

Research Article

The effect of eight weeks of interval training on plasma levels of FoxN1 and blood pressure indices in middle-aged men with hypertension

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Abstract

High blood pressure or hypertension has become the most common cardiovascular and renal risk factor among people around the world and is mainly associated with an inactive lifestyle and unhealthy diet. The aim of the present study was to investigate the effect of eight weeks of moderate-intensity interval training on plasma levels of FoxN1 and blood pressure indices in middle-aged men with hypertension. In the present quasi-experimental study, 32 middle-aged men with an age range of 50-60 years and with high blood pressure were purposefully selected and then randomly assigned to two control (n=15) and experimental (n=17) groups. The experimental group performed interval training for eight weeks with a frequency of three sessions per week and an intensity of 50-75% of heart rate reserve based on the principle of gradual overload, while the control group did not participate in any training program. Plasma levels of FoxN1 were measured by the ELISA protein assay. Systolic, diastolic and mean arterial blood pressure were also measured in the subjects of the two groups before and after the training period. To evaluate the normality of the data, the Shapiro-Wilk test was used, and the homogeneity of variances was assessed with the Levene test. The analysis of covariance (ANCOVA) test was also used to compare the variables in the two groups. The data were analyzed at a significance level of 0.05 and using SPSS-23 software. The results showed that eight weeks of moderate-intensity interval training led to a significant increase in FoxN1 ($p < 0.05$). Also, a significant decrease was observed in systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure after eight weeks of interval training ($p < 0.05$). According to the results of the present study, it is recommended that people with high blood pressure perform moderate-intensity interval training to control blood pressure, reduce inflammation, and improve immune function.

Key Words: Interval training, Hypertension, FoxN1, Cardiovascular

Introduction

High blood pressure or Hypertension (HBP) is a systemic disease that damages target organs, including the heart, brain, and kidneys, and increases the risk of cardiovascular, renal, and cerebrovascular events (Cavasin et al., 2007). Hypertension is a multifactorial disease involving various cell types and is mainly influenced by environmental factors, especially sedentary lifestyle, psychological stress, and unhealthy diet (Charchar et al., 2024). Hypertension has also been identified as an immune-related disease, and the thymus gland has been shown to play a critical role in the pathogenesis of hypertension (Dai et al., 2017). The thymus is a primary immune organ where T cells are produced and mature (Walters et al., 2014). The thymus is mainly composed of hematopoietic thymocytes (TECs) and non-hematopoietic thymic epithelial cells (nTECs), which are essential for the regulation of thymic function (Xu et al., 2017). In the pathological conditions of hypertension, functional defects in TECs have been observed, suggesting a link between hypertension and immune dysfunction (Kadouri et al., 2020). As an immune regulatory factor, the thymic transcription factor forkhead box protein N1 (FoxN1) (Burnley et al.; Chen et al.) plays a critical role in the proliferation, differentiation, and homeostasis of TECs and the maintenance of overall thymic function (Burnley et al., 2013; Chen et al., 2009) increased expression of FoxN1 can enhance thymic function and even lead to thymic regeneration (Bredenkamp et al., 2014). Thymic epithelial cell differentiation, growth and function depend on the expression of the transcription factor FoxN1 (Žuklys et al., 2016).

Forkhead box protein N1 (FoxN1) is a major thymic transcription factor that plays an important role in the physiological function of the thymus (Bredenkamp et al., 2014). Thymic atrophy leads to a decrease in FoxN1 expression, and it has been shown that thymic atrophy and, consequently, a decrease in FoxN1 expression are observed in hypertension (Fukuda et al., 2004). Recent evidence suggests that the adaptive immune response plays an important role in the pathogenesis of hypertension. Various hypertensive stimuli activate and infiltrate T cells into

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target organs such as the vasculature and kidney, leading to vascular dysfunction and hypertension (Vinh et al., 2010). The FoxN1 is expressed in thymic epithelium and the earliest known thymus marker that Loss of it results in thymus degeneration and reduced T-cell production, suggesting that FoxN1 is required for functional maintenance thymus (Vaidya et al., 2016). Previous studies have found that thymus is involved in the process of hypertension and the control of the high blood pressure is associated with improved thymus function and increased the FoxN1 expression (Dai et al., 2023).

