生理学报 *Acta Physiologica Sinica*, June 25, 2020, 72(3): 371–381
DOI: 10.13294/j.aps.2020.0030 http://www.actaps.com.cn

综 述

热量限制对能量代谢的影响及其机制

樊晓娜，陈琳茜，许戈阳*

暨南大学基础医学院生理学系，广州 510632

摘 要：热量限制(caloric restriction, CR)是在保证机体不产生营养不良的前提下限制机体的热量摄入。CR能够影响体内各种代谢产物水平，如脂类、游离脂肪酸、酮体、胆汁酸和氨基酸等，被认为可延长生物寿命，推迟和降低多种与老龄相关疾病(如2型糖尿病、肿瘤、心血管疾病)的发病。CR所产生的功效与其对机体能量代谢的调节效应密不可分，其作用机制与生物钟、激素、胃肠道菌群及炎症都密切相关。本文简要总结CR对能量代谢的影响及其作用机制。

关键词：热量限制；能量代谢；激素；生物钟；胃肠道菌群；炎症
中图分类号：Q411；Q48；Q591；R151.1；R335

The effects and mechanism of caloric restriction on energy metabolism

FAN Xiao-Na, CHEN Lin-Xi, XU Ge-Yang*
Department of Physiology, School of Medicine, Jinan University, Guangzhou 510632, China

Abstract: Caloric restriction (CR) is explored to limit the caloric intake without malnutrition. CR can affect the levels of various metabolites in organism, such as lipids, free fatty acids, ketones, bile acids and amino acids, etc, and is thought being able to extend the lifespan, postpone and reduce the incidence of age-related disorders (e.g., type 2 diabetes, cancer and cardiovascular diseases). These effects are mainly attributed to the role of CR in energy metabolism. The mechanism of CR on energy metabolism is closely related to biological clock, hormonal production, gastrointestinal flora and inflammation. Here we briefly review the effects and mechanism of CR on energy metabolism.

Key words: caloric restriction; energy metabolism; hormone; biological clock; gastrointestinal flora; inflammation

热量限制 (caloric restriction, CR) 指在提供生物体足够的营养成分，如必需氨基酸、维生素等，保证机体不发生营养不良的情况下，限制每日摄取的总热量 [1]。CR 策略主要有三种 (图 1)。(1) 不改变进食频率，减少每次进食热量。狭义的 CR 即这种策略。本文中将此种策略称为节食 (caloric decline, CD)，以示区别。减少进食热量的方法包括改变饮食结构，或是减少每种饮食组成的量。(2) 间断禁食 (intermittent fasting, IF)，即每周中的 1~3 天完全或部分限制热量摄入，其余天数随意进食。(3) 限时进食 (time-restricted feeding, TRF)，指不减少摄入热量，在一天的短时间内如 3~4、7~9 或 10~12 h 内随意进食，而余下的 12~21 h 内禁食；这种策略有的文献中把它归入 IF [2]。尽管有报道称这三种策略的作用机制不尽相同，作用效果也有细微差异 [3]，但它们都能有效地预防和改善代谢性疾病。因而，本文中的 CR 指的是包含这三种策略的、广义上的 CR。

CR 能降低体重和减少体脂，在增加糖酵解和糖异生的同时，促使体内甘油三酯转化为游离脂肪

Received 2019-09-17 Accepted 2020-02-04
Research from the corresponding author's laboratory was supported by a grant from the National Natural Science Foundation of China (No. 81770794).
*Corresponding author. Tel: +86-20-85220260; E-mail: xugeyangliang@163.com

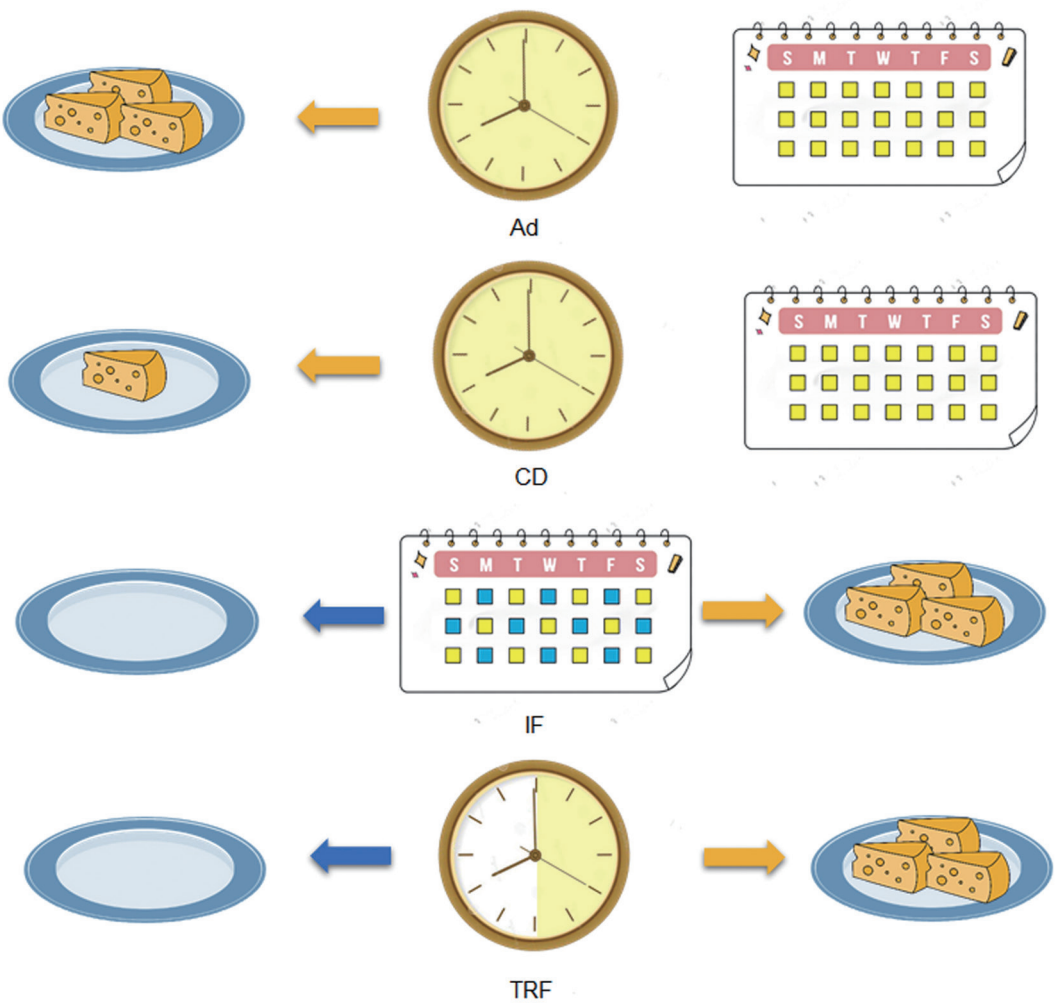

图 1. 热量限制的三种策略

Fig. 1. The three strategies of caloric restriction. Ad: *ad libitum*; CD: caloric decline; IF: intermittent fasting; TRF: time-restricted feeding.

