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Correlating Serum Adropin Levels with Blood Coagulation Indices across Physical Activity Levels in Young Adults

Hamid Rajabi [1]✉, **Seyed Sarmad Zahmatkeshan** [1], **Azam Ahmadi** [1]

[1] Department of Exercise physiology, Faculty of Physical Education and Sport Sciences, Kharazmi University, Tehran, Iran

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✉ ***Correspondence to:***
Hamid Rajabi
Department of Exercise physiology, Faculty of Physical Education and Sport Sciences, Kharazmi University, Tehran, Iran

Email:
hrajabi1346@gmail.com

A B S T R A C T

Introduction: Evidence suggests a link between serum adropin levels and coagulation factors, with physical activity boosting adropin circulation. This study investigates the correlation between adropin and blood coagulation factors in young adults at varying activity levels.

Material & Methods: Fifty healthy young adults were divided into active and inactive groups using the Baecke questionnaire. Blood samples assessed adropin and coagulation factors. Statistical tests included Mann-Whitney and independent t-tests for comparison, with Spearman's correlation coefficient determining strength.

Results: Active participants exhibited significantly lower fibrinogen ($p<0.05$) and higher adropin levels ($p<0.05$) compared to inactive peers. Physical activity correlated negatively ($r=-0.27$, $p=0.05$) with fibrinogen but not with adropin and other coagulation factors.

Conclusion: Elevated physical activity levels correlate with heightened serum adropin and reduced serum fibrinogen. Moreover, serum fibrinogen, a critical coagulation factor influencing blood clot formation, appears particularly sensitive to the effects of physical activity.

Keywords: Adropin, Blood Coagulation Factors, Exercise

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Introduction

Adropin is considered as a biomarker for the early diagnosis of cardiovascular diseases (1) because its low concentration is regarded as a risk factor for coronary heart disease (2, 3). Researchers indicated that blood adropin levels decrease in diseases such as coronary artery disease, heart disease, and endothelial dysfunction (4, 5). Adropin protein is encoded by the Enho gene, which is mostly expressed in the brain and liver. However, the above-mentioned protein is found in various tissues such as the lung, central part of the kidney, muscles, blood connective mononuclear cells, breast cancer cells, heart, and blood vessels, as well (6). Adropin in endothelial cells (ECs) increases the expression level of endothelial nitric oxide synthase (eNOS) by activating vascular endothelial growth factor receptor 2 (VEGFR2) and PI3K-Akt and ERK1/2 pathways (7, 8).

In fact, adropin can phosphorylate Akt at Ser473 and eNOS at Ser177 through VEGFR2-PI3K-Akt and VEGFR2-ERK1/2 signaling pathways, as well as upregulating skeletal muscle to increase the ratio of phosphorylated eNOS (p-eNOS)/eNOS and raise vascular nitric oxide (NO) production and bioavailability to protect blood vessels (9-12). Thus, an increase in NO in endothelial cells leads to a decrease in vascular stiffness and subsequent improvement of angiogenesis, resulting in affecting endothelial function (7, 13). NO, which is mainly generated from L-arginine and oxygen molecules by the endothelial enzyme eNOS in the blood vessel wall (14), is considered as a strong inhibitor of platelet adhesion to the vessel wall and platelet aggregation and prevents more platelets from being recruited for the formation of growing thrombosis (15). Endothelial cells are regarded as essential components in the blood coagulation system, the integrity and function of which play a critical role in maintaining homeostasis and preventing platelet activation and thrombosis (16).

Based on the evidence, the release of NO from endothelial cells inhibits the function of platelets and prevents coagulation disorders related to cardiovascular diseases (17). Park et al. argued that NO can affect the coagulation process (15). However, Armand et al. did not observe any effect of internal (endogen) or external origin (exogen) NO on blood coagulation factors (18).

Old and recent evidence indicate that an active lifestyle during youth and throughout life plays a significant role in managing the primary risk factors of diseases including diabetes and cardiovascular diseases (19, 20). Based on some studies, regular exercise leads to an increase in enzymes related to the synthesis and formation of nitric oxide and a rise in the plasma level of nitric oxide metabolites (21). Different types of exercise and physical activities create appropriate alterations in blood coagulation indicators (fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)), and fibrinolysis reduces the risk of cardiovascular diseases (21-23).

