Impact of microbiome on sexual health: Where do we stand?

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Introduction

- Many researchers have investigated gut microbiome in various disorders
  - Aging, obesity, hypertension, cardiovascular disease and chronic kidney disease and diabetes mellitus

    Science (80-) 350:1214–1215, Nutr Clin Pract 30:787–797, J Am Heart Assoc 4:e002699, Microbiome 5:14, Int Urol Nephrol 50:1453–1466, BMC Microbiol 19:191

  - Some bacterial genera which produce beneficial substances for human health
    - Bifidobacterium, Faecalibacterium, Lactobacillus, Alistipes
  - Pathogens for human being
    - Clostridium species, Escherichia/Shigella, and Klebsiella

- Sexual health
  - Erectile and ejaculatory function, testosterone, fertility
- Erectile dysfunction is prevalent in over middle-aged men and can notably affect their quality of life
  - Strongly associated with **aging**, smoking, **obesity**, **hypertension,** LUTS, **DM, CKD**, mental status, and a history of **CVD**
- Relationship of ED and gut microbiome remains unknown.
  - Men with ED might have a decrease of some beneficial genera or increase of some harmful genera

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UROLOGY - ORIGINAL PAPER

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The association between gut microbiome and erectile dysfunction: a community-based cross-sectional study in Japan

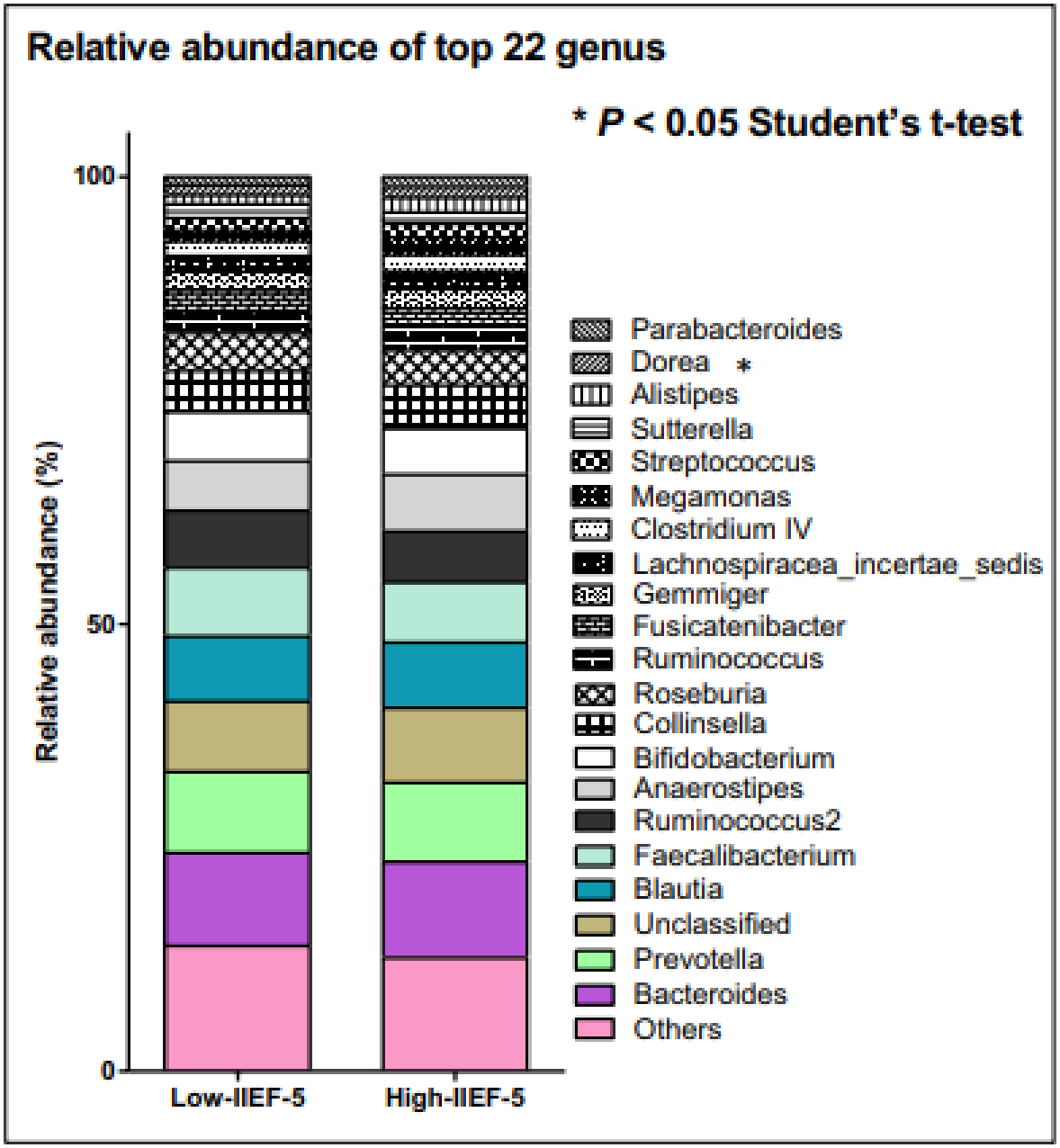
Teppei Okamoto[1] · Shingo Hatakeyama[1] · Atsushi Imai[2] · Hayato Yamamoto[1] · Tohru Yoneyama[2] · Kazuyuki Mori[1] · Takahiro Yoneyama[1] · Yasuhiro Hashimoto[2] · Shigeyuki Nakaji[3] · Chikara Ohyama[1,2]