Numerous studies have been conducted on exercise and immune function, and it has been proven that the effect of exercise on the immune system depends on the intensity of exercise, such that moderate-intensity exercise enhances immune function, while intense exercise reduces it (AKAMA et al., 2003). Despite extensive studies on exercise and the immune system, limited studies have examined the effect of exercise on thymus function and factors secreted from this organ, including FoxN1. One of the most important strategies for controlling blood pressure is lifestyle modification with regular physical activity. Analysis of previous large-scale studies has reported significant reductions in systolic and diastolic blood pressure (SBP and DBP) in various types of exercise (Cornelissen & Smart, 2013). Although the effects of exercise on various aspects of blood pressure have been investigated, the effects of exercise on immune indices in blood pressure have been less studied. Therefore, the aim of the present study was to investigate the effect of eight weeks of moderate-intensity interval training on plasma levels of FoxN1 in men with hypertension.

Materials and methods

Subjects

This study is a quasi-experimental and applied study that studied the effect of eight weeks of moderate-intensity interval training on plasma FoxN1 levels in men with hypertension. The statistical population of this study included all inactive hypertensive men aged 50 to 60 years in Ahvaz city that 32 of them were selected through convenience sampling after screening and then divided into two groups by simple random sampling. Also, the sample size was estimated using the Cochran formula with adjustment for the error rate.

Interval training group: This group consisted of 17 middle-aged men with hypertension, whose blood samples were taken 48 hours before the start of the training period, and they performed moderate-intensity interval training for eight weeks, and again 48 hours after the last training session to assess the effect of training on the variables under study.

Control group: This group consisted of 15 middle-aged men with

hypertension, who served as the control group and had their blood samples taken at the same times as the experimental group and in two pre-test and post-test sessions. This group did not participate in any training intervention and they were asked not to participate in any other training program during the study period.

Interval training protocol

The training program included interval training for eight weeks, with a frequency of three sessions per week. Each training session lasted 60 minutes and included 15 minutes of warm-up (general and specific) and 35 minutes of interval running (7 repetitions of 5-minute interval running with 2.5-minute active rest intervals) at an intensity of 50-75% of heart rate reserve, followed by a 10-minute cool-down. Warm-up and cool-down of each training session included stretching exercises and slow running. The subjects were advised not to participate in any other physical activity during the eight weeks of the training program. The initial training intensity for the first week was determined at an intensity of 50% of heart rate reserve. After measuring the subjects' resting heart rate in the supine position and based on the maximum heart rate formula based on age, the training intensity was calculated using the Karonen formula. Activity heart rate was also measured to assess training intensity using a Polar heart rate monitor. Based on the principle of gradual overload, the training intensity was increased by 5% each week until the training intensity reached 70% of the heart rate reserve in weeks five and six, and finally, in weeks seven and eight, the training intensity ended with 75% of the heart rate reserve (Barron-Cabrera et al., 2023). A summary of the training program is given in Table 1.

Blood pressure measurement

The subjects' systolic and diastolic blood pressures were measured and recorded at the pre-test stage and at the end of each exercise session, as well as 48 hours after the last exercise session to eliminate the acute effect of exercise. An Omron digital blood pressure monitor (M6 comfort, made in Vietnam) was used to measure blood pressure. To measure resting blood pressure, the subjects sat on a chair in a comfortable position, with their back straight and supported, for one minute, and then their blood pressure was measured at rest. All measurements were taken

Table 1. The training program in different weeks

week	Intensity (heart rate reserve)	Number of activity intervals	Active rest (s)	Frequency
1	50	7	150	3
2	55	7	150	3
3	60	7	150	3
4	65	7	150	3
5	70	7	150	3
6	70	7	150	3
7	75	7	150	3
8	75	7	150	3

from the subjects' right arm, and their arm was placed parallel to the level of their heart. After measuring systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean arterial blood pressure (MAP) was also calculated and recorded using the following formula: $MAP = DBP + 1/3(SBP - DBP)$.

