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REVIEW

How Metabolomics Could Contribute to Advancing the Field of Sport and Exercise Medicine: A Clinician Perspective

EXERCISE IS MEDICINE

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Abstract

Metabolomics is a system biology approach that aims to analyze the metabolome comprehensively. The metabolome is defined as the complete set of metabolites within a given biological system. Metabolomics can identify the unique metabolic fingerprint underlying complex phenotypes in physiological and pathological conditions. Interestingly, metabolites are not only essential fuels in cellular energetics and key building blocks of cell components but also serve as important signaling molecules. In addition, changes recorded in the metabolome reflect the influence of the genome, the lifestyle, and the environment. In that way, metabolomics offers a unique opportunity to upgrade sport and exercise medicine knowledge by investigating mechanisms underlying body adaptations to exercise. In this short review, we want to introduce clinicians to selected findings recently issued from applying metabolomics in the sport and exercise medicine field.

Résumé

La métabolomique est une approche de biologie systémique qui vise à analyser de manière exhaustive le métabolome. Le métabolome est défini comme l'ensemble des métabolites d'un système biologique donné. Ainsi, la métabolomique peut identifier l'empreinte métabolique unique qui sous-tend des phénotypes complexes dans des conditions tant physiologiques que pathologiques. En plus, d'être des carburants essentiels à la production d'énergie et des éléments constitutifs clés des composants cellulaires, les métabolites jouent également un rôle clé de molécules de signalisation. De manière intéressante, les changements enregistrés dans le métabolome reflètent non seulement l'influence du génome, mais aussi du mode de vie et de l'environnement. Ainsi, la métabolomique offre une occasion unique d'améliorer les connaissances en médecine du sport et de l'exercice en étudiant les mécanismes qui sous-tendent les adaptations du corps à l'exercice. Dans cette brève revue, nous souhaitons présenter une sélection de résultats récemment obtenus par l'application de la métabolomique dans le domaine de la médecine du sport et de l'exercice.

Introduction

Metabolomics is a system biology approach aiming to analyze the metabolome comprehensively [1]. The metabolome is defined as the complete set of small molecules (lighter than 15'000 Dalton), known as metabolites, and their interaction within a given biological system, such as a cell, a tissue, or a whole organism [1]. From simple molecules like glucose or amino acids to very complex lipids such as sphingolipids, metabolites are extraordinarily diverse both from a structural and functional point of view [2]. More than 8'300 endogenous human metabolites and even more exogenous ones are indexed in the Human Metabolite Database [2]. In addition to being the building blocks of living organisms, metabolites hold crucial physiological roles such as producing and storing energy and molecular signaling [3]. Conversely to the genome, the metabolome reflects our genetics, lifestyle, and environment [1]. As indicated in Figure 1, the metabolome is the final *'ome* level before the phenome and provides the most direct and sensitive measure of changes driving *who we are* (i.e., the phenome) [1]. Consequently, each individual yields a unique metabolome, which can be compared to a personal metabolic fingerprint [4]. In clinical practice, we still capture a very narrow part of the information encompassed in the metabolome to

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evaluate health and disease states (for instance, cholesterol and triglycerides to assess the cardiovascular risk) [5]. In that way, applying metabolomics in clinical medicine could meaningfully contribute to developing *personalized medicine* (also known as *precision medicine)* [4]. Importantly, metabolomics approaches can be applied to any biofluid and tissue (blood, saliva, urine, muscle, fat, bone, etc.) [1].
The increasing surge of interest in metabolomics and its application also gained traction in sport and exercise medicine. In this short review, we want to introduce clinicians to selected findings recently issued from applying metabolomics in the sport and exercise medicine field.