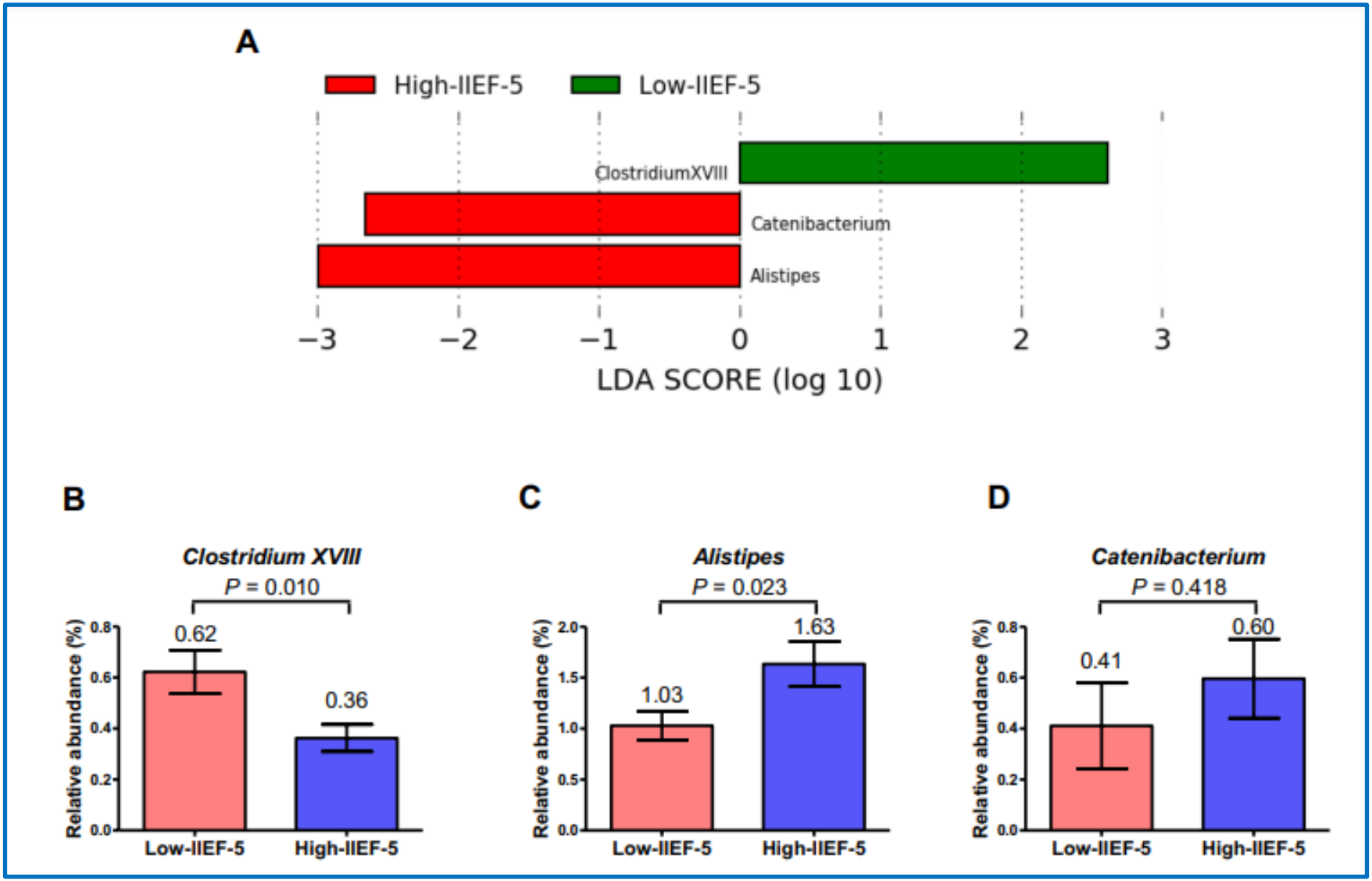
- Iwaki Health Promotion Project Database
  - Designed to evaluate the etiology of lifestyle-related diseases,
    - HTN, CVD, type 2 DM, and metabolic syndrome
  - Role of lifestyle factors
    - Body mass index and smoking status
  - The goal was to prevent lifestyle-associated diseases
    - Promote health of the people in Hirosaki City
- Present or past medical history, smoking, alcohol drinking, dietary intake, physical activity, mental health status, and occupation
- Blood sampling, body measurements, and physiological tests

