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Evaluation of Exercise Time and Cardiac Autonomic Responses with an Exercise Stress Test in Primary Adrenal Insufficiency

ABSTRACT

Objective: The aim was to evaluate autonomic dysfunction by investigating exercise time, the chronotropic index (CI), and heart rate recovery (HRR) during an exercise stress test (EST) in patients with primary adrenal insufficiency, also called Addison's disease (AD).

Methods: Twenty-two patients with adrenal insufficiency and 25 healthy controls were included in this study. The data from the patients who underwent an EST were collected, analyzed, and reported.

Results: The mean ages and genders of the patients with AD and the controls were insignificant. The baseline systolic and diastolic blood pressures (SBP and DBP) were significantly lower in the patients with AD compared to the controls before the EST. According to exercise-induced data, the SBP, DBP, and CI were insignificant for females and males between the groups. The exercise time, HRR1, and HRR2 were significantly decreased in the patients with AD compared to the controls. When the patients and controls were evaluated by gender, other than the HRR1 of the females, there were no differences between both genders. Additionally, a multiple logistic regression analysis showed that exercise time was independent and negatively related to the CI, HRR1, and HRR2 in the patients with AD.

Conclusion: Exercise time and cardiac autonomic dysfunction in patients with AD may be related to mortality and morbidity. However, further studies and detailed analyses are needed on this subject.

Keywords: Exercise time, heart rate recovery, primary adrenal insufficiency

Introduction

Primary adrenal insufficiency [also known as Addison's disease (AD)] is a rare but severe clinical condition because it is potentially life-threatening. It is characterized by the insufficient secretion of hormones [glucocorticoids (GCs), mineralocorticoids, and sex steroids] of the adrenal cortex. The incidence and prevalence of AD in the developed world have been estimated as 0.8 cases and 4-11 cases per 100 000, respectively. Infection diseases, especially tuberculosis, are the most common cause of AD worldwide, whereas autoimmune adrenalitis is the predominant cause in the Western world.[1]

A significant number of patients with AD die within 2 years of diagnosis before GCs are available and used.[2] Currently, treatment and management with GCs can be made easily after diagnosis. Patients with AD have a significantly increased life expectancy and quality of life with replacement therapies. Nevertheless, there is significant morbidity, and the risk ratio for mortality is more than 2-fold excess despite treatment. The increased mortality is associated with cardiovascular, malignancy, and infectious diseases.[3]

An exercise stress test (EST) is simple and widely used to evaluate patients with cardiovascular disease due to its availability and low cost. Exercise stress tests are easy to administer, perform, and interpret. Also, they are flexible and adaptable.[4] Exercise stress tests are useful for evaluating, managing, and predicting prognosis in cardiovascular diseases and reveal possible risks in asymptomatic individuals. In addition to analyzing the ST segment, an EST provides information about functional capacity, ventricular ectopy, chronotropic index (CI), and heart rate recovery (HRR).[5]

The heart rate (HR) increases during exercise due to inactive parasympathetic and active sympathetic tonus. Under normal circumstances, when exercise terminates, the process reverses and HR decreases. The HRR is the rate of HR decline. It is a powerful indicator of fitness and a

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partial mediator of the autonomic nervous system. An abnormal HRR is related to increased all-cause mortality in asymptomatic individuals and patients with known heart disease.[4]

Many studies reveal that impaired exercise capacity, HRR, and chronotropic incompetence during an EST, as autonomic dysfunction parameters, are associated with poor long-term outcomes and all-cause death. Cardiovascular risk factors are also one of the triggering reasons for premature mortality in patients with AD. This study aimed to investigate the data from ESTs (CI, HRR, exercise time, and blood pressure) and find an association between autonomic dysfunction and AD.

