Article Classification:
Discussion article

SODIUM NITRITE (E250) AND ZINC AS MODULATORS OF THE BIOMECHANICAL PROPERTIES OF BLOOD IN SPORTS

Ivan Ivanov[1], Yordanka Gluhcheva[2], Emilia Petrova[2]

[1] National Sports Academy "Vassil Levski", Sofia, Bulgaria
[2] Institute of Experimental Morphology, Pathology, and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia, Bulgaria

OPEN ACCESS

ORCID
Ivan Ivanov
https://orcid.org/0000-0001-7519-9657
Yordanka Gluhcheva
https://orcid.org/0000-0001-5929-4697
Emilia Petrova
https://orcid.org/0000-0001-6971-1183

Cite this article as:
Ivanov, I., Gluhcheva, Y., Petrova, E. (2024). Sodium Nitrite (E250) and Zinc as modulators of the biomechanical properties of blood in sports. *Journal of Applied Sports Sciences*, Vol. 1, pp. 91 - 101.
DOI: *10.37393/JASS.2024.01.7*

ABSTRACT

Nutritional supplements are often used by athletes to support their performance. However, if there is no nutrient deficiency, supplementation may not improve performance and may even have a detrimental effect on both performance and health. The aim of this study was to review the influence of sodium nitrite ($NaNO_2$) and zinc (Zn) on the hemorheological status of different types of blood cells with application in sports. Sodium nitrite, known as food preservative E250, and zinc are proven modulators of the biomechanical properties of blood, influencing its hematometric and hemorheological properties. Our previous experimental results demonstrated that intraperitoneal injection of $NaNO_2$ in mature rats had a diverse effect on the leukocyte and platelet populations. After the treatment, the number of monocytes and granulocytes decreased significantly, thus increasing the susceptibility to infections. The number of platelets increased, altering the coagulation status of blood. Scientific research data show that the proper intake of $NaNO_2$ and Zn improves glucose metabolism, a key factor in maintaining energy levels during physical activity, muscle strength, and endurance. Zn also exhibits protective effects against bone loss. Excessive intake of zinc for long periods may interfere with other essential elements of metabolism. This review proves that hemorheological parameters such as whole blood viscosity, plasma viscosity, as well as the main hematometric indices are suitable quantitative biological markers for monitoring nitrite and/or zinc supplementation.

Keywords*: Sodium nitrite, zinc, biomechanical properties of blood, physical performance*

INTRODUCTION

Sports and an active lifestyle are very important factors in maintaining good health and a high quality of life for modern people. Regular, moderate-intensity exercise is known to reduce the likelihood of death from a general cardiovascular event (Ivanov et al., 2016). Analyzes by Brandt & Pedersen (2010) and Nocon et al. (2008) proved that physical activity reduces the risk of death from cardiovascular disorders by 35% and the risk of death of a general nature – by 33%. Studies have also reported that diet and moderate physical activity protect patients with impaired glucose tolerance from developing type 2 diabetes (Brandt & Pedersen, 2010; Knowler et al., 2002). In the specialized medical scientific literature, the term "diseases of physical inactivity" encompasses diseases such as type 2 diabetes, cardiovascular diseases, colon and breast cancer, dementia, etc. (Pedersen, 2009; Hotamisligil, 2006).

Nutritional supplements are often used by athletes to support their performance, enhance

recovery and immune function, or improve overall health (Peeling, 2019). However, athletes should consider that supplement use exposes them to the risk of ingesting banned substances or precursors of prohibited substances (Garthe, 2018).

The aim of this study was to review the influence of sodium nitrite ($NaNO_2$) and zinc (Zn) on the hemorheological status of different types of blood cells in sports.

Sodium nitrite – properties and physiological effects

Sodium nitrite is a water-soluble, white-yellow-colored crystalline powder used as a food preservative and coloring agent. It is also a corrosion inhibitor found in pharmaceutical antifreeze and an antidote for cyanide poisoning (Albano et al., 2024). $NaNO_2$ blocks the development of bacteria that cause botulism and prevents meat from spoiling. It also gives cured meats a characteristic color and flavor (American Meat Institute). It is well-known as a preservative E250 in the food industry (Figure 1).

The vasodilator effect of sodium nitrite has been proven in active athletes and helps to improve their sports performance. Anti-doping authorities do not ban nitrites, but their prolonged use has caused increased attention and concern from these institutions (Petróczi, Naughton, 2010).