- ✓ 431 men were screened for participation
- ✓ Exclusion
  - History of receiving prostate cancer treatments
    - androgen-deprivation therapy, radical prostatectomy, and radiotherapy
- ✓ Metabolic equivalent (MET) to evaluate the energy expenditure for daily physical activities
- ✓ Mental health status
  - 36-Item Short-Form Health Survey Questionnaire Mental Component Summary (SF-36 MCS)
- ✓ lower urinary tract symptoms (IPSS)
- ✓ International Index of Erectile Function 5 (IIEF-5)
  - Men were divided into the **low IIEF-5** (IIEF-5<16) and **high IIEF-5** (IIEF>16)
- ✓ The analysis of gut microbiome
  - 3g of fecal samples were collected by participants

Table 1 Comparison of characteristics between the low-IIEF-5 and high-IIEF-5 groups

	High-IIEF-5 (IIEF-5 > 16)	**Low-IIEF-5 (IIEF-5 ≤ 16)**	***P value***
Number of participants	96	96	–
Age† (years) (mean, SD)	50 (13)	51 (13)	*0.923*
History of CVD‡ (presence), *n* (%)	7 (7.3%)	8 (8.3%)	*1.000*
CKD‡ (presence), *n* (%)	11 (12%)	15 (16%)	*0.528*
DM‡ (presence), *n* (%)	8 (8.3%)	9 (9.4%)	*1.000*
HTN‡ (presence), *n* (%)	30 (31%)	30 (31%)	*1.000*
Current smoking‡ (presence), *n* (%)	62 (65%)	62 (65%)	*1.000*
Habitual drinking‡ (presence), *n* (%)	64 (67%)	67 (75%)	*0.757*
Metabolic syndrome‡ (presence), *n* (%)	13 (14%)	13 (14%)	*1.000*
Use of anticholinergic drugs and/or mirabegron‡ (presence), *n* (%)	1 (1.0%)	1 (1.0%)	*1.000*
Use of α 1-receptor antagonists and/or dutasteride and/or tadalafil	5 (5.2%)	3 (3.1%)	*0.500*
Total METs/week* (median, IQR)	168 (104–271)	161 (89–291)	*0.770*
IPSS ≥ 8 ‡ (presence), *n* (%)	11 (12%)	24 (26%)	*0.014*
SF-36 MCS* (median, IQR)	52 (46–60)	52 (44–57)	*0.232*
BMI† (kg/m^2) (mean, SD)	23.3 (2.5)	23.7.1 (3.3)	*0.359*
Total testosterone* (ng/dL) (median, IQR)	585 (444–702)	607 (464–802)	*0.724*
HbA1c† (%) (mean, SD)	5.7 (0.4)	5.7 (0.5)	*0.965*
High-density lipoprotein cholesterol* (mg/dL) (median, IQR)	60 (52–70)	59 (52–70)	*0.960*
Low-density lipoprotein cholesterol* (mg/dL) (median, IQR)	116 (102–131)	118 (97–138)	*0.637*
Triglyceride* (g/dL) (median, IQR)	100 (65–147)	94 (66–139)	*0.630*
Total cholesterol* (mg/dL) (median, IQR)	204 (183–217)	207 (175–231)	*0.578*


Relative abundance of top 22 genus
* P < 0.05 Student's t-test
Relative abundance (%)
100
50
0
Low-IIEF-5
High-IIEF-5
Parabacteroides
Dorea *
Alistipes
Sutterella
Streptococcus
Megamonas
Clostridium IV
Lachnospiracea_incertae_sedis
Gemmiger
Fusicatenibacter
Ruminococcus
Roseburia
Collinsella
Bifidobacterium
Anaerostipes
Ruminococcus2
Faecalibacterium
Blautia
Unclassified
Prevotella
Bacteroides
Others



