腸内フローラと糖質制限ダイエット

Antonio Paoli
パドヴァ大学　生物化学分野　イタリア

略歴：

1989年に体育専門大学（Istituto Superiore di Educazione Fisica; ISEF）を卒業後、2004年にパドヴァ大学（イタリア）で医学、2008年にパヴィア大学（イタリア）でスポーツ医学の学位を取得。2011年からパドヴァ大学・人体解剖生理学部のスポーツ科学の助教を務めた。2013年には同大学のバイオメディカルサイエンス学部・運動スポーツ科学科の准教授、2018年には正教授／学科長に就任した。ムルシア・カトリック大学（UCAM；スペイン）の筋力トレーニング／スポーツ栄養学科教授／学科長、ロバチェフスキー大学（ロシア）のヒト健康研究室長、さらにはイタリアスポーツ運動科学学会（SISMES）および欧州スポーツ栄養学会（ESNS）の学会長も務める。パドヴァ大学のスポーツ・ウェルネス担当として、2015年10月から2021年まで学長補佐、2021年以降は副学長を務め、学生や教員、職員のためのスポーツ・ウェルネス・健康関連活動の運営に従事している。

現在はパドヴァ大学・バイオメディカルサイエンス学部の栄養・運動生理学研究所長を務め、ヒト運動学の学士課程、予防・リハビリ運動学の修士課程を統括する。主な研究テーマは、ケトン食と断食、腸内細菌叢、運動・食事と骨格筋代謝との相互作用、運動トレーニングに対する適応の分子的機序、様々な筋力トレーニング法が若年者と成人の健康指標と体組成に及ぼす影響など。これまでに国際学術雑誌にて査読付き論文218報を発表し、被引用数は3957件、h指数は34である。学術雑誌Nutrients、Medicina（リトアニア）、Frontiers in Physiology、Sport Science for Health、Journal of Translational Medicineの編集委員であり、Journal of Human KineticsとAging, Clinical and Experimental Researchの共同編集者も務める。2017年にはEuropean Journal of Sport Science（EJSS）の年間ベストペーパー賞を共同受賞し、同年European College of Sport Science（ECSS）学会ではGatorade Sports Science Institute（GSSI）賞1位を受賞した。また、イタリアとヨーロッパの研究助成プロジェクトにおいて数々の研究を主導した。

要約：

ヒトの腸管は、宿主に共生する膨大な数の微生物集団（マイクロバイオータ）とそれらの遺伝子（マイクロバイオーム）で構成されている。近年、ヒトの健康における微生物叢の重要性に対する関心は非常に高まっており、マイクロバイオーム研究は生命科学の中でも重点分野となっている［1］。年齢、環境、出産経路、母乳育児、抗生物質、食生活、運動などの内因性および外因性の要因が腸内細菌叢の構成と機能に影響を及ぼし、中でも食事と運動が主要な因子である［2-5］。栄養に関しては、炭水化物、タンパク質、脂質の総摂取量および／または摂取比率が菌叢構成に大きく影響する。例えば、炭水化物が腸内細菌叢に与える影響は、一般的に食物繊維と呼ばれる、腸内に届き菌に利用される炭水化物（MACs）の含有量と種類に大きく左右される。MACsは植物、動物組織、食物由来微生物など様々な食品に含まれ、腸内細菌にとって代謝可能な炭水化物供給源となる。MACsは大腸内生態系における「第一発酵槽」として、一般的にバクテロイデスやアクチノバク