$NaNO_2$ interferes with red blood cells binding to oxygen. The iron component of hemoglobin becomes oxidized from ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), converting hemoglobin to methemoglobin (Lee et al., 2017). Methemoglobin cannot bind oxygen, impairing oxygen transport and causing subsequent hypoxia and lactic acidosis. The physical symptoms of $NaNO_2$ poisoning vary depending on the concentration of methemoglobin and include fatigue, difficulty/irregular breathing, tachycardia, impaired mental status, nausea, and vomiting. More than 50% of the patients develop symptoms of severe tissue hypoxia, such as cardiac arrhythmias, seizures, coma, and death (Zerbo et al., 2023). If not treated, this condition can be fatal in severe cases. Self-poisoning with sodium nitrite represents an increasing trend in nitrate-related deaths (Khan et al., 2024). A similar trend has recently been reported in the United States, Portugal, and the Republic of Korea (Albano et al., 2024).

In adults, the daily intake of $NaNO_2$ varies between 1.8 and 8.4 mg, depending on various factors. Many authors claim that increased consumption of red and processed meats leads to an increased risk of cancer and chronic lung diseases (Hord et al., 2009; Ivanov et al., 2016; Norat et al., 2005; Santarelli et al., 2008; Varraso et al., 2007; Jiang et al., 2007). The American Institute for Cancer Research recommends the following: "Reduce consumption of red meats (beef, pork, and lamb) and limit canned meats. To reduce your risk of cancer, consume no more than 18 oz. (0.5102 kg weight after cooking) per week of red meat (beef, pork, and lamb) and refrain from canned meats such as ham, salami, hot dogs, sausage" (World Cancer Research Fund. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Second Expert Report, 2007).

It is known that the presence of increased levels of nitrates (NO_3^-) and nitrites (NO_2^-) in food is associated with an increased risk of developing gastrointestinal cancer and methemoglobinemia in infants (Hord et al., 2009). Approximately 80% of dietary nitrates come from fruits, vegetables, and canned meats.

Nitrite is synthesized endogenously by oxidation of nitric oxide (NO) and by reduction of nitrate by parasitic bacteria present in the oral cavity and gastrointestinal tract (Hord et al., 2009). It is also known that there are three ways to increase the amount of nitrites (the main part of which is $NaNO_2$) in the body:

- endogenous – by oxidation of nitric oxide, synthesized by endothelial cells in the walls of blood vessels, under different conditions;
- by converting the ingested nitrates to nitrites – by available parasitic bacteria in the oral cavity and gastrointestinal tract;
- oral intake through food, mainly meat with E250 preservative, and medication (used for doping in specific concentrations and with intake protocols).

Consuming foods rich in $NaNO_2$ and intravenous sodium nitrite infusion may also be beneficial (Ormerod et al., 2015). Jones et al. (2013) reported the benefits of sodium nitrite consumption in the treatment of heart attacks, cerebral aneurysms, elevated pulmonary pressure in infants, and infections caused by the bacterium *Pseudomonas aeruginosa* (Jones et al., 2013; Omar & Webb, 2014).

Studies have shown that the vasodilator effect of $NaNO_2$ helps treat so-called "pulmonary hypertension" (Hunter et al., 2004), posthemorrhagic cerebral vasospasm (Pluta et al., 2005), myocardial infarction (Webb et al., 2004), and plasma peroxynitrite levels in well-trained subjects (Gholami et al., 2019).

Knowing the benefits and drawbacks of increased or decreased sodium nitrite consumption is important. The mechanisms of influence of this metal compound on the morphology, rheology, and biomechanics of human blood cells and whole blood as fluids need to be studied and elucidated. Numerous studies are available in the literature regarding the biomechanical changes in the blood in the presence, intake, and synthesis of sodium nitrite in the body.

Our previous studies in an experimental rat model of $NaNO_2$-induced hypoxia (Ivanov et al., 2014; Ivanov et al., 2016) showed interesting results regarding the influence of $NaNO_2$ on the rheological properties of blood and the biomechanical and hematometric parameters of the three types of blood cells – erythrocytes, leukocytes and platelets. These results are also directly related to physical activity and sports achievements because hemoglobin is the primary transporter of oxygen to the tissues. The reported quantitative values of the hematometric indices in this experimental model can serve to predict the effects of sodium nitrite over time - on specific indicators of the blood and, from there on, the sports results of elite athletes.

Our data also showed a significantly decreased number of monocytes at various earlier stages of $NaNO_2$ treatment (1 h, 5 h, 24 h, and 48 h). Monocyte count recovered up to 20 days after treatment. Our results confirmed those of Abuharfeil et al. (2001), which demonstrated an immunosuppressive effect of $NaNO_2$ in subchronic treatment of mice.