Linear discriminant effect size (LEfSe) analysis

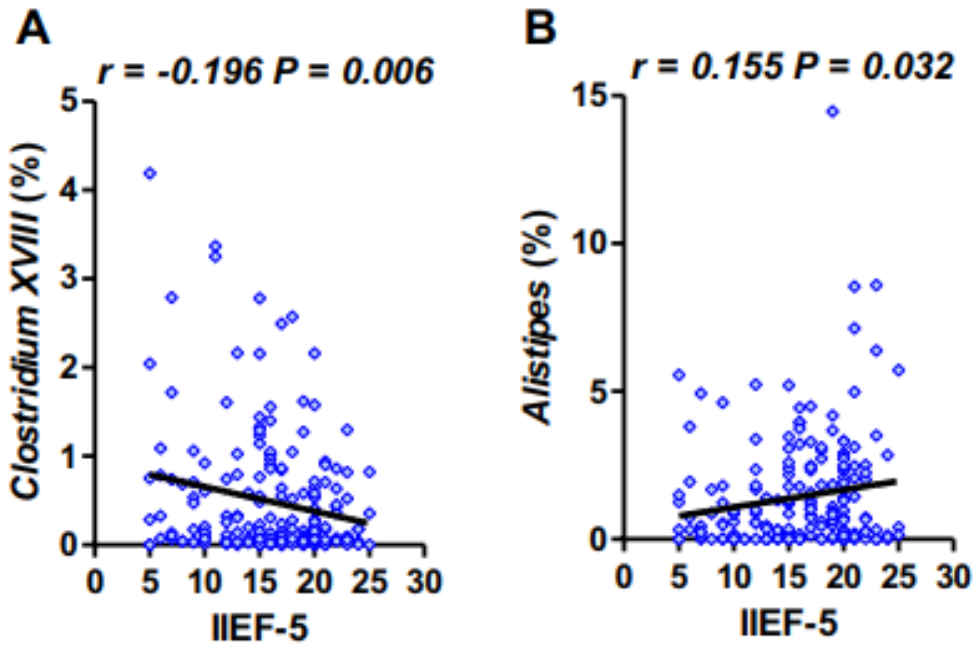


Table 2 Background adjusted-multivariate logistic analysis for low-IIEF-5 (IIEF-5 ≤ 16)

Variable	Risk factor	*P* value	OR	95% CI
IPSS ≥ 8	Presence	*0.008*	3.23	1.36–7.68
Clostoridium XVIII (%)	Continuous	*0.009*	2.06	1.20–3.55
Alistipes (%)	Continuous	*0.040*	0.81	0.66–0.99

SCIENTIFIC REPORTS

OPEN

Sulfonolipids as novel metabolite markers of *Alistipes* and *Odoribacter* affected by high-fat diets

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Alesia Walker[1], Barbara Pfitzner[2], Mourad Harir[1,6], Monika Schaubeck[3], Jelena Calasan[3], Silke S. Heinzmann[1], Dmitrij Turaev[4], Thomas Rattei[4], David Endesfelder[5], Wolfgang zu Castell[5], Dirk Haller[3,7], Michael Schmid[2], Anton Hartmann[2] & Philippe Schmitt-Kopplin[1,6,7]

The gut microbiota generates a huge pool of unknown metabolites, and their identification and characterization is a key challenge in metabolomics. However, there are still gaps on the studies of gut microbiota and their chemical structures. In this investigation, an unusual class of bacterial sulfonolipids (SLs) is detected in mouse cecum, which was originally found in environmental microbes. We have performed a detailed molecular level characterization of this class of lipids by combining high-resolution mass spectrometry and liquid chromatography analysis. Eighteen SLs that differ in their capnoid and fatty acid chain compositions were identified. The SL called "sulfobacin B" was isolated, characterized, and was significantly increased in mice fed with high-fat diets. To reveal bacterial producers of SLs, metagenome analysis was acquired and only two bacterial genera, i.e., *Alistipes* and *Odoribacter*, were revealed to be responsible for their production. This knowledge enables explaining a part of the molecular complexity introduced by microbes to the mammalian gastrointestinal tract and can be used as chemotaxonomic evidence in gut microbiota.

- Sulfonolipids
  - Antagonist on the von Willebrand factor receptor and suppressing tumor necrosis factor alpha (TNF-α)

    Int J Mol Med 26:751–758
  - Severity of ED was inversely correlated with von Willebrand factor and TNF-α.

    Eur Urol 52:1590–1600
    - Micro-inflammation and vascular endothelial dysfunction.

      J Antibiot (Tokyo) 48:924–928
- CVD patients have lower abundance of Alistipes

  Nat Commun 8:845A
  - Because ED may be an early phase of a generalized vascular disease and be an independent risk for CVD,
    - lower abundance of Alistipes in men with ED may be associated with the risk of future CVD.

- Clostridium XVIII might have negative impacts on human health in terms of bowel movement and erectile function.
  - Clostridium XVIII may be related with bowel movement disorders.
    - Clostridium XVIII was signifcantly more abundant in autistic children with constipation and DM patients with diarrhea and constipation

      United Eur Gastroenterol J 5:898–907
    - Clostridium species belonging to Clostridium XVIII were increased in patients with irritable bowel syndrome (IBS)

      Gastroenterology 141:1792–1801
  - Men with IBS were 2.12–2.38 times more likely to develop ED than those without.