For example, Zantini et al. observed a decrease in blood fibrinogen after 12 weeks of aerobic training in people aged 22-50 years with resting diastolic blood pressure between 90-104 mm Hg (24). However, Furkva et al. did not observe an alteration in fibrinogen level compared to the control group after 12 weeks of walking in women aged 32-57 years (25). Based on some studies, resting and post-exercise PTT, PT activities are not affected by long-term endurance training programs, and no difference is reported between sedentary and athletic samples (22, 26, 27). In another study, a significant decrease was observed in fibrinogen levels, PTT, PT after four weeks of aerobic and strength training on elderly people, and increased D-Dimer levels were reported (28).

Adropin is considered a candidate for NO regulation, influenced by physical activity and exercise. Additionally, Parlek et al. claimed that low and moderate-intensity swimming exercise is associated with increased adropin levels in aged rats (29).

According to studies, continuous endurance and interval training can serve as intervention strategies to effectively stimulate adropin release into the bloodstream (9). Overall, a correlation is observed between serum adropin levels and coagulation factors, given that adropin correlates positively with NO, which inhibits blood coagulation and reduces the factors involved in this process (20). Future research should explore the relationship between coagulation factors and adropin in youth and whether the level of exercise activity among young adults correlates with these factors. The present study aims to investigate the correlation between adropin and blood coagulation factors among young adults with varying levels of physical activity.

Materials and methods

The study included 50 healthy young adults, comprising 25 men and 25 women, with an average age of 28.23 ± 2.28 years, height of 170 ± 9 cm, and body mass index of 24.71 ± 4.88 kg/m², who volunteered to participate. Participants were categorized into active and inactive groups using the questionnaire by Baecke et al. (1982) (30), which assesses physical activity levels in work, sports, and leisure time. Prior to blood sample collection, participants were briefed on the study protocol and provided written consent to participate. They retained the option to withdraw from the study at any point. The research proposal was submitted to the Ethics Committee of the Sports Sciences Research Institute and received approval (SSRI.REC-2306-2288 (R1)) (Figure 1).

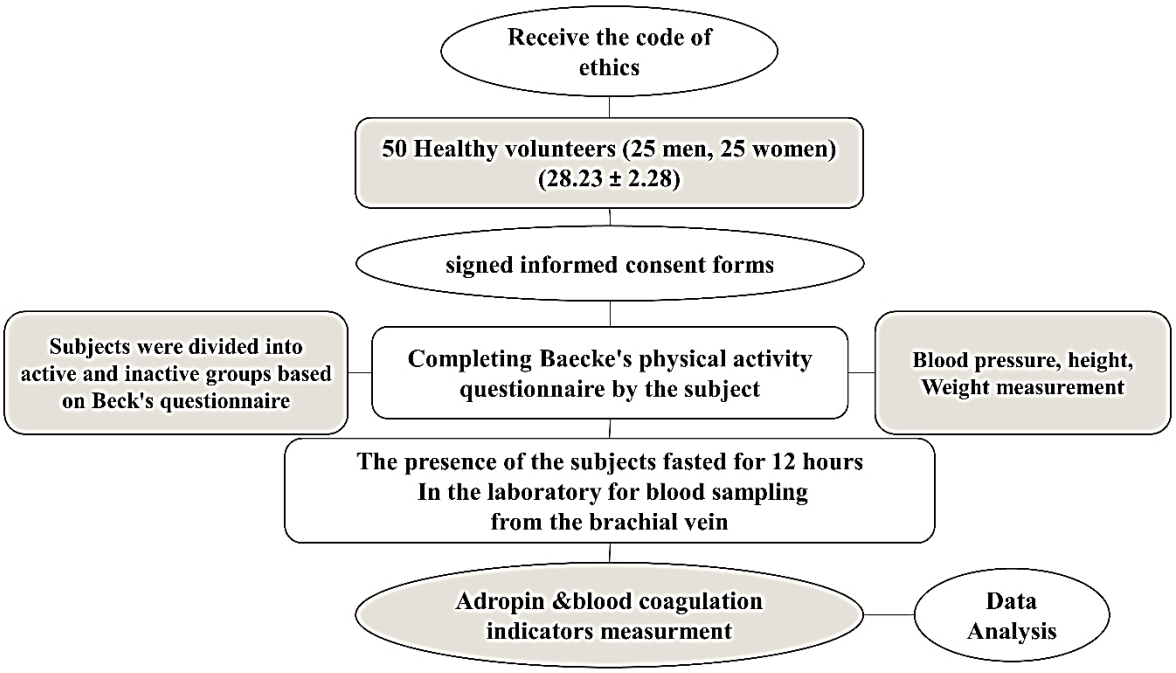

Figure 1. Research protocol

Baecke questionnaire

The Baecke questionnaire serves as a tool to assess individuals' physical activity over the preceding 12 months. Comprising 16 questions, it encompasses three primary activity domains: occupational, sports, and recreational activities within the past year. The initial section of the questionnaire, consisting of eight questions, pertains to various body positions and movements typically encountered during work. The subsequent segment addresses individuals involved in both primary and secondary sports activities. The final part focuses on leisure-time physical activity. Subsequently, scores from the three sections are aggregated to determine an individual's overall