Sodium nitrite had the opposite effect on platelet parameters. The platelet count (PLT) was significantly increased at all stages of the $NaNO_2$ treatment studied, except for the 20th day after exposure. The increase was likely also due to the decreased platelet volume (MPV) found in the study. The increased platelet number, in turn, leads to a significant increase in the platelet crit (PCT). There was no effect on platelet distribution width (PDW), as PDW values were close to the control ones. The results suggested that $NaNO_2$ affected platelet activity, possibly with implications for blood coagulation. Thus, our data confirmed those of Dautov et al. (2014), who reported reduced platelet aggregation under NO_2-induced hypoxic conditions. According to Srihirun et al. (2012), nitrite inhibits platelet aggregation in the presence of erythrocytes, which may explain the increased number of platelets in our samples. Sodium nitrite treatment in our study had diverse effects on the leukocyte and platelet populations. The number of phagocytizing cells – monocytes and granulocytes

– decreased statistically significantly, leading to increased susceptibility to infections. Hematometric indices for platelets showed a significant increase in PLT and PCT.

The results of our experimental studies showed that hemorheological parameters such as whole blood viscosity (WBV) and plasma viscosity (PV), as well as the main hematometra indices (Hb, HCT, MCV, MCHC, and others), are suitable quantitative biological markers for monitoring nitrite intoxication in medical toxicology (Ivanov et al., 2014; Ivanov et al., 2016).

Acute exposure to NO_2^- has also been reported to increase Ca^{2+} in isolated skeletal muscle fibers during tetanic contractions (Andrade et al., 1998).

$NaNO_2$ exposure is shown to delay *ex vivo* fatigue development in single intact mammalian skeletal muscle fibers at a near-physiological oxygen partial pressure (PO_2) and repeated isometric contractions (Bailey et al., 2019).

Singamsetty et al. (2015) found that nitrite improves glucose tolerance and insulin sensitivity in genetically obese mice.

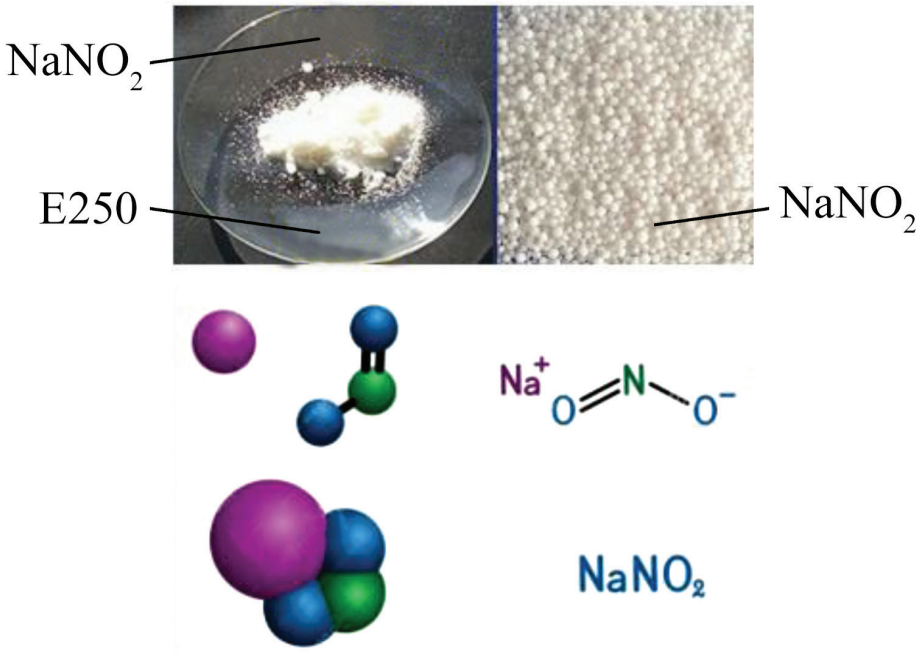


Figure 1. *Sodium nitrite – real species, molecule, and structural chemical formula.*

Justice et al. (2015) provided the first evidence that sodium nitrite improves motor and cognitive function in healthy middle-aged and older adults. The authors postulated that these improvements were associated with and predicted by the plasma metabolome. These findings provide important support for larger clinical trials on this promising pharmacological strategy for preserving physiological function with aging.

Another research group demonstrated that $NaNO_2$ enhanced cardiac output reserve, which improved with exercise. In addition, $NaNO_2$ normalized the increase in cardiac output relative to oxygen consumption (Borlaug et al., 2015).

$NaNO_2$ serves therapeutically as a hypoxic vasodilator with efficacy for improving exercise performance in patients with cardiovascular disease (Colburn, 2016).