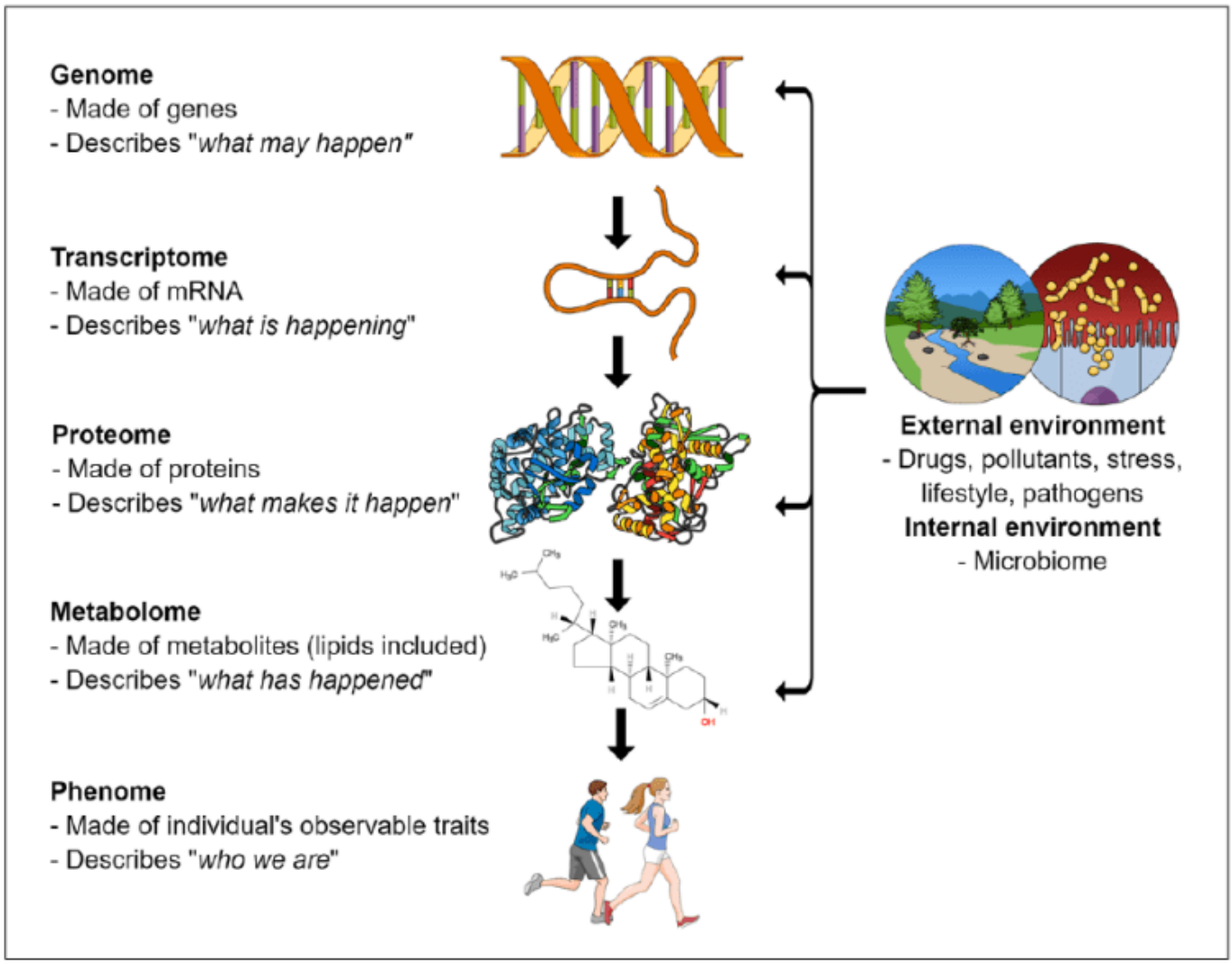

Figure 1: Overview of the interrelations between the different 'omics levels (genome, transcriptome, proteome, metabolome, and phenome) and the external and internal environments. The figure was inspired from [1-3].

Metabolomics applied to Exercise Medicine

Exercise medicine is based on the evidence that prescription of physical activity can prevent and treat chronic diseases [6,7]. In conditions such as cancer, atherosclerosis, type 2 diabetes mellitus, heart failure, and neurodegenerative disorders, metabolic disturbances are believed to play an essential role in disease

