

Yeong Yeh LEE

Submitted: 11 Dec 2014
Accepted: 15 Dec 2014

Sub-Editor (Medical Base), Malaysian Journal
of Medical Sciences, Universiti Sains Malaysia
Health Campus, 16150 Kubang Kerian,
Kelantan, Malaysia



Abstract

Obesity is a fast-emerging epidemic in the Asia-Pacific region, with numbers paralleling the rising global prevalence within the past 30 years. The landscape of gut diseases in Asia has been drastically changed by obesity. In addition to more non-specific abdominal symptoms, obesity is the cause of gastro-oesophageal reflux disease, various gastrointestinal cancers (colorectal cancer, hepatocellular carcinoma, oesophageal adenocarcinoma, gastric cardia adenocarcinoma, pancreatic cancer and gallbladder cancer) and non-alcoholic fatty liver disease. Abnormal cross-talk between the gut microbiome and the obese host seems to play a central role in the pathogenesis, but more studies are needed.

Keywords: obesity, gastrointestinal tract, Asia-Pacific, microbiota, disease

The Rising Numbers of Obesity in the Asia-Pacific

Recently rightfully recognised as a disease, obesity is probably the greatest threat to humankind, not just now but also in the coming years. The World Health Organization (WHO) estimates that at least 2.8 million people die from obesity each year and that 35.8 million of global disability-adjusted life years (DALYs) are the result of obesity (1). The worldwide prevalence of obesity (BMI ≥ 30 kg/m²) nearly doubled from 1980 to 2008, with 10% of men and 14% of women affected in 2008 compared with 5% of men and 8% of women in 1980 (1).

The Asia-Pacific is fast catching up with obesity data from the Asia Pacific Cohort Studies Collaboration (APCSC), showing increases of 46% in Japan and 414% in China (2). Malaysia has not escaped the epidemic, with a national prevalence of 11.7% in those aged 15 years and above in 2004 compared with data from the Second National Health and Morbidity Survey (NHMS), indicating 4.4% in 1996 (3). The more recent Third NHMS reported a prevalence of 7.4% in men and 13.8% in women (4).

Gut Diseases Arising from the Epidemic of Obesity

The landscape of gut diseases has shifted

in parallel with the rising trend in obesity. A meta-analysis of 21 studies found that obesity was associated with various gastrointestinal (GI) symptoms, including upper abdominal pain, gastro-oesophageal reflux (GOR), diarrhoea, chest pain, vomiting, and incomplete evacuation (5). Bypass surgery can improve GI symptoms, providing proof that obesity is responsible for the various GI complaints (6). Obese Asian adults may also have more frequent functional pain syndrome (7), but more data are needed.

Obese individuals have more acid reflux episodes, a longer reflux time, and a longer time at pH < 4 in addition to having more reflux symptoms and complications, including erosive oesophagitis and Barrett's oesophagus (8). The excess in oesophageal acid exposure in obesity is mostly due to increased intra-abdominal pressure, which in turn increases transient lower oesophageal sphincter relaxations, causing mechanical disruption of the gastro-oesophageal junction (GOJ) in early stages (partial hiatus hernia) and then permanent hiatal hernia in the later stages (9,10). A recent ecological study of 49 studies from Europe, the United States, Japan, and Australia found an inverse correlation between *Helicobacter pylori* prevalence and body mass index (BMI), but studies from populations with coronary heart disease and an extremely low prevalence of *Helicobacter pylori* did not find such a correlation (11,12).

Emerging evidence has also implicated obesity as a cause of various GI cancers, among which are colorectal carcinoma, oesophageal adenocarcinoma, gastric cardia adenocarcinoma, hepatocellular carcinoma, pancreatic cancer, and gallbladder cancer (13). What drives carcinogenesis in obesity is still unclear, but a number of mechanisms may be important, including insulin resistance, which increases insulin-like growth factor levels and chronic inflammation. The latter is associated with an increase in the secretion of pro-inflammatory adipokines (leptin and adiponectin) and various other inflammatory cytokines (13).