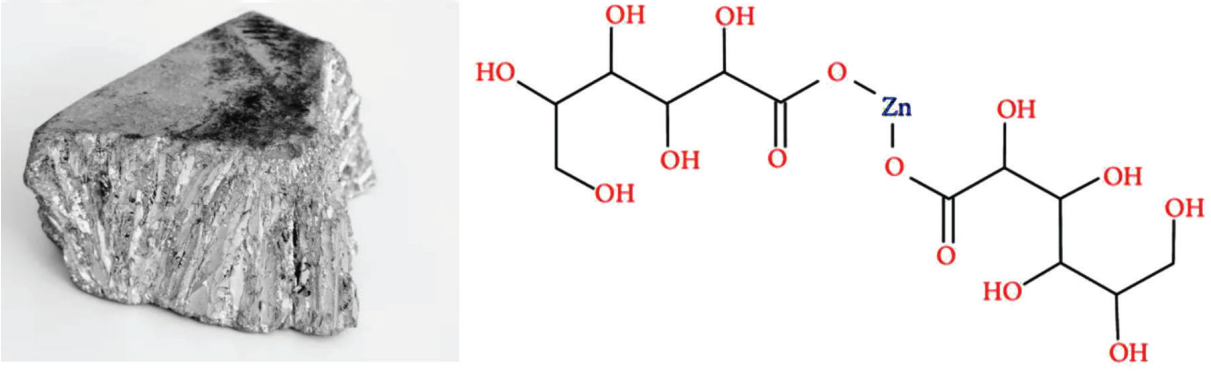
Zinc – properties and physiological effects

Food quality, quantity, and composition are other important factors determining human health and leading to better performance in athletes. From this point of view, Zn is a

trace element of great importance to the body and is necessary for the health of the human immune system. Such effects were observed after treatment with zinc gluconate (Zavros et al., 2023) (Figure 2). Zinc insufficiency may lead to an increased likelihood of a number of diseases.

The human body does not produce zinc naturally, so people must obtain it through food or supplements.

Zinc participates in essential processes in the body, regulating basic functions of the endocrine and immune systems. Its ability to weaken the catabolite effect of proteins and thus exert an anabolic effect on the muscle is also important (Figure 2).



A. B.

Figure 2. *Zinc. A.) Natural specimen; B.) Zinc gluconate (Araujo-Lima et al., 2017).*

Zinc is the second most abundant trace metal in the human body and is a biologically important cation, which makes it an important mediator of hemostasis and thrombosis. Approximately 10–15% of human genes encode proteins that utilize Zn^{2+} as a cofactor. These include transcription factors, enzymes, and structural and signaling proteins (Taylor, 2016). Zn^{2+} modulates platelet function and may contribute to pathophysiological thrombus formation (Taylor, 2016). According to Vu et al. (2013), zinc is an effector of coagulation, anticoagulation, and fibrinolysis. Zinc status may influence blood rheology during exercise, altering RBC flexibility (Khaled, 1997).

Another vital contribution of zinc is detoxifying ammonia. Without sufficient Zn, the concentration of ammonia in the muscles increases. The metal works in sync with vitamin B6 in the human body, playing a vital role in both glycogen storage processes and amino acid metabolism. Vitamin A or zinc deficiency is a prerequisite for a breakdown in the functions of the immune system.

Zinc is essential for energy metabolism, muscle repair, and immune system (Ravindra et al., 2022; Prasad, 2013). Zinc insufficiency may disrupt thyroid hormone levels, thus affecting metabolic rate and sports performance (Prasad, 2013).

Elite athletes' nutritional habits during training and competition completely differ from the recommended diet. Their diet often includes excess carbohydrates, low proteins, and fat, which may lead to suboptimal zinc intake in 90% of athletes. Mild zinc deficiency is difficult to detect because of the lack of definitive indicators of zinc status. In athletes, zinc deficiency can lead to anorexia, significant body weight loss, risk of osteoporosis, etc. (Micheletti et al., 2001).

The role of zinc in the synthesis of the three most important anabolic hormones - growth hormone, insulin, and testosterone - has been well studied. Zinc is essential for the production of Human growth hormone. It is also needed

for the accumulation or secretion of insulin in the pancreas. Zinc has also been shown to increase testosterone levels in various diseases. All the above shows zinc's importance for athletes practicing sports with increased intensity.

The scientific database has examined serum zinc concentrations in athletes - gymnasts, soccer players, and other elite athletes (Khaled et al., 1997; Brun al., 1995).

Zn also exhibits protective effects against bone loss by suppressing osteoclastogenesis (Amin et al., 2020).

A number of specialized studies have highlighted the influence of zinc on erythrocyte biorheology (Khaled et al., 1997; Dash et al., 1974; Brun et al., 1991). *In vitro*, Zn has been shown to increase erythrocytes' deformability following experimentally induced cell membrane rigidity (Brun et al., 1991). Of interest is the hemorheological influence of zinc in two classic hemorheological conditions: hyperviscosity of blood induced by excessive physical activity (Ernst et al., 1991; Brun et al., 1993) and reduced blood viscosity – fitness-induced in trained athletes (Brun et al., 1995). In this sense, the importance of zinc in sports medicine is constantly increasing as a specific nutritional biofactor that positively affects the rheology of blood and blood cells and is of fundamental importance in systematic training and physical exercises.