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development [8-14]. Through large-scale metabolic phenotyping of health and diseases, metabolomics not only allows the discovery of novel and likely more sensitive biomarkers of human health but also enables a mechanistic understanding of exercise physiology and the pathophysiology of many chronic conditions [15]. To date, molecular mechanisms through which physical activity positively impacts global human health and modulates disease development remain insufficiently understood [16]. This is where metabolomics comes into play, as such a comprehensive approach can aid in shedding light on the systemic adaptions to exercise without having to focus *a priori* on a particular molecular pathway [16]. Recently, a milestone study comprehensively investigated the molecular response to a single session of moderate-intensity continuous exercise training [17]. Thousands of molecular changes were identified, indicating a fine-regulated response to exercise on many biological levels, such as energy metabolism, inflammation, oxidative stress, and tissue repair [17]. We acknowledge that the results of this study might seem very theoretical and far from our daily practice. However, unraveling short-term exercise effects on the human body is particularly relevant as signaling molecules are released in response to exercise and convey messages to other organs distant from the exercising tissues [18]. In addition, the authors found that the observed changes were dampened or even reversed in patients with insulin-resistance [17]. This highlights that molecular exercise studies are valuable in identifying mechanisms underlying insulin resistance (or other metabolic condition) [17]. Such findings could lead to a better-tailored exercise prescription and pave the way for the discovery of novel pharmaceutical targets [19].
Cardiorespiratory fitness (CRF), defined as the peak oxygen uptake, is widely recognized as a powerful health marker [20]. The American Heart Association even recommends monitoring CRF as a vital sign in clinical practice [20]. CRF is negatively associated with the incidence of cancer, cardiometabolic diseases, and all-cause mortality [20,21]. More importantly, CRF improvement lowers the incidence of stroke, type 2 diabetes mellitus, dementia, and all-cause mortality [22-24]. A recent systematic review highlighted that CRF was significantly associated with a unique panel of lipid species [25]. Concretely, specific circulating glycerolipids, acylcarnitines, and ceramides were negatively related to cardiorespiratory fitness, featuring poor cardiometabolic health [25]. Conversely, particular glycerophosphocholines and cholesterol esters were positively associated with cardiorespiratory fitness, indicating a potential role in health maintenance [25]. It is interesting that circulating ceramides, thanks to metabolomics-based studies, are increasingly recognized as novel biomarkers of cardiometabolic health and even predict cardiovascular risk beyond traditional cholesterol and risk estimation scores [26,27]. Together, these studies suggest a molecular explanation of why improvement in CRF leads to improved cardiometabolic health.

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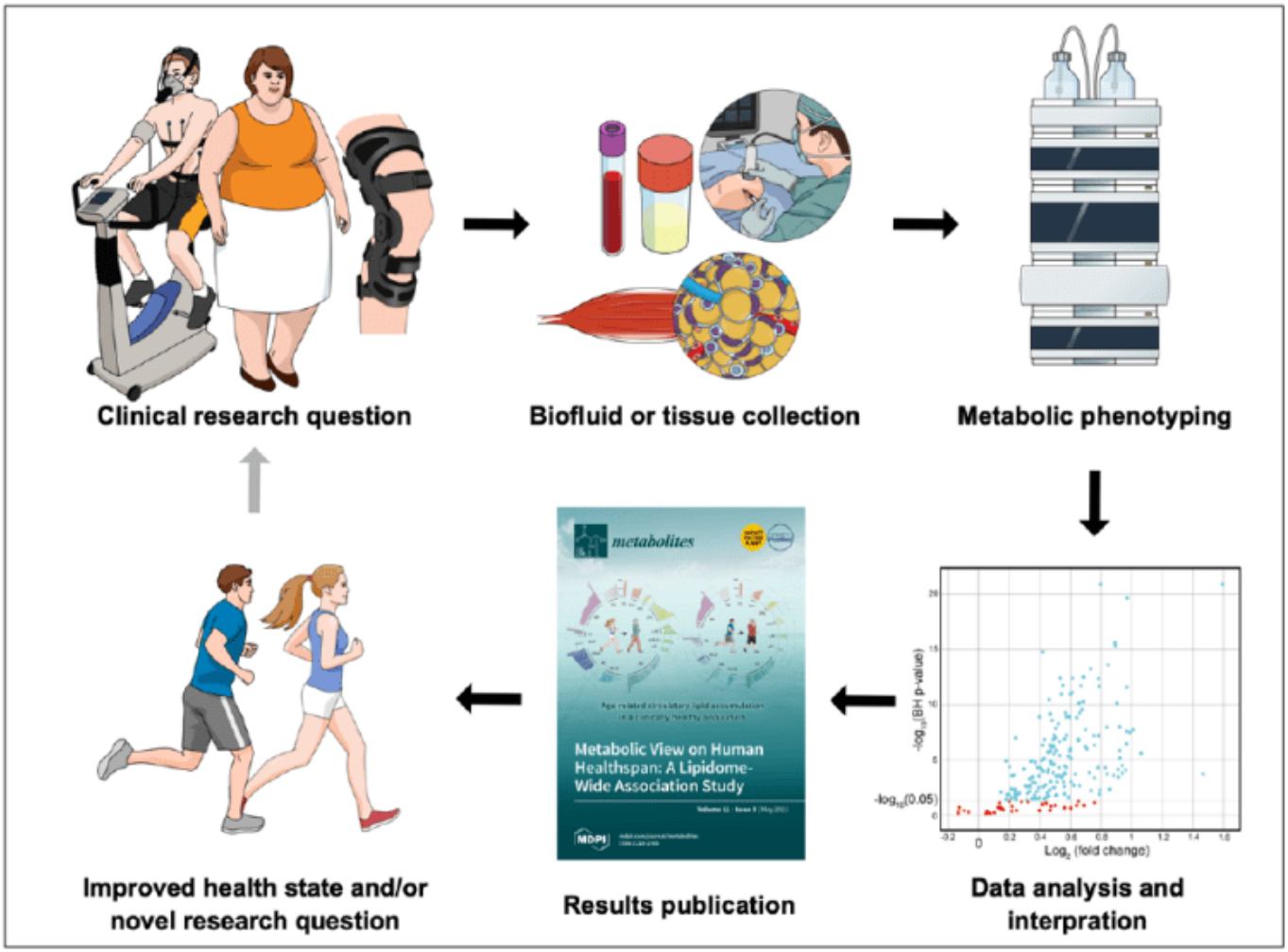