Blood collection and measurement of biochemical variables

48 hours before the first training session and 48 hours after the last training session, blood samples were taken from the subjects in both groups by a laboratory technician; then the sample was centrifuged at 3000 rpm for 10 minutes and the blood plasma of the samples was separated. The resulting plasma was poured into 1 ml microtubes and transported to the laboratory for further steps and stored at -80°C (frozen). Blood was collected after 12 hours of overnight fasting and in a resting state, and 5 cc each time was taken from the anterior vein of the left hand of the subjects in a sitting position. The blood was poured into sterile tubes containing an Ethylenediamin Tetera acetic Acid (EDTA). After collecting the samples in the post-test stage, all blood samples were removed from the freezer on the same day and the desired test was performed according to the relevant protocols. To measure plasma FoxN1 levels, ELISA was used using a human kit from mybiosource with a sensitivity of 5.0 pg/ml.

Ethical Approval: Given that the present study was conducted on human samples with exercise intervention over a relatively long period of time, in full compliance with the ethical principles of research, approval was received from the ethics committee with the ID number IR.IAU.AHVAZ.REC.1404.192 from the Islamic Azad University, Ahvaz Branch.

Statistical analysis

In the present study, the mean \pm standard deviation was used to describe the data. The normality of the data distribution was assessed using the Shapiro and Wilk test and the homogeneity

Table 2. Distribution of age, height and weight and BMI of the subjects in the two groups.

Group	N	Age (year)	Height (cm)	Weight (kg)	Body mass index(BMI)
Interval training	17	53.42 \pm 2.37	178.35 \pm 5.29	88.51 \pm 7.92	27.82 \pm 3.18
Control	15	54.61 \pm 3.19	179.12 \pm 6.38	86.33 \pm 8.24	26.90 \pm 3.35

of variances was assessed using the Levene test. Also, for intragroup comparison, the dependent t test and the analysis of covariance (ANCOVA) test were used for intergroup comparison. The data were analyzed by SPSS-23 software at a significance level of 0.05.

Results

Descriptive data: Descriptive data related to the frequency, mean and standard deviation of age, height, weight and body mass index (BMI) of the subjects in the two groups are presented in Table 2.

Changes in systolic, diastolic and mean arterial blood pressure: To investigate the effect of eight weeks of interval training on systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) in middle-aged men with hypertension, analysis of covariance (ANCOVA) was used. The results of this test showed that eight weeks of interval training resulted in a significant reduction in SBP ($p=0.015$, $F=84.21$), DBP ($p=0.031$, $F=61.83$) and MAP ($p=0.021$, $F=70.14$).

The changes of FoxN1

Analysis of covariance (ANCOVA) was also used to investigate the effect of eight weeks of interval training on FoxN1 plasma levels in middle-aged men with hypertension. After confirming the assumptions of this test and adjusting for baseline values, it was observed that eight weeks of interval training resulted in a significant increase in FoxN1 plasma levels in middle-aged men with hypertension ($p=0.027$, $F=76.40$). Figure 1 (A, B, C, and D) shows changes in systolic, diastolic, and mean arterial blood pre-

Table 3. The results of the analysis of covariance for between-group comparison of variables

