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Analysis Of Plasma Myokines Levels In Response To Race: Implications For Physiometabolic Health In Active Individuals

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Abstract:
Background: *Considering the growing body of scientific evidence, it is supported that physical exercise, whether acute or chronic, confers substantial health benefits, mitigating the risk of various diseases. The benefits are attributed, in part, to the exercise's ability to modulate immune function through adaptations that include the production of specific cytokines secreted by skeletal muscle tissue, called myokines. However, the underlying mechanisms of these benefits remain partially understood. The study aimed to understand how specific myokines respond to aerobic exercise, providing insights into the physiological and metabolic impacts of running.*

Materials and Methods: *For this purpose, nine male participants aged between 22 and 34 years (mean ± 32.21), all regular runners of 10 km, were included. They were non-smokers and physically fit as determined by a pre-exercise readiness questionnaire. Blood samples were collected before the run, immediately after the run, and 24 hours after the run to measure changes in myokine levels. The exercise protocol involved a single 10 km run completed in an average of 49.85 minutes.*

Results: *Significant increases in several myokines were observed. Interleukin-6 (IL-6) levels increased notably from 0.94 pg/ml before the run to 2.82 pg/ml after the exercise, illustrating the acute inflammatory response and metabolic activation due to running. Similarly, Interleukin-15 (IL-15) and Brain-Derived Neurotrophic Factor (BDNF) also showed significant increases, suggesting enhanced muscular and neurotrophic responses. Interestingly, Irisin levels peaked 24 hours post-exercise, highlighting a delayed response potentially linked to enhanced fat oxidation and improved metabolic health.*

Conclusion: *Thus, the study confirmed that a 10 km run can significantly affect plasma myokine levels, with IL-6, IL-15, Irisin, and BDNF showing marked changes. These myokines play crucial roles in tissue repair, cell proliferation, and metabolic regulation, which are beneficial for tissue protection and metabolic health. This research contributes to a better understanding of the systemic benefits of regular moderate running, advocating its role in maintaining health and preventing diseases.*

Key Word: *Physical Exercises; Race; Myokines; Physiometabolism; Health Benefits*

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I. Introduction

Regular physical exercise, encompassing various forms such as aerobic, anaerobic, resistance, strength, or flexibility, has been shown to improve numerous emerging and increasingly prevalent clinical conditions [1]. The literature emphasizes that moderate physical exercise plays a crucial role in stimulating the immune system, providing protection against chronic diseases such as diabetes, hypertension, obesity, and diverse types of cancer [2]. Conversely, a sedentary lifestyle is associated with reduced life expectancy in the population [3].

Physical exercise challenges bodily homeostasis, inducing changes in various physiological aspects, such as increased cardiac output, respiratory rate, glucose production, and mobilization of free fatty acids [4].

Skeletal muscle is now recognized as an endocrine organ, in addition to its role in the locomotor system. During physical exercise, muscle contraction releases myokines, specific cytokines that play autocrine, paracrine, and endocrine roles. These myokines are involved in muscle hypertrophy, lipid metabolism, and adaptation to physical training [2,5].

Studies have revealed compelling findings about the relationship between excessive training and participation in marathons, indicating a decrease in the benefits of exercise. In contrast, moderate training demonstrates a more favorable impact on health. A significant subsequent finding is observed in the realization that, although regular marathon practice can provide various health benefits, these do not completely neutralize the harmful effects associated with prolonged exposure to a sedentary and unhealthy lifestyle [6].

The influence of myokines extends to the acute and chronic beneficial effects of exercise, playing a significant role in protection against diseases associated with inflammation, insulin resistance, and hyperlipidemia, such as cardiovascular diseases, type II diabetes, and cancer[3].

Street running, the focus of this study, is classified as predominantly aerobic, considering the duration and distance traveled [7] thus, the responses observed during and after physical exercise are categorized as acute responses induced by the exercise protocol [4].