Non-alcoholic fatty liver disease (NAFLD) is also closely linked with obesity and other components of metabolic syndrome. In a population-based study using magnetic resonance spectroscopy in Hong Kong, the prevalence of NAFLD was 27.3%, and the risk increased in a dose-dependent manner. In subjects having all five components of metabolic syndrome, the prevalence of NAFLD was above 80%, compared with only 4.5% in those without any component (14). Although the majority of patients with NAFLD have simple steatosis, NAFLD can progress to a more severe form, or non-alcoholic steatohepatitis (NASH), in one third of patients, which increases the risk of cirrhosis and liver cancer (15). What drives the progression from simple steatosis to NASH is still incompletely understood, and better diagnostic and prognostic biomarkers are clearly needed.

Alterations in the Gut Microbiome Play a Central Role in Pathogenesis

A major breakthrough in recent years has been a better understanding of the role of the gut microbiome in health and in disease. Beyond being highly complex and diverse, the microbiome has a density that greatly outnumbers that of human cells by a factor of ten. While there are inter-individual variations, the composition of the gut microbiome is relatively stable and resilient to changes and may vary with the mode of delivery, age, and geographical area (16). Only limited data are available for the normal composition of the gut microbiome among Asian populations, but the available evidence indicates a difference at the phylum and genus levels (17). Obesity reduces the diversity of the gut microbiome, with a greater proportion of Firmicutes than Bacteroidetes (18), but more recent data may not support this observation (19).

The gut flora plays an important role in energy harvest from indigestible dietary nutrients, and nutrient overload can induce rapid changes in the gut microbial composition (increased Firmicutes/Bacteroidetes ratio). Dysbiosis in obesity is driven by the consumption of a high-fat diet (20), which in turn increases the systemic levels of lipopolysaccharide (LPS), promoting inflammation (termed as metabolic endotoxaemia), and increasing intestinal permeability. Other mechanisms of dysbiosis include low-grade inflammation through increases in toll-like receptor activity and the production of more short-chain fatty acids, and especially propionate, rather than butyrate and bile acid dysmetabolism (21).

A number of studies have suggested that intestinal dysbiosis is an important factor in the pathogenesis of inflammatory bowel disorders (Crohn's disease and ulcerative colitis) and irritable bowel syndrome (21). Intestinal dysbiosis and altered gut interactions with the host through defective inflammasome sensing were recently found to play a central role in the progression of NAFLD (22). Significant microbial dysbiosis is also a signature feature of colon cancer (21).

Conclusions

There is clearly an emerging epidemic of obesity within the Asia-Pacific, and there is strong evidence for obesity being a major factor in diseases of the gut that have been relatively uncommon in this part of the world in the past. Alterations in the gut environment, and especially in the gut microbiome, seem to play a central role in the pathogenesis of obesity in gut diseases. Further studies are needed, especially in Asia, to better understand the cross-talk between the gut microbiome and the obese host.

Correspondence

Associate Professor Dr Lee Yeong Yeh
MD (USM), MRCP (UK), DTM & H (Lond), MMed
(Internal Medicine) (USM), PhD (Glasgow), FACP,
FRCPE, FRCP, FACG
Malaysian Journal of Medical Sciences
Universiti Sains Malaysia
Health Campus, 16150 Kubang Kerian
Kelantan, Malaysia
Tel: +609-767 6571
Fax: +609-767 3949
Email: yylee@usm.my