Variable	Source	Type III Sum of Square	df	Mean Square	F	Sig
FoxN1 (ng/ml)	Pre-test	12.548	1	12.548	8.309	0.254
	groups	115.371	1	115.371	76.404	0.027*
	Error	45.32	30	1.510		
SBP (mmhg)	Pre-test	12.251	1	12.251	4.939	0.527
	groups	458.376	1	458.376	184.829	0.001*
	Error	74.428	30	2.480		
DBP (mmhg)	Pre-test	10.348	1	10.348	5.328	0.435
	groups	339.125	1	339.125	174.626	0.001*
	Error	58.267	30	1.942		
MAP (mmhg)	Pre-test	12.573	1	12.573	5.919	0.380
	groups	385.561	1	385.561	181.525	0.001*
	Error	63.734	30	2.124		

*Significant difference in level of 0.05

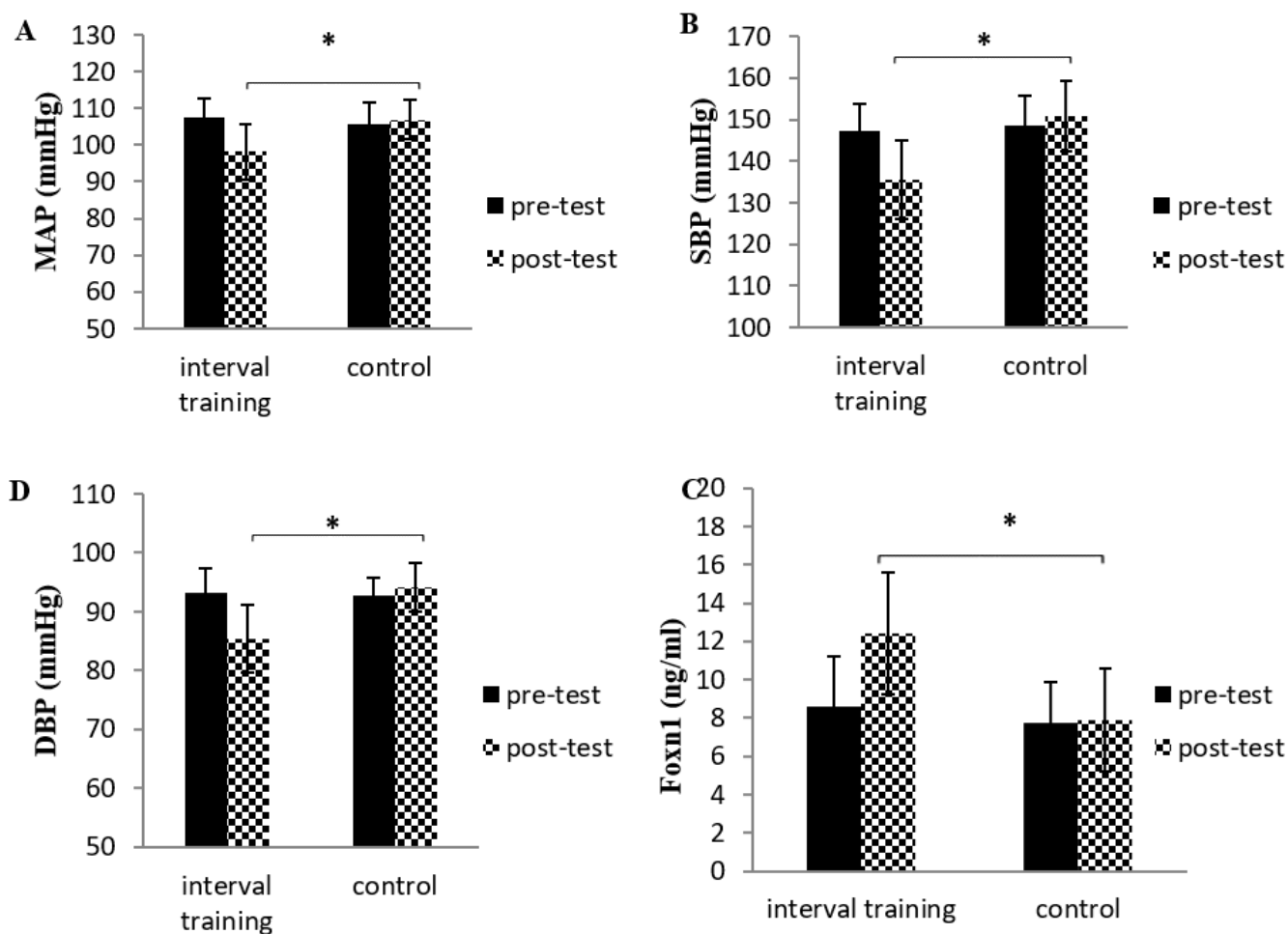


Figure 1. Comparison of A: Changes in systolic blood pressure (SBP), B: Changes in mean arterial pressure (MAP), C: Changes in diastolic pressure (DBP), and D: Changes in FoxN1 plasma levels in middle-aged men with hypertension in the two-interval training and control groups. * Indicates a significant difference between the groups post-test $p < 0.05$.

shows changes in systolic, diastolic, and mean arterial blood pressure, as well as changes in FoxN1 plasma levels in middle-aged men with hypertension.

Discussion

In the present study, it was observed that eight weeks of interval training significantly increased plasma levels of FoxN1 in middle-aged men with hypertension. The FoxN1 transcription factor plays an important role in some functions of tissues such as thymus and epidermis and is a key factor for the proliferation of thymic epithelial progenitor cells (Senoo et al., 2007). Thymus function is affected in some pathological conditions such as hypertension, and the FoxN1 transcription factor is negatively regulated. Given that limited studies have been conducted on the effect of exercise on the FoxN1 transcription factor, the discussion on the mechanism of the effect of exercise on this factor requires further studies.

One of the most important factors affecting thymus function is exercise. Exercise plays an important role in thymus function by

increasing pulmonary ventilation. The results of a research study showed that in mice that had a regular exercise program (8 weeks of exercise, 5 sessions per week, 30 minutes per session, speed 30 m/min and 8 degrees of incline) and then had a 72-hour rest period, the percentage of L3T4 was positive and thymus cells increased by 29% compared to a sedentary control group (Hoffman-Goetz et al., 1989). In obese individuals or those with high blood pressure, there is a marked deregulation of immune responses, which leads to fewer circulating T cells and reduces the response to pathogens, exercise can play an important role in blood pressure control by increasing circulating T cells and increasing FoxN1 levels. Increased FoxN1 levels caused by interval training lead to reduced vascular inflammatory responses and consequently reduced blood pressure (Dai et al., 2023).

In the present study, it was shown that eight weeks of interval training resulted in significant reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in middle-aged men with hypertension. Blood pressure is influenced by blood volume, cardiac output,

and total peripheral resistance (TPR). The mechanisms of blood pressure reduction induced by exercise include neurohormonal, vascular, and structural adaptations, reductions in catecholamines and total peripheral resistance, and changes in vasodilators and vasoconstrictors. These changes may partly explain the antihypertensive effects of exercise. This reduction in blood pressure occurs through a significant reduction in circulating catecholamine levels (Green et al., 2017).

Recent studies suggest that low- to moderate-intensity exercise (35 to 79% of maximum heart rate or 30 to 74% of maximum oxygen uptake) may be more effective in reducing blood pressure than higher intensities. The results of the present study are consistent with the findings of Pitsavos et al (Pitsavos et al., 2011), who investigated the effects of a moderate-intensity aerobic exercise program on left ventricular mass, exercise capacity, and blood pressure response during a treadmill test in men with hypertension. They evaluated 40 men with a mean age of 53 years and moderate blood pressure on an exercise program that included 16 weeks of treadmill training at an intensity of 60 to 80% of maximum heart rate. At baseline, there was no difference in left ventricular mass index and blood pressure values at rest and during the treadmill test between the experimental and control groups, but after 16 weeks of the training program, systolic and diastolic blood pressure, resting heart rate, and left ventricular mass index were significantly lower in the experimental group compared to the control group.