According to Khaled et al. (1997), erythrocyte stiffness and blood viscosity (with a corrected hematocrit of 45%) are increased in "hypo-zincemic athletes." The authors hypothesize that athletes' "zinc status" affects their sports form precisely through positive hemorheological effects.

Eskici et al. (2016) found that when zinc is supplemented to athletes, the relation between the duration and dose of supplementation is important. However, excess zinc in the diet can result in a secondary copper deficiency (McDonald et al., 1988). Kilic et al. (2004) show that zinc supplementation positively affects hematological parameters in wrestlers.

Cinar et al. (2018) demonstrated that the groups' total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride decreased after zinc supplementation. In contrast, high-density lipoprotein (HDL) cholesterol levels increased following six weeks of zinc administration and training.

Applied as zinc chloride ($ZnCl_2$), it improves glucose homeostasis in high-fat-fed mice by a mechanism that enhances β-cell function (Cooper-Capetini, 2017). Excessive zinc intake for extended periods may interfere with the metabolism of iron and copper, which can affect the immune system and reduce HDL-cholesterol concentrations (Cooper-Capetini, 2017). However rare intoxication by excessive exposure is, zinc deficiency is widespread and has a detrimental impact on growth, neuronal development, and immunity, and in severe cases, its consequences are lethal. Zinc deficiency caused by malnutrition and foods with low bioavailability, aging, certain diseases, or deregulated homeostasis is a far more common risk to human health than intoxication (Plum, 2010).

Sinan et al. (2023) show that Zn incubation increased deformability and decreased aggregation in thalassemic erythrocytes.

CONCLUSIONS

Food quality and composition are other vital factors determining human health and leading to better athlete performance. Sodium nitrite (known as food preservative E250) and zinc are proven modulators of the biomechanical properties of blood, influencing its hematometric and hemorheological properties. The proper intake of $NaNO_2$ and Zn improves glucose metabolism, muscle strength, and endurance, but long-term supplementation may

induce severe side effects. Zn also exhibits protective effects against bone loss. Excessive zinc intake for extended periods may interfere with other essential elements of metabolism.

The scientific literature presents a great deal of evidence for sodium nitrite and zinc's effects on human body hemorheological status and exercise performance. They demonstrate beneficial effects on tissue oxygen supply and in delaying skeletal muscle fatigue, which is important for athletes' performance and recovery. The proper intake of $NaNO_2$ and Zn improves muscle strength and endurance.

Our previous experimental results demonstrate that intraperitoneal injection of $NaNO_2$ in mature rats has a diverse effect on the leukocyte and platelet populations. After the treatment, the number of monocytes and granulocytes decreases statistically significantly, thus increasing the susceptibility to infections. The number of platelets increases, altering the coagulation status of blood.

This review demonstrates that hemorheological parameters such as whole blood viscosity, plasma viscosity, and the main hematometric indices are suitable quantitative biological markers for monitoring nitrite and/or zinc supplementation.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Dr. Elissaveta Zvetkova from the Bulgarian Academy of Sciences for her valuable advice and in-depth analysis.

REFERENCES

Abuharfeil, N., Sarsour, E. & Hassuneh, M. (2001). The effect of sodium nitrite on some parameters of the immune system. *Food Chem Toxicol, 39*(2),119-124.

Albano, G.D., La Spina, C., Buscemi, R., Palmeri, M., Malandrino, G., Licciardello, F., Midiri, M., Argo, A., Zerbo, S. (2024). Systematic Review of Fatal Sodium Nitrite Ingestion Cases: Toxicological and Forensic Implications. *Toxics, 12*(2), 124.

Amin, N., Clark, C.C.T., Taghizadeh, M., Djafarnejad, S. (2020). Zinc supplements and bone health: The role of the RANKL-RANK axis as a therapeutic target. *J Trace Elem Med Biol*, *57*:126417.

Andrade, F.H., Reid, M.B., Allen, D.G. & Westerblad, H. (1998). Effect of nitric oxide on single skeletal muscle fibers from the mouse. *J Physiol, 509*, 577–586.

Araujo-Lima, C. F., Nunes, R. J., Carpes, R. M., Aiub, C. A., & Felzenszwalb, I. (2017). Pharmacokinetic and toxicological evaluation of a zinc gluconate-based chemical sterilant using in vitro and in silico approaches. *BioMed Research International*, *2017*(1), 5746768.

Bailey, S.J., Gandra, P.G., Jones, A.M., Hogan, M.C., Nogueira, L. (2019). Incubation with sodium nitrite attenuates fatigue development in intact single mouse fibers at physiological PO2. *J Physiol, 597*(22), 5429-5443.

Borlaug, B. A., Koepp, K. E., & Melenovsky, V. (2015). Sodium nitrite improves exercise hemodynamics and ventricular performance in heart failure with preserved ejection fraction. *Journal of the American College of Cardiology, 66*(15), 1672-1682.