Materials and Methods

In this retrospective study, patients over the age of 18 with AD who received physiologic GC and mineralocorticoid doses of replacement therapy and were followed by the endocrinology departments of the University of Health Sciences, Antalya Training and Research Hospital and University of Uşak, Uşak Training and Research Hospital were evaluated. The EST data from the patients with AD were examined using retrospective records. The data available from the patients were compared with the data from the controls. None of the recruited patients or controls had an anamnesis of ischemic cardiovascular diseases, diabetes mellitus, hypertension, or severe systemic diseases. The mean follow-up period could not be evaluated because the patients' diagnosis date was not clear, the reliability of the anamnesis was insufficient, and they applied to different hospitals during follow-up. The study is a cross-sectional study. There were no signs of electrolyte imbalance in the laboratory and clinical evaluation of the patients before the EST protocol. At the same time, patients were informed about taking their medication regularly. However, electrolytes were not checked on the day of the test. This study was approved by the Ethics Committee of the University of Health Sciences, Antalya Training and Research Hospital (date number: September 21, /2017-13/08) and was conducted in accordance with the government policies and the Declaration of Helsinki. Written informed consent was obtained from all the study groups.

According to the EST protocol suggested by the American College of Cardiology/American Heart Association, the subjects in the study groups rested in the supine position for 10 minutes. They were asked not to use cigarettes or caffeine 48 hours before the testing due to its effect on HR. Initially, the subjects were walked slowly for 3 minutes at 1.7 m/h at a 10% grade. Later, the speed and grade of walking were increased every 3 minutes until the patient was exhausted. Data such as electrocardiogram, HR, and blood pressure were registered during the last minute of each stage. The exercise was stopped when the subjects reached their target HR (85% of their age and sex predicting maximal HR). Finally, the subjects got off the treadmill and rested in a supine position. The test was ceased earlier in cases of limited fatigue, dyspnea, and chest or leg discomfort. Exercise time, exercise capacity, and HRR were evaluated by performing a symptom-limited treadmill exercise test following the standard multistage Bruce protocol.[6]

The chronotropic response is described as the percentage of the HR reserve used at peak exercise. The CI is calculated using the following formula: (HR peak − HR baseline)/(220 − age − HR baseline) × 100. If the CI is below 0.8, it is defined as chronotropic incompetence. At the end of the exercise, the HR was obtained by an electrocardiographic monitor when the subject was resting in a supine position for 10 minutes. The HR was recorded every minute during the recovery period. The HRR was formulated as peak HR during exercise—HR at recovery minute. The HRs at the first and second minute of recovery were defined as HRR1 and HRR2, respectively. Both chronotropic incompetence and HRR are associated with all-cause mortality.[7]

Statistical Analysis

Statistically, all data were analyzed using the Statistical Package for the Social Sciences Statistics software for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared with the Pearson chi-square test. The normality assumptions were controlled by the Shapiro–Wilk test. The differences between the 2 groups were evaluated with a Student's *t*-test for the normally distributed data or a Mann–Whitney *U*-test for the non-normally distributed data. A multiple logistic regression analysis was used to determine the relationship between study parameters measured in AD patients. The data are shown as the n (%), the mean ± SD, or the median (minimum–maximum), as appropriate. $P < .05$ were considered statistically significant. A post hoc power analysis was used in the G*Power 3.1.9 program. A large effect size ($P = .8$) was calculated.[8] The minimum number of samples to be included in the study was determined as 42 patients for 80% statistical power with 0.05 alpha significance level and a CI of 95%.

Results

Twenty-two patients (8 females and 14 males) with AD and 25 (9 females and 16 males) age- and gender-compatible healthy controls were enrolled in the study. The mean ages were 44.9 ± 14.7 in patients and 49.8 ± 11.5 in controls, and the difference between groups was not statistically significant ($P = .213$). Similarly, the mean ages of the females and males in the patients versus controls were not significantly different [46.9 (30-64) vs. 49.0 (30-68), $P = .773$ in females; 43.8 (22-73) vs. 50.2 (27-77), $P = .163$ in males]. Baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) before EST were significantly lower in AD patients compared to controls [110 (75-140), 120 (110-140), $P = .007$ vs. 70 (60-90), 75 (60-98), $P = .003$; respectively]. The SBP was not significant between groups for the females with AD than the controls [108 (75-130) vs. 127 (110-140), $P = .064$] but was significant for the males [111 (90-140) vs. 121 (110-140), $P = .028$]. The DBP was not significant between groups for the females with AD than the controls [69 (60-80) vs. 74 (60-80), $P = .198$] but was significant for the males [69 (60-90) vs. 77 (68-98), $P = .008$] (Table 1).