In healthy individuals, diastolic blood pressure changes little during dynamic aerobic exercise. Diastolic blood pressure normally does not change or may decrease slightly by less than 10 mmHg or increase by 10-20 mmHg during exercise, which may be due to obstruction of blood flow by strong contractions of the active muscles. The slight decrease in diastolic blood pressure is mainly due to the dilation of the arteries during exercise. Therefore, an increase in the diameter of the arteries can cause a drop in blood pressure in the diastolic phase. An increase in diastolic blood pressure of more than 10 mmHg during or after exercise indicates an unstable form of hypertension and may be related to coronary artery disease (Collier et al., 2008).

Exercise training causes a significant increase in blood pressure immediately after exercise, which is due to increased sympathetic nervous system activity during exercise. This increase in sympathetic nervous system activity is due to increased heart rate and peripheral vascular resistance, resulting in an increase in blood pressure immediately after exercise, but after cessation of exercise, with a decrease in sympathetic nervous system activity and an increase in parasympathetic nervous system activity, a decrease in resting heart rate and an increase in stroke volume, blood pressure decreases after exercise (Besler et al., 2012). After some time after exercise, the activity of antioxidant

enzymes increases, which causes a decrease in blood pressure. Blood pressure begins to decrease from 20 minutes after exercise, and after 30 minutes of exercise, blood pressure decreases significantly. The most important reason that exercise is a suitable stimulus for improving blood pressure is that exercise causes more stress on the vascular bed, thus being a good stimulus for improving endothelial function. Exercise intensity is an important determining factor in increasing endothelial cell function. Moderate-intensity exercise, neither at low nor at high intensities, promotes endothelium-dependent vasodilation through increased nitric oxide production. In total, various mechanisms explain the effect of exercise on reducing resting blood pressure, including decreased sympathetic tone, weight loss, decreased serum insulin levels, weakening of baroreceptors, secretion of endogenous opioids, and changes in systemic vascular resistance (Whelton et al., 2002). Finally, given that this research was conducted on human subjects, one of the limitations of the present study was the inability to evaluate hematopoietic thymocytes cells (TECs). therefore, it is recommended that in future studies, in addition to examining FoxN1, researchers also evaluate the thymus cells along with their histology.

Conclusion

In the present study, eight weeks of interval training reduced blood pressure indices such as systolic blood pressure, diastolic blood pressure, and mean arterial pressure in men with hypertension and led to a significant increase in FoxN1 plasma levels. Therefore, it is recommended that people with hypertension use moderate-intensity interval training to help manage blood pressure, which could reduce the risk of long-term complications.

What is already known on this subject?

Hypertension has also been identified as an immune-related disease, and the thymus gland has been shown to play a critical role in the pathogenesis of hypertension.

What this study adds?

Eight weeks of interval training reduced blood pressure indices such as systolic blood pressure, diastolic blood pressure, and mean arterial pressure in men with hypertension and led to a significant increase in FoxN1 plasma levels.

Organ Cross-Talk Tips:

- Muscle activity from training improves cardiovascular health and immune markers.
- Training reduces inflammation, a key link between better heart health and immune function.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest in the present research.

Ethical approval Given that the present study was conducted on human samples with exercise intervention over a relatively long period of time, in full compliance with the ethical principles of research, approval was received from the ethics committee with the ID number IR.IAU.AHVAVZ.REC.1404.192 from the Islamic Azad University, Ahvaz Branch.

Informed consent Performed.