physical activity level. The maximum attainable score on this questionnaire is 15.

To effectively differentiate between active and inactive groups, individuals scoring nine or higher were categorized as the active group (n=9), while those scoring below six were classified as the inactive group (n=11).

Thus, the first objective of the study was to examine the differences in variables between the active and inactive groups. Furthermore, both active and inactive participants (totaling 20 individuals) as well as the entire cohort (50 individuals) were included in the statistical analysis to assess the correlation between variables.

Measuring blood factors and anthropometric indices

The subjects' height was measured using a stadiometer (cm), and body weight (kg) was measured with an electronic scale prior to blood sampling. Subsequently, the body mass index was calculated by dividing body weight (kg) by the square of height (m).

Next, participants were instructed to fast for 12 hours, consuming only water, before blood collection at the Navid Pathology Laboratory. Blood samples (5 cc) were drawn from the brachial vein of participants and collected in tubes containing anticoagulant (Trisodium citrate). The serum was separated from the blood samples using a Hettich centrifuge (Germany) at 3000 rpm for 15 minutes.

Prothrombin time (PT) and partial thromboplastin time (PTT) were manually measured using a Fisher kit. Fibrinogen levels were determined using a coagulometer, while D-Dimer levels were assessed using an Immulite device (Germany).

Finally, serum adropin levels were measured using the Zelbio ELISA kit (manufactured in Germany), and the values were recorded using a Plate Reader device (manufactured in the United States).

Statistical analysis

The data were analyzed using SPSS software version 23. Normality of the data was assessed using the Kolmogorov-Smirnov test. Results were presented as mean ± standard deviation (SD) ($P < 0.05$).

To compare average variables of fibrinogen, PT, PTT, PT activity, and D-Dimer between active and inactive groups, the Mann-Whitney test was employed, considering the non-normal distribution of the data.

For comparing adropin values between active and inactive groups, the independent t-test was utilized, given the normal distribution of the data.

Spearman's correlation coefficient was calculated to determine correlation coefficients ($P < 0.05$).

Results

Table 1 presents the general characteristics of the subjects overall and separately for the active and inactive groups. No significant difference was observed between the active and inactive groups in terms of average age, weight, and body mass index ($P > 0.05$).

Table 1. Characteristics of Subjects: Mean and Standard Deviation for Separate Groups and Total Active and Inactive Subjects.

Groups	Age (year)	Weight (kg)	Height (meters)	Body mass index (kilograms per square meter)
Active (9 people)	22.74 ± 2.78	67.50 ± 10.35	1.72 ± 0.12	22.74 ± 2.78

Inactive (11 people)	23.73 ± 2.31	77.53 ± 25.44	1.70 ± 0.09	26.23 ± 6.02
The total number of subjects (20 people)	23.28 ± 2.78	72.88 ± 19.12	1.70 ± 0.09	24.71 ± 4.88

As depicted in Table 2, coagulation factors, including PT, PT activity, PTT, and D-Dimer, did not exhibit statistical significance between the active and inactive groups, showing no significant difference between the two groups. However, serum fibrinogen levels were significantly higher in the inactive group (Figure 2) ($P < 0.05$). Additionally, the average serum adropin level was notably higher in the active group compared to the inactive group (Figure 3) ($P < 0.05$).

Table 2. Mean and Standard Deviation of Coagulation Factors and Adropin in Active and Inactive Groups.