Figure 2: Overview of a typical metabolomics discovery cycle. After establishing a specific clinical question, working with an interdisciplinary team to develop an appropriate study design, collect biological samples, choose an adequate metabolomics approach, and conduct suitable data analysis is essential. Study results are usually published in peer-reviewed journals, should advance current knowledge, and might lead to a novel clinical research question.

Metabolomics applied to Sport Medicine

Sport medicine is internationally defined as the medical discipline that aims to diagnose and manage musculoskeletal pathologies and medical conditions associated with physical activity [6]. The term *sportomics* was recently coined and refers to the application of metabolomics in the field of sport medicine and science to study the impact of sport on human metabolism [28]. *Sportomics* has the potential to advance many areas of sport medicine. For instance, following athletes' metabolic profiles throughout a season could ensure that they positively adapt to their training load [29]. Concretely, *sportomics* could allow for early detection of metabolic maladaptation to training and avoid the occurrence of non-functional overreaching or overtraining syndrome [30].

Researchers of the F. C. Barcelona examined the urine metabolome of professional football players throughout one season [31]. They found that alterations in the urinary level of several metabolites issued from the steroid hormone, tryptophan, and tyrosine metabolic pathways were significantly associated with external training load. Further, players who sustained muscle injury throughout the season shared

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similar urinary metabolic fingerprints. Therefore, urinary metabolic profiling could be a promising non-invasive tool to monitor long-term adaptation to training in athletes. Another research group reported that a salivary profile composed of metabolites of the urea and Krebs cycles could distinguish between female volleyball players with high and low sleep quality [32]. Thus, applied-metabolomics studies could also contribute to improving molecular mechanisms underlying recovery processes in athletes.
Finally, research in sport medicine has traditionally focused on males [33]. For convenience, female-specific methodical challenges (menstrual cycle, hormonal contraceptive use, pregnancy, or menopause) have too rarely been considered in study designs. Consequently, sport medicine needs more high-quality data on females [33]. Due to their comprehensiveness, high-throughput metabolomics approaches could speed up female-specific data and knowledge acquisition in sport medicine [34]. Indeed, it has been shown that females and males display distinct blood metabolic fingerprints in physiological and pathological conditions [35-37]. To develop study designs appropriate for females and males, we highly recommend working with an interdisciplinary team, including metabolomics specialists, data science specialists, statisticians, physiologists, and clinicians. Indeed, applying metabolomic approaches is challenging and demands expertise in post-genomic science, including method development, data acquisition, computational skills in data processing, quality assessment, metabolite annotation, and clinical/physiological interpretation [1]. Figure 2 illustrates some essential steps of a typical metabolomics workflow, highlighting the need for various specialized skills.