酸并刺激脂肪酸的 β- 氧化 [4]，引起代谢产物的组成发生变化 (表 1)。CR 被认为是迄今为止最有效地降低代谢性疾病发生率和死亡率的生活方式 [5]。1935 年 McCay 首次报道 CR 能延长大鼠寿命 [6]，其后，CR 对机体健康影响的相关研究报道不断涌现。对多种实验动物，如鱼 [7]、仓鼠 [8]、小鼠 [9]、大鼠 [10]、狗 [11] 和兔 [12] 等进行大量深入的研究，表明 CR 能改善心血管状态、减轻体重、增加胰岛素敏感性，对糖尿病控制、认知能力提高和癌症预防都有积极的作用。对灵长类动物和人的实验也显示同样的有利作用 [13, 14]。

近年来研究表明，CR 调节机体能量代谢的机制主要涉及四个方面，包括生物钟、激素、胃肠道菌群和炎症。本综述从这四个方面对 CR 影响能量代谢的机制进行总结。

1 CR与生物钟

生物钟又称生物节律，是生物适应环境周期性变化而发生的生理学、生物化学和行为活动的周期性变化。生物钟包括下丘脑视交叉上核 (suprachiasmatic nucleus, SCN) 的中央生物钟和外周代谢相关器官 (如肝脏、脂肪、肌肉、心脏和肾脏) 中的多个外周生物钟，在光照调节下按照一定节律运转。

大量研究表明，生物钟的正常运行对维持机体代谢健康十分重要。哺乳动物的生物钟由 2 个转录反馈环路组成 (图 2)。最主要的环路是两个转录因子 CLOCK 和 BMAL1 组成的复合体调节其它生物钟基因，如 *Periods* (*Per1*、*Per2* 和 *Per3*) 和 *Crypto-*

表1. 受热量限制影响的代谢产物

Table 1. The metabolites affected by caloric restriction (CR)

Types	Increased after CR	Decreased after CR
Lipids	High density lipoprotein [10, 15]	Low density lipoprotein [10, 15], very low density lipoprotein [10, 15], choline [14], glycerylphosphorylcholine [15], phosphorylcholine [15], sphingomyelin [15], lysophosphatidylcholines (lysoPCs) [15], diglyceride [15], triglyceride [15]
Free fatty acids		n-6 polyunsaturated fatty acids [16], palmitic acid [16], heptadecenoic acid [16], γ-linoleic acid [16], dihomo-γ-linolenic acid [16]
Ketone bodies	Acetoacetic acid [14], 3-hydroxybutyric acid [14]	Pyruvic acid [10]
Bile acids	Taurocholic acid [17], tauroursodeoxycholic acid [17], deoxycholic acid [17], lithocholic acid [17], ω-muricholic acid [17], hyodeoxycholic acid [17]	
Amino acids	Glutamate [18], methionine [18], glutamine [18], alanine [18]	Branched-chain amino acid [19, 20], aromatic amino acids [19, 20]
Others	Citric acid [16], succinic acid [16], 2-ketolvalic acid [16], cis-aconitic acid [16], gluconate [21]	

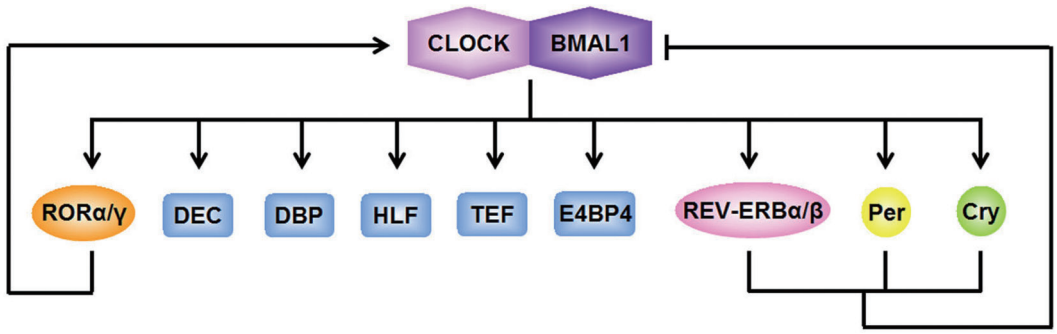

图 2. 生物钟转录水平的2个反馈环路

Fig. 2. The two feedback loops of transcripts of biologic clock.

chromes (*Cry1* 和 *Cry2*) 的转录；其产物反过来又抑制 CLOCK:BMAL1 的转录活性和表达，形成一个负反馈机制 [22]。另一个环路 (也称辅助环路) 由 REV-ERBS (α 和 β) 和视黄酸受体 (RORα 和 RORγ) 组成，分别作为转录抑制因子和激活因子，控制 *Bmal1* 的表达 [22]。此外，CLOCK:BMAL1 复合体驱动着钟控转录因子 DEC1、DEC2、DBP、HLF、TEF 和 E4BP4 (由 *Nfil3* 编码) 的表达 [22]。

生物钟尤其是 SCN 生物钟主要受到环境光线的影响。食物摄入，包括摄入总热量、饮食结构和进食时间，虽不能影响 SCN 生物钟，但对外周生物钟有极大影响。

CD 可以通过 BMAL1 依赖和 BMAL1 非依赖通路极大地影响生物钟 [23]。有报道称在分子水平上 CD 对生物钟的影响与 TRF 不同，CD 使肝脏中 *Bmal1*、*Per1*、*Per2*、*Per3* 和 *Cry2* 生物钟基因的表达明显增加，而 TRF 对其表达影响不大 [23]。热量摄入减少时，生物钟基因 *Cry1*、*Rev-Erbα* 和 *Rorγ* 在小鼠肝脏中的表达雌雄有差别。*Cry1* 的表达在雄性小鼠中增加，在雌性小鼠中不受影响；*Rev-Erb* 的表达在雄性小鼠中仅在时间点 ZT6 (光照开启时间为 ZT0，光照熄灭时间为 ZT12，进食时间为 ZT14) 时增加，在雌性小鼠中在三个时间点 ZT2、ZT6 和 ZT10 都大大增加；*Ror* 的表达在雄性小鼠中在时间点 ZT22 增加，在雌性小鼠中在三个时间点 ZT6、ZT14 和 ZT18 都增加 [24]。*Bmal1*、*Per1*、*Per2*

和 *Per3* 在小鼠肝脏中的表达在热量摄入减少时均增加，没有性别差异。其中，*Bmal1* 在时间点 ZT2 和 ZT22，*Per1* 在 ZT10 和 ZT14，*Per2* 在 ZT18，*Per3* 在 ZT10 表达增加 [24]。钟控基因 *Fmo3*、*Mup4*、*Cyp412b* 和 *Serpina12* 的表达在热量摄入减少时有性别差异：*Fmo3* 在雄性和雌性 CR 小鼠中在所有时间点的表达均增加，但相比随意进食小鼠，雄性 CR 小鼠的增加幅度为 600~3 000 倍，而雌性 CR 小鼠仅为 2~5 倍；*Mup4*、*Cyp412b* 和 *Serpina12* 在 CR 后表达的减少仅在雄性小鼠中观察到 [24]。