テリアなどの有益な短鎖脂肪酸産生菌を増加させる［6］。一方で、タンパク質摂取量の増加は、クロストリジウムやプロテオバクテリアの増殖による過剰なタンパク質発酵を引き起こす可能性がある。栄養と腸内菌叢との関連において、ケトン食（KD）は一つの実例的な課題といえる。KD は高脂肪、適度なタンパク質と一日 20 グラム以下（または一日のエネルギー摂取量の 5%）の炭水化物からなる食事プロトコルである［7］。この栄養学的アプローチは 1920 年代から難治性てんかんの治療法として用いられており［8］、その後肥満や代謝性疾患への治療効果が期待できるとしてさらに広まった［9］。実際に KD が体組成を適正化し健康を維持するための効果的で安全な方法であることを示唆する報告も増えつつある一方で、KD の腸内細菌叢に対する影響について重要な問題を提起する研究者もいる。高脂肪食の腸内細菌に対する影響を調査した研究は多数あるが［10-13］、これらは精製高脂肪 - 低繊維食を与えたマウスと水溶性繊維を多く含む標準飼料を与えたマウスを用いた実験モデルでのみ検証されている。そのため、これらの動物実験で得られた結果をケトン食の効果やそれに関連する腸内細菌叢への影響の予測に外挿することはできない［14］。ヒトでは近年、ケトン食が高脂肪食とは異なる腸内細菌叢構成の変化をもたらし、さらにケトン食に限って消化管関連の全身的指標を改善することが確認されている［15］。単なる高脂肪食と KD に多くの根本的な違いがあることは明らかである。KD の腸内細菌叢に対する特異的な代謝作用は、インスリンとグルコース値の低下および β ヒドロキシ酪酸の上昇によって説明できるかもしれない。実際に Turnbaugh らは、KD が宿主内のケトン体、特に β ヒドロキシ酪酸の産生を介して腸内生態系に良い影響を及ぼすことを確認した［15］。研究者らは、KD に関連した消化管内と脂肪組織における炎症性 Th17 細胞の減少が、ケトン食の代謝に対する効果に寄与する潜在的なメカニズムではないかと考察し、KD がより「全身的に」作用する可能性があることを強調した。また、脂質の量だけでなく、脂質の種類や質も考慮されるべきである。実際に、脂肪の種類が異なれば腸内細菌叢への影響も異なり、結果として腸管および全身性の炎症への影響も異なる［16-18］。飽和脂肪がヒトにおける菌叢多様性の低下と体内 LPS 量の増加に関連する一方で［19］、オメガ 3 などの多価不飽和脂肪は菌叢の多様性と豊富さには影響を与えないものの短鎖脂肪酸（SCFAs）の産生を通じて腸管上皮の完全性と胃腸炎を改善した［20］。さらに、KD と腸内細菌叢の相互作用が KD の効果に極めて重要な役割を果たすことは特筆すべきであり［21-23］、この相互作用は抗けいれん効果や神経血管機能改善などの効果をもたらすために必要なものである［24-26］。我々は最近、植物抽出物と良質な脂質を含む KD をサッカー選手が摂取することで、有害事象や腸内細菌叢プロファイルへの悪影響なしに腸内細菌叢の特性が維持されることを示したが、一方で KD が腸内細菌叢プロファイルに影響し、その変化が KD の有効性に重要な役割を果たすとの報告もある［21-23］。KD の腸内細菌叢への影響に関する様々な結果（マイナス効果、プラス効果、または変化なし）を理解することは、これらの結果に影響する栄養因子（タンパク質・脂質の量と質、MACs、プレバイオティクス、プロバイオティクスなど）を解明するために不可欠である。結論として、ヒトにおけるケトン食介入法をより腸内細菌叢を考慮した形で確立するためには、長期的な臨床試験を含むさらなる研究が必要である。