The Role Of Myokines In Physiometabolic Health

Interleukin-6 (IL-6) is a myokine that plays a fundamental role in modulating the inflammatory response and metabolic regulation during physical exercise. IL-6 is rapidly released by muscles in response to contraction, acting as a critical mediator in the interaction between inflammation, metabolism, and physical activity. Previous studies suggest that IL-6 promotes lipolysis and fat oxidation, in addition to improving insulin sensitivity, highlighting its dual role as both pro-inflammatory and anti-inflammatory [8].

Interleukin-15 (IL-15), known for its anabolic properties, is crucial for muscle hypertrophy and the maintenance of muscle mass. Beyond its functions in the muscle, IL-15 influences metabolic and immune health, promoting the function of natural killer cells and the regulation of adipose tissue mass. Studies highlight its role in improving cardiac function and protecting against cardiovascular diseases, demonstrating the complexity of its systemic actions [9].

Brain-Derived Neurotrophic Factor (BDNF), considered an important neurotrophin, is involved in the survival and differentiation of neurons in the central nervous system. In the context of exercise, BDNF is released by muscle tissue and contributes to neuroplasticity and cognitive function. The increase in BDNF levels following physical activity suggests a mechanism by which exercise improves brain function and neural resilience [10].

Irisin, recently discovered, is a myokine that transforms white adipose tissue into brown, increasing thermogenesis and contributing to the reduction of fat mass. Additionally, it plays a role in regulating glucose and lipid metabolism, offering promising prospects for the treatment of metabolic diseases such as diabetes and obesity [11].

These findings underscore the importance of myokines as mediators of the benefits of physical exercise on metabolic and immune health, justifying the focus of this study on analyzing the responses of these peptides to aerobic exercise.

II. Material And Methods

Sample Characterization

The study included nine male participants, aged between 22 and 34 years, physically active, non-smokers, with an average weight of 78.80 ± 9.30 kg (as shown in Table 1). All were regular runners of 10 km and met the readiness criteria for physical activity as assessed by the Physical Activity Readiness Questionnaire (PAR-Q). The volunteers were recruited through the dissemination of the study's intent via the author's digital channels (social media). After receiving clarification on all procedures to be performed in the study, they signed an Informed Consent Form, approved by the Research Ethics Committee (CEP) of the Santa Casa de Misericórdia Hospital in Belo Horizonte, in accordance with resolution 196/96, under protocol 466/2012, no. 074/2007, and followed the 1964 Helsinki Declaration.

Aerobic Exercise Protocol (10 km Run)

Participants underwent three distinct phases: 1) an initial interview, 2) an outdoor running session, and 3) a second blood sample collection. The experimental 10 km runs, aimed at performance optimization, were conducted at 8:00 AM. Blood samples were taken pre-exercise, immediately post-exercise, and 24 hours after the end of the exercise. Prior to the run, volunteers consumed their usual breakfast. Instructions were strictly provided for individuals to abstain from any physical activity and alcohol consumption in the 72 hours preceding the 10 km run and the subsequent 24-hour post-exercise sample collection.

Tabela nº 1: Características dos participantes (n=9)

	Média		**(DP)**
Peso (kg)	78,8	±	9,3
Altura (cm)	174,4	±	4,4
Índice de massa corporal (kg/m²)	25,9	±	3,2
Idade (anos)	32,21	±	10,24
Percentual de gordura corporal (%BF)	16,49	±	4,65
Frequência cardíaca de repouso (bpm)	59,78	±	5,98
Tempo correndo 10 km (min)	49,8	±	7

Font: Prepered by the authors.

Human Myokine Analysis Protocol

For the evaluation of myokines in this study, the MILLIPLEX® MAP Human Myokine Magnetic Beads Panel HMYOMAG-56K and Luminex® technology were used, following the manufacturer's guidelines.