Groups	Prothrombin time (Sec)	PT activity (%)	PTT (sec)	Fibrinogen (mg/dl)	D-Dimer (ng/ml)	Adropin (ng/l)
Active (9 people)	12.62 ± 0.17	99.05 ± 1.36	31.11 ± 2.36	*330.44 ± 58.92	90.50 ± 92.23	*131.62 ± 15.84
Inactive (11 people)	12.55 ± 0.15	99.58 ± 1.14	30.90 ± 3.33	408.00 ± 60.34	86.86 ± 67.21	92.55 ± 22.81

*: Statistically significant between groups

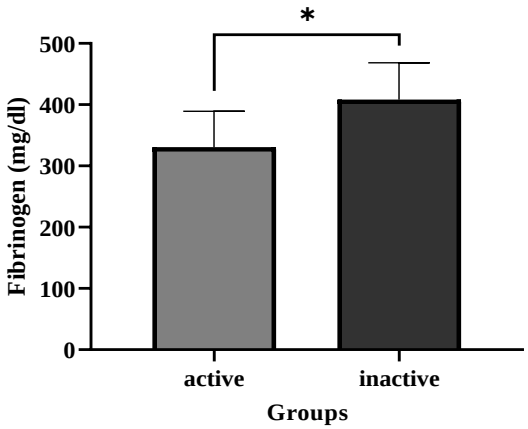

Figure 2. Fibrinogen difference between active and inactive groups

Table 3 illustrates the Spearman correlation coefficients between the measured variables in individuals. A positive and weak correlation is observed between serum adropin values and D-Dimer, PTT, and Prothrombin Time. Additionally, a negative and weak correlation is noted between serum adropin values and Fibrinogen and PT activity; however, these correlations are not statistically significant in both cases.

Table 3. Correlation Coefficient Between Coagulation Factors and Adropin (n=50).

Variable	Prothrombin time	PT activity	PTT	Fibrinogen	D-Dimer	Adropin
Adropin	0.13	- 0.13	0.05	- 0.08	0.01	1
Significant degree	0.37	0.37	0.74	0.58	0.93	

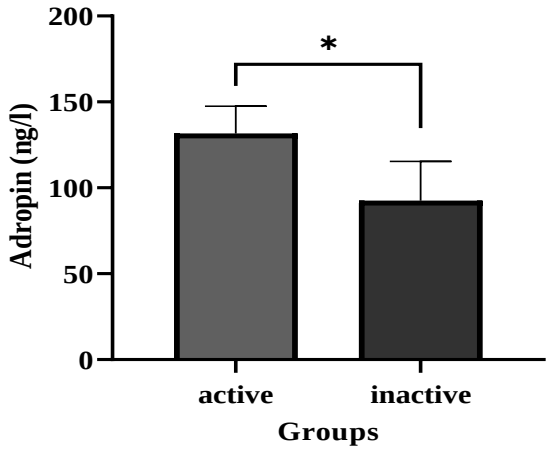

Figure 3. Adropin difference between active and inactive groups

Table 4 presents the correlation between physical activity and coagulation factors for all subjects (n=50). A positive and weak correlation is reported between the amount of physical activity and PT and PTT. Furthermore, a negative and weak correlation is observed between physical activity and D-Dimer, Fibrinogen, and PT activity, none of which are statistically significant. However, Table 5 indicates a significant correlation between fibrinogen and physical activity ($P < 0.05$).

Table 4. Correlation Coefficient Between Coagulation Factors and Physical Activity (n=50).

Variable	Prothrombin time	PT activity	PTT	Fibrinogen	D-Dimer	Physical Activity
Physical Activity	0.14	- 0.14	0.01	- 0.27	- 0.1	1
Significant degree	0.32	0.37	0.92	0.05	0.48	

Table 5. Correlation Coefficient Between Coagulation Factors and Physical Activity (n=20).

Variable	Prothrombin time	PT activity	PTT	Fibrinogen	D-Dimer	Physical Activity
Physical Activity	0.24	- 0.24	0.03	* - 0.46	- 0.05	1
Significant degree	0.30	0.30	0.89	0.04	0.83	

*Statistically significant correlation

Discussion

Based on the results, no significant correlation was found between the subjects' physical activity levels, as measured by the Baecke questionnaire, and the values of PT, PTT, PT activity, and D-Dimer, which are among the blood coagulation indicators. This lack of differentiation in coagulation system indicators between active and inactive individuals may be attributed to the young and healthy nature of the subjects.

These findings align with those reported by van den Berg et al., who similarly observed no effect on blood coagulation factors following training in healthy subjects (26, 31). Additionally, Rezaian et al. did not observe any impact on PT in healthy subjects after an 8-week period of submaximal aerobic training on a bicycle, although they did report a significant decrease in PTT and fibrinogen levels (32).