参考文献

1. Lynch SV, Pedersen O: **The Human Intestinal Microbiome in Health and Disease**. *N Engl J Med* 2016, **375** (24):2369-2379.
2. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA *et al*: **Diet rapidly and reproducibly alters the human gut microbiome**. *Nature* 2014, **505** (7484):559-563.
3. Scheiman J, Luber JM, Chavkin TA, MacDonald T, Tung A, Pham LD, Wibowo MC, Wurth RC, Punthambaker S, Tierney BT *et al*: **Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism**. *Nat Med* 2019, **25** (7):1104-1109.
4. Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, Hayes P, O'Reilly M, Jeffery IB, Wood-Martin R *et al*: **Exercise and associated dietary extremes impact on gut microbial diversity**. *Gut* 2014, **63** (12):1913-1920.
5. Barton W, Penney NC, Cronin O, Garcia-Perez I, Molloy MG, Holmes E, Shanahan F, Cotter PD, O'Sullivan O: **The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level**. *Gut* 2018, **67** (4):625-633.
6. Sonnenburg ED, Sonnenburg JL: **Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates**. *Cell Metab* 2014, **20** (5):779-786.
7. Paoli A, Bianco A, Grimaldi KA: **The Ketogenic Diet and Sport: A Possible Marriage?** *Exerc Sport Sci Rev* 2015, **43** (3):153-162.
8. Cooder HR: **Epilepsy in Children: With Particular Reference to the Ketogenic Diet**. *Cal West Med* 1933, **39** (3):169-173.
9. Perez-Guisado J: [**Ketogenic diets: additional benefits to the weight loss and unfounded secondary effects**]. *Arch Latinoam Nutr* 2008, **58** (4):323-329.
10. Singh RP, Halaka DA, Hayouka Z, Tirosh O: **High-Fat Diet Induced Alteration of Mice Microbiota and the Functional Ability to Utilize Fructooligosaccharide for Ethanol Production**. *Front Cell Infect Microbiol* 2020, **10**:376.
11. Daniel H, Gholami AM, Berry D, Desmarchelier C, Hahne H, Loh G, Mondot S, Lepage P, Rothballer M, Walker A *et al*: **High-fat diet alters gut microbiota physiology in mice**. *ISME J* 2014, **8** (2):295-308.
12. Xiao L, Sonne SB, Feng Q, Chen N, Xia Z, Li X, Fang Z, Zhang D, Fjaere E, Midtbo LK *et al*: **High-fat feeding rather than obesity drives taxonomical and functional changes in the gut microbiota in mice**. *Microbiome* 2017, **5** (1):43.
13. Serino M, Luche E, Gres S, Baylac A, Berge M, Cenac C, Waget A, Klopp P, Iacovoni J, Klopp C *et al*: **Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota**. *Gut* 2012, **61** (4):543-553.
14. Morrison KE, Jasarevic E, Howard CD, Bale TL: **It's the fiber, not the fat: significant effects of dietary challenge on the gut microbiome**. *Microbiome* 2020, **8** (1):15.
15. Ang QY, Alexander M, Newman JC, Tian Y, Cai J, Upadhyay V, Turnbaugh JA, Verdin E, Hall KD, Leibel RL *et al*: **Ketogenic Diets Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells**. *Cell* 2020, **181** (6):1263-1275 e1216.
16. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Backhed F: **Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling**. *Cell Metab* 2015, **22** (4):658-668.
17. Huang EY, Leone VA, Devkota S, Wang Y, Brady MJ, Chang EB: **Composition of dietary fat source shapes gut microbiota architecture and alters host inflammatory mediators in mouse adipose tissue**. *JPEN J Parenter Enteral Nutr* 2013, **37** (6):746-754.
18. Paoli A, Mancin L, Bianco A, Thomas E, Mota JF, Piccini F: **Ketogenic Diet and Microbiota: Friends or Enemies?** *Genes (Basel)* 2019, **10** (7).
19. Wolters M, Ahrens J, Romani-Perez M, Watkins C, Sanz Y, Benitez-Paez A, Stanton C, Gunther K: **Dietary fat, the gut microbiota, and metabolic health - A systematic review conducted within the MyNewGut project**. *Clin Nutr* 2019, **38** (6):2504-2520.
20. Costantini L, Molinari R, Farinon B, Merendino N: **Impact of Omega-3 Fatty Acids on the Gut Microbiota**. *Int J Mol Sci* 2017, **18** (12).
21. Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY: **The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet**. *Cell* 2018, **174** (2):497.
22. Newell C, Bomhof MR, Reimer RA, Hittel DS, Rho JM, Shearer J: **Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder**. *Mol Autism* 2016, **7** (1):37.
23. Xie G, Zhou Q, Qiu CZ, Dai WK, Wang HP, Li YH, Liao JX, Lu XG, Lin SF, Ye JH *et al*: **Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy**. *World J Gastroenterol* 2017, **23** (33):6164-6171.
24. Lindefeldt M, Eng A, Darban H, Bjerkner A, Zetterstrom CK, Allander T, Andersson B, Borenstein E, Dahlin M, Prast-Nielsen S: **The ketogenic diet influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy**. *NPJ Biofilms Microbiomes* 2019, **5**:5.
25. Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY: **The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet**. *Cell* 2018, **173** (7):1728-1741 e1713.
26. Zhang Y, Zhou S, Zhou Y, Yu L, Zhang L, Wang Y: **Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet**. *Epilepsy Res* 2018, **145**:163-168.