Conclusion

Metabolomics offers the unique opportunity to scratch beneath the surface of what is currently known in sport and exercise medicine by providing extensive metabolic phenotyping of complex physiological and pathological states. Specifically, metabolomics applications will likely contribute to advancing knowledge in various fields, such as exercise prescription for health, training monitoring, and female athletes.

Practical implications

- Metabolomics is a powerful tool to unravel molecular mechanisms underlying complex phenotypes. It offers a unique opportunity to scratch beneath the surface of what is currently known in sport and exercise medicine.
- Large-scale metabolic profiling is a promising non-invasive tool to monitor long-term adaptation to training in athletes.
- Working with a highly skilled interdisciplinary team is necessary to conduct metabolomics studies in sport and exercise medicine.

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References

1. Ivanisevic J, Thomas A. Metabolomics as a Tool to Understand Pathophysiological Processes. In: Giera M, editor. Clinical Metabolomics: Methods and Protocols. New York, NY: Springer New York; 2018. p. 3-28.
2. Wishart DS, Guo A, Oler E, Wang F, Anjum A, Peters H, et al. HMDB 5.0: the Human Metabolome Database for 2022. Nucleic Acids Res. 2021;50(D1):D622-D31.
3. Rinschen MM, Ivanisevic J, Giera M, Siuzdak G. Identification of bioactive metabolites using activity metabolomics. Nat Rev Mol Cell Biol. 2019;20(6):353-67.
4. Beger RD, Dunn W, Schmidt MA, Gross SS, Kirwan JA, Cascante M, et al. Metabolomics enables precision medicine: "A White Paper, Community Perspective". Metabolomics. 2016;12(10):149.
5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.
6. Jaques R, Loosemore M. Sports and exercise medicine in undergraduate training. The Lancet. 2012;380(9836):4-5.
7. Pedersen BK, Saltin B. Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports. 2015;25 Suppl 3:1-72.
8. Chen X, Liu L, Palacios G, Gao J, Zhang N, Li G, et al. Plasma metabolomics reveals biomarkers of the atherosclerosis. Journal of separation science. 2010;33(17-18):2776-83.
9. Park JY, Lee SH, Shin MJ, Hwang GS. Alteration in metabolic signature and lipid metabolism in patients with angina pectoris and myocardial infarction. PLoS One. 2015;10(8):e0135228.
10. Zordoky BN, Sung MM, Ezekowitz J, Mandal R, Han B, Bjorndahl TC, et al. Metabolomic fingerprint of heart failure with preserved ejection fraction. PLoS One. 2015;10(5):e0124844.
11. Wishart DS. Emerging applications of metabolomics in drug discovery and precision medicine. Nat Rev Drug Discov. 2016;15(7):473-84.
12. van der Velpen V, Teav T, Gallart-Ayala H, Mehl F, Konz I, Clark C, et al. Systemic and central nervous system metabolic alterations in Alzheimer's disease. Alzheimers Res Ther. 2019;11(1):93.
13. Chen ZZ, Gerszten RE. Metabolomics and Proteomics in Type 2 Diabetes. Circ Res. 2020;126(11):1613-27.
14. Kumar A, Misra BB. Challenges and Opportunities in Cancer Metabolomics. Proteomics. 2019;19(21-22):e1900042.
15. Wishart DS. Metabolomics for Investigating Physiological and Pathophysiological Processes. Physiol Rev. 2019;99(4):1819-75.
16. Hoffman NJ. Omics and Exercise: Global Approaches for Mapping Exercise Biological Networks. Cold