References

1. World Health Organization. Obesity: situation and trends. Geneva (CH): World Health Organization; 2014.
2. Tofield A. Creeping epidemic of obesity hits Asia Pacific region. *Eur Heart J*. 2013;**34**(24):1768–1769.
3. Rampal L, Rampal S, Khor GL, Zain AM, Ooyub S Bin, Rahmat R Bin, et al. A national study on the prevalence of obesity among 16,127 Malaysians. *Asia Pac J Clin Nutr*. 2007;**16**(3):561–566.
4. Khambalia AZ, Seen LS. Trends in overweight and obese adults in Malaysia (1996-2009): A systematic review. *Obes Rev*. 2010;**11**(6):403–412. doi: 10.1111/j.1467-789X.2010.00728.x.
5. Eslick GD. Gastrointestinal symptoms and obesity: a meta-analysis. *Obes Rev*. 2012;**13**(5):469–479. doi: 10.1111/j.1467-789X.2011.00969.x.
6. Petereit R, Jonaitis L, Kupčinskas L, Maleckas A. Gastrointestinal symptoms and eating behavior among morbidly obese patients undergoing Roux-en-Y gastric bypass. *Medicina (Kaunas)*. 2014;**50**(2):118–23. doi: 10.1016/j.medici.2014.06.009.
7. Lee YY, Wahab N, Mustaffa N, Daud N, Mohd Noor N, Shaaban J, et al. A Rome III survey of functional dyspepsia among the ethnic Malays in a primary care setting. *BMC Gastroenterol*. 2013;**13**:84. doi: 10.1186/1471-230X-13-84.
8. Derakhshan MH, Robertson E V, Fletcher J, Jones G-R, Lee YY, Wirz AA, et al. Mechanism of association between BMI and dysfunction of the gastro-oesophageal barrier in patients with normal endoscopy. *Gut*. 2012;**61**(3):337–343. doi: 10.1136/gutjnl-2011-300633.
9. Lee YY, Wirz AA, Whiting JGH, Robertson E V., Smith D, Weir A, et al. Waist belt and central obesity cause partial hiatus hernia and short-segment acid reflux in asymptomatic volunteers. *Gut*. 2014;**63**(7):1053–1060. doi: 10.1136/gutjnl-2013-305803.
10. Lee YY, McColl KEL. Disruption of the gastroesophageal junction by central obesity and waist belt: role of raised intra-abdominal pressure. *Dis Esophagus*. 2014: Early View. doi: 10.1111/dote.12202.
11. Bezmin Abadi AT, Lee YY. Helicobacter pylori vacA as marker for gastric cancer and gastroduodenal diseases: One but not the only factor. *J Clin Microbiol*. 2014;**52**(12):4451. doi: 10.1128/JCM.02640-14.
12. Lee YY, Mahendra Raj S, Graham DY. Helicobacter pylori Infection - A Boon or a Bane: Lessons from Studies in a Low-Prevalence Population. *Helicobacter*. 2013;**18**(5):338–346. doi: 10.1111/hel.12058.
13. Goh LY, Goh KL. Obesity: an epidemiological perspective from Asia and its relationship to gastrointestinal and liver cancers. *J Gastroenterol Hepatol*. 2013;**28**(Suppl 4):54–58. doi: 10.1111/jgh.12293.
14. Wong VW-S, Chu WC-W, Wong GL-H, Chan RS-M, Chim AM-L, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. *Gut*. 2012;**61**(3):409–415. doi: 10.1136/gutjnl-2011-300342.
15. Dietrich P, Hellerbrand C. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. *Best Pract Res Clin Gastroenterol*. 2014;**28**(4):637–653. doi: 10.1016/j.bpg.2014.07.008.
16. Yatsunenکو T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;**486**(7402):222–227. doi: 10.1038/nature11053.
17. Nam Y-D, Jung M-J, Roh SW, Kim M-S, Bae J-W. Comparative analysis of Korean human gut microbiota by barcoded pyrosequencing. *PLoS One*. 2011;**6**(7):e22109. doi: 10.1371/journal.pone.0022109.
18. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006;**444**(7122):1022–1023. doi: 10.1038/4441022a.
19. Finucane MM, Sharpton TJ, Laurent TJ, Pollard KS. A taxonomic signature of obesity in the microbiome? Getting to the guts of the matter. *PLoS One*. 2014;**9**(1):e84689. doi: 10.1371/journal.pone.0084689.
20. Serino M, Luche E, Gres S, Baylac A, Bergé M, Cenac 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. doi: 10.1136/gutjnl-2011-301012.
21. Moran CP, Shanahan F. Gut microbiota and obesity: Role in aetiology and potential therapeutic target. *Best Pract Res Clin Gastroenterol*. 2014;**28**(4):585–597. doi: 10.1016/j.bpg.2014.07.005.
22. Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature*. 2012;**482**(7384):179–185. doi: 10.1038/nature10809.