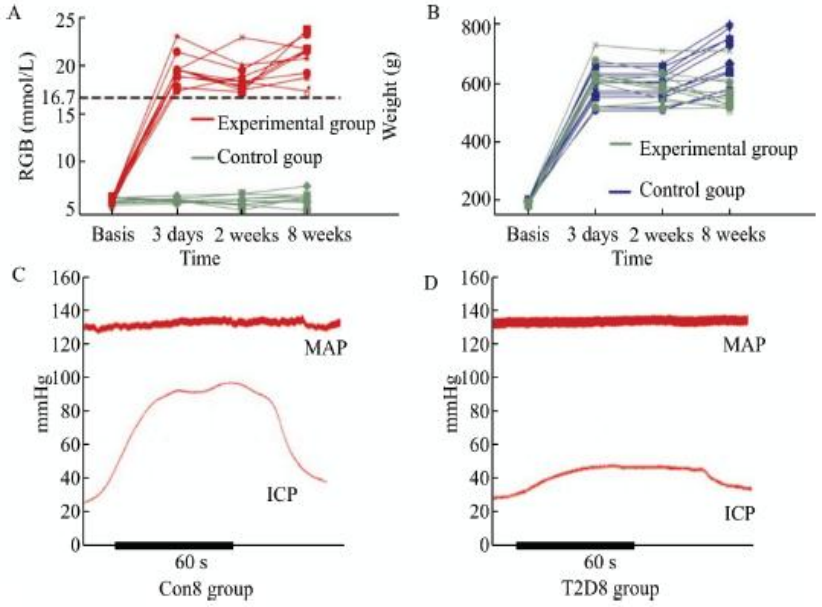
    Int J Impot Res 27:233–238

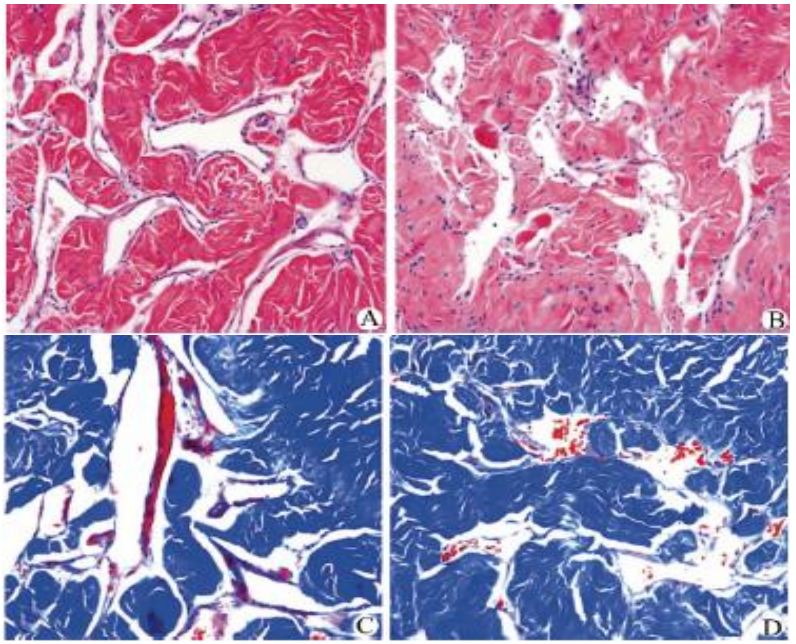
J Huazhong Univ Sci Technol［Med Sci］ 37(4):523-530,2017
DOI 10.1007/s11596-017-1767-z

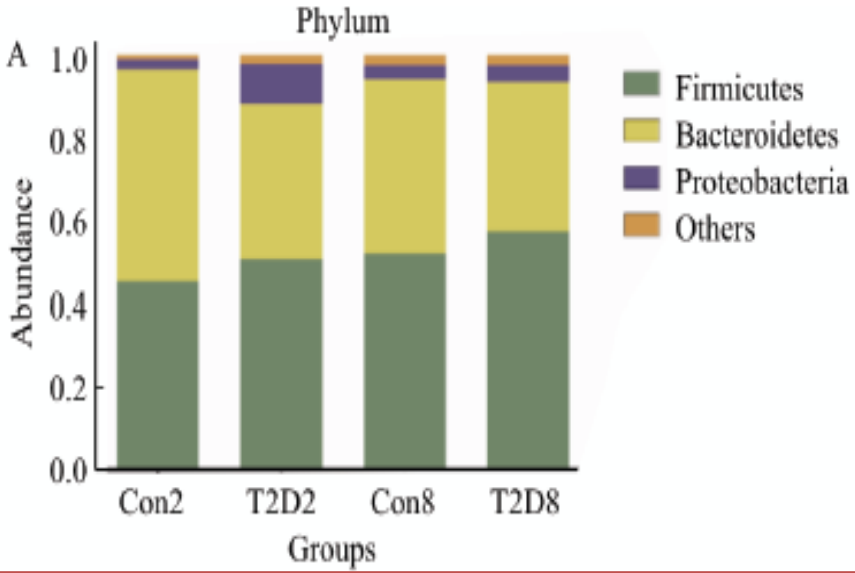
Relationship between Gut Microbiota and Type 2 Diabetic Erectile Dysfunction in Sprague-Dawley Rats*