According to exercise-induced data, SBP, DBP, and CI were insignificant for females and males between the groups. The exercise time, HRR1, and HRR2 were significantly decreased in the patients with AD than the controls [(5.4 ± 2.2 vs. 10 ± 3.2, $P < .001$); (10 (2-28) vs. 26 (2-43), $P = .002$); and (26 (11-56) vs. 39 (10-59), $P = .002$), respectively].

MAIN POINTS

- Primary adrenal insufficiency is a rare disease that requires lifelong medication and follow-up.
- There are various factors affecting the quality of life, mortality, and morbidity of adrenal insufficiency patients.
- The effect of exercise time and cardiac autonomic dysfunction on life in patients with primary adrenal insufficiency is an issue that needs to be examined in detail.

Table 1. Demographic Data of Patients with Addison's Disease and Controls Before Exercise Stress Test

	Patients (n = 22)	Controls (n = 25)	*P*
Sex, n (%)			
Female	8 (36.4)	9 (36)	
Male	14 (63.6)	16 (64)	
Age (SD), total, years	44.9 (14.7)	49.8 (11.5)	.213
Female (minimum–maximum)	46.9 (30-64)	49.0 (30-68)	.773
Male (minimum–maximum)	43.8 (22-73)	50.2 (27-77)	.163
SBP (mmHg), all (minimum–maximum)	110 (75-140)	120 (110-140)	**.007**
Female (minimum–maximum)	108 (75-130)	127 (110-140)	.064
Male (minimum–maximum)	111 (90-140)	121 (110-140)	**.028**
DBP (mmHg), all (minimum–maximum)	70 (60-90)	75 (60-98)	**.003**
Female (minimum–maximum)	69 (60-80)	74 (60-80)	.198
Male (minimum–maximum)	69 (60-90)	77 (68-98)	**.008**

Values are expressed as mean (SD) and median (minimum–maximum). Bold values emphasize statistical significance.
DBP, diastolic blood pressure; SBP, systolic blood pressure.

When these parameters were compared among the females and males in the patients and controls, except for the HRR1 in females ($P = .458$), they were significantly lower ($P = .004$ in females, $P < .001$ in males for exercise time; $P = .002$ in males for HRR1; $P = .044$ in females, $P = .022$ in males for HRR2) (Table 2).

Based on the multiple logistic regression analysis, exercise time was independently and negatively related to CI, HRR1, and HRR2 in the patients with AD (odds ratio 0.581, CI 0.381-0.884; $P = .011$) (Table 3).

Discussion

During exercise, needed cardiovascular adjustments should be made to meet metabolic demands and maintain thermoregulation. Cardiac autonomic regulation and HR maintain a balanced parasympathetic (at rest and during low-intensity exercise) and sympathetic neural activity (during high-intensity exercise) while exercising. As the exercise intensity increases, the cardiac parasympathetic activity reduces and sympathetic activity increases. After exercise cessation starts, the post-exercise cardio-deceleration time profile starts. Initially, the HR decreases as a "fast phase" of cardio-deceleration, predominantly mediated by an activating parasympathetic effect. Then, the recovery continues as a 'slow phase'. During this phase, progressive parasympathetic reactivation and sympathetic withdrawal are observed.[9] The HRR indicates that the HR declines after exercise. The recovery period continues until the baseline HR, blood pressure, and electrocardiogram are reached. An impaired HRR after exercise indicates an abnormal vagal tonus and is determined by many cardiological exams. The most commonly accepted values for an abnormal HRR are <12 beats/min at the 1 minute postexercise cooldown period, <18 beats/min at 1 minute with an immediate cessation of movement into either the supine or the sitting position, and <22 beats/min at 2 minutes post exercise.[4,10]

