Title:

Gut Microbiota: Implications for Sports and Exercise Medicine.

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INTRODUCING THE GUT MICROBIOTA

Technological progress in high-throughput sequencing and advanced bioinformatic techniques, have facilitated a deeper understanding of the gut microbial influence on human health. Collectively known as the gut microbiota, the trillions of microbes including bacteria, viruses and fungi, which reside within the gut, are now recognized as significant contributors to human (host) health. Patients with non-communicable diseases such as metabolic syndrome, obesity and inflammatory bowel disease, demonstrate distinct microbial alterations. This has prompted vigorous pursuit of the mechanisms by which this microbial "organ" influences host health. This branch of medicine has already revealed exciting avenues for disease treatment, from the discovery of novel antibiotics to the treatment of recurrent *Clostridium difficile* infection.[1]

The scale and spectrum of microbial influence is substantial and elegant studies have linked the presence or absence of specific microbes with immunity,[2] neuro-development, and even behavioral disturbances.[3] The potential impact of microbiome science extends to the specialties of Sports Medicine and particularly to Exercise Medicine.

EXERCISING YOUR MICROBIOTA

The development of a mature enteric microbiota is subject to modifiable and non-modifiable factors, including diet and host genetics.[4] The gut microbiota is perturbed by antibiotic usage and is influenced by short- and long-term dietary trends. Recently, the interaction between exercise and the gut microbiota has been highlighted following identification of correlations between cardio-respiratory fitness and health-associated gut microbial parameters such as taxonomic diversity and richness.[5 6] It is

unknown whether improvements in cardio-respiratory fitness achieved during adulthood can shift the gut microbiota toward a more healthy compositional profile. Evidence suggests that physical activity in childhood and adolescence supports the development of a diverse core microbiota that promotes psychological and metabolic health.[7] However, longitudinal studies are required to establish or challenge this hypothesis.

In determining the true or specific effect of exercise on the composition and activity of the gut microbiota, significant impediments must be addressed. First, there is the confounding influence of subconscious or intentional dietary and lifestyle changes, which commonly accompany changes in physical activity. Secondly, there are the uncertain effects of fitness-industry targeted dietary supplements, including energy bars, caffeine, and whey protein, on gut microbiota status and on human health and performance. These effects are of particular interest to elite sport, where attention to detail and marginal gains are perceived as pivotal to competitive success.

MICROBIAL LESSONS FOR THE ELITE ATHLETE

Recognition of the need to prevent illness in athletes has heightened, with emphasis on nutrition and workload monitoring central to illness prevention strategies. Microbes in the gut transduce functional nutritional signals to enhance not only energy input but also immune and metabolic welfare. Simply stated, athletes need to know that when they eat and drink, they are feeding not only themselves, but also their microbes! Dietary supplementation, although commonplace, is generally adopted with poor understanding of how supplements influence gut microbial health and performance. Furthermore, knowledge of the impact of sports drinks on the oral microbiota of athletes is limited, yet may be significant considering the high

prevalence of dental caries and periodontal disease witnessed in this population, and the potential for oral microbiota to affect both systemic and oral health.

As microbiome science advances, there is likely to be improved standardization and dietary design with due regard for host-microbe interactions under varying levels of physical activity. Previously, we characterized the microbiota of a professional international rugby union squad demonstrating a distinct compositional profile compared to non-athletes.[6] The elite athlete microbiota is diverse and its characteristics are associated with positive health indicators, including favorable metabolic and inflammatory profiles. The compositional and functional characteristics of the elite athlete microbiota are likely the cumulative result of years of optimized nutrition and high-degrees of physical conditioning, through youth, adolescence and into the professional sporting milieu. Athletes' microbial potential may also be shaped by their own genotype.[8] However, longitudinal studies are needed to resolve many gaps in knowledge, as most of the available data on exercise and the microbiota are cross-sectional.

In summary, there is significant potential for microbiota research to contribute to the specialty of Sports and Exercise Medicine. In addition, Sports and Exercise Medicine represents a model or platform to facilitate studies of the interplay between human physiology, host and microbial genetics, and diet. The gut microbiota is implicated in areas vital to elite sport; these include immunity, defence against gastro-intestinal infections, and energy provision. Microbiome science even embraces cerebral function, cognition and behavior. To exploit the microbial contribution to athlete performance, prospective studies are required to bridge the gap between correlation and causation, and the interactions among biological co-variables and the microbiota.[4] Athletes of the future will continue to measure many parameters of

fitness and amongst these will be microbial indicators of health and nutritional welfare.

Conflicts of interest:

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References:

1. Drekonja D, Reich J, Gezahegn S, et al. Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. *Ann Intern Med* 2015;162(9):630-8. doi: 10.7326/m14-2693 [published Online First: 2015/05/06]

2. Schuijt TJ, Lankelma JM, Scicluna BP, et al. The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia. *Gut* 2016;65(4):575-83. doi: 10.1136/gutjnl-2015-309728 [published Online First: 2015/10/30]

3. Hoban AE, Moloney RD, Golubeva AV, et al. Behavioral and neurochemical consequences of chronic gut microbiota depletion during adulthood in the rat. *Neuroscience* 2016 doi: 10.1016/j.neuroscience.2016.10.003 [published Online First: 2016/10/23]

4. Debelius J, Song SJ, Vazquez-Baeza Y, et al. Tiny microbes, enormous impacts: what matters in gut microbiome studies? *Genome Biol* 2016;17(1):217. doi: 10.1186/s13059-016-1086-x [published Online First: 2016/10/21]

5. Estaki M, Pither J, Baumeister P, et al. Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. *Microbiome* 2016;4(1):42. doi: 10.1186/s40168-016-0189-7 [published Online First: 2016/08/10]

6. Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut* 2014;63(12):1913-20. doi: 10.1136/gutjnl-2013-306541

7. Mika A, Fleshner M. Early-life exercise may promote lasting brain and metabolic health through gut bacterial metabolites. *Immunol Cell Biol* 2016;94(2):151-7. doi: 10.1038/icb.2015.113 [published Online First: 2015/12/10]

8. Bonder MJ, Kurilshikov A, Tigchelaar EF, et al. The effect of host genetics on the gut microbiome. *Nat Genet* 2016;48(11):1407-12. doi: 10.1038/ng.3663 [published Online First: 2016/10/28]