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# The Long-term Effects of Colostrum Supplementation and Sprint-Endurance Training on Plasma VEGF Levels in Male Wistar Rats

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## Abstract

**Introduction:** Bovine colostrum is an antioxidant material, however, its potential impact along with various methods of physical exercise on changes in vascular endothelial growth factor (VEGF)is unclear. The aim of this study was to evaluate the long-term effects of colostrum supplementation and sprint-endurance training on plasma VEGF levels in male Wistar rats.

**Methods:** In our study, 48 male Wistar rats were used. The rats were assigned into 6 groups (control, colostrum supplementation, aerobic exercise, anaerobic exercise, colostrum supplementation-aerobic exercise, and colostrum supplementation-anaerobic exercise). Groups receiving colostrum were orally administrated 300 mg/kg/d bovine colostrum for 10 weeks. Training groups received sprint-endurance training, 3 times a week for a period of 10 weeks, with specified intensity and duration. In all the groups, blood samples were taken in the morning on an empty stomach 24 hours after the last training session. Data were analyzed using SPSS version 19 software and the Kolmogorov-Smirnov (K-S), one-way analysis of variance (ANOVA), and Tukey tests at $\alpha < 0.05$.

**Results:** The findings showed that colostrum supplementation for 10 weeks with dose of 300 mg/kg significantly increased VEGF levels in all the study groups compared to the control group receiving normal saline ($P < 0.05$). Moreover, colostrum supplementation along with sprint-endurance training increased VEGF levels more effectively compared to other groups receiving sprint-endurance training along with normal saline.

**Conclusion:** The findings indicated that intake of colostrum, as a strong antioxidant supplement having enzymatic and non-enzymatic antioxidants, along with sprint-endurance training for 10 weeks increased plasma VEGF levels, thereby playing a possible significant role in vascular angiogenesis.

**Keywords:** Bovine colostrum, Endurance training, Sprint training, Vascular endothelial growth factor (VEGF), Wistar rats

## Introduction

Regular physical exercise reduces cardiovascular diseases, diabetes, and cancer,[1,2] while intense contractions and production of large amounts of free radicals induce lipid membrane peroxidation, damage of cellular proteins and DNA, and ultimately, cell death.[3,4] Athletes consume antioxidant supplements especially vitamin E to reduce and remove free radicals.[4] It has recently been revealed that although high levels of free radicals could cause cellular damage, moderate to low levels of oxidants play several regulatory roles in the cell, such as regulation of force production in skeletal muscle, control of gene expression, and regulation of cellular signaling pathways.[5] Angiogenesis [Angiogenesis refers to the increased density of capillaries in cardiac and skeletal muscle] is one of the major signaling pathways in which free radicals are involved.[3,5] Angiogenesis requires

the involvement of various cells, signaling pathways, growth factors and receptors,[6] and eventually induces the growth of new blood vessels from pre-existing vessels via the 2 sprouting[7,8] and longitudinal splitting[1] modes. Vascular endothelial growth factor (VEGF) is the main mitogen involved in angiogenesis. VEGF is a 45 kDa glycoprotein mostly secreted from endothelial cells[8] and tumor cells.[3,9,10] It leads to the survival, proliferation, and migration of endothelial cells, and ultimately, formation of new blood vessels by binding to its receptor, which is, VEGF receptor-2 (VEGFR-2).[7,11] For binding of VEGF, an optimal level of antioxidants must exist on the outer surface of the cell, since these antioxidants mediate the binding of VEGF to VEGFR-2.[5] However, it has been shown that binding of VEGF to VEGFR-2 activates NADPH oxidase and consequently produces oxidants necessary for angiogenic response to VEGF signaling.[9]

Angiogenesis is a multistep process including migration and proliferation of endothelial cells and organization of cell masses as tube-like structures, interconnection of tube-like structures, and finally, maturity and stability of the forming vessel.[12,13] Sprouting refers to the process of branching and budding of new capillaries from pre-existing vessels. Excessive proliferation of endothelial cells is an essential prerequisite for this event.[14] On the contrary, bisection refers to the longitudinal splitting and division of a capillary into 2 new capillaries.[15] Proliferation, differentiation, and migration of vascular endothelial cells (in both methods) is a prerequisite for the formation of new vessels,[16] which occurs through a series of growth factors.[17] Angiogenic factors are agents directly or indirectly involved in the formation of new capillaries, helping in the formation and evolution of blood vessels to such a degree that the absence of any of these factors would disrupt the formation and evolution of capillaries.[18] VEGFs perform their biological actions on target cells through interaction with existing receptor tyrosine kinases (RTKs) in the cell plasma membrane. These receptors bind to ligands, then form dimmers and are phosphorylated, thereby inducing an intracellular signaling cascade.[19] Through up-regulation of anti-apoptotic factors,[20] DNA synthesis, degradation of the basement membrane, and also phosphorylation of endothelial intercellular adhesive components and tight junctions, VEGF promotes the survival, proliferation, migration, and permeability of vascular endothelial cells, respectively, and ultimately leads to the formation of new blood vessels.[21]