IF 对小鼠昼夜节律的影响取决于喂养时间。在 IF 方案中，当在白天光照期间引入食物时，小鼠仍然是夜间活动，但不利于小鼠肝脏中的生物钟基因的表达。IF 抑制了 *mPer1*、*mCry1* 和 *mBmal1* 的昼夜节律性表达，*mPer2* 和 *mClock* 仍然在 IF 下表现出昼夜节律表达，但幅度降低并且相位超前。与白天喂养不同，夜间喂养产生的节律类似于随意喂养时产生的节律 [25]。

进食时间对生物钟影响更明显。实验表明，TRF 使得叙利亚仓鼠 [26]、兔 [27] 和小鼠 [28] 的生物钟受到影响。在大鼠中，TRF 对生物钟的影响甚至能与昼夜影响持平 [29]。在持续光照条件下，长期的限时饮食还能缩短光导引起搏 (light entrainment pacemaker, LEP) 的时间 [30]。进食时间不当可以改变外周器官和大脑中的生物钟 [31]，从而对代谢健康不利 [32]。吃夜宵被发现与人体的体重增加、能量消耗失调、食欲、压力和睡眠激素分泌的节律紊乱相关 [33]。

大量动物实验结果提示 [34–37]，饮食引起的生物钟紊乱可能是形成代谢性疾病的因素之一。而通过对进食时间的严格控制，尤其是在晚餐之后不进食，可以维持生物钟的正常功能，并预防和改善代谢性疾病。其可能原因是空腹时间延长使得肝糖原贮存耗尽，脂肪和胆固醇合成和贮存受阻，而脂肪酸氧化生成的脂肪和脂肪酸的下游产物酮体被调用作为能量的来源 [38]。当小鼠的进食时间被控制在 8~12 h 内时，其消耗的食物与随意进食的小鼠几乎一致，而高脂、高蔗糖或高果糖饮食导致的肥胖、葡萄糖耐受、瘦素抵抗、脂肪肝和组织炎症相比不限时随意进食的小鼠都减轻，且代谢改善程度与空腹时间成正比 [34, 38]。给予 C57BL/6 小鼠随意进食高脂食物，它们发生高胰岛素血症、肥胖和全身炎症；而不限制进食量，把它们的进食时间控制在每天 8 h 内，则能预防这些疾病发生。其原因可能是 TRF 促进了 CREB、mTOR 和 AMPK 通路的功能、改善生物钟节律以及相关基因的表达。而这些代谢和合成代谢通路的改变使得肝脏代谢组发生变化，营养物质的利用和能量消耗也得到改善 [34]。Sutton 等对男性前期糖尿病患者进行了为期 5 周的 TRF 实验：给予同样的食物，实验组每天给予 6 h 进食时间，且晚餐在 3 p.m. 之前，对照组每天给予 12 h 进食时间。结果表明，TRF 能明显改善机体的胰岛素敏感性、β 细胞反应性、血压、炎症、氧化应激性和食欲。其原因可能是实验组进食和空腹的时间正好和代谢的生物钟节律一致 [2]。

综上，CD 和严格控制进食时间都能影响外周生物钟，调节生物钟基因和相关基因的表达，预防和改善代谢性疾病。

2 CR对激素合成和分泌的影响

除了胰岛素外，食欲和胃肠激素在调节机体能量摄入、食欲和系统能量稳态中也发挥重要作用 [39, 40]。这些激素包括生长激素释放肽 (ghrelin)、脂联素 (adiponectin)、瘦素 (leptin)、胰高血糖素 (glucagon)、胰高血糖素样肽 -1 (glucagon-like peptide-1, GLP-1)、肾上腺皮质激素 (glucocorticoids)、多肽 YY (peptide YY, PYY)、胰多肽 (pancreatic polypeptide, PP) 和肠抑胃肽 (gastric inhibitory polypeptide, GIP) 等。CR 可影响这些激素的合成和分泌。

2.1 胰岛素

胰岛素由胰腺 β 细胞合成分泌，其主要作用是“允许”循环系统中的葡萄糖进入肝脏和肌肉细胞，转化为糖原或作为能量“烧掉”。若胰岛素的分泌或机体对胰岛素的反应出现问题，则机体摄入的葡萄糖将不能被正常处置，表现为血液中的葡萄糖或 (和) 胰岛素水平升高，出现高血糖症或 (和) 高胰岛素血症等代谢性疾病。如果血液中葡萄糖累积，还会产生过多的氧自由基和非酶糖基化产物，破坏蛋白等大分子。许多研究报道 CR 能降低小鼠 [41]、恒河猴 [42] 和人 [43] 循环血中胰岛素样生长因子 1 (insulin-like growth factor 1, IGF-1)、胰岛素和葡萄糖的水平，从而改善胰岛素的敏感性，以免血液中葡萄糖的累积。CR 也能减少氧自由基的生成 [44] 和非酶糖基化 [45]，进一步减少葡萄糖累积对蛋白大分子的破坏。

胰岛素受体通路被激活是机体对胰岛素敏感性增加的原因之一，该激活具有组织特异性：骨骼肌

的胰岛素结合能力增加，而心肌的结合能力降低。胰岛素受体被激活后，激活了典型磷脂酰肌醇 -3- 激酶 (PI3K) 和丝氨酸 - 苏氨酸蛋白激酶 (Akt-1/Akt-2/protein kinase B) 信号通路 (PI3K/Akt)[46]。CR 通过增加沉默信息调节因子 2 相关酶 1 (sirtuin 1, SIRT1) 介导的信号转导及转录激活蛋白 3 (signal transducer and activator of transcription 3, STAT3) 脱乙酰化，增强了小鼠骨骼肌 PI3K 信号转导效率和胰岛素作用 [47]。CR 还能降低胰岛素激活的硫氧还蛋白相互作用蛋白 (thioredoxin interacting protein, TXNIP) 水平，加强非氧化葡萄糖利用过程，从而增加外周组织对胰岛素的敏感性 [48]。

2.2 脂联素

脂联素是一种脂肪分泌蛋白，在血液中以多聚体的形式，激活机体组织中的脂肪代谢，并能增加细胞对胰岛素的敏感性，减少血液中胰岛素的水平和 β 细胞功能异常。糖尿病患者的脂联素水平较低 [49]。动物和人体实验数据表明，脂联素能促进心血管健康 [50]。其有利作用是通过激活 cAMP 依赖的蛋白激酶 (Akt) 通路 [51]，减少 *Hif-1* 的表达 [52]。CD 和 IF 都能提升循环系统中的脂联素水平 [53, 54]，且在 CR 后的前 16 周脂联素浓度升高的程度大于 16 周之后 [55]。而这些增加的脂联素主要来自于内分泌器官 —— 骨髓脂肪组织 (marrow adipose tissue, MAT) [56]。也有报道称，CR 对脂联素在体内总量的影响不大，而是通过影响脂联素形成的高分子量的多聚体的分布以发挥脂联素的正常功能 [57]。脂联素受体被激活后，激活下游的代谢调节因子腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK) [58]，促进 NAD 补救通路的重要酶烟酰胺磷酸核糖转移酶 (nicotinamide phosphoribosyltransferase, NAMPT) 的表达，激活 NAD 依赖的去乙酰化酶 SIRT1，正调节过氧化物酶体增殖物活化受体 γ 协同激活因子 1α (peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α) [59]。CR 使得这四种代谢调节因子的表达水平都上调 [60]。有研究认为脂联素分泌的决定因素是摄入的热量，不是食物中脂肪成分的含量 [61]。也有报道称给予实验动物富含饱和脂肪酸的高脂饮食会减少脂联素水平，而给予富含多聚不饱和脂肪酸并补充 omega-3 和二十碳五烯酸能上调脂联素的表达及其在血清中的浓度 [62]。

