc), Glutamylcysteine ligase modulatory (GCLm), and Catalase (CAT) were higher in 6 hours exercise group.[26] Based on these researches, it is accepted that the longer the exercise duration the higher the NRF2 response.

According to intensity of exercise, research using a mouse model reported muscle stimulation of high (100 Hz) and low (50 Hz) frequency in a mouse's limb is effective to increase NRF2 activity. In addition, stimulation in high intensity also affects the contralateral unstimulated limb suggesting that there is a threshold for intensity to affect NRF2 activation. Moreover, the higher intensity may increase NRF2 activity by placing a greater demand on antioxidant enzymes.[27,28]

c. Recommendation of exercise to increase NRF2

Mitohormesis is recognized as a mechanism to restore redox homeostasis and protect muscle against age-related weakness. It has been declared that aerobic exercise promotes the mitohormesis mechanism via NRF2 activity. NRF2 increases mitochondrial mitohormesis, especially in producing ATP, as an energy store that impacts function, endurance, maintains muscle mass, and is an indicator of longevity.[2] Novel findings indicate that, exercise recovery in a hypoxic environment may attenuate oxidative stress responses and selected redox dependent adaptation compared to normoxic condition.[29]

Based on age, it is found that ROS accumulation is higher in the elderly compared to younger people which lead to age-related disease including cardiovascular disease and osteoporosis. Several studies showed an increase in reactive oxygen (ROS) accumulation in cardiomyocytes during the aging process.[28,30] Moderate-intensity exercise training (MET) in long term successfully stabilizes NRF signaling and increases AREs-dependent antioxidants in the myocardium of aged mice. Old mice were highly susceptible to oxidative stress following high endurance exercise stress but showed the improvement of adaptive redox homeostasis after moderate exercise training (MET; 10m/min for 45 min/day) for 6 weeks.[31,32] A 1-hour daily treadmill increases NRF2, cardiac function, femoral bone mass, trabecular microstructure, and corrects epigenetic changes.[30,33,34]

An important fact to note is that tiresome exercise increases the production of excessive ROS and carries the risk of structural damage and impaired muscle contraction resulting in muscle weakness, fatigue, and reduction of endurance and performance.[35]

In addition, intake of Sulforaphane (SFN), a phytochemical that activates NRF2, 2 weeks before to 4 days after the exhaustive exercise promoted NQO1, a target gene of NRF2, thus reducing delay onset muscle soreness (DOMS).[36] Moreover, supplementation of Q10 coenzyme can increase NFκB, IκB, NRF2, and HO-1 expression after training.[37] In contrast, administration of single high-dose Genistein showed no effect in reducing ROS generation after exercise.[38] Similar to SFN, several substances contribute to the increase of NRF2. Vitamin D, Isothiocyanates, Curcumin, Rosemary, Wasabi, and Sesamin are responsible to increase NRF2 while Cinnamaldehyde activates NRF2 and inhibits fibrosis through inhibition of TGF-β1 and IL-13.[39,40]

CONCLUSION

It's known that NRF2 is responsible for maintaining and managing many antioxidant genes and its deficiency causes mitochondrial dysfunction and skeletal muscle atrophy via the increase of oxidative stress.

Several studies showed that exercise plays an important role in increasing NRF2 response, thus reducing oxidative stress. Moreover, previous experimental studies within 10 years conclude that duration and intensity of exercise affect the activation of NRF2. Longer duration and higher intensity results in a better response of NRF2.

According to the type of exercise, we found that daily moderate 1-hour aerobic exercise is recommended in promoting mitohormesis via enhancement of NRF2 expression. Moreover, we found

that several supplements, including Sulforaphane, vitamin D, and Ubiquinone taken at the same time as exercise causes a better increase in NRF2 levels and fights oxidative stress.

Based on the results of research we found during the last 10 years, it is expected in the future, many similar studies will be conducted regarding the relationship between exercise that increases NRF2, especially in the elderly. Scientific research on exercise that induces NRF2 in the elderly has never been carried out in the territory of Indonesia, considering the increase in the number of elderly people in Indonesia.

CONFLICT OF INTEREST

The author declares no conflict of interest.

CONFESSION

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