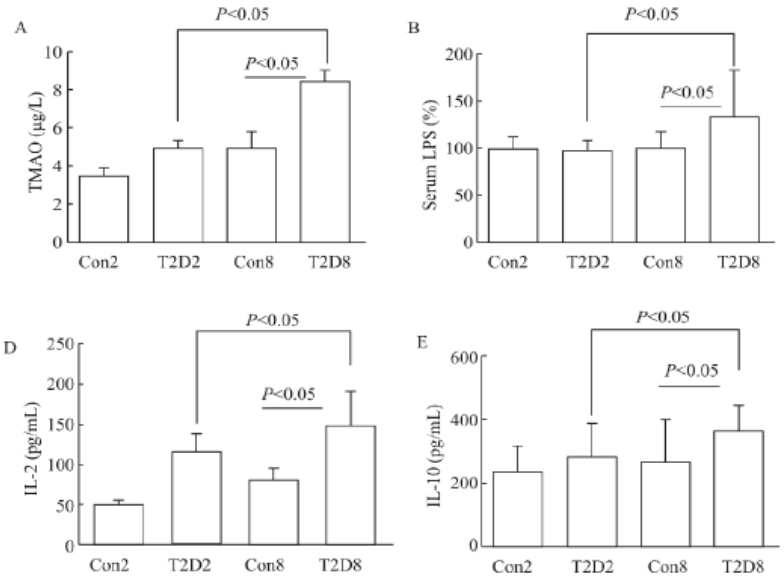
Hao LI (李 浩)[1†], Tao QI (齐 涛)[1†], Zhan-sen HUANG (黄展森)[1†], Ying YING (应 颖)[2], Yu ZHANG (张 宇)[1], Bo WANG (王 博)[1], Lei YE (叶 雷)[1], Bin ZHANG (张 滨)[1], Di-ling CHEN (陈地灵)[3#], Jun CHEN (陈 俊)[1#]

- 35 SD rats were randomly divided into two groups:
  - Control group (n=15) with normal diet,
  - Experimental group (n=20) with construction of T2D model.
- Fecal and serum samples at 2nd and 8th week
  - Fecal samples
    - Analysis of gut microbiota
  - Serum samples
    - Trimethylamine N-oxide (TMAO), lipopolysaccharide (LPS), and IL-1, IL-2, IL-10, and monocyte chemoattractantprotein-1 (MCP-1)