Table 2. Exercise-Induced Data of Patients of Addison's Disease and Controls

	Patients (n = 22)	Controls (n = 25)	*P*
SBP (mmHg), all (minimum–maximum)	158 (94-191)	142.5 (120-220)	.626
Female (minimum–maximum)	154 (94-168)	141 (120-165)	.569
Male (minimum–maximum)	158 (124-191)	150 (130-220)	.746
DBP (mmHg), all (minimum–maximum)	84 (50-92)	86 (55-104)	.118
Female (minimum–maximum)	77 (50-90)	85 (55-104)	.571
Male (SD)	82.2 (8.5)	85.3 (9.9)	.386
Chronotropic index, all (minimum–maximum)	73 (23-170)	92 (35-177)	.052
Female (minimum–maximum)	79 (40-170)	89 (67-177)	.427
Male (minimum–maximum)	73 (23-130)	96.5 (35-114)	.085
Exercise time, all (SD)	5.4 (2.2)	10 (3.2)	**<.001**
Female (minimum–maximum)	4.1 (2.5-6.5)	9.1 (5.5-11)	**.004**
Male (SD)	5.9 (2.4)	11.2 (3.4)	**<.001**
HRR1, all (minimum–maximum)	10 (2-28)	26 (2-43)	**.002**
Female (minimum–maximum)	11 (4-23)	16 (2-43)	.458
Male (minimum–maximum)	9 (2-28)	26 (4-39)	**.002**
HRR2, all (minimum–maximum)	26 (11-56)	39 (10-59)	**.002**
Female (minimum–maximum)	22 (13-56)	35 (26-57)	**.044**
Male (minimum–maximum)	26.5 (11-48)	41.5 (10-59)	**.022**

Values are expressed as mean (SD) and median (minimum–maximu). Bold values emphasize statistical significance.
DBP, diastolic blood pressure; HRR, heart rate recovery; SBP, systolic blood pressure.

Many studies demonstrate that a low HRR after an EST predicts autonomic dysfunction and mortality risk in healthy and some patient groups. Data from 2 large prospective cohort studies in which people with no known diseases were followed up reported that the risk of mortality in the low fitness and low HRR groups is approximately 7 times higher than the risk in the high fitness and high HRR groups, and abnormal HRR is an independent predictor of mortality.[11,12] A prospective cohort study meta-analysis evaluated the relationship

Table 3. Multiple Logistic Regression Test in Addison's Patient Group

Variables	Odds Ratio (95% CI)	*P*
Chronotropic index	0.996 (0.969-1.024)	.777
Exercise time	0.581 (0.381-0.884)	**.011**
HRR1	0.951 (0.837-1.080)	.439
HRR2	1.024 (0.912-1.150)	.683

Bold values emphasize statistical significance. HRR, heart rate recovery.

between HRR and mortality in patient groups (e.g., cardiovascular, cerebral, and renal diseases and cancer). This study demonstrated that the higher risk of cardiovascular events and all-cause mortality compared to general population reference data was correlated with HRR. The increase in risk for every 10 beats per minute decrease in HRR was 13% and 9%, respectively. The authors emphasized that HRR and the risk of fatal cardiovascular events and all-cause mortality were observed as inverse associations independent of the known metabolic factors for cardiovascular disease.[13]

Our study is a rare cardiovascular investigation in patients with AD. Our knowledge of cardiovascular events and death in AD is very limited. We examined CI, exercise time, and HRR values (the first and second minutes during the recovery period) after an EST in patients with AD and controls. The SBP and DBP before the EST were decreased in the patients with AD, but after the EST, they were not significant between the groups. We found that exercise time, HRR1, and HRR2 were lower in the patients with AD than the control participants. Also, the CI was not significantly different between the groups. Additionally, the multiple linear regression analysis revealed that the exercise time of AD patients was lower, and CI, HRR1, and HRR2 were negatively independent.