2.3 瘦素

瘦素，同脂联素一样，也是由脂肪细胞合成的一种激素，传递能量储存不足的信号，平衡脂肪代谢，调节体内能量平衡和葡萄糖稳态。瘦素主要作用于弓状核，影响外周组织，能够抑制食欲和刺激能量消耗 [63]。当瘦素作用于中枢下丘脑受体时，是骨骼肌对胰岛素敏感的增强剂；而当瘦素直接作用于外周比目鱼肌时，对胰岛素有拮抗作用 [64]。瘦素在 CR 发挥功效中十分重要。甘油三酯 / 游离脂肪酸循环是保护心脏免受脂肪累积危害的一条关键通路。该通路是一个瘦素依赖的循环：缺乏瘦素的参与，CR 就不能改善心肌脂变 [65]。CR 能降低血清瘦素水平 [66] 和皮下脂肪中瘦素的表达 [67]，但是不影响循环系统中瘦素表达的周期性变化 [68]。血清中的瘦素水平在 CR 的前期 (6 周内) 主要受到饮食的影响，而后期则与身体脂肪重量高度相关 [69]。对空腹瘦素水平的研究显示，其影响因素主要是摄入总热量，与进食频率关系不大 [70]。CR 能以一种耐受的方式降低血清瘦素浓度，从而抑制性腺轴、生长轴和甲状腺轴，激活肾上腺轴 [71]，增加能量消耗。

2.4 其它激素

GLP-1 [72]、PYY [73]、PP [74] 和生长激素释放肽 [72] 被认为能促进饱腹感，降低食欲。GIP 能促进葡萄糖依赖的胰岛素释放和脂肪组织对营养的吸收 [75]。实验表明，增加进食频率，把同样的低热量饮食分为一天 6 次摄入，相比一天 2 次摄入，空腹血清中 GIP、GLP-1、PYY 和 PP 的水平降低，而生长激素释放肽的水平升高；餐后 GLP-1、PYY 和 PP 的水平升高，而生长激素释放肽水平下降 [70]。

综上，CR 能调节胰岛素的分泌和增加胰岛素的敏感性，提高循环系统中脂联素的水平，降低血清瘦素水平以及影响其它胃肠激素的分泌，从而改善代谢。

3 CR对胃肠道菌群的影响

目前研究最多的与饮食相关的胃肠道微生物有三种：益生菌菌株、短链脂肪酸 (short chain fatty acids, SCFAs) 生成微生物以及具有氨基酸降解功能的微生物。

受广泛关注的益生菌菌株有乳酸杆菌和双歧杆菌。益生菌通过与免疫细胞的直接作用，保护胃肠屏障不受病原损伤、抑制病原黏附到肠道管壁、并减少炎症因子，维护胃肠道免疫学平衡 [76]。对实验动物和人进行的 CR 实验均表明，CD 和降低饮食中脂肪含量均能增加机体胃肠道中益生菌的数量。

Zhang 等对小鼠和大鼠进行终身的 CD (不考虑饮食结构) 干预后，发现其胃内双歧杆菌和乳酸杆菌的数量显著增加 [77, 78]。对肥胖患者进行为期 10 周的 CR 治疗后，用 PCR 方法分析其胃中微生物，结果显示，在体重减轻 > 4.0 kg 的患者中，乳酸杆菌的数量显著增加 [79]。双歧杆菌和乳酸杆菌的增加与体重减轻、总胆固醇和总甘油三酯水平降低相关，从而减少了代谢性功能紊乱的可能性 [78, 80]。

哺乳动物胃肠道生存着超过 100 万亿微生物细胞的复杂群落。这些微生物能使膳食纤维发酵生成 SCFAs，这些 SCFAs 是维持宿主体内脂肪稳态和减轻炎症的内源信号。厚壁菌门 (Firmicutes, F) 和拟杆菌门 (Bacteroidetes, B) 是宿主胃内产生 SCFAs 的两种主要微生物门。F/B 比例的变化长期以来都被认为与肥胖 (高 F/B 比例) 和体重减轻 (低 F/B 比例) 相关 [81]。对大鼠 [82] 和小鼠 [83] 的研究均显示，CR 能增加拟杆菌的数量，并减少厚壁菌的数量。Ruzi 等对肥胖青少年进行为期一年的低脂和低碳水化合物饮食干预后，发现他们胃内的 F/B 比例显著下降 [84]。此外，奶犊牛实验显示肠内分泌细胞中丁酸盐增加 GLP-1/2 的分泌，改善机体对血糖和胰岛素的响应 [85]。

CR 干预能改变胃中与氨基酸代谢相关的菌株的功能 [86]。其中，必需氨基酸的微生物代谢改变显著，如赖氨酸生物合成增加、苯丙氨酸和色氨酸合成减少、支链氨基酸降解增加。

综上，CR 能增加胃肠道内益生菌数量，改变不同 SCFAs 生成微生物的相对数量和微生物降解氨基酸的功能，从而改善机体代谢。

4 CR与炎症

轻度炎症是一种亚临床炎症状态，是发生胰岛素耐受和继之而来的 2 型糖尿病的先兆，也能促使心血管疾病的发生。脱硫弧菌科、链球菌科 [87] 和 TM7 科 [88] 的某些胃内微生物能释放一种叫脂多糖 (lipopolysaccharide, LPS) 的内毒素。当这些有害微生物数量增加，或胃屏障受损、渗透性变大时，微生物产生的 LPS 从胃中转移到血液中的数量也就增加。血液循环系统中过多的 LPS 会造成机体的轻度炎症，增加肥胖、糖尿病和炎性黏膜的发生几率 [89, 90]。研究显示，过度饮食尤其是高脂饮食，能减少甚至消灭对胃屏障起保护作用的双歧杆菌，使内毒素对胃的渗透性增加，宿主炎症发生的几率增加 [91]。实验证明，对 C57BL/6J 小鼠进行 CR 干预 (减少 30% 随意进食量且低脂饮食)，平衡了胃内微生物的组成结构，减少了进入血清中的 LPS [77]。同样的现象在人体中也有报道。Ott 等对肥胖成年女性进行为期 28 天的超低热量饮食治疗 (very low calory diets，VLCD，800 kcal/ 天) 后，发现其血液中 LPS 结合蛋白 (血液循环系统中 LPS 量的生化指标) 大大减少 [67]。