Ketogenic diet and microbiota

Antonio Paoli
Department of Biomedical Sciences-University of Padua, Italy

Brief curriculum vitae:

Antonio Paoli graduated in physical education (ISEF) in 1989, then in 2004 in Medicine (Padova University) and in in 2008 he earned the specialization in Sport Medicine (University of Pavia). He became assistant professor of Sport Sciences in 2011 at the Department of Human Anatomy and Physiology, University of Padova (Italy). In 2013 he became associate professor and in 2018 full professor and chair of Exercise and Sport Sciences at the Department of Biomedical Sciences, University of Padova. He is Director and Professor of Strength Training and Sport Nutrition at the University UCAM (Murcia, Spain) and Head of Human Health Laboratory Lobachevsky University - Niznij Novgorod - Russia. He is President of the Italian Society of Sport and Exercise Science (SISMES) and the European Sport Nutrition Society (ESNS). From October, 2015 to 2021, Antonio Paoli has served as Rector's Delegate for Sport and Wellness of the University of Padova, and from 2021 he became Vice Rector for Wellness and Sport , being in charge for managing sport and wellness-health related activities for students, faculties and employees.

He is currently Director of the Nutrition & Exercise Physiology Laboratory of the Department of Biomedical Sciences, University of Padova, Italy, Dean of the Bachelor Degree in Human Movement Science and Dean of the Master Degree in Preventive and Adapted Physical Activity. His laboratory research interests include ketogenic diet and fasting, gut-microbiota, the interaction of exercise and diet on skeletal muscle metabolism, the molecular bases of exercise training adaptation and the effects of different methodology of resistance training on health parameters and body composition in young and adults. Antonio Paoli published 218 papers in international peer reviewed, indexed journals, with 3957 citations and an H-Index of 34. He serves as member of editorial board for Nutrients, Medicina - Lituania, Frontiers in Physiology, Sport Science for Health, Journal of Translational medicine and as associate editor for Journal of Human Kinetics, and Aging, Clinical and Experimental Research. He was the co-recipient of the 2017 year's EJSS Best Paper Award and the recipient of the 1st place of the GSSI Award at the 2017 ECSS conference. Antonio Paoli leaded many work packages for Italian and European grants.

Five recent publications

Paoli A, Cenci L, Pompei P, Sahin N, Bianco A, Neri M, Caprio M, Moro T. Effects of Two Months of Very Low Carbohydrate Ketogenic Diet on Body Composition, Muscle Strength, Muscle Area, and Blood Parameters in Competitive Natural Body Builders. Nutrients. 2021 Jan 26;13 (2):374

Mancin L, Rollo I, Mota JF, Piccini F, Carletti M, Susto GA, Valle G, **Paoli A**. Optimizing

Microbiota Profiles for Athletes: Dream or Reality? Exerc Sport Sci Rev. 2021 Jan;49(1):42-49

Paoli A, Mancin L, Caprio M, Monti E, Narici MV, Cenci L, Piccini F, Pincella M, Grigoletto D, Marcolin G. Effects of 30 days of ketogenic diet on body composition, muscle strength, muscle area, metabolism, and performance in semi-professional soccer players. J Int Soc Sports Nutr. 2021 Sep 16;18 (1):62.

Paoli A, Mancin L, Bianco A, Thomas E, Mota JF, Piccini F. Ketogenic Diet and Microbiota: Friends or Enemies? Genes (Basel). 2019 Jul 15;10 (7):534.

Paoli A, Mancin L, Giacona MC, Bianco A, Caprio M. Effects of a ketogenic diet in overweight women with polycystic ovary syndrome. J Transl Med. 2020 Feb 27;18 (1):104

Abstract :

The human intestinal tract is composed of a considerable population of microorganisms (microbiota) and its corresponding gene complement (microbiome), that symbiotically live within the host. In recent years, the awareness of the importance of microbial community in human health has increased tremendously, making the science of microbiome a key area for life sciences [1]. Intrinsic and extrinsic factors including age, environment, birth delivery route, breastfeeding, antibiotics, dietary factors, and exercise, impact the microbial composition and function, with the diet and exercise act as primary modulators [2-5]. Regarding nutrition the total amount and/or the relative percentage of carbohydrate/protein and fat has a great influence on microbiota composition. Indeed, the effect of carbohydrates on the gut microbiota differs widely as a function of microbiota-accessible carbohydrates (MACs) commonly referred to as dietary fiber, content and types. Dietary MACs are found in a variety of sources including plants, animal tissue, or food-borne microbes and represent the source of carbohydrates that are metabolically available for gut microbes. MACs hold a role of "primary fermenters" within the colonic ecosystem and generally tend to increase the production of the beneficial short chain fatty acids (SCFAs) producing bacteria such as Bacteroides and Actinobacteria [6]. Differently, an increased consumption of protein, may lead to an excessive protein fermentation associated with the increased abundance of related taxa such as Clostridium and Proteobacteria. In this regard, ketogenic diet (KD) may represent a paradigmatic example. KD is a dietary protocol consisting of high-fat, adequate protein and less than 20g of carbohydrate daily (or 5% of total daily energy) [7]. This nutritional approach has been used since the 1920s as a treatment for refractory epilepsy [8] and it has gained popularity as a potential treatment for obesity and related metabolic disorders [9]. Indeed, increased amount of evidence point out that KD may represent an efficient and safe solution to get adequate body composition and maintain a general good health, whilst some researchers raised important issues about KD effects on microbiota. As a matter of fact, many studies