Brandt, C., & Pedersen, B. K. (2010). The role of exercise-induced myokines in muscle homeostasis and the defense against chronic diseases. *Journal of Biomedicine and Biotechnology*.

Brun, J. F., Fons, C., Fussellier, M., Bardet, L., & Orsetti, A. (1991). Zinc salts improve in vitro erythrocyte flexibility. *Rev. Port. Hemorreol, 5*, 231-238.

Brun, J. F., Fons, C., Supparo, I., Mallard, C., & Orsetti, A. (1993). Could exercise-induced increase in blood viscosity at high shear rate be entirely explained by hematocrit and plasma viscosity changes?. *Clinical Hemorhe-*

ology and Microcirculation, 13(2), 187-199.

Brun, J. F., Dieu-Cambrezy, C., Charpiat, A., Fons, C., Fedou, C., Micallef, J. P., ... & Orsetti, A. (1995). Serum zinc in highly trained adolescent gymnasts. *Biological Trace Element Research, 47*(1), 273-278.

Cinar, V., Akbulut, T., Kilic, Y., Özdal, M., Sarikaya, M. (2018). The effect of 6-week zinc supplement and weight training on the blood lipids of the sedentaries and athletes. *Cell Mol Biol (Noisy-le-grand), 64*(11), 1-5.

Colburn, T. D. (2016). *Sodium nitrite impacts the peripheral control of contracting skeletal muscle microvascular oxygen pressure in healthy rats* (Doctoral dissertation, Kansas State University).

Cooper-Capetini, V., de Vasconcelos, D.A.A., Martins, A.R., Hirabara, S.M., Donato, J. Jr., Carpinelli, A.R., Abdulkader, F. (2017). Zinc Supplementation Improves Glucose Homeostasis in High Fat-Fed Mice by Enhancing Pancreatic β-Cell Function. *Nutrients, 9*(10), 1150.

Dash, S., Brewer, G. J., & Oelshlegel, F. J. (1974). Effect of zinc on hemoglobin binding by red blood cell membranes. *Nature, 250*(5463), 251-252.

Dautov, R. F., Stafford, I., Liu, S., Cullen, H., Madhani, M., Chirkov, Y.Y. & Horowitz, J. D. (2014). Hypoxic potentiation of nitrite effects in human vessels and platelets, *Nitric Oxide,40*, 36–44.

Ernst, E., Daburger, L., & Saradeth, T. (1991). The kinetics of blood rheology during and after prolonged standardized exercise. *Clinical Hemorheology and Microcirculation, 11*(5), 429-439.

Eskici, G., Gunay, M., Baltaci, A.K., Mogulkoc, R. (2016). The effect of zinc supplementation on the urinary excretion of elements in female athletes. *Pak J Pharm Sci, 29*(1), 125-129.

Garthe, I., Maughan, R.J. (2018). Athletes and Supplements: Prevalence and Perspectives. *Int J Sport Nutr Exerc Metab, 28*(2),126–138.

Gholami, F., Rahmani, L., Amirnezhad, F., & Cheraghi, K. (2019). High doses of sodium nitrate prior to exhaustive exercise increases plasma peroxynitrite levels in well-trained subjects: randomized, double-blinded, cross-over study. *Applied Physiology, Nutrition, and Metabolism, 44*(12), 1305-1310.

Hord, N. G., Tang, Y., & Bryan, N. S. (2009). Food sources of nitrates and nitrites: the physiologic context for potential health benefits. *The American Journal of Clinical Nutrition, 90*(1), 1–10.

Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. *Nature, 444*(7121), 860-867.

Hunter, C. J., Dejam, A., Blood, A. B., Shields, H., Kim-Shapiro, D. B., Machado, R. F., Tarekegn, S., Mulla, N., Hopper, A. O., Schechter, A. N., Power, G. G., & Gladwin, M. T. (2004). Inhaled nebulized nitrite is a hypoxia-sensitive NO-dependent selective pulmonary vasodilator. *Nature Medicine, 10*(10), 1122–1127. DOI: 10.1038/nm1109

Ivanov, I., Gluhcheva, Y., Petrova, E., & Antonova, N. (2014). Hemorheological changes and hematometric erythrocyte characteristics in rats after sodium nitrite intoxication. *Korea-Australia Rheology Journal, 26*(2), 225-228.

Ivanov, I., Gluhcheva, Y., Petrova, E., & Gikova, M. (2016). Food preservatives and sport. Sodium nitite (E250) ‘s influence on hematometrical parameters of white blood cells and platelets in rats. *Research in Kinesiology, 44*(1), 67-70.