CR 可以降低炎症，防止与年龄有关的疾病。低度慢性炎症与多种年龄相关的慢性疾病的发病机制和衰老本身的生物学密切相关 [92]。血清 C 反应蛋白 (C-reactive protein，CRP，一种高度特异性的炎症系统标志物) 和 TNF-α (一种强大的促炎细胞因子) 的浓度增高都与发生胰岛素抵抗、2 型糖尿病 [93] 和心血管疾病的风险增加有关 [94, 95]。对肥胖个体进行的减肥研究的数据表明，CR 降低了总白细胞计数、白细胞介素 1β、白细胞介素 6 和 TNF-α [96]。对健康人群进行 24 个月 25% 的 CR 后，血清 CRP 和 TNF-α 浓度分别降低约 40% 和 50%，总白细胞、淋巴细胞和单核细胞计数显著减少，中性粒细胞也显示出减少的强烈趋势 [97]。此外，CR 可以降低血清胎球蛋白 -A [98]。胎球蛋白 -A 是一种源自肝脏的促炎蛋白，与代谢性疾病如胰岛素抵抗和非酒精性脂肪性肝病 (non-alcoholic fatty liver disease, NAFLD) 密切相关 [99]。胎球蛋白 -A 水平与 NAFLD 的早期指标正相关 [100]。CR 可以降低小鼠胎球蛋白 -A 水平，减轻小鼠肝脏脂肪变性 [98]。

综上，CR 能降低炎症因子在循环系统中的水平，从而减少代谢性疾病的发生。

5 小结

CR 对机体代谢的影响是研究的热点，几乎没有报道否认 CR 对健康代谢的有利作用。但由于代谢过程本身的复杂性，使得 CR 对代谢的影响机制成为研究的难点。如前所述，CR 可以通过影响生物钟、激素、胃肠道菌群和炎症使得机体达到代谢平衡，而这四种因素又是相互交织、相互影响的。目前的研究结果只是冰山一角。不过，影响机制的复杂性也意味着我们可能通过 CR 获得众多的可能方法，从分子水平上预防和治疗代谢性疾病。

参考文献

1 Mattson MP, Longo VD, Harvie M. Impact of intermittent

fasting on health and disease processes. Ageing Res Rev 2017; 39: 46–58.
2 Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. Cell Metab 2018; 27(6): 1212–1221.
3 Antoni R, Johnston KL, Collins AL, Robertson MD. Intermittent v. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in overweight/obese participants. Br J Nutr 2018; 119(5): 507–516.
4 Collet TH, Sonoyama T, Henning E, Keogh JM, Ingram B, Kelway S, Guo L, Farooqi IS. A metabolomic signature of acute caloric restriction. J Clin Endocrinol Metab 2017; 102(12): 4486–4495.
5 Golbidi S, Daiber A, Korac B, Li H, Essop MF, Laher I. Health benefits of fasting and caloric restriction. Curr Diab Rep 2017; 17(12): 123.
6 McCay CM, Crowell MF, Maynard LA. The effect of retarded growth upon the length of life span and upon the ultimate body size. J Nutr 1935; 10: 63–79.
7 Roohinejad S, Koubaa M, Barba FJ, Saljoughian S, Amid M, Greiner R. Application of seaweeds to develop new food products with enhanced shelf-life, quality and health-related beneficial properties. Food Res Int 2017; 99(Pt 3): 1066–1083.
8 Siutz C, Millesi E. Torpor patterns in common hamsters with and without access to food stores. J Comp Physiol B 2017; 187(5–6): 881–888.
9 Rubovitch V, Pharayra A, Har-Even M, Dvir O, Mattson MP, Pick CG. Dietary energy restriction ameliorates cognitive impairment in a mouse model of traumatic brain injury. J Mol Neurosci 2019; 67(4): 613–621.
10 Nestor G, Eriksson J, Sandstrom C, Malmlof K. Nuclear magnetic resonance-based blood metabolic profiles of rats exposed to short-term caloric restriction. Anal Lett 2015; 48(16): 2613–2625.
11 Chapman M, Woods GRT, Ladha C, Westgarth C, German AJ. An open-label randomised clinical trial to compare the efficacy of dietary caloric restriction and physical activity for weight loss in overweight pet dogs. Vet J 2019; 243: 65–73.
12 Makovicky P, Tumova E, Volek Z, Makovicky P, Arnone JM, Svecova I, Samasca G. The influence of food restriction on the small bowel: Does intensive shortterm food restriction lead to weight loss? Bratisl Lek Listy 2017; 118(6): 361–365.
13 Mattison JA, Colman RJ, Beasley TM, Allison DB, Kemnitz JW, Roth GS, Ingram DK, Weindruch R, de Cabo R, Anderson RM. Caloric restriction improves health and survival of rhesus monkeys. Nat Commun 2017; 8: 14063.
14 Schmedes MS, Yde CC, Svensson U, Hakansson J, Baby S, Bertram HC. Impact of a 6-week very low-calorie diet and weight reduction on the serum and fecal metabolome of overweight subjects. Eur Food Res Technol 2015; 240(3): 583–594.
15 Kim M, Lee SH, Lee JH. Global metabolic profiling of plasma shows that three-year mild-caloric restriction lessens an age-related increase in sphingomyelin and reduces L-leucine and L-phenylalanine in overweight and obese subjects. Aging Dis 2016; 7(6): 721–733.
16 Wu JF, Yang L, Li SF, Huang P, Liu Y, Wang YL, Tang HR. Metabolomics insights into the modulatory effects of long-term low calorie intake in mice. J Proteome Res 2016; 15(7): 2299–2308.
17 Fu ZD, Klaassen CD. Increased bile acids in enterohepatic circulation by short-term calorie restriction in male mice. Toxicol Appl Pharmacol 2013; 273(3): 680–690.
18 Selman C, Kerrison ND, Cooray A, Piper MD, Lingard SJ, Barton RH, Schuster EF, Blanc E, Gems D, Nicholson JK, Thornton JM, Partridge L, Withers DJ. Coordinated multitissue transcriptional and plasma metabonomic profiles following acute caloric restriction in mice. Physiol Genomics 2006; 27(3): 187–200.
19 Haufe S, Engeli S, Kaminski J, Witt H, Rein D, Kamlage B, Utz W, Fuhrmann JC, Haas V, Mahler A, Schulz-Menger J, Luft FC, Boschmann M, Jordan J. Branched-chain amino acid catabolism rather than amino acids plasma concentrations is associated with diet-induced changes in insulin resistance in overweight to obese individuals. Nutr Metab Cardiovasc Dis 2017; 27(10): 858–864.
20 Shah SH, Crosslin DR, Haynes CS, Nelson S, Turer CB, Stevens RD, Muehlbauer MJ, Wenner BR, Bain JR, Laferrere B, Gorroochurn P, Teixeira J, Brantley PJ, Stevens VJ, Hollis JF, Appel LJ, Lien LF, Batch B, Newgard CB, Svetkey LP. Branched-chain amino acid levels are associated with improvement in insulin resistance with weight loss. Diabetologia 2012; 55(2): 321–330.
21 Rezzi S, Martin FP, Shanmuganayagam D, Colman RJ, Nicholson JK, Weindruch R. Metabolic shifts due to long-term caloric restriction revealed in nonhuman primates. Exp Gerontol 2009; 44(5): 356–362.
22 Sato TK, Yamada RG, Ukai H, Baggs JE, Miraglia LJ, Kobayashi TJ, Welsh DK, Kay SA, Ueda HR, Hogenesch JB. Feedback repression is required for mammalian circadian clock function. Nat Genetics 2006; 38(3): 312–319.
23 Patel SA, Velingkaar N, Makwana K, Chaudhari A, Kondratov

R. Calorie restriction regulates circadian clock gene expression through BMAL1 dependent and independent mechanisms. Sci Rep 2016; 6: 25970.