Considering the data on the relationship between HRR and mortality, our data were remarkable in patients with AD. Cardiovascular disease is significant when studies evaluate the causes of mortality and morbidity in primary or secondary adrenal insufficiency.[14-16] In 2006, Bergthorsdotti et al[3] reported a population-based, retrospective, observational study with an end of follow-up or death in patients with AD covering the period from 1987 to 2001. They noticed that the risk ratio for all-cause mortality was increased in genders (2.19 for men, 2.86 for women) in Sweden. The excess mortality was associated with cardiovascular, malignant, and infectious diseases. Another Swedish study reached a similar conclusion, showing a 2-fold increased mortality in autoimmune AD.[17] In contrast, another population study from a Norwegian survey revealed no significant difference in mortality in the general population of patients but increased mortality in patients diagnosed younger than 40 years old due to adrenal failure, infections, and sudden death.[18]

Along with the increased mortality rates, comorbidities related to cardiovascular or other causes (infections, malignancy, osteoporosis, stroke, autoimmune disease, etc.) are also high in adrenal insufficiency.[3,14-19] In particular, cardiovascular risk factors and events are at the forefront of the comorbidities. Ischemic heart disease is the most common cardiovascular cause of death in a Swedish population study.[3] In 2017, Dalin et al[20] evaluated cardiovascular risk factors in AD compared to controls. The patients had a significantly low body mass index and a lower prevalence of hypertension than the controls, but the incidence of hyperlipidemia and type 2 diabetes mellitus was not different. In a Korean survey study, Hong et al[21] revealed that hypertension and type 2 diabetes mellitus increased during the follow-up period (median, 60.2 months). On the other hand, the prevalence of arrhythmias, ischemic heart disease, stroke, and heart failure were not significantly different in the follow-up.[21]

A few studies have evaluated inflammatory, proinflammatory, and proatherogenic risk factors in AD. However, our knowledge of the association between cardiovascular diseases and mortality and morbidity in AD is limited. It is alleged that this relationship is based on pharmacological GC treatments. Ueland and Husebye,[22] in their review, reported that increased mortality in cardiovascular disease is associated with adverse metabolic effects, such as hypertension, diabetes, hyperlipidemia, and weight gain, in patients with primary and secondary adrenal insufficiency in registry studies. They pointed out that patients with AD had less hypertension and a lower body mass index than the controls. The effects of physiological replacement therapy on long-term cardiovascular morbidity and mortality in AD patients are still unclear.

Our knowledge about the pathophysiology and results of cardiac manifestations in AD is still incomplete. Addison's disease presents metabolic disturbances such as hyponatremia, hyperpotassaemia, and intravascular volume depletion because of hypocortisolaemia. Cortisol has a permissive effect on the synthesis of catecholamines and agonizes the sympathetic nervous system adrenergic receptors. Therefore, it may have direct inotropic effects. Cortisol encourages the synthesis of epinephrine from the adrenal medulla and inhibits catechol-O-methyltransferase, an enzyme that inactivates epinephrine. At the same time, cortisol is required to carry out the functions of the adrenergic receptors, as it induces the transcription and expression of α1-adrenergic receptors in smooth muscle cells.[23] Considering these effects of cortisol, it may be an essential factor affecting acute clinical outcomes, such as sudden death, cardiac arrest, and electrocardiographic abnormalities in the adrenal crisis (e.g., prolonged QT, ST-T wave changes), especially in untreated AD patients. The literature reveals that congestive heart failure, dilated cardiomyopathy, ischemic heart disease, and arrhythmias are cardiovascular outcomes in the chronic process.

In 2016, van der Valk et al[24] reported physical activity and debilitating fatigue data in 328 patients with AD. Standard physical activity was lower in the patients than in the controls. There were no predictors for lower physical activity and no significant difference in physical activity between the quartiles of the total daily dose of GCs in the further analysis. The evaluation of the fatigue score showed that 48% of the patients were abnormally fatigued, while 61% had severe fatigue. The patients' fatigue scores were significantly higher than the controls. Another study examined the cardiovascular system functions by submaximum bicycle ergometry in 48 patients with AD. The authors reported that the working capacity of these patients was lower, and the total volume of work done, loading power, and maximum oxygen consumption were also reduced.[25]

The most common symptoms of adrenal insufficiency are weakness, tiredness, and fatigue, accompanied by muscle and joint pain. In this regard, a low exercise capacity is not a surprising result. When stress factors, such as trauma, sepsis, and infections, increase, regulating the dose of the GCs and mineralocorticoids used in the treatment is recommended. In addition to these stress factors, Bonnecaze et al[26] suggested that the dosage should be adjusted in the case of intensive endurance exercise in AD. In another study, Simunkova et al[27] investigated the effects of a pre-exercise hydrocortisone dose response to short-term strenuous physical activity in 10 females with AD in a randomized controlled study. They revealed that the additional dose of hydrocortisone was not beneficial.