Jiang, R., Paik, D. C., Hankinson, J. L., & Barr, R. G. (2007). Cured meat consumption, lung function, and chronic obstructive pulmonary disease among United States adults. *American Journal of Respiratory and Critical Care Medicine, 175*(8), 798–804. DOI:

10.1164/rccm.200607-969OC

Jones, D. A., Andiapen, M., Van-Eijl, T. J. A., Webb, A. J., Antoniou, S., Schilling, R. J., ... & Mathur, A. (2013). The safety and efficacy of intracoronary nitrite infusion during acute myocardial infarction (NITRITE-AMI): study protocol of a randomized controlled trial. *BMJ Open, 3*(4), e002813.

Justice, J. N., Johnson, L. C., DeVan, A. E., Cruickshank-Quinn, C., Reisdorph, N., Bassett, C. J., Evans, T. D., Brooks, F. A., Bryan, N. S., Chonchol, M. B., Giordano, T., McQueen, M. B., & Seals, D. R. (2015). Improved motor and cognitive performance with sodium nitrite supplementation is related to small metabolite signatures: a pilot trial in middle-aged and older adults. *Aging, 7*(11), 1004–1021. DOI: 10.18632/aging.100842

Khaled, S., Brun, J. F., Micallef, J. P., Bardet, L., Cassanas, G., Monnier, J. F., & Orsetti, A. (1997). Serum zinc and blood rheology in sportsmen (football players). *Clinical Hemorheology and Microcirculation, 17*(1), 47-58.

Khan, H., Barber, C., & Azrael, D. (2024). Suicide by sodium nitrite poisoning: Findings from the National Violent Death Reporting System, 2018-2020. *Suicide & Life-threatening Behavior, 54*(2), 310–316. DOI: 10.1111/sltb.13043

Kilic, M., Baltaci, A. K., & Gunay, M. (2004). Effect of zinc supplementation on hematological parameters in athletes. *Biological Trace Element Research, 100*(1), 31–38. DOI: 10.1385/BTER:100:1:031

Knowler, W. C., Barrett-Connor, E., Fowler, S. E. et al. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine, vol. 346*, no. 6, pp. 393–403.

Lee, C., Jang, E.J., Yum, H., Choi, Y.S., Hong, J. (2017). Unintentional mass sodium nitrite poisoning with a fatality. *Clinical Toxicology, 55*, 678–679.

McDonald, R., & Keen, C. L. (1988). Iron, zinc and magnesium nutrition and athletic performance. *Sports Medicine (Auckland, N.Z.), 5*(3), 171–184. DOI: 10.2165/00007256-198805030-00004

Micheletti, A., Rossi, R., & Rufini, S. (2001). Zinc status in athletes: relation to diet and exercise. *Sports medicine*, *31*, 577-582.

Nocon, M., Hiemann, T., Müller-Riemenschneider, F., Thalau, F., Roll, S., & Willich, S. N. (2008). Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 15*(3), 239–246. DOI: 10.1097/HJR.0b013e3282f55e09.

Norat, T., Bingham, S., Ferrari, P., Slimani, N., Jenab, M., Mazuir, M., Overvad, K., Olsen, A., Tjønneland, A., Clavel, F., Boutron-Ruault, M. C., Kesse, E., Boeing, H., Bergmann, M. M., Nieters, A., Linseisen, J., Trichopoulou, A., Trichopoulos, D., Tountas, Y., Berrino, F., … Riboli, E. (2005). Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *Journal of the National Cancer Institute, 97*(12), 906–916. DOI: 10.1093/jnci/dji164

Omar, S. A., & Webb, A. J. (2014). Nitrite reduction and cardiovascular protection. *Journal of Molecular and Cellular Cardiology, 73*, 57–69. DOI: 10.1016/j.yjmcc.2014.01.012

Ormerod, J. O., Arif, S., Mukadam, M., Evans, J. D., Beadle, R., Fernandez, B. O., Bonser, R. S., Feelisch, M., Madhani, M., & Frenneaux, M. P. (2015). Short-term intravenous sodium nitrite infusion improves cardiac and pulmonary hemodynamics in heart failure patients. *Circulation. Heart Failure, 8*(3), 565–571. DOI: 10.1161/CIRCHEARTFAILURE.114.001716

Pedersen B. K. (2009). The diseasome of physical inactivity--and the role of myokines in muscle--fat cross talk. *The Journal of Physiology, 587*(Pt 23), 5559–5568. DOI: 10.1113/jphysiol.2009.179515

Peeling, P., Castell, L. M., Derave, W., de Hon, O., & Burke, L. M. (2019). Sports Foods and Dietary Supplements for Optimal Function and Performance Enhancement in Track-and-Field Athletes. *International Journal of Sport Nutrition and Exercise Metabolism, 29*(2), 198–209. DOI: 10.1123/ijsnem.2018-0271