24 Astafev AA, Patel SA, Kondratov RV. Calorie restriction effects on circadian rhythms in gene expression are sex dependent. Sci Rep 2017; 7(1): 9716–9724.

25 Froy O, Chapnik N, Miskin R. Effect of intermittent fasting on circadian rhythms in mice depends on feeding time. Mech Ageing Dev 2009; 130(3): 154–160.

26 Mistlberger RE. Scheduled daily exercise or feeding alters the phase of photic entrainment in Syrian hamsters. Physiol Behav 1991; 50(6): 1257–1260.

27 Jilge B, Stahle H. Restricted food access and light-dark: impact of conflicting zeitgebers on circadian rhythms of the rabbit. Am J Physiol 1993; 264: R708–R715.

28 Mendoza J, Graff C, Dardente H, Pevet P, Challet E. Feeding cues alter clock gene oscillations and photic responses in the suprachiasmatic nuclei of mice exposed to a light/dark cycle. J Neurosci 2005; 25(6): 1514–1522.

29 Challet E, Jacob N, Vuillez P, Pevet P, Malan A. Fos-like immunoreactivity in the circadian timing system of calorie-restricted rats fed at dawn: daily rhythms and light pulse-induced changes. Brain Res 1997; 770(1–2): 228–236.

30 Cambras T, Vilaplana J, Diez-Noguera A. Effects of long-term restricted feeding on motor activity rhythm in the rat. Am J Physiol 1993; 265(2 Pt 2): R467–R473.

31 Feillet CA, Mendoza J, Albrecht U, Pevet P, Challet E. Forebrain oscillators ticking with different clock hands. Mol Cell Neurosci 2008; 37(2): 209–221.

32 McHill AW, Phillips AJ, Czeisler CA, Keating L, Yee K, Barger LK, Garaulet M, Scheer FA, Klerman EB. Later circadian timing of food intake is associated with increased body fat. Am J Clin Nutr 2017; 106(5): 1213–1219.

33 Allison KC, Goel N. Timing of eating in adults across the weight spectrum: Metabolic factors and potential circadian mechanisms. Physiol Behav 2018; 192: 158–166.

34 Hatori M, Vollmers C, Zarrinpar A, DiTacchio L, Bushong EA, Gill S, Leblanc M, Chaix A, Joens M, Fitzpatrick JAJ, Ellisman MH, Panda S. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab 2012; 15(6): 848–860.

35 Su W, Xie Z, Guo Z, Duncan MJ, Lutshumba J, Gong MC. Altered clock gene expression and vascular smooth muscle diurnal contractile variations in type 2 diabetic db/db mice. Am J Physiol Heart Circ Physiol 2012; 302(3): H621–H633.

36 Vieira E, Ruano E, Figueroa AL, Aranda G, Momblan D, Carmona F, Gomis R, Vidal J, Hanzu FA. Altered clock gene expression in obese visceral adipose tissue is associated with metabolic syndrome. PLoS One 2014; 9(11): e111678.

37 Anton SD, Moehl K, Donahoo WT, Marosi K, Lee SA, Mainous AG 3rd, Leeuwenburgh C, Mattson MP. Flipping the metabolic switch: understanding and applying the health benefits of fasting. Obesity (Silver Spring) 2018; 26(2): 254–268.

38 Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metab 2014; 20(6): 991–1005.

39 Perry B, Wang Y. Appetite regulation and weight control: the role of gut hormones. Nutr Diabetes 2012; 2: e26.

40 Xu G, Li Y, An W, Li S, Guan Y, Wang N, Tang C,Wang X, Zhu Y, Li X, Mulholland M, Zhang W. Gastric mammalian target of rapamycin signaling regulates ghrelin production and food intake. Endocrinology 2009; 150(8): 3637–3644.

41 Mitchell SE, Delville C, Konstantopedos P, Derous D, Green CL, Wang Y, Han JD, Promislow DE, Douglas A, Chen L, Lusseau D, Speakman JR. The effects of graded levels of calorie restriction: V. Impact of short term calorie and protein restriction on physical activity in the C57BL/6 mouse. Oncotarget 2016; 7(15): 19147–19170.

42 Kemnitz JW, Roecker EB, Weindruch R, Elson DF, Baum ST, Bergman RN. Dietary restriction increases insulin sensitivity and lowers blood glucose in rhesus monkeys. Am J Physiol 1994; 266(4 Pt 1): E540–E547.

43 Meehan CA, Cochran E, Mattingly M, Gorden P, Brown RJ. Mild caloric restriction decreases insulin requirements in patients with type 2 diabetes and severe insulin resistance. Medicine (Baltimore) 2015; 94(30): e1160.

44 Qiu X, Brown K, Hirschey MD, Verdin E, Chen D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. Cell Metab 2010; 12(6): 662–667.

45 Caro P, Gomez J, Sanchez I, Naudi A, Ayala V, Lopez-Torres M, Pamplona R, Barja G. Forty percent methionine restriction decreases mitochondrial oxygen radical production and leak at complex I during forward electron flow and lowers oxidative damage to proteins and mitochondrial DNA in rat kidney and brain mitochondria. Rejuvenation Res 2009; 12(6): 421–434.

46 Granado M, Amor S, Martin-Carro B, Guerra-Menendez L, Tejera-Munoz A, Gonzalez-Hedstrom D, Rubio C, Carrascosa JM, Garcia-Villalon AL. Caloric restriction attenuates aging-induced cardiac insulin resistance in male Wistar rats through activation of PI3K/Akt pathway. Nutr Metab Cardiovasc Dis 2019; 29(1): 97–105.