published online on 01.12.2022
https://doi.org/10.34045/SEMS/2022/24

Spring Harb Perspect Med. 2017;7(10).
17. Contrepois K, Wu S, Moneghetti KJ, Hornburg D, Ahadi S, Tsai MS, et al. Molecular Choreography of Acute Exercise. Cell. 2020; 181(5):1112-30.e16.
18. Chow LS, Gerszten RE, Taylor JM, Pedersen BK, van Praag H, Trappe S, et al. Exerkines in health, resilience and disease. Nature Reviews Endocrinology. 2022;18(5):273-89.
19. Tippetts TS, Holland WL, Summers SA. Cholesterol – the devil you know; ceramide – the devil you don't. Trends Pharmacol Sci. 2021;42(12):1082-95.
20. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. Circulation. 2016; 134(24):e653-e99.
21. Robsahm TE, Falk RS, Heir T, Sandvik L, Vos L, Erikssen JE, et al. Measured cardiorespiratory fitness and self-reported physical activity: associations with cancer risk and death in a long-term prospective cohort study. Cancer Med. 2016;5(8):2136-44.
22. Prestgaard E, Mariampillai J, Engeseth K, Erikssen J, Bodegård J, Liestøl K, et al. Change in Cardiorespiratory Fitness and Risk of Stroke and Death. Stroke. 2018:Strokeaha118021798.
23. de Lannoy L, Sui X, Lavie CJ, Blair SN, Ross R. Change in Submaximal Cardiorespiratory Fitness and All-Cause Mortality. Mayo Clin Proc. 2018;93(2):184-90.
24. Tari AR, Nauman J, Zisko N, Skjellegrind HK, Bosnes I, Bergh S, et al. Temporal changes in cardiorespiratory fitness and risk of dementia incidence and mortality: a population-based prospective cohort study. Lancet Public Health. 2019;4(11):e565-e74.
25. Carrard J, Guerini C, Appenzeller-Herzog C, Infanger D, Königstein K, Streese L, et al. The Metabolic Signature of Cardiorespiratory Fitness: A Systematic Review. Sports Med. 2021.
26. Laaksonen R, Ekroos K, Sysi-Aho M, Hilvo M, Vihervaara T, Kauhanen D, et al. Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol. Eur Heart J. 2016;37(25):1967-76.
27. Berkowitz L, Cabrera-Reyes F, Salazar C, Ryff CD, Coe C, Rigotti A. Sphingolipid Profiling: A Promising Tool for Stratifying the Metabolic Syndrome-Associated Risk. Frontiers in Cardiovascular Medicine. 2022;8.
28. Bongiovanni T, Pintus R, Dessì A, Noto A, Sardo S, Finco G, et al. Sportomics: metabolomics applied to sports. The new revolution? Eur Rev Med Pharmacol Sci. 2019;23(24):11011-9.
29. Bragazzi NL, Khoramipour K, Chaouachi A, Chamari K. Toward Sportomics: Shifting From Sport Genomics to Sport Postgenomics and Metabolomics Specialties. Promises, Challenges, and Future Perspectives. Int J Sports Physiol Perform. 2020;15(9):1201-2.
30. Carrard J RA-C, Hinrichs T, Appenzeller-Herzog C, Schmidt-Trucksäss A. Diagnosing overtraining syndrome: a scoping review protocol. 2020.
31. Quintas G, Reche X, Sanjuan-Herráez JD, Martínez H, Herrero M, Valle X, et al. Urine metabolomic analysis for monitoring internal load in professional football players. Metabolomics. 2020;16(4):45.
32. Akazawa N, Kobayashi N, Nakamura Y, Kumagai H, Choi Y, Maeda S. Effect of sleep efficiency on salivary metabolite profile and cognitive function during exercise in volleyball athletes. Eur J Appl Physiol. 2019;119(10):2215-23.
33. Elliott-Sale KJ, Minahan CL, de Jonge X, Ackerman KE, Sipilä S, Constantini NW, et al. Methodological Considerations for Studies in Sport and Exercise Science with Women as Participants: A Working Guide for Standards of Practice for Research on Women. Sports Med. 2021;51(5):843-61.
34. Costanzo M, Caterino M, Sotgiu G, Ruoppolo M, Franconi F, Campesi I. Sex differences in the human metabolome. Biol Sex Differ. 2022;13(1):30.
35. Krumsiek J, Mittelstrass K, Do KT, Stückler F, Ried J, Adamski J, et al. Gender-specific pathway differences in the human serum metabolome. Metabolomics. 2015;11(6):1815-33.
36. Carrard J, Gallart-Ayala H, Infanger D, Teav T, Wagner J, Knaier R, et al. Metabolic View on Human

published online on 01.12.2022
https://doi.org/10.34045/SEMS/2022/24

Healthspan: A Lipidome-Wide Association Study. Metabolites. 2021;11(5):287.
37. Chary S, Amrein K, Lasky-Su JA, Dobnig H, Christopher KB. Metabolomic differences between critically Ill women and men. Sci Rep. 2021;11(1):3951.

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