Furthermore, Fathi et al. observed non-significant alterations in fibrinogen and D-dimer levels, along with increased PT and PTT factors, after 4 weeks of resistance training in inactive subjects (33). These findings suggest that not all cardiovascular risk factors carry equal weight in indicating risk status, with factors such as fibrinogen potentially demonstrating higher sensitivity in this regard.

However, numerous epidemiological studies have consistently shown a strong and clear relationship between certain risk factors for cardiovascular diseases and improvements in individuals' fitness, physical activity levels, and adoption of a healthy lifestyle (34).

Firstly, the correlation between physical activity and coagulation factors was examined among all subjects, revealing a weak relationship in this context. However, the results indicated that the Baecke questionnaire may lack high sensitivity in distinguishing between active and inactive individuals. Consequently, 60% of subjects with intermediate scores were excluded from the correlation analysis to enhance the certainty of determining individuals' active or inactive status.

With this adjustment, the correlation results saw a slight increase, particularly in the relationship between physical activity and fibrinogen, which became statistically significant. However, other factors did not exhibit a statistically significant correlation with the level of physical activity. Notably, factors such as PT, partial thromboplastin time (PTT), PT activity, and D-dimer appeared unaffected by individuals' physical activity levels, which were not high (maximum score of 12 out of 15).

It's worth noting that the size of the studied population may impact the results, suggesting the need for larger sample sizes in future studies. Additionally, alongside the Baecke questionnaire, incorporating physical fitness tests could offer a more accurate determination of individuals' physical activity levels, a consideration for future research endeavors.

An increase in endothelial nitric oxide synthase (eNOS) levels is among the mechanisms that reduce

the risk of cardiovascular diseases among active individuals due to its beneficial effects on the vessel wall (35). Numerous reports have highlighted the impact of exercise training on coagulation, fibrinolysis, and platelet activity. Several studies have demonstrated improvements in fibrinolysis capacity and reductions in plasma fibrinogen levels following long-term regular exercise, emphasizing the role of exercise as an antithrombotic agent (22, 36).

For example, Hilberg et al. observed a decrease in prothrombin time (PT) in both healthy and hypertensive subjects after an exercise test (37). However, conflicting results across different studies may stem from variations in exercise protocols or programs, study populations (e.g., age, gender, presence of coronary heart disease), and analytical methods employed (25, 46). Notably, some studies have shown that elderly individuals exhibit more pronounced alterations in D-dimer levels compared to younger individuals (38).

The results of the present study indicated significant differences in fibrinogen and adropin levels between the active and inactive groups. Specifically, blood adropin levels were significantly higher in the active group compared to the inactive group, consistent with findings from previous studies demonstrating that exercise and physical activity increase serum adropin levels (6, 39, 40). Additionally, fibrinogen values were higher in the inactive group, aligning with results reported by Manuel et al., who found a significant relationship between fibrinogen values and physical activity in adults without chronic diseases (41).

Furthermore, Koing et al. investigated the correlation between plasma fibrinogen levels and physical activity over a one-year period (12 months) and observed a significant decrease in fibrinogen levels (42). Additionally, Eberhardt et al. found a significant relationship between physical activity and low aerobic endurance with high fibrinogen levels, consistent with the findings of the present study (43). However, Ponji et al. reported no alteration in plasma fibrinogen levels among men and women after 24 weeks of training (44).

According to some studies, the decrease in fibrinogen levels due to physical activity may be attributed to reductions in individuals' weight and percentage of body fat (28). In the present study, although the difference was not statistically significant, the inactive group exhibited higher weight and BMI compared to the active group. Nevertheless, this slight difference may potentially influence fibrinogen levels. Weight gain and obesity are associated with inflammation, which can stimulate fibrinogen production (45). Furthermore, some studies suggest that the reduction in fibrinogen levels among active individuals may be linked to a decrease in the secretion of pro-inflammatory cytokines (33). Another possible mechanism for fibrinogen reduction due to exercise is the increase in plasma volume and its transfer from the intravascular space to the extravascular space (46).

Conclusion

Based on the findings, no significant correlation was observed between participants' physical activity levels, as measured by Baecke's questionnaire, and variables such as PT, PTT, PT activity, and D-Dimer. However, physical activity did show an impact on the levels of fibrinogen and adropin. Specifically, higher levels of physical activity were associated with increased serum adropin levels and lower fibrinogen levels, suggesting a healthier cardiovascular and coagulation system.

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

HR contributed to the study design and manuscript revision. SSZ was involved in data collection, laboratory testing, and data analysis. AA contributed to data analysis and manuscript writing.

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