

# Animal Studies for Effect of Exercise to Postmenopausal Women



**Denny Agustiningsih\***

*Department of Physiology, Universitas Gadjah Mada, Indonesia*

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**\*Corresponding author:** Denny Agustiningsih, Department of Physiology, Faculty of Medicine, Universitas Gadjah Mada, Indonesia, Email: denny\_agustiningsih@ugm.ac.id

## Abstract

Postmenopausal women had more than 20 years life remaining with various menopausal-related health conditions and symptoms which can reduce personal and social life. Recommendation for postmenopause management including lifestyle changes i.e. nutrition and exercise, systemic menopausal hormone therapy (MHT), nonhormonal therapies, alternative and complementary therapies. The recommendations of exercise for humans made by the American College of Sports Medicine (ACSM) are based primarily on epidemiological or prevalence studies. However, basic research is not entirely consistent with the effects of specific exercise protocols related to menopause. Several limitations about menopause-related effect of exercise include studying organ-specific changes following interventions which require invasive procedures or organ isolation, procedures that are best undertaken in a laboratory setting to animal models. Animal research enables a deeper understanding of how exercise can induce changes at the molecular, cellular and neural circuit levels and how these may impact organ body system functions. There are still many possibilities to discuss whether animal studies can reveal the mechanism of exercise as an alternative in the management of postmenopausal and propose some recommendations for how the evidence from animal research might be strengthened with a view to improving success in the area of exercise for postmenopausal translational medicine. When experimental results have been generated in an animal model they have to be validated with respect to their applicability to human.

**Keywords:** Exercise; Menopause; Animal model

**Abbreviations:** ACSM: American College of Sport Medicine; EMAS: European Menopause and Andropause Society; MHT: Menopausal Hormone Therapy; NICE: National Institute for Health and Care Excellence

## Introduction

Life expectancy has increased remarkably in recent years and based on the World Health Organization (WHO) women live longer than men. Life expectancy for women 73 years and 6 months and the average age of menopause was about 52 years old. By the year 2025, the number of postmenopausal women is expected to rise to 1.1 billion worldwide [1]. The cessation of menstrual cycling and reduction of ovarian hormones are related to the increased risk of several diseases such as cardiovascular disease, diabetes, osteoporosis, metabolic syndrome and ovarian cancer. Postmenopausal women had more than 20 years life remaining with various menopausal-related health conditions and symptoms which can reduce personal and social life. Management for postmenopausal women based on the evidence presented in the several documents: EMAS position statements and clinical guides, published in Maturitas between 2010 and 2016 [1], a guideline from the UK National Institute for Health

and Care Excellence (NICE) [2], a clinical practice guideline from the Endocrine Society [3], a practitioner's toolkit for managing the midlife women produced by the North American Menopause Society [4]. Lifestyle changes including nutrition and exercise, systemic menopausal hormone therapy (MHT), nonhormonal therapies including phytoestrogens, alternative and complementary therapies. The salutary relevance of replacement therapy is far from being clearly defined and remains a complex and controversial issue.

The recommendations of exercise for humans made by the American College of Sports Medicine (ACSM) are based primarily on epidemiological or prevalence studies [5,6]. However, until now, basic research is not entirely consistent with the effects of specific exercise protocols related to gender and age differences, specifically for menopause. Several types of research have been done to reveal the mechanism of exercise as one of the

management of menopause. Those studies have some advantages and disadvantages. Several limitations about menopause-related diseases include studying organ-specific changes following interventions which require invasive procedures or organ isolation, procedures that are best undertaken in a laboratory setting to animal models [7]. Animal research enables a deeper understanding of how exercise can induce changes at the molecular, cellular and neural circuit levels and how these may impact organ body system functions. Exercise is simple, low-cost lifestyle intervention that can be quantified in a straightforward manner in both animals and humans. Since the 1980s, Koch and Britton have been developing rat models to resolve the connection between the capacity to convert stored energy into movement and health. Since there was a strong statistical association between exercise capacity and all-cause morbidity and mortality which wanting to understand how the scientific reasoning [8].