Author contributions

Conceptualization: M.Gh., M.B., Methodology: M.Gh., M.B., Software: M.Gh., M.B., Validation: M.Gh., M.B., Formal analysis: M.Gh., M.B., Investigation: M.Gh., M.B., Resources: M.Gh., M.B., Data curation: M.Gh., M.B., Writing - original draft: M.Gh., M.B., Writing–review & editing: M.Gh., M.B., Visualization: M.Gh., M. B, Supervision: M.B.; Project administration: M.Gh., M.B., Funding acquisition: M.B.

References

AKAMA, T., KIMURA, F., AKIMOTO, T., & KONO, I. (2003). Effects of exercise on immune function in elderly persons. *Japanese Journal of Physical Fitness and Sports Medicine*, 52(Supplement), 65–71. https://doi.org/10.7600/jspfsm1949.52.Supplement_65

Barron-Cabrera, E., Soria-Rodriguez, R., Amador-Lara, F., & Martinez-Lopez, E. (2023). Physical activity protocols in non-alcoholic fatty liver disease management: A systematic review of randomized clinical trials and animal models. *Healthcare*. <https://doi.org/10.3390/healthcare11141992>

Besler, C., Lüscher, T. F., & Landmesser, U. (2012). Molecular mechanisms of vascular effects of high-density lipoprotein: alterations in cardiovascular disease. *EMBO molecular medicine*, 4(4), 251–268. <https://doi.org/10.1002/emmm.201200224>

Bredenkamp, N., Nowell, C. S., & Blackburn, C. C. (2014). Regeneration of the aged thymus by a single transcription factor. *Development*, 141(8), 1627–1637. <https://doi.org/10.1242/dev.103614>

Burnley, P., Rahman, M., Wang, H., Zhang, Z., Sun, X., Zhuge, Q., & Su, D. (2013). Role of the p63-FoxN1 regulatory axis in thymic epithelial cell homeostasis during aging. *Cell death & disease*, 4(11), e932–e932. <https://doi.org/10.1038/cddis.2013.460>

Cavasin, M. A., Liao, T.-D., Yang, X.-P., Yang, J. J., & Carretero, O. A. (2007). Decreased endogenous levels of Ac-SDKP promote organ fibrosis. *Hypertension*, 50(1), 130–136. <https://doi.org/10.1161/HYPERTENSIONAHA.106.084103>

Charchar, F. J., Prestes, P. R., Mills, C., Ching, S. M., Neupane, D., Marques, F. Z., Sharman, J. E., Vogt, L., Burrell, L. M., & Korostovtseva, L. (2024). Lifestyle management of hypertension: International Society of Hypertension position paper endorsed by the World Hypertension League and European Society of Hypertension. *Journal of hypertension*, 42(1), 23–49. <https://doi.org/10.1097/HJH.0000000000003563>

Chen, L., Xiao, S., & Manley, N. R. (2009). Foxn1 is required to maintain the postnatal thymic microenvironment in a dosage-sensitive manner. *Blood, The Journal of the American Society of Hematology*, 113(3), 567–574. <https://doi.org/10.1182/blood-2008-05-156265>

Collier, S., Kanaley, J., Carhart, R., Frechette, V., Tobin, M., Hall, A., Luckenbaugh, A., & Fernhall, B. (2008). Effect of 4 weeks of aerobic or resistance exercise training on arterial stiffness, blood flow and blood pressure in pre-and stage-1 hypertensives. *Journal of human hypertension*, 22(10), 678–686. <https://doi.org/10.1038/jhh.2008.36>

Cornelissen, V. A., & Smart, N. A. (2013). Exercise training for blood pressure: a systematic review and meta-analysis. *Journal of the American heart association*, 2(1), e004473. <https://doi.org/10.1161/JAHA.112.004473>

Dai, X., Huang, S., He, Z., Wu, F., Ding, R., Chen, Y., Liang, C., & Wu, Z. (2017). Dysfunction of the thymus in mice with hypertension. *Experimental and Therapeutic Medicine*, 13(4), 1386–1392. <https://doi.org/10.3892/etm.2017.4125>