Multiple studies have shown that endurance training produces positive effects on angiogenesis in healthy humans, and the role of exercise in increasing capillary growth in skeletal muscles is well known.[22] Studies conducted in this field indicate that skeletal muscle capillary density, both in animal and human models, is increased in response to exercise training.[23,24] Although physical exercise can regulate serum levels of angiogenic factors, to prevent creation of pathological conditions such as arteriosclerosis and arthritis, molecular mechanism of capillary network growth in response to exercise training should be elucidated.[25] As shown in some previous studies, serum VEGF values increased after exercise,[26,28] whereas other studies reported no changes in serum VEGF levels after acute exercise.[8,27] In addition, Gu et al reported reduced serum VEGF concentration after exercise.[29] Several studies have also contemplated the effect of free radicals on angiogenesis. Zhao et al, analyzing the effect of reactive oxygen species (ROS) on cardiac angiogenesis following myocardial infarction (MI), found that angiogenesis occurs in the first week of MI, developed in spatio-temporal symmetry with ROS.[30] Chen et al, through the expression of NADPH oxidase subunits, detected sprouting and budding of rat aortic rings from suppressed vessels.[31]

Colostrum is a nutrient that is produced by the mammary glands of female mammals and is the first breast milk secreted immediately after delivery. Colostrum contains lower fat and higher protein compared to breast milk. Many properties and benefits have been enumerated for colostrum and it has been recommended since earlier times.[32] More recently, colostrum has been used as a substance with immunomodulatory properties as well as antibacterial, anti-inflammatory, and antioxidative properties in patients with rheumatoid arthritis. It is also considered as one of the compounds used in the preparation of vaccines.[33] Akin to human colostrum, bovine colostrum has numerous bioactive compounds, and research has shown that immune factors in the bovine colostrum far exceed those in the human colostrum.[34] Colostrum also consists of several growth factors such as VEGF.[35] Moreover, athletes tend to use antioxidants to remove and scavenge free radicals which act as cellular mediators in the process of vascularization.[3,5] This can reduce vascularization in athletes taking antioxidant supplements. Even despite all the studies conducted on colostrum and accessibility to sports supplements enriched with colostrum, there are no studies on the interactive effects of colostrum supplementation and exercise training on VEGF in a controlled manner and in an experimental design (animal model). This study aimed to address the question of whether intake of bovine colostrum can change VEGF levels after physical exercises.

## Methods

For this experimental study, 48 male Wistar rats with the weight range of 200-250 g were purchased from the Animal Laboratory for Experimental Medicine Research Center, Birjand University of Medical Sciences. The aforesaid animals were kept in cages made of polyethylene for 1 week without any intervention for adaptation to the laboratory environment in standard conditions (12-hour light/dark cycle, free access to animal food and healthy tap water, and temperature range of 22-25°C).

Accordingly, laboratory experiment was designed and performed on animals based on the ethics checklist for experiments involving animals issued by the Ministry of Health and Medical Education, which is focused on using the minimum number of animals and minimizing animal pain in different stages of the study.

After 1 week, the animals were randomly divided into 6 groups as follows: group 1 (control) receiving 1 mL of normal saline per day; group 2 (endurance training) receiving 1 mL of normal saline per day along with 3 sessions of aerobic exercise training per week; group 3 (sprint training) receiving 1 mL of normal saline per day along with 3 sessions of anaerobic exercise training per week; group 4 (supplementation without training) receiving 300 mg/kg colostrum powder per day; group 5 (supplementation with endurance training) receiving 300 mg/kg colostrum powder per day along with 3 sessions of aerobic exercise training per week; and group 6 (supplementation along with sprint training) receiving 300 mg/kg colostrum powder per day along with 3 sessions of anaerobic exercise training per week.

Colostrum was obtained from Holstein cows in less than 6 hours after delivery, immediately transferred to sterile containers and then frozen at temperatures below -80°C. The frozen samples were powdered using Freeze Dryer (Dena Co., Iran). Efficiency of this method was 25%.