[10-13] investigating the effect of a high-fat diet on gut microbiota, but it has been tested only on mouse models fed a refined high-fat, low fiber diet with animals fed a standard chow diet, high in soluble fibers. For this reason, the conclusions arising from these animal studies cannot be adopted to predict the outcomes of a ketogenic diet and, consequently, its associated effect on gut microbiome [14]. In humans, it has been recently confirmed [15] that ketogenic diets differentially alter the composition of gut microbiota when compared to high-fat diet and, further, only ketogenic diet was able to provide positive gut-associated systemic outcomes [15]. It is of evidence that there are many, fundamental differences between a normal CHO/high fat diet and a KD. The low level of insulin and glucose and the high level of beta-hydroxybutyrate may help to explain the peculiar metabolic effect of KD on microbiota. Indeed, Turnbaugh and colleagues confirmed that KD positively affected the gut ecosystem with a mechanism involving the concomitant host production of ketone bodies and particularly of beta-hydroxybutyrate [15]. The authors hypothesized that the KD-associated decreases in pro-inflammatory Th17 cell levels, both in gut and adipose tissues, might have represented a potential mechanism contributing to some metabolic positive effects of ketogenic diet; highlighting that KD might have act as more "systemically". Moreover, not only the amount of fat should be considered, but also the different type/quality of fats. Indeed, different types of fat are associated with different effects on the gut microbiome and consequential effects on intestinal and systemic inflammation [16-18]. If on one side saturated fat is associated with decreased microbiome diversity and increased availability of LPS [19] in humans, polyunsaturated fat such as omega-3 did not affect microbial diversity and richness. Indeed, polyunsaturated fats improved gut epithelial integrity and gastrointestinal inflammation through the production of short chain fatty acids (SCFAs) [20]. Additionally, it is essential to point out that the interplay between KD and microbiota, plays a pivotal role on the KD's effects [21-23] ; this interaction it is necessary in order to provide positive effects such the anti-seizure effect and amelioration of neurovascular function [24-26]. Even though, we recently demonstrated that a KD with phytoextracts and good quality fats is able to maintain, in a population of soccer players, microbiota characteristics without any harmful effect or negative modification of microbiome profile, there are other data actually showing an the effects of KD on microbiome profile and these changes plays a positive, pivotal role on the itself activity of KD itself [21-23]. Understanding the different outcomes induced by a KD on microbiota (negative, positive, or no effects) is mandatory to understand the nutritional variables influencing these results (amount/quality of protein and fats, MACs, prebiotics and probiotics, etc). In conclusion, further researches with long-term clinical trials has to be performed in order to establish more precisely microbiota-oriented ketogenic diet interventions in humans.