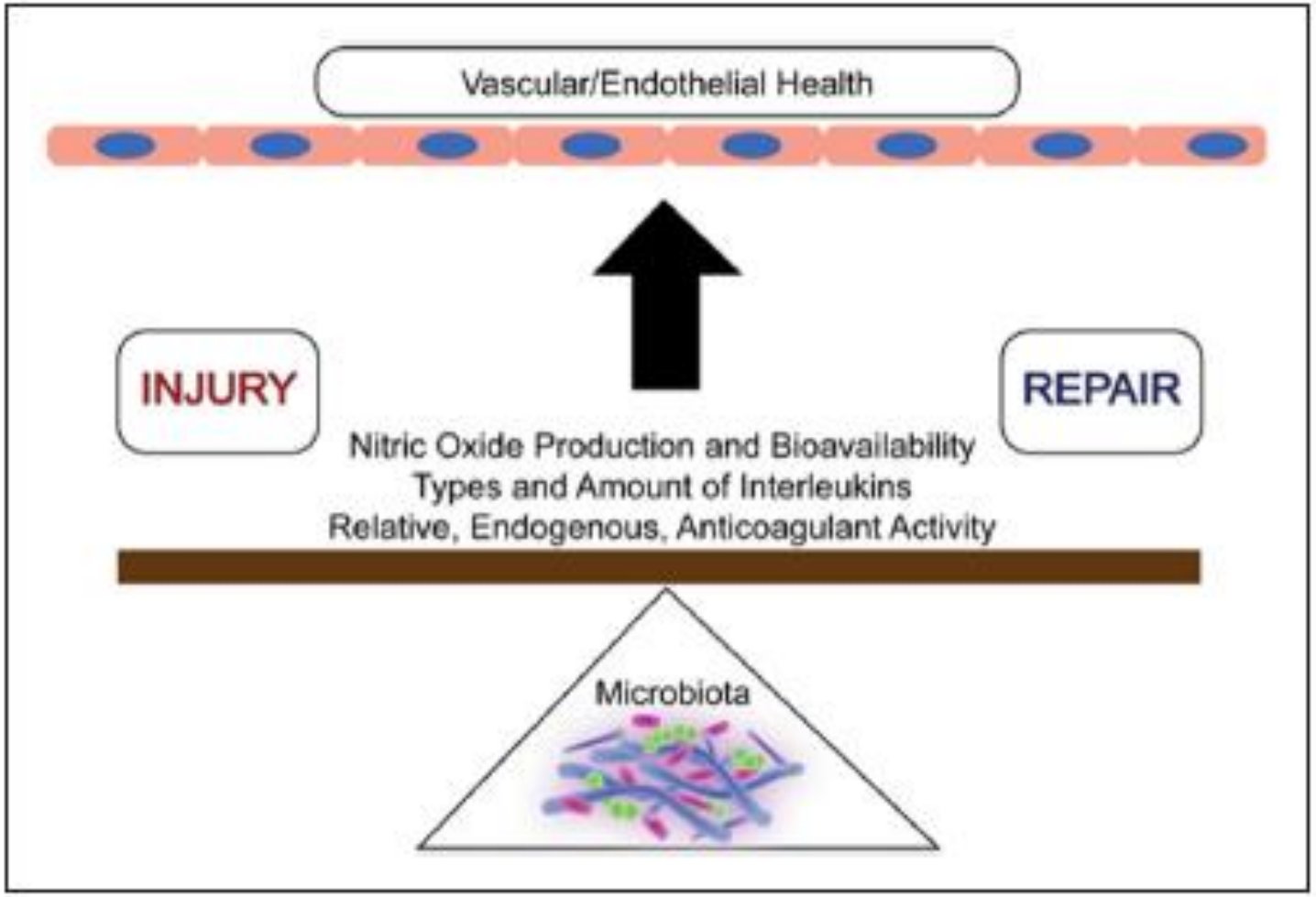

A
RGB (mmol/L)
25
20
16.7
15
10
5
Experimental group
Control goup
Basis 3 days 2 weeks 8 weeks
Time
B
Weight (g)
800
600
400
200
Experimental group
Control goup
Basis 3 days 2 weeks 8 weeks
Time
C
160
140
120
100
80
60
40
20
0
mmHg
MAP
ICP
60 s
Con8 group
D
160
140
120
100
80
60
40
20
0
mmHg
MAP
ICP
60 s
T2D8 group


A
B
C
D


Phylum
A
1.0
0.8
0.6
0.4
0.2
0.0
Abundance
Firmicutes
Bacteroidetes
Proteobacteria
Others
Con2
T2D2
Con8
T2D8
Groups


A
TMAO (μg/L)
P<0.05
P<0.05
10
8
6
4
2
0
Con2
T2D2
Con8
T2D8
B
Serum LPS (%)
P<0.05
P<0.05
200
150
100
50
0
Con2
T2D2
Con8
T2D8
D
IL-2 (pg/mL)
P<0.05
P<0.05
250
200
150
100
50
0
Con2
T2D2
Con8
T2D8
E
IL-10 (pg/mL)
P<0.05
P<0.05
600
400
200
0
Con2
T2D2
Con8
T2D8

Endothelial function and microbiome



Gut microbiome and sexual hormones

- Men have considerably less variety of gut microbiota than women.

  PLoS One. 2015;10(4):e0124599.

- Numerous studies have also confirmed other differences in gut microbiota between gender.

  PLoS One. 2016;11(5):e0154090.

  J Microbiol Biotechnol. 2017;27(12):2228-2236.

  Proc Natl Acad Sci USA. 2011;108(Suppl 1):4539-4546

  - *Prevotella* has a strong positive correlation with testosterone and is therefore more abundant in men than in women.
  - Females had higher abundance of *Bacteroides*
  - Males had lower abundance of *Clostridia*, *Methanobrevibacter*, and *Desulfovibrio*.
  - Differences in sex hormones appear to be somewhat responsible for this occurrence
    - Pathways involved remain unclear