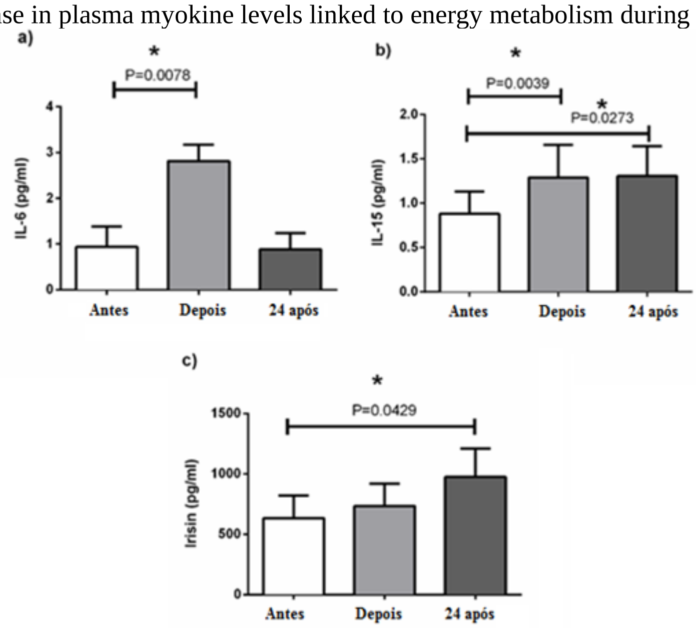
Statistical Analysis

The results are presented as mean ± standard error of the mean. The omnibus D'Agostino & Pearson normality test, with an alpha significance level of 0.01, was used to verify the normality of the data. Normalized variables were subjected to One-Way Analysis of Variance (ANOVA), and differences between time points were assessed using Fisher's LSD test. For data without normal distribution, Wilcoxon tests were used. Statistical significance was established for p-values less than 0.05 (Graph pad Prism 9.0).

III. Results

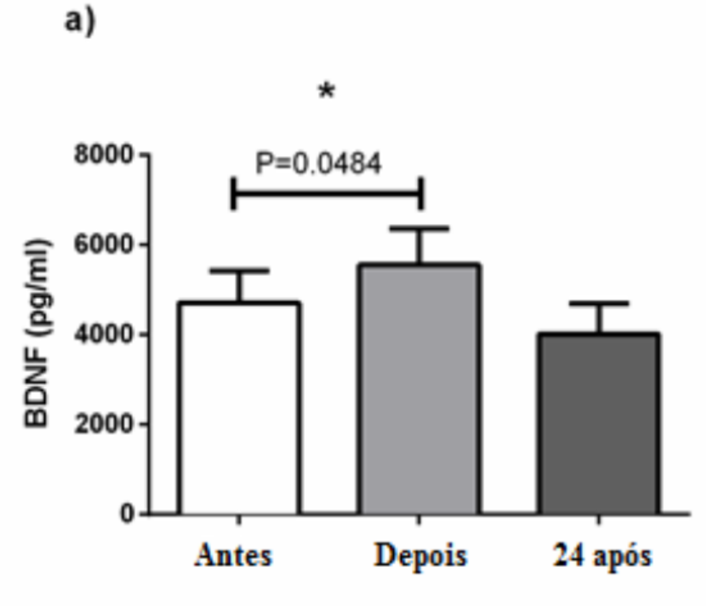
The plasma levels of myokines associated with tissue repair and cell proliferation showed a notable increase following the completion of the 10 km run. The participants completed the running protocol in an average time of 49.8 ± 7.0 minutes. Interleukin-6 (IL-6) (Figure 1) recorded an increase from 0.94 ± 0.4 to 2.82 ± 0.3 pg/ml after exercise, returning to initial levels 24 hours after the end of physical activity. Intriguingly, Irisin showed a subsequent increase, ranging from 632.60 ± 188.40 to 974.70 ± 232.30 pg/ml, 24 hours after exercise, demonstrating a unique temporal dynamic. Myokines related to neurogenesis also exhibited an increase in response to the 10 km run. The exercise protocol induced an immediate increase in the plasma levels of Brain-Derived Neurotrophic Factor (BDNF) (Figure 2), rising from 4719.00 ± 701.80 to 5557.00 ± 810.30 pg/ml, returning to initial levels 24 hours after the completion of the exercise session.