**Table 1.** Endurance Training Protocol

| Training Weeks | Training Speed (m/min) | Vo2max (≈%) | Training Duration (min) |
|---|---|---|---|
| First | 15 | 55 | 15 |
| Second | 15 | 55 | 15 |
| Third | 20 | 70 | 20 |
| Fourth | 20 | 70 | 25 |
| Fifth | 25 | 78 | 30 |
| Sixth | 25 | 78 | 40 |
| Seventh | 30 | 85 | 50 |
| Eighth | 30 | 85 | 60 |
| Ninth | 30 | 85 | 60 |
| Tenth | 30 | 85 | 60 |

The subjects were orally fed colostrum supplements and normal saline via gavage per day for 10 weeks The aforesaid groups received sprint-endurance training,[36,37] by a special treadmill for rodents (Tajhiz Gostar Omid Iranian Co., Iran) based on the training protocols illustrated in Tables 1 and 2.

Changes in VEGF levels were measured in order to evaluate the angiogenic effectiveness of colostrum in this study. Twenty-four hours after the last training session, all the groups were anaesthetized with inhalation anesthetics (diethyl ether) in the morning on an empty stomach. Blood samples were taken directly by a veterinary surgeon from the hearts of 8 rats in each group. Then, the blood samples were transferred to labeled test tubes containing EDTA anticoagulant and centrifuged at 3000 rpm for 15 minutes. After preparing the plasma, VEGF values were measured by ELISA kits (eBioscience Co.) in Autoanalyzer (Tekken-Japan). Data were analyzed using SPSS version 19.0 and their normal distribution was determined by the Kolmogorov-Smirnov (K-S) test. Data were further analyzed using one-way analysis of variance (ANOVA) and Tukey test at $P<0.05$ level of significance.

## Results

Distribution of VEGF values determined by the K-S test was normal ($P>0.05$). Comparison of the aforesaid groups using one-way ANOVA revealed a significant difference in the mean values of VEGF ($P=0.001$); thus, groups were compared using Tukey test and 95% CI. Figure 1 illustrates the mean and standard deviation of VEGF values. The results of this study showed that VEGF values of rats in the groups 2 (endurance training+saline), 3 (sprint training+saline), 5 (endurance training+colostrum supplementation), and 6 (sprint training+colostrum supplementation) significantly increased compared to those in the control group ($P=0.001$). VEGF values in group 4 (colostrum supplementation) also significantly increased compared to those in the control group ($P=0.033$). Results indicated greater increases of VEGF values in training groups receiving colostrum supplements

**Table 2.** Sprint Training Protocol

| Training Weeks | Treadmill Incline (grade) | Recycling (s) | Vo2max (≈%) | Speed (m/min) | Intervals of 40 s |
|---|---|---|---|---|---|
| First | 5 | 100 | 95 | 35 | 3 |
| Second | 5 | 100 | 100 | 40 | 4 |
| Third | 5 | 100 | 100 | 45 | 5 |
| Fourth | 5 | 100 | 100 | 50 | 6 |
| Fifth | 5 | 100 | >100 | 55 | 6 |
| Sixth | 10 | 100 | >100 | 55 | 6 |
| Seventh | 10 | 120 | >100 | 55 | 7 |
| Eighth | 10 | 120 | >100 | 60 | 8 |
| Ninth | 15 | 120 | >100 | 60 | 8 |
| Tenth | 15 | 120 | >100 | 60 | 8 |

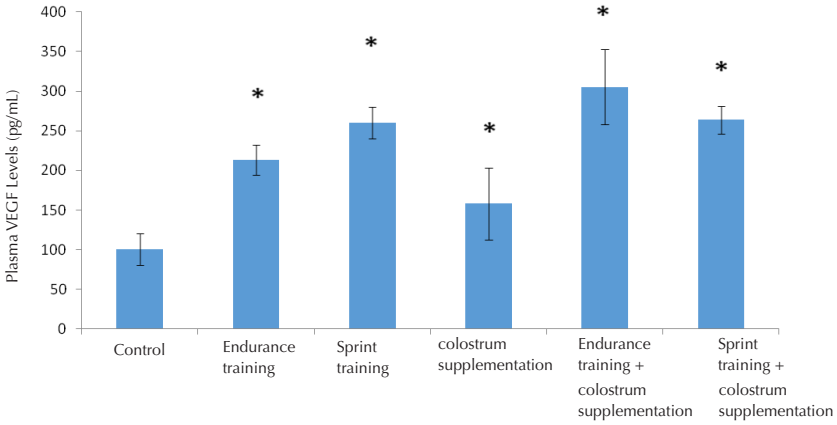


**Figure 1.** Comparison of the Mean and Standard Deviation of Plasma VEGF Levels (pg/mL) in Study Groups.

compared to training groups receiving saline; however, this increase was not significant (Figure 1).