References

1. Lynch SV, Pedersen O: **The Human Intestinal Microbiome in Health and Disease**. *N Engl J Med* 2016, **375** (24):2369-2379.
2. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA *et al*: **Diet rapidly and reproducibly alters the human gut microbiome**. *Nature* 2014, **505** (7484):559-563.
3. Scheiman J, Luber JM, Chavkin TA, MacDonald T, Tung A, Pham LD, Wibowo MC, Wurth RC, Punthambaker S, Tierney BT *et al*: **Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism**. *Nat Med* 2019, **25** (7):1104-1109.
4. Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, Hayes P, O'Reilly M, Jeffery IB, Wood-Martin R *et al*: **Exercise and associated dietary extremes impact on gut microbial diversity**. *Gut* 2014, **63** (12):1913-1920.
5. Barton W, Penney NC, Cronin O, Garcia-Perez I, Molloy MG, Holmes E, Shanahan F, Cotter PD, O'Sullivan O: **The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level**. *Gut* 2018, **67** (4):625-633.
6. Sonnenburg ED, Sonnenburg JL: **Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates**. *Cell Metab* 2014, **20** (5):779-786.
7. Paoli A, Bianco A, Grimaldi KA: **The Ketogenic Diet and Sport: A Possible Marriage?** *Exerc Sport Sci Rev* 2015, **43** (3):153-162.
8. Cooder HR: **Epilepsy in Children: With Particular Reference to the Ketogenic Diet**. *Cal West Med* 1933, **39** (3):169-173.
9. Perez-Guisado J: [**Ketogenic diets: additional benefits to the weight loss and unfounded secondary effects**]. *Arch Latinoam Nutr* 2008, **58** (4):323-329.
10. Singh RP, Halaka DA, Hayouka Z, Tirosh O: **High-Fat Diet Induced Alteration of Mice Microbiota and the Functional Ability to Utilize Fructooligosaccharide for Ethanol Production**. *Front Cell Infect Microbiol* 2020, **10**:376.
11. Daniel H, Gholami AM, Berry D, Desmarchelier C, Hahne H, Loh G, Mondot S, Lepage P, Rothballer M, Walker A *et al*: **High-fat diet alters gut microbiota physiology in mice**. *ISME J* 2014, **8** (2):295-308.
12. Xiao L, Sonne SB, Feng Q, Chen N, Xia Z, Li X, Fang Z, Zhang D, Fjaere E, Midtbo LK *et al*: **High-fat feeding rather than obesity drives taxonomical and functional changes in the gut microbiota in mice**. *Microbiome* 2017, **5** (1):43.
13. Serino M, Luche E, Gres S, Baylac A, Berge M, Cenac C, Waget A, Klopp P, Iacovoni J, Klopp C *et al*: **Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota**. *Gut* 2012, **61** (4):543-553.
14. Morrison KE, Jasarevic E, Howard CD, Bale TL: **It's the fiber, not the fat: significant effects of dietary challenge on the gut microbiome**. *Microbiome* 2020, **8** (1):15.
15. Ang QY, Alexander M, Newman JC, Tian Y, Cai J, Upadhyay V, Turnbaugh JA, Verdin E, Hall KD, Leibel RL *et al*: **Ketogenic Diets Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells**. *Cell* 2020, **181** (6):1263-1275 e1216.
16. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Backhed F: **Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling**. *Cell Metab* 2015, **22** (4):658-668.
17. Huang EY, Leone VA, Devkota S, Wang Y, Brady MJ, Chang EB: **Composition of dietary fat source shapes gut microbiota architecture and alters host inflammatory mediators in mouse adipose tissue**. *JPEN J Parenter Enteral Nutr* 2013, **37** (6):746-754.
18. Paoli A, Mancin L, Bianco A, Thomas E, Mota JF, Piccini F: **Ketogenic Diet and Microbiota: Friends or Enemies?** *Genes (Basel)* 2019, **10** (7).
19. Wolters M, Ahrens J, Romani-Perez M, Watkins C, Sanz Y, Benitez-Paez A, Stanton C, Gunther K: **Dietary fat, the gut microbiota, and metabolic health - A systematic review conducted within the MyNewGut project**. *Clin Nutr* 2019, **38** (6):2504-2520.
20. Costantini L, Molinari R, Farinon B, Merendino N: **Impact of Omega-3 Fatty Acids on the Gut Microbiota**. *Int J Mol Sci* 2017, **18** (12).
21. Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY: **The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet**. *Cell* 2018, **174** (2):497.
22. Newell C, Bomhof MR, Reimer RA, Hittel DS, Rho JM, Shearer J: **Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder**. *Mol Autism* 2016, **7** (1):37.
23. Xie G, Zhou Q, Qiu CZ, Dai WK, Wang HP, Li YH, Liao JX, Lu XG, Lin SF, Ye JH *et al*: **Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy**. *World J Gastroenterol* 2017, **23** (33):6164-6171.
24. Lindefeldt M, Eng A, Darban H, Bjerkner A, Zetterstrom CK, Allander T, Andersson B, Borenstein E, Dahlin M, Prast-Nielsen S: **The ketogenic diet influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy**. *NPJ Biofilms Microbiomes 2019*, **5**:5.
25. Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY: **The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet**. *Cell* 2018, **173** (7):1728-1741 e1713.
26. Zhang Y, Zhou S, Zhou Y, Yu L, Zhang L, Wang Y: **Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet**. *Epilepsy Res* 2018, **145**:163-168.