Gut Microbes

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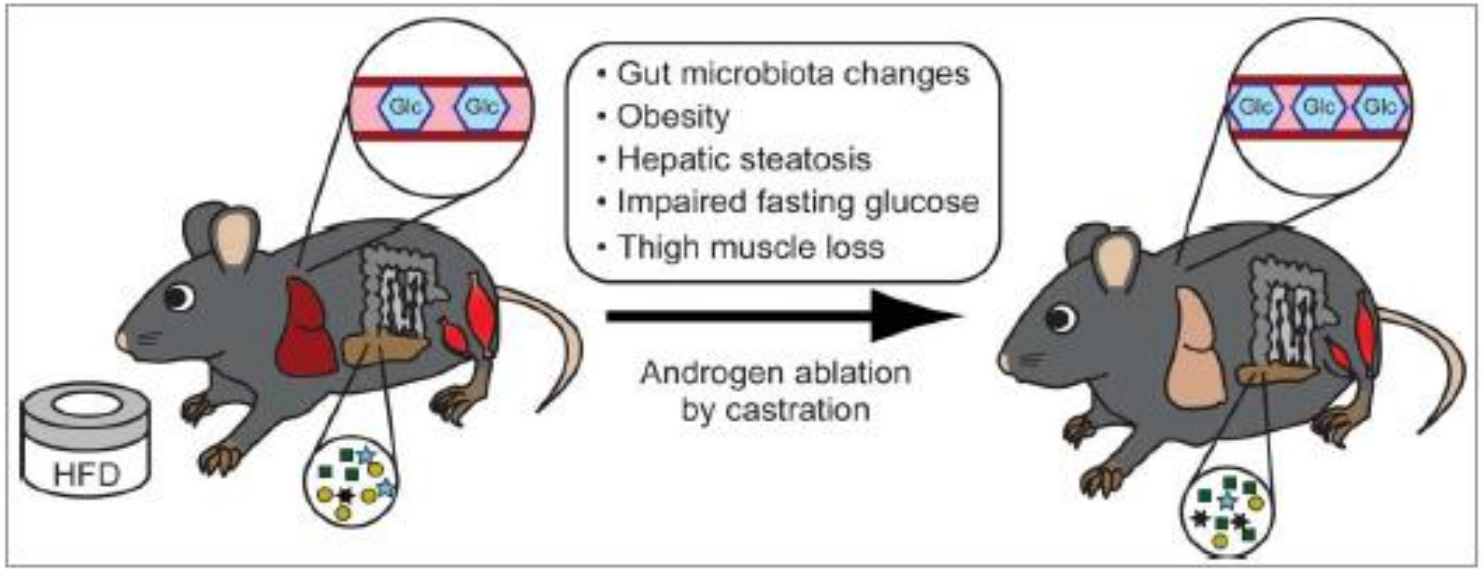
Hypogonadism alters cecal and fecal microbiota in male mice



GUT MICROBES 2016, VOL. 7, NO. 6, 533–539

Beneficial Microbes, 2017; 8(2): 193-206

Wageningen Academic Publishers

Probiotic administration improves sperm quality in asthenozoospermic human donors

- Two selected antioxidant probiotics strains
  - Lactobacillus rhamnosus CECT8361, Bifidobacterium longum CECT7347
- Evaluation of sperm quality parameters in males
  - WHO standards (WHO, 2010) after 3 pre-asthenozoospermic analysis (P1, P2 and P3) motility evaluations by the CASA
  - 9 asthenozoospermic men w/o any medical treatment

Analysis	Concentration | Volume | Motility [CASA] | Viability [flow cyclometry (PI-H33342)] DNA fragmentation [flow cytometry (SCSA)] | Intracellular H_2O_2 [flow cytometry (DCF)]

- Sperm motility was drastically improved after the treatment
- DNA fragmentation was statistically reduced after probiotic administration
- Intracellular H_2O_2 level was decreased.

- Probiotics could be administrated to improve motility and decrease DNA fragmentation and ROS levels in asthenozoospermic human males.

Summary

- Few clinical and animal studies about the association between erectile function and microbiome.
  - In clinical study, significant association between the erectile function and gut microbiomes
    - *Alistipes* and *Clostoridium XVIII*
  - In animal study, deterioration of gut microbiota led to the increase in the serum TMAO level, promoted vascular inflammation.
    - Damage of corpus cavernosum and smooth muscle cells.
    - Occurrence and development of ED
- The gut microbiome can serve as a fulcrum in the ongoing battle of vascular injury and repair that determines overall endothelial health.

Summary

- Gender differences impact the composition of the gut flora
  - Androgen could markedly remodel the gut microbiota
    - Castration influenced the gut microbiota in male mice in the high-fat diet-dependent manner.
      - Obesity, hepatic steatosis, thigh muscle loss, impaired fasting glucose
- In clinical study, probiotics could be administrated to improve motility and decrease DNA fragmentation and ROS levels in asthenozoospermic human males.
- Gut microbiota may have a causal role in male sexual health
  - Supplementation with appropriate probiotics could be undertaken as a complementary treatment.
  - Future studies should be designed