47 Schenk S, McCurdy CE, Philp A, Chen MZ, Holliday MJ, Bandyopadhyay GK, Osborn O, Baar K, Olefsky JM. Sirt1 enhances skeletal muscle insulin sensitivity in mice during

caloric restriction. J Clin Invest 2011; 121(11): 4281–4288.
48 Johnson ML, Distelmaier K, Lanza IR, Irving BA, Robinson MM, Konopka AR, Shulman GI, Nair KS. Mechanism by which caloric restriction improves insulin sensitivity in sedentary obese adults. Diabetes 2016; 65(1): 74–84.
49 Alnaggar A, Sayed M, El-Deena KE, Gomaa M, Hamed Y. Evaluation of serum adiponectin levels in diabetic nephropathy. Diabetes Metab Syndr 2019; 13(1): 128–131.
50 Kyrou I, Tsantarlioti O, Panagiotakos DB, Tsigos C, Georgousopoulou E, Chrysohoou C, Skoumas I, Tousoulis D, Stefanadis C, Pitsavos C, group As. Adiponectin circulating levels and 10-year (2002-2012) cardiovascular disease incidence: the ATTICA Study. Endocrine 2017; 58(3): 542–552.
51 Gonon AT, Widegren U, Bulhak A, Salehzadeh F, Persson J, Sjoquist PO, Pernow J. Adiponectin protects against myocardial ischaemia-reperfusion injury via AMP-activated protein kinase, Akt, and nitric oxide. Cardiovasc Res 2008; 78(1): 116–122.
52 Natarajan R, Salloum FN, Fisher BJ, Kukreja RC, Fowler AA 3rd. Hypoxia inducible factor-1 upregulates adiponectin in diabetic mouse hearts and attenuates post-ischemic injury. J Cardiovasc Pharmacol 2008; 51(2): 178–187.
53 Wan RQ, Ahmet I, Brown M, Cheng AW, Kamimura N, Talan M, Mattson MP. Cardioprotective effect of intermittent fasting is associated with an elevation of adiponectin levels in rats. J Nutr Biochem 2010; 21(5): 413–417.
54 Park CY, Park S, Kim MS, Kim HK, Han SN. Effects of mild calorie restriction on lipid metabolism and inflammation in liver and adipose tissue. Biochem Biophys Res Commun 2017; 490(3): 636–642.
55 Salehi-Abargouei A, Izadi V, Azadbakht L. The effect of low calorie diet on adiponectin concentration: a systematic review and meta-analysis. Horm Metab Res 2015; 47(8): 549–555.
56 Cawthorn WP, Scheller EL, Learman BS, Parlee SD, Simon BR, Mori H, Ning XM, Bree AJ, Schell B, Broome DT, Soliman SS, DelProposto JL, Lumeng CN, Mitra A, Pandit SV, Gallagher KA, Miller JD, Krishnan V, Hui SK, Bredella MA, Fazeli PK, Klibanski A, Horowitz MC, Rosen CJ, MacDougald OA. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. Cell Metab 2014; 20(2): 368–375.
57 Xu XJ, Babo E, Qin F, Croteau D, Colucci WS. Short-term caloric restriction in db/db mice improves myocardial function and increases high molecular weight (HMW) adiponectin. IJC Metab Endocr 2016; 13: 28–34.
58 Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, Yamaguchi M, Tanabe H, Kimura-Someya T, Shirouzu M, Ogata H, Tokuyama K, Ueki K, Nagano T, Tanaka A, Yokoyama S, Kadowaki T. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature 2013; 503(7477): 493–499.
59 Fulco M, Cen Y, Zhao P, Hoffman EP, McBurney MW, Sauve AA, Sartorelli V. Glucose restriction inhibits skeletal myoblast differentiation by activating SIRT1 through AMPK-mediated regulation of Nampt. Dev Cell 2008; 14(5): 661–673.
60 Ma LN, Wang R, Dong W, Zhao ZW. Caloric restriction can improve learning and memory in C57/BL mice probably via regulation of the AMPK signaling pathway. Exp Gerontol 2018; 102: 28–35.
61 Nakamura T, Funayama H, Kubo N, Yasu T, Kawakami M, Saito M, Momomura S, Ishikawa SE. Association of hyperadiponectinemia with severity of ventricular dysfunction in congestive heart failure. Circ J 2006; 70(12): 1557–1562.
62 Reis CE, Bressan J, Alfenas RC. Effect of the diet components on adiponectin levels. Nutr Hosp 2010; 25(6): 881–888.
63 Ahima RS, Lazar MA. Adipokines and the peripheral and neural control of energy balance. Mol Endocrinol 2008; 22(5): 1023–1031.
64 De Solis AJ, Fernandez-Agullo T, Garcia-SanFrutos M, Perez-Pardo P, Bogonez E, Andres A, Ros M, Carrascosa JM. Impairment of skeletal muscle insulin action with aging in Wistar rats: role of leptin and caloric restriction. Mech Ageing Dev 2012; 133(5): 306–316.
65 Rame JE, Barouch LA, Sack MN, Lynn EG, Abu-Asab M, Tsokos M, Kern SJ, Barb JJ, Munson PJ, Halushka MK, Miller KL, Fox-Talbot K, Zhang JH, Hare JM, Solomon MA, Danner RL. Caloric restriction in leptin deficiency does not correct myocardial steatosis: failure to normalize PPAR alpha/PGC1 alpha and thermogenic glycerolipid/fatty acid cycling. Physiol Genomics 2011; 43(12): 726–738.
66 Page-Wilson G, Nguyen KT, Atalayer D, Meece K, Bainbridge HA, Korner J, Gordon RJ, Panigrahi SK, White A, Smiley R, Wardlaw SL. Evaluation of CSF and plasma biomarkers of brain melanocortin activity in response to caloric restriction in humans. Am J Physiol Endocrinol Metab 2017; 312(1): E19–E26.
67 Ott B, Skurk T, Hastreiter L, Lagkouvardos I, Fischer S, Buttner J, Kellerer T, Clavel T, Rychlik M, Haller D, Hauner H. Effect of caloric restriction on gut permeability, inflammation markers, and fecal microbiota in obese women. Sci Rep 2017; 7(1): 11955.
68 Lecoultre V, Ravussin E, Redman LM. The fall in leptin concentration is a major determinant of the metabolic adaptation induced by caloric restriction independently of the

changes in leptin circadian rhythms. J Clin Endocrinol Metab 2011; 96(9): E1512–E1516.

69 Wadden TA, Considine RV, Foster GD, Anderson DA, Sarwer DB, Caro JS. Short- and long-term changes in serum leptin dieting obese women: effects of caloric restriction and weight loss. J Clin Endocrinol Metab 1998; 83(1): 214–218.

70 Belinova L, Kahleova H, Malinska H, Topolcan O, Windrichova J, Oliyarnyk O, Kazdova L, Hill M, Pelikanova T. The effect of meal frequency in a reduced-energy regimen on the gastrointestinal and appetite hormones in patients with type 2 diabetes: A randomised crossover study. PLoS One 2017; 12(4): e0174820.

71 Legradi G, Emerson CH, Ahima RS, Flier JS, Lechan RM. Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. Endocrinology 1997; 138(6): 2569–2576.

72 Xu G, Li Z, Ding L, Tang H, Guo S, Liang H, Wang H, Zhang W. Intestinal mTOR regulates GLP-1 production in mouse L cells. Diabetologia 2015; 58(8): 1887–1897.

73 Neary NM, Small CJ, Druce MR, Park AJ, Ellis SM, Semjonous NM, Dakin CL, Filipsson K, Wang F, Kent AS, Frost GS, Ghatei MA, Bloom SR. Peptide YY3-36 and glucagon-like peptide-17-36 inhibit food intake additively. Endocrinology 2005; 146(12): 5120–5127.

74 Batterham RL, Le Roux CW, Cohen MA, Park AJ, Ellis SM, Patterson M, Frost GS, Ghatei MA, Bloom SR. Pancreatic polypeptide reduces appetite and food intake in humans. J Clin Endocrinol Metab 2003; 88(8): 3989–3992.