Petróczi, A., & Naughton, D. P. (2010). Potentially fatal new trend in performance enhancement: a cautionary note on nitrite. *Journal of the International Society of Sports Nutrition, 7*, 25. DOI: 10.1186/1550-2783-7-25

Plum, L. M., Rink, L., & Haase, H. (2010). The essential toxin: impact of zinc on human health. *International Journal of Environmental Research and Public Health, 7(*4), 1342–1365. DOI: 10.3390/ijerph7041342

Pluta, R. M., Dejam, A., Grimes, G., Gladwin, M. T., & Oldfield, E. H. (2005). Nitrite infusions to prevent delayed cerebral vasospasm in a primate model of subarachnoid hemorrhage. *JAMA, 293*(12), 1477–1484. DOI: 10.1001/jama.293.12.1477

Prasad A. S. (2013). Discovery of human zinc deficiency: its impact on human health and disease. *Advances in nutrition (Bethesda, Md.), 4(*2), 176–190. DOI: 10.3945/an.112.003210

Ravindra, P. V., Janhavi, P., Divyashree, S., & Muthukumar, S. P. (2022). Nutritional interventions for improving the endurance performance in athletes. *Archives of Physiology and Biochemistry, 128*(4), 851–858. DOI: 10.1080/13813455.2020.1733025

Santarelli, R. L., Pierre, F., & Corpet, D. E. (2008). Processed meat and colorectal cancer: a review of epidemiologic and experimental evidence. *Nutrition and Cancer, 60*(2), 131–144. DOI: 10.1080/01635580701684872

Sinan, M., Yalcin, O., Karakas, Z., Goksel, E., & Ertan, N. Z. (2023). Zinc improved erythrocyte deformability and aggregation in patients with beta-thalassemia: An in vitro study. *Clinical Hemorheology and Microcirculation, 85*(1), 1–12. DOI: 10.3233/CH-221452

Singamsetty, S., Watanabe, Y., Guo, L., Corey, C., Wang, Y., Tejero, J., McVerry, B. J., Gladwin, M. T., Shiva, S., & O'Donnell, C. P. (2015). Inorganic nitrite improves components of the metabolic syndrome independent of weight change in a murine model of obesity and insulin resistance. *The Journal of Physiology, 593*(14), 3135–3145. DOI: 10.1113/JP270386

Srihirun, S., Sriwantana, T., Unchern, S., Kittikool, D., Noulsri, E., Pattanapanyasat, K., Fucharoen, S., Piknova, B., Schechter, A. N., & Sibmooh, N. (2012). Platelet inhibition by nitrite is dependent on erythrocytes and deoxygenation. *PloS One, 7*(1), e30380. DOI: 10.1371/journal.pone.0030380

Taylor, K. A., & Pugh, N. (2016). The contribution of zinc to platelet behaviour during haemostasis and thrombosis. *Metallomics: Integrated Biometal Science, 8*(2), 144–155. DOI: 10.1039/c5mt00251f

Webb, A., Bond, R., McLean, P., Uppal, R., Benjamin, N. & Ahluwalia, A. (2004). Reduction of nitrite to nitric oxide during ischemia protects against myocardial ischemia-reperfusion damage. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 13683–13688.

Varraso, R., Jiang, R., Barr, R. G., Willett, W. C., & Camargo, C. A., Jr (2007). Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *American Journal of Epidemiology, 166*(12), 1438–1445. DOI: 10.1093/aje/kwm235

Vu, T. T., Fredenburgh, J. C., & Weitz, J. I. (2013). Zinc: an important cofactor in haemostasis and thrombosis. *Thrombosis and*

Haemostasis, 109(3), 421–430. DOI: 10.1160/TH12-07-0465

Zavros, A., Andreou, E., Aphamis, G., Bogdanis, G. C., Sakkas, G. K., Roupa, Z., & Giannaki, C. D. (2023). The Effects of Zinc and Selenium Co-Supplementation on Resting Metabolic Rate, Thyroid Function, Physical Fitness, and Functional Capacity in Overweight and Obese People under a Hypocaloric Diet: A Randomized, Double-Blind, and Placebo-Controlled Trial. *Nutrients, 15*(14), 3133. DOI: 10.3390/nu15143133

Zerbo, S., Spanò, M., Albano, G. D., Buscemi, R., Malta, G., & Argo, A. (2023). A fatal suicidal sodium nitrite ingestion determined six days after death. *Journal of Forensic and Legal Medicine, 98,* 102576. DOI: 10.1016/j.jflm.2023.102576

Corresponding author:

Ivan M. Ivanov, PhD
Anatomy and Biomechanics Department
National Sports Academy "Vassil Levski"
21, Acad. Stefan Mladenov Str.
Studentski grad, 1700
Sofia, Bulgaria
E-mail: ivanmirchev@abv.bg