The data from our study are noteworthy, as this is the first study to evaluate the duration of exercise time and cardiac autonomic responses with EST in patients with adrenal insufficiency. In this study, we found that exercise time was reduced in patients with AD compared to healthy controls matched for age and sex. A decreased

exercise time in the patients was expected and is compatible with the data from the clinical symptoms of AD. Moreover, except for HRR1 in the females, we calculated lower HRR1 and HRR2 values in the patients than in the controls after an exercise-induced EST. We anticipate that an impaired HRR is an indicator of autonomic dysfunction and might be an early marker of cardiac dysfunction in patients with AD.

To the best of our knowledge, there were no studies in the medical literature about the association between adrenal insufficiency and autonomic dysfunction based on the cardiovascular system. However, the small sample size was the most significant limitation of our study. Second, we did not examine etiologic factors, treatment protocols, and durations in the AD patients in this study. Third, the comparisons and interpretations were insufficient due to the lack of studies on this subject in literature. Finally, our study was conducted on patients who received their treatment regularly, and cardiac functional tests were performed once. The evaluated cardiac functions of the patients and the morbidity–mortality relationship could be examined at diagnosis or with unethical discontinuation of treatment or could be repeated more than once over the years. Despite these limitations, we hope our data will enlighten a different perspective on comorbidities in patients with AD.

In conclusion, the life expectancy and quality of life of patients with adrenal insufficiency increase with applied replacement therapies. In line with the data of our study, decreased exercise time and cardiac autonomic dysfunction are present in patients with primary adrenal insufficiency. These attributes may be direct or indirect underlying reasons for possible mortality and morbidity in patients with adrenal insufficiency. However, further clinical studies at larger scales are needed to support our data on cardiac autonomic function in patients with adrenal insufficiency.

Ethics Committee Approval: This study was approved by Ethics committee of University of Health Sciences, Antalya Training and Research Hospital (Approval No: 13/08, Date: September 21, 2017).