75 Hoizumi M, Sato T, Shimizu T, Kato S, Tsukiyama K, Narita T, Fujita H, Morii T, Sassa MH, Seino Y, Yamada Y. Inhibition of GIP signaling extends lifespan without caloric restriction. Biochem Biophys Res Commun 2019; 513(4): 974–982.

76 Zareie M, Johnson-Henry K, Jury J, Yang PC, Ngan BY, McKay DM, Soderholm JD, Perdue MH, Sherman PM. Probiotics prevent bacterial translocation and improve intestinal barrier function in rats following chronic psychological stress. Gut 2006; 55(11): 1553–1560.

77 Zhang C, Li S, Yang L, Huang P, Li W, Wang S, Zhao G, Zhang M, Pang X, Yan Z, Liu Y, Zhao L. Structural modulation of gut microbiota in life-long calorie-restricted mice. Nat Commun 2013; 4: 2163.

78 Fraumene C, Manghina V, Cadoni E, Marongiu F, Abbondio M, Serra M, Palomba A, Tanca A, Laconi E, Uzzau S. Caloric restriction promotes rapid expansion and long-lasting increase of Lactobacillus in the rat fecal microbiota. Gut Microbes 2018; 9(2): 104–114.

79 Santacruz A, Marcos A, Warnberg J, Marti A, Martin-Matillas M, Campoy C, Moreno LA, Veiga O, Redondo-Figuero C, Garagorri JM, Azcona C, Delgado M, Garcia-Fuentes M, Collado MC, Sanz Y, Grp ES. Interplay between weight loss and gut microbiota composition in overweight adolescents. Obesity 2009; 17(10): 1906–1915.

80 Sun J, Buys N. Effects of probiotics consumption on lowering lipids and CVD risk factors: a systematic review and meta-analysis of randomized controlled trials. Ann Med 2015; 47(6): 430–440.

81 Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature 2006; 444(7122): 1022–1023.

82 Tanca A, Abbondio M, Palomba A, Fraumene C, Marongiu F, Serra M, Pagnozzi D, Laconi E, Uzzau S. Caloric restriction promotes functional changes involving short-chain fatty acid biosynthesis in the rat gut microbiota. Sci Rep 2018; 8(1): 14778.

83 Xu J, Galley JD, Bailey MT, Thomas-Ahner JM, Clinton SK, Olivo-Marston SE. The impact of dietary energy intake early in life on the colonic microbiota of adult mice. Sci Rep 2016; 6: 19083.

84 Ruiz A, Cerdo T, Jauregui R, Pieper DH, Marcos A, Clemente A, Garcia F, Margolles A, Ferrer M, Campoy C, Suarez A. One-year calorie restriction impacts gut microbial composition but not its metabolic performance in obese adolescents. Environ Microbiol 2017; 19(4): 1536–1551.

85 Hatew B, Inabu Y, Sugino T, Steele M. Effects of pulse-dose ruminal infusion of butyrate on plasma glucagon-like peptide 1 and 2 concentrations in dairy calves. J Dairy Sci 2019; 102(3): 2254–2265.

86 Pataky Z, Genton L, Spahr L, Lazarevic V, Terraz S, Gaia N, Rubbia-Brandt L, Golay A, Schrenzel J, Pichard C. Impact of hypocaloric hyperproteic diet on gut microbiota in overweight or obese patients with nonalcoholic fatty liver disease: a pilot study. Dig Dis Sci 2016; 61(9): 2721–2731.

87 Price LB, Liu CM, Melendez JH, Frankel YM, Engelthaler D, Aziz M, Bowers J, Rattray R, Ravel J, Kingsley C, Keim PS, Lazarus GS, Zenilman JM. Community analysis of chronic wound bacteria using 16S rRNA gene-based pyrosequencing: impact of diabetes and antibiotics on chronic wound microbiota. PLoS One 2009; 4(7): e6462.

88 Kuehbacher T, Rehman A, Lepage P, Hellmig S, Folsch UR, Schreiber S, Ott SJ. Intestinal TM7 bacterial phylogenies in active inflammatory bowel disease. J Med Microbiol 2008; 57(12): 1569–1576.

89 Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, Gibson GR, Delzenne NM. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia 2007; 50(11): 2374–2383.

90 Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmee E, Cousin B, Sulpice T, Chamontin B, Ferrieres J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007; 56(7): 1761–1772.

91 Zhang CH, Zhang MH, Wang SY, Han RJ, Cao YF, Hua WY, Mao YJ, Zhang XJ, Pang XY, Wei CC, Zhao GP, Chen Y, Zhao LP. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. ISME J 2010; 4(2): 232–241.

92 Howcroft TK, Campisi J, Louis GB, Smith MT, Wise B, Wyss-Coray T, Augustine AD, McElhaney JE, Kohanski R, Sierra F. The role of inflammation in age-related disease. Aging (Albany NY) 2013; 5(1): 84–93.

93 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286(3): 327–334.

94 Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol 2013; 168(6): 5126–5134.

95 Sulistyoningrum DC, Susilowati R, Huriyati E, Witari NPD, Luglio HF, Julia M. Tumour necrosis factor-alpha and risk of cardiovascular disease among overfat Indonesian adolescents. Asia Pac J Clin Nutr 2017; 26(Suppl 1): S50–S56.

96 Chae JS, Paik JK, Kang R, Kim M, Choi Y, Lee SH, Lee JH. Mild weight loss reduces inflammatory cytokines, leukocyte count, and oxidative stress in overweight and moderately obese participants treated for 3 years with dietary modification. Nutr Res 2013; 33(3): 195–203.

97 Meydani SN, Das SK, Pieper CF, Lewis MR, Klein S, Dixit VD, Gupta AK, Villareal DT, Bhapkar M, Huang M, Fuss PJ, Roberts SB, Holloszy JO, Fontana L. Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: a randomized controlled trial in non-obese humans. Aging (Albany NY) 2016; 8(7): 1416–1431.

98 Choi KM, Han KA, Ahn HJ, Lee SY, Hwang SY, Kim BH, Hong HC, Choi HY, Yang SJ, Yoo HJ, Baik SH, Choi DS, Min KW. The effects of caloric restriction on Fetuin-A and cardiovascular risk factors in rats and humans: a randomized controlled trial. Clin Endocrinol 2013; 79(3): 356–363.

99 Haukeland JW, Dahl TB, Yndestad A, Gladhaug IP, Loberg EM, Haaland T, Konopski Z, Wium C, Aasheim ET, Johansen OE, Aukrust P, Halvorsen B, Birkeland KI. Fetuin A in non-alcoholic fatty liver disease: *in vivo* and *in vitro* studies. Eur J Endocrinol 2012; 166(3): 503–510.

100 Huang Y, Huang X, Ding L, Wang P, Peng K, Chen Y, Dai M, Zhang D, Xu M, Bi Y, Wang W. Serum Fetuin-A associated with fatty liver index, early indicator of nonalcoholic fatty liver disease: a strobe-compliant article. Medicine (Baltimore) 2015; 94(39): e1517.