Dai, X., Zhao, J., Hua, L., Chen, H., & Liang, C. (2023). Thymus transplantation regulates blood pressure and alleviates hypertension-associated heart and kidney damage via transcription factors FoxN1 pathway. *International Immunopharmacology*, 116, 109798. <https://doi.org/10.1016/j.intimp.2023.109798>

Fukuda, S., Tsuchikura, S., & Iida, H. (2004). Age-related changes in blood pressure, hematological values, concentrations of serum biochemical constituents and weights of organs in the SHR/lzm, SHRSP/lzm and WKY/lzm. *Experimental animals*, 53(1), 67–72. <https://doi.org/10.1538/expanim.53.67>

Green, D. J., Hopman, M. T., Padilla, J., Laughlin, M. H., & Thijssen, D. H. (2017). Vascular adaptation to exercise in humans: role of hemodynamic stimuli. *Physiological reviews*, 97(2), 495–528. <https://doi.org/10.1152/physrev.00014.2016>

Hoffman-Goetz, L., Thorne, R., Simpson, J., & Arumugam, Y. (1989). Exercise stress alters murine lymphocyte subset distribution in spleen, lymph nodes and thymus. *Clinical and Experimental Immunology*, 76(2), 307. PMC1541822

Kadouri, N., Nevo, S., Goldfarb, Y., & Abramson, J. (2020). Thymic epithelial cell heterogeneity: TEC by TEC. *Nature Reviews Immunology*, 20(4), 239–253. <https://doi.org/10.1038/s41577-019-0238-0>

Pitsavos, C., Chrysohoou, C., Koutroumbi, M., Aggeli, C., Kourlaba, G., Panagiotakos, D., Michaelides, A., & Stefanadis, C. (2011). The impact of moderate aerobic physical training on left ventricular mass, exercise capacity and blood pressure response during treadmill testing in borderline and mildly hypertensive males. *Hellenic J Cardiol*, 52(1), 6–14. PMID: 21292602

Senoo, M., Pinto, F., Crum, C. P., & McKeon, F. (2007). p63 Is essential for the proliferative potential of stem cells in stratified epithelia. *Cell*, 129(3), 523–536. <https://doi.org/10.1016/j.cell.2007.02.045>

Vaidya, H. J., Briones Leon, A., & Blackburn, C. C. (2016). FOXP1 in thymus organogenesis and development. *European journal of immunology*, 46(8), 1826–1837. 10.1002/eji.201545814

Vinh, A., Chen, W., Blinder, Y., Weiss, D., Taylor, W. R., Goronzy, J. J., Weyand, C. M., Harrison, D. G., & Guzik, T. J. (2010). Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. *Circulation*, 122(24), 2529–2537. <https://doi.org/10.1161/CIRCULATIONAHA.109.930446>

Walters, S. N., Webster, K. E., Daley, S., & Grey, S. T. (2014). A role for intrathymic B cells in the generation of natural regulatory T cells. *The Journal of Immunology*, 193(1), 170–176. <https://doi.org/10.4049/jimmunol.1302519>

Whelton, S. P., Chin, A., Xin, X., & He, J. (2002). Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Annals of internal medicine*, 136(7), 493–503. <https://doi.org/10.7326/0003-4819-136-7-200204020-00006>

Xu, M., Zhang, X., Hong, R., Su, D.-M., & Wang, L. (2017). MicroRNAs regulate thymic epithelium in age-related thymic involution via Down-or upregulation of transcription factors. *Journal of Immunology Research*, 2017(1), 2528957. <https://doi.org/10.1155/2017/2528957>

Žuklys, S., Handel, A., Zhanybekova, S., Govani, F., Keller, M., Maio, S., Mayer, C., Teh, H., Hafen, K., & Gallone, G. (2016). Foxn1 regulates in postnatal thymic epithelial cells key target genes essential for T cell development. *Nature Immunology*, 17. <https://doi.org/10.1038/ni.3537>