Informed Consent: Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

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References

1. Newell-Price JDC, Auchus RJ. The adrenal cortex. In: Melmed S, Auchus RJ, Goldfine AB, Koening RJ, Rosen CJ, eds. *Williams Textbook of Endocrinology*. Amsterdam: Elsevier; 2020:480-541.
2. Dunlop D. Eight-six cases of Addison's disease. *Br Med J*. 1963;2(5362):887-891. [CrossRef]
3. Bergthorsdottir R, Leonsson-Zachrisson M, Odén A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. *J Clin Endocrinol Metab*. 2006;91(12):4849-4853. [CrossRef]
4. Balady GJ, Morise AP. Exercise electrocardiographic testing. In: Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Amsterdam: Elsevier; 2019:154-173.
5. Lauer M, Froelicher ES, Williams M, Kligfield P, American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. *Circulation*. 2005;112(5):771-776. [CrossRef]
6. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines) [published correction appears in J Am Coll Cardiol. 2006 Oct 17;48(8):1731]. *J Am Coll Cardiol*. 2002;40(8):1531-1540. [CrossRef]
7. Myers J, Tan SY, Abella J, Aleti V, Froelicher VF. Comparison of the chronotropic response to exercise and heart rate recovery in predicting cardiovascular mortality. *Eur J Cardiovasc Prev Rehabil*. 2007;14(2):215-221. [CrossRef]
8. Tyagi A, Girotra G, Mohta M, Bhardwaj R, Sethi AK. Autonomic dysfunction and adrenal insufficiency in thoracic spine tuberculosis. *Clin Orthop Relat Res*. 2007;460:56-61. [CrossRef]
9. Michael S, Graham KS, Davis GM. Cardiac autonomic responses during exercise and post-exercise recovery using heart rate variability and systolic time intervals-A review. *Front Physiol*. 2017;8:301. [CrossRef]
10. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation*. 2011;123(9):1010-1020. [CrossRef]
11. Kokkinos P, Myers J, Doumas M, et al. Heart rate recovery, exercise capacity, and mortality risk in male veterans. *Eur J Prev Cardiol*. 2012;19(2):177-184. [CrossRef]
12. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA*. 2000;284(11):1392-1398. [CrossRef]
13. Qiu S, Cai X, Sun Z, et al. Heart rate recovery and risk of cardiovascular events and all-cause mortality: a meta-analysis of prospective cohort studies. *J Am Heart Assoc*. 2017;6(5):e005505. [CrossRef]
14. Castinetti F, Sahnoun M, Albarel F, et al. An observational study on adrenal insufficiency in a French tertiary centre: real life versus theory. *Ann Endocrinol (Paris)*. 2015;76(1):1-8. [CrossRef]
15. Chabre O, Goichot B, Zenaty D, Bertherat J. Group 1. Epidemiology of primary and secondary adrenal insufficiency: prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. *Ann Endocrinol (Paris)*. 2017;78(6):490-494. [CrossRef]
16. Quinkler M, Ekman B, Zhang P, Isidori AM, Murray RD, EU-AIR Investigators. Mortality data from the european adrenal insufficiency registry-patient characterization and associations. *Clin Endocrinol (Oxf)*. 2018;89(1):30-35. [CrossRef]
17. Bensing S, Hulting AL, Husebye ES, Kämpe O, Løvås K. Management of endocrine disease: epidemiology, quality of life and complications of primary adrenal insufficiency: a review. *Eur J Endocrinol*. 2016;175(3):R107-R116. [CrossRef]
18. Erichsen MM, Løvås K, Fougner KJ, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. *Eur J Endocrinol*. 2009;160(2):233-237. [CrossRef]
19. Iwasaku M, Shinzawa M, Tanaka S, Kimachi K, Kawakami K. Clinical characteristics of adrenal crisis in adult population with and without predisposing chronic adrenal insufficiency: a retrospective cohort study. *BMC Endocr Disord*. 2017;17(1):58. [CrossRef]
20. Dalin F, Nordling Eriksson G, Dahlqvist P, et al. Clinical and immunological characteristics of autoimmune Addison disease: a nationwide Swedish multicenter study. *J Clin Endocrinol Metab*. 2017;102(2):379-389. [CrossRef]
21. Hong AR, Ryu OH, Kim SY, Kim SW, Korean Adrenal Gland and Endocrine Hypertension Study Group, Korean Endocrine Society. Characteristics of Korean patients with primary adrenal insufficiency: a registry-based nationwide survey in Korea. *Endocrinol Metab (Seoul)*. 2017;32(4):466-474. [CrossRef]

22. Ueland GA, Husebye ES. Metabolic complications in adrenal insufficiency. *Front Horm Res*. 2018;49:104-113. [CrossRef]
23. Schumaecker MM, Larsen TR, Sane DC. Cardiac manifestations of adrenal insufficiency. *Rev Cardiovasc Med*. 2016;17(3-4):131-136. [CrossRef]
24. van der Valk ES, Smans LC, Hofstetter H, et al. Decreased physical activity, reduced QoL and presence of debilitating fatigue in patients with Addison's disease. *Clin Endocrinol (Oxf)*. 2016;85(3):354-360. [CrossRef]
25. Zelinskiĭ BA, Vernigorodskaia MV, Vernigorodskiĭ VS, Gamarnik LV, Palamarchuk AV. Assessment of the working capacity of patients with chronic cortico-adrenal insufficiency. *Ter Arkh*. 1987;59(11):132-134.
26. Bonnecaze AK, Reynolds P, Burns CA. Stress-dosed glucocorticoids and mineralocorticoids before intensive endurance exercise in primary adrenal insufficiency. *Clin J Sport Med*. 2019;29(6):e73-e75. [CrossRef]
27. Simunkova K, Jovanovic N, Rostrup E, et al. Effect of a pre-exercise hydrocortisone dose on short-term physical performance in female patients with primary adrenal failure. *Eur J Endocrinol*. 2016;174(1):97-105. [CrossRef]