There are still many possibilities to discuss whether animal studies can reveal the mechanism of exercise as an alternative in the management of postmenopausal and propose some recommendations for how the evidence from animal research might be strengthened with a view to improving success in the area of exercise for postmenopausal translational medicine. One of the problems in animal postmenopause-model is how accurately does the animal model replicate postmenopausal symptoms and disturbances? The hypoestrogenic condition due to natural or surgical menopause results in dramatic changes in the function of estrogen-sensitive tissues i.e. pituitary, uterus, breast, bone, heart, and brain. These events are noted both in women and rodents. It is believed that neuronal changes in the hypothalamus initiate transition into reproductive decline early in the aging process, leading to reproductive senescence. There are major differences in the mechanisms of age-related reproductive senescence of female rats and women. In women, as aging ensues, serum levels of estrogen and progesterone decline due to decreased ovarian follicular reserves. Thus, hormone loss during natural, nonsurgical menopause is ultimately due to ovarian follicle depletion. In contrast, the aging rat undergoes estropause, a persistent estrus state due to slightly elevated estrogen levels and chronic anovulation followed by a persistent diestrus state characterized by high progesterone levels due to increased activity of corpora lutea. These changes in ovarian-derived hormone release are primarily due to alterations in the hypothalamic/pituitary axis. Thus, the primary mechanism that ultimately results in reproductive senescence in the woman is ovarian follicle depletion, whereas in the rat it is the hypothalamic-pituitary axis. Differences in etiology and processes of menopause should be taken into consideration when we conclude the effect of exercise [9-11]. There are several advantages gained by research on model animals, which are (a) The homogeneity of the study subjects can be measured both genetically and physiologically. The results of the experiments on

animal models were similar to the results of research on human subjects. As stated by Goutianos, et al., (2015) [12] which directly comparing the results of blood chemistry analysis between rats and humans. Both subjects, done similar physical exercise (using treadmills in equal intensity and duration). The results show that rats adequately have a blood biochemical profile response (iron status, lipid profile, glucose regulation, protein metabolism, hepatic function and kidney function) to physical exercise similar on the quality and quantity characteristics to humans. (b) Animal models are easily modified genetically, and (d) Animal models are easy to observe their daily activities, including kind and amount of food, sleep duration etc.

In addition to the advantageous things, the selection of rats as animal models has several disadvantages, which are (a). several physiological differences between rats and humans, including skeletal muscle isoforms [13], muscle fibers numbers and types [14], also the rat locomotion is different from humans [15], (b) The response to stress due to physical exercise is different from humans. Feeding as a reward for stress-fighting in experimental animals can lead to different outcomes. To increase the animal motivation for doing exercise, a researcher is often given stimuli such as electric foot shock or air with high-pressure. Unfortunately, those treatments can trigger stress on the experimental animals and act as confounding factors which can cause different results with humans [16]. The most important factors to consider is almost all of disturbances of the body systems is no longer considered a single disorder; rather, it is a collection of different disease phenotypes that share certain clinical and pathological features. Consequently the responses to treatment, including exercise, and indeed the appropriate therapeutic targets may be quite distinct. Suggested clinically relevant stratification approaches into those disturbances phenotypes that may warrant distinct therapeutic strategies. In the case of postmenopausal disturbances, the choice of an 'appropriate' animal model will strongly depend on which type of human body system one wishes to replicate. Indeed, a lot of studies in genetically modified rats have mimicking symptoms and disturbances of postmenopausal. But sometimes have a difference in the outcome because an intervention can be effective for one disturbance but not to another. Finding an appropriate model for human menopause has been difficult for several reasons. Previously, researchers have used nonhuman primates, dogs, cats, rabbits, guinea pigs, pigs, and minipigs, each these animal models possesses certain advantages and disadvantages. Primates are the closest to female human menopause due to the fact that they are the only species to undergo menstrual sloughing of the endometrial lining. But it is important to note that female primates do not experience menopause. Also, primates research is ethically difficult to perform and costly [17].

In order to select an appropriate animal model for a given study, the investigator must take into consideration a wide variety of factors: 1) appropriateness as a model for estrogen

deficiency, 2) genetic homogeneity of organism, 3) background knowledge of biological properties, 4) cost and availability, 5) ease of experimental manipulation, 6) ecological considerations, and 7) ethical and societal implications. It is of great importance that the model selected does not add too many new variables to an already complex problem. Therefore, ideally, the model chosen should closely mimic human diseases in its induction, progression, and pathology. Obviously, no animal model can meet every criterion. In real life, compromises must be made and the best possible model is selected [18]. When experimental results have been generated in an animal model they have to be validated with respect to their applicability to human. Extrapolation is generally not performed in its mathematically sense where data fit a certain function that may be described graphically to describe a situation of observation. What laboratory animal experimentation is about the similarity with other types of experiments. The scientists aim to obtain answers to specific questions before deciding on its potential usefulness in human conditions. Although the predictive value of animal studies may seem high if they are conducted thoroughly and have included several species, uncritical reliance on the results of animal tests can be misleading to human health in several cases. Several studies have shown that even the most promising findings from animal research often fail in human trials and are rarely adopted into clinical practice. The genomic and inherent differences between rodent and human physiology are increasingly acknowledged and even nonhuman primates have many differences in the epigenomic that fundamentally affect the functionality of the genome and may account for the lack of success in predicting clinical response. Even if the research was conducted faultlessly, animal models might still have limited success in predicting human responses to drugs and disease because of inherent inter-species differences in molecular and metabolic pathways [19].

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