Figure 1. Increase in plasma myokine levels linked to energy metabolism during physical activity.



a) There was a threefold increase in IL-6 levels after exercise; b) IL-15 showed a 1.5-fold increase after exercise; Irisin recorded a 1.5-fold increase 24 hours after the completion of the exercise. Source: Prepared by the authors.

Figure 2 – Myokine related to tissue repair and cell proliferation.



a) BDNF levels increased immediately after the completion of the exercise. Source: Prepared by the authors.

IV. Discussion

Well-established in the literature, IL-6, a myokine derived from exercise, exerts anti-inflammatory effects by regulating the release of IL-10 and IL-1ra. Moreover, the paracrine effects of IL-6 not only include lipolysis but also contribute to improving insulin sensitivity [8,12]. Studies indicate that IL-6 induces myogenic differentiation and the expression of myotubular proteins in muscle cells [13,14]. In animal models, IL-6 activates M2 macrophages, promoting angiogenesis, tissue repair, and myonuclear increase [15,16].

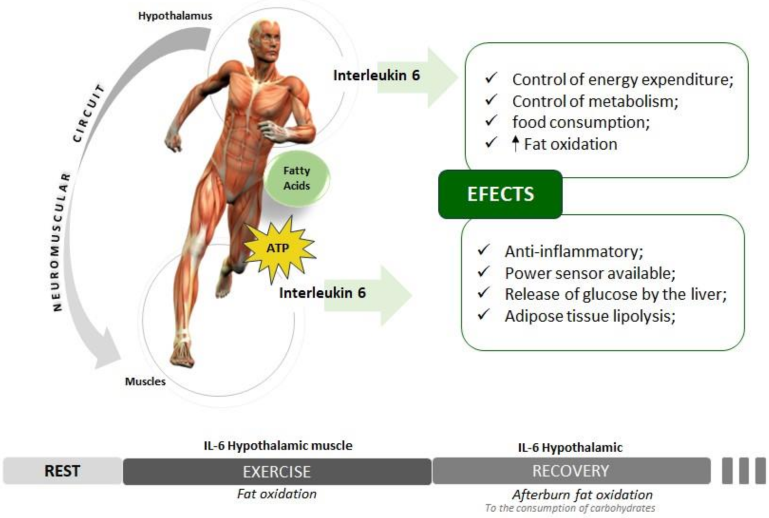
In the present study, we observed a significant increase, approximately threefold, in plasma IL-6 concentrations compared to baseline levels, suggesting considerable intensity in the 10 km run and notable energy recruitment, in line with previously attributed properties of IL-6. This finding is supported by previous research [17]. It is important to note that the increase in plasma IL-6 after exercise is not directly linked to muscle tissue damage; only muscular activities can instigate the production of IL-6, resulting in the observed peak in blood concentration. This elevation can be explained by the specific characteristics of the metabolic pathway involved in the exercise (as shown in the Figure 3).

Interleukin-15 (IL-15) presents as a pro-inflammatory cytokine of pleiotropic nature, sharing structural similarity with IL-2. This compound predominantly induces anabolic effects, promoting tissue protection by attenuating apoptosis of cardiac myocytes, mobilizing endothelial and mesenchymal progenitor cells, reducing oxidative stress, and enhancing myocardial function. In hypoxic environments, cardiac myocytes express the protective receptor for IL-15, providing them protection against injuries [18].

