New Insights into the Mechanisms of High-Fat Diet Mediated Gut Microbiota in Chronic Diseases

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➢ Dietary characteristics in most patients with chronic diseases:
  • excessive sugar,
  • excessive saturated fat intake,
  • low total carbohydrate and fiber intake.
(As a risk factor for chronic diseases, HFD should be of high concern.)

➢ Gut microbiota dysbiosis may deliver a profound negative impact on the aggravation of chronic diseases, such as obesity, diabetes, cardiovascular diseases (CVDs), gastrointestinal diseases, and central nervous system disorders.

➢ However, the current review remains with a lack of discussion of the latest research on the changes in characteristic microorganisms and bacterial metabolites induced by HFD and its corresponding mechanisms in major chronic diseases.

HFD, High-fat diet
Roles of gut microbiota in chronic diseases induced by HFD

HFD (high lipid, less fiber, less vitamin, and less mineral)

- Obesity:
  - ↑ F/B ratio
  - ↑ LPS-producing bacteria
  - ↑ SCFAs-producing bacteria
  - ↑ Chronic inflammation

- Diabetes:
  - ↑ F/B ratio
  - ↑ Gram-positive bacteria in blood
  - ↑ Chronic inflammation
  - ↓ SCFAs

- Cardiovascular diseases:
  - ↓ Butyric acid-producing bacteria
  - ↑ Opportunistic pathogen
  - ↑ Blood TMAO level
  - Bile acid metabolism disorder

- Gastrointestinal diseases:
  - ↓ Lactate-producing bacteria
  - ↑ Opportunistic pathogen
  - Immune cell infiltration
  - Gut barrier damage

- Neurodegenerative diseases:
  - ↑ LPS-producing bacteria
  - ↑ Intestinal permeability
  - ↑ Opportunistic pathogen
  - ↑ TMAO level in cerebrospinal fluid
  - ↑ Oxidative stress
  - ↓ BDNF level in brain and blood
  - Blood-brain barrier damage
Roles of gut microbiota in chronic diseases induced by HFD

- **Obesity**
  - F/B ratio↑
  - LPS-producing bacteria↑
  - SCFAs-producing bacteria↓
  - Chronic inflammation↑

- **Diabetes**
  - F/B ratio↑
  - Gram-positive bacteria in blood↑
  - Chronic inflammation↑
  - SCFAs↓

- **Cardiovascular diseases**
  - Butyric acid-producing bacteria↓
  - Opportunistic pathogen↑
  - Intestinal permeability↑
  - Blood TMAO level↑

- **Gastrointestinal diseases**
  - Lactate-producing bacteria↑
  - Opportunistic pathogen↑

- **Neurodegenerative diseases**
  - LPS-producing bacteria↑
  - Intestinal permeability↑
  - Opportunistic pathogen↑
  - TMAO level in cerebrospinal fluid↑

- **Innate immune response**
  - Metabolic endotoxemia↑
  - Cholesterol metabolism disorder↑

- **Blood-brain barrier damage**
  - Oxidative stress↑
  - BDNF level in brain and blood↓

HFD (high lipid, less fiber, less vitamin, and less mineral)
Mechanism

Reveal microbial markers and bacterial metabolites and its role in HFD-induced chronic diseases.

Discuss possibility of synergistic mechanisms among those metabolites (bile acids, LPS, SCFAs, and TMAO) and characteristic microbes in the context of HFD-induced chronic diseases.

HFD, High-fat diet
Potential mechanisms of interaction between HFD and chronic diseases via bile acid

- Bile acids
  - Eubacterium
  - Clostridium
  - Ruminococcaceae
  - Blautia

- 7α-dehydroxylation reaction

- Pathogens

- DCA
- UDCA

- Secondary bile acids

- Gut barrier dysfunction

- Intestinal lumen

- Enterocyte
- Immune cell
- White adipose
- Beige adipocyte
- Muscle
- Liver
- Pancreas

- FXR
- TGR5

- Immune-cell infiltration
- Insulin secretion
- Insulin resistance
- Lipid metabolism
- Lipid metabolism
Potential mechanisms of interaction between HFD and chronic diseases via LPS

- Enterobacteriaceae
- Desulfovibrionaceae

- LPS

- CD14
- TLR4

- Immune cell activation
- NF-κB activation

- Proinflammatory cytokines, like TNF-α, IL-6, IL-1β

- BDNF

- CREB phosphorylation

- Synapsin-1

- Enterocyte
- Immune cell
- Epithelial cell
- Adipose cell
- Neuron
Potential mechanisms of interaction between HFD and chronic diseases via SCFAs
Potential mechanisms of interaction between HFD and chronic diseases via TMAO
Potential biomarkers

HFD induced obesity and diabetes are exhibited highly commonality and features on the influences of the composition of gut microbiota, accompany with the increase of F/B ratio, metabolic endotoxemia, and chronic inflammation.

Butyric acid producing bacteria, opportunistic pathogen, Lachnoclostridium, and unidentified Enterobacteriaceae are identified as the characteristic microbes in HFD induced cardiovascular diseases.

Lactate-producing bacteria and opportunistic pathogens are treated as the common microbial markers in HFD induced gastrointestinal diseases including Proteobacteria, Escherichia coli-Shigella, and Allobaculum.

LPS-producing bacteria and opportunistic pathogens also identified as the general microbial markers in HFD induced neurodegenerative diseases, including E. coli, Desulfovibrio, and unidentified Enterobacteriaceae.

Potential biomarkers
Conclusion

Systematic review
The influences of HFD on the composition of gut microbiota toward corresponding chronic diseases.

Prospective challenge
In-depth studies at the genetic and functional levels of bacteria based on metagenome sequencing deems very important. Single-microbe genomics shows unique insights into further strain-level variations.

New insights
Mechanisms among microbiota, metabolites, and immune responses during HFD-induced chronic diseases.

Potential biomarkers
The suggestion of potential biomarkers may improve holistic thinking about the issues surrounding long-term care and disease management.

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