## Discussion

The results obtained for this study showed that colostrum supplementation for 10 weeks along with sprint-endurance training had a significant effect on the plasma VEGF levels in all study groups compared to the control group. Greater increases of plasma VEGF levels were reported for sprint-endurance training groups receiving colostrum supplements than for sprint-endurance training groups receiving saline (without supplementation); however, this increase was not significant.

In regard to the effects of physical exercise on VEGF levels, several studies have been conducted which have yielded contradictory results. Results of the present study revealed increased VEGF levels for sprint-endurance training groups without supplementation, which are consistent with the results of some studies[23,25,28] while different from the results of some other studies.[8,29] The specific training method applied in this study could account for such contradictory results. In addition to the aforesaid training method, different timings of the blood sample collection may also account for the contradictory results of the present study and the study conducted by Thorell et al.[17] In fact, in the latter study blood sampling was performed 1 hour after exercise, whereas in the present study blood samples were collected 24 hours after the last training session and in the morning on an empty stomach. It was revealed that glycogen levels in skeletal muscle dropped during exercise, thereby resulting in increased cAMP phosphorylation; then, increased PGC-1α led in turn to the increase of VEGF gene expression.[38] In this regard, an inverse relationship was reported to exist between the level of interleukin-6 (IL-6) released from the skeletal muscle in the last stages of exercise and muscle glycogen content after exercise. More precisely, the less the muscle glycogen storage is at the end of exercise, the more the IL-6 release from skeletal muscles would be in the last stages of exercise.[39] Schulze-Tanzil et al reported a positive correlation between the secretion and increase of interleukin-1 beta (IL-1 beta), tumor necrosis factor-alpha (TNF-α), IL-6, and VEGF after exercise-induced muscle and tendon cell damages.[40]

Exercise-induced VEGF expression may be increased by several mechanisms. The hypoxia-inducible factor (HIF) is elevated in exercise-induced hypoxic-ischemic conditions.[41] VEGF gene is partially affected by this factor, thereby increasing the gene expression. In addition, the accumulation of lactate and adenosine increases along with elevated intensity of exercise. Adenosine increases the cAMP concentration, and consequently, mRNA of VEGF through the activation of alpha-2 (α2) receptor.[21] Moreover, adenosine has been effective in the induction of cellular VEGF.[42] During exercise, tissue blood flow increases and exerts a hydrodynamic-frictional force on the vessel wall. Acute exertion of this force increases the expression of vasodilators, especially nitric oxide (NO), prostacyclin, and prostanoids. The above factors could increase VEGF gene expression. However, few similar studies have evaluated the effects of antioxidant supplementation coupled with exercise on VEGF levels, the results of which seem to contradict the findings of the present study in sprint-endurance training groups with colostrum supplementation.

Rodrıguez et al, through 9-week vitamin E supplementation for pigs with hypercholesterolemia, observed decreased expression of VEGF and VEGF-2 levels.[43] Woodson et alfound a correlation between long-term alpha-tocopherol (vitamin E) supplementation and reduced serum VEGF levels.[44] In a study conducted by Norshahi et al concerning the effect of vitamin E supplementation on angiogenic factor response to exhaustive exercise, supplementation with 400 IU for 14 days did not appear to have a significant effect on serum levels of VEGF at rest and exhaustive exercise-induced VEGF levels.[45]

Nevertheless, the existing VEGF in colostrum may probably account for contradictory results of this study and previous studies concerning the effect of antioxidant supplements on VEGF values, because antioxidant

supplements used in previous studies did not have such properties. The results of this study in training groups without supplementation seem to contradict the results obtained for previous studies; this could also be attributed to the duration of the training protocol, the specific training method applied, and the study population.

## Conclusion

The findings indicated that intake of colostrum, as a strong antioxidant supplement having enzymatic and non-enzymatic antioxidants, along with sprint-endurance training for 10 weeks increases plasma VEGF levels, thereby playing a significant role in vascular angiogenesis.

## Ethical Approval

Our study was based on the ethics standards for experiments involving animals issued by the Ministry of Health and Medical Education.

## Competing Interests

Authors declare that they have no competing interests.

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