IL-15, by activating signaling through the β and common γ (γc) chains of the IL-2 receptor, supports the survival and activation of natural killer cells while effectively suppressing oxidative stress. However, IL-15 regulates the chemotaxis of natural killer cells, influencing their adhesion to the vascular endothelium. Unlike IL-8, IL-15 stands out as a growth factor widely expressed in skeletal muscle, inducing muscle hypertrophy through the activation of its specific receptor, IL-15R. Demonstrating anabolic impact both in vitro and in vivo, IL-15 plays a crucial role in regulating the mass of white adipose tissue (WAT) [9].

In our investigation, we identified significant disparities in circulating IL-15 levels immediately and 24 hours after exercise, compared to baseline levels. The results of Rinnov et al. (2014)[19] showed that resistance training induces an upregulation in baseline levels of IL-15, indicating a possible correlation of this myokine with adaptation to training. We further suggest that the immediate increase in IL-15 is likely attributable to the predominant energy pathway during exercise, while the persistence of this response may be related to the continuous need for protein synthesis 24 hours after the 10 km run.

Figure 3: Interleukin 6 (IL-6) effects in the body during and after aerobic exercises.



Font: Prepared by the authors.

Recently discovered in 2012, irisin, when exposed to physical activities, stimulates an increase in the expression of PGC-1α, elevating thermogenic genes. This results in significant loss of visceral fat through an anti-inflammatory state, which in turn leads to the browning of white adipose tissue (WAT), reducing the composition of visceral adipose tissue (VAT). This phenomenon enables the oxidation of free fatty acids, allowing for hypertrophy and reducing substrates for lipogenesis. Moreover, irisin may contribute to the reduction of fat mass, as its antioxidant and anti-inflammatory effects act on hepatocytes, reducing hepatic steatosis [11].

Our findings point to a distinct temporal response of irisin, a myokine that stood out with a significant difference. This unique phenomenon suggests that irisin may require specific cellular signaling stimuli, such as the exercise-induced cytokine, whose expression may not be induced by other types of inflammation. This characteristic highlights the complexity and specificity of the responses to myokines, demanding a more in-depth analysis for a comprehensive understanding of their release mechanisms and action.

Brain-Derived Neurotrophic Factor (BDNF), a component of the neurotrophins family, plays a crucial role in regulating neural processes related to neurogenesis, like other members of its family [10]. When produced and secreted in muscle tissue, this molecule exhibits metabolic properties that enhance fat oxidation, mediated by the activation of AMPK. Additionally, in the context of skeletal muscle, BDNF plays a fundamental role in regulating satellite cell differentiation and the regeneration of skeletal muscle tissue [20].

Our research reveals a statistically significant difference in blood BDNF concentrations immediately after the run, in line with the findings of Roh et al. (2017)[21], who investigated the effects of treadmill running and observed significant variations in plasma BDNF levels immediately after exercise in groups subjected to different intensities. Thus, the results presented indicate that the 10 km run can induce an increase in BDNF levels, suggesting that the chronic adaptations resulting from this stimulus may be advantageous for practitioners of this type of physical activity.

V. Conclusion

The results of this study point to significant health benefits for regular practitioners of 10 km running. The immediate and subsequent elevations in plasma myokine concentrations, such as IL-6, IL-15, Irisin, and BDNF, suggest adaptive responses of the body to exercise. These myokines, involved in tissue repair, cell proliferation, and metabolic regulation, stand out as mediators of the beneficial effects of running, contributing to the homeostasis of the immune system, tissue protection, and improvement of the metabolic profile.

However, it is essential to acknowledge some inherent limitations of this study that may influence the interpretation and application of our results. As mentioned, "the study focused on specific myokines such as IL-6, IL-15, Irisin, and BDNF. Including a more comprehensive analysis of other relevant myokines could provide a fuller understanding of the effects of the 10 km run on plasma myokine levels." We recommend that future research expand the analysis to include a broader spectrum of myokines, to enrich the understanding of these complex physiological mechanisms associated with the practice of 10 km running. Despite these limitations, the findings reinforce the importance of regular practice of this type of exercise in promoting health and well-being in individuals.

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