The energy-rush and insulin model of obesity

Hangxing Jia

The energy-rush and insulin model of obesity

Hangxing Jia [‡]

‡ Key Laboratory of Zoological Systematics and Evolution & State Key Laboratory of Integrated Management of Pest Insects and Rodents, Institute of Zoology, Chinese Academy of Sciences, Beijing, China

Corresponding author: Hangxing Jia (jiahangxing@163.com)

Reviewable   v 1

Abstract

Obesity has been a global health problem since the 1980s. Despite the intensive research, there is no scientific consensus on the onset of obesity. The energy balance model (EBM) and the carbohydrate-insulin model (CIM) are two competing obesity theories, each with supporting and conflicting evidence. In this essay, I propose a new model, the energy-rush and insulin model (ERIM) which integrates not only the energy intake and expenditure but also the food composition and digestibility, to explain how the high energy-rush and insulin secretion contribute to the development of obesity. The ERIM offers a novel framework to explain how obesity occurs and proposes new recommendations for obesity management which may reverse the obesity epidemic In the future.

Keywords

EBM, CIM, ERIM, energy-rush, insulin secretion, obesity, food digestibility, GLP-1

Overview and background

Obesity can induce and increase the risk of many diseases (Ghaus et al. 2021, Kivimaki et al. 2022). Until 2016, approximately 40% of adults worldwide are overweight or obese, including about 1.9 billion adults (OECD and WHO 2020). The rapid prevalence of obesity and recent studies suggest that environmental factors, rather than genetic factors, are primarily to blame for the obesity epidemic (Blüher 2019). Although many environmental factors including overeating, the type of food, lack of physical activity, alcohol consumption, lack of sleep, intestinal microbiota, soft drinks, and so on have been reported to be associated with the obesity epidemic (Safaei et al. 2021), the question of how obesity occurs remain unresolved. There are currently two mainstream theoretical models, the energy balance model (EBM) (Hall et al. 2022) and the carbohydrate-insulin model (CIM) (Ludwig and Ebbeling 2018, Ludwig et al. 2021), that attempt to explain the onset of obesity.

However, there are several conflicts between the EBM and CIM (Ludwig and Ebbeling 2018, Ludwig et al. 2021, Ludwig et al. 2022, Hall et al. 2022). Firstly, the EBM claims that excessive energy intake drives additional fat deposition, while the CIM suggests that excessive fat accumulation causes additional energy intake; secondly, the EBM emphasizes "a calorie is a calorie" without considering food composition, whereas the CIM underlines that a high intake of carbohydrates is the leading cause of obesity; thirdly, the EBM recommends a low-fat diet to reduce the consumption of energy-dense foods for weight loss, yet the CIM advocates a low-carbohydrate diet to reduce fat deposition.

Recent studies have shown that both low-fat and low-carbohydrate diets can effectively lose weight (Chawla et al. 2020, Ge et al. 2020). These findings both support and contradict the claims of the EBM and CIM. Also, the CIM claims that a high-carbohydrate diet can lead to cellular internal starvation and a decrease in metabolic rate (Ludwig and Ebbeling 2018), which is not supported by recent studies (Speakman and Hall 2021). Therefore, the EBM and CIM are like two sides of the same coin, each revealing some but not all of the truth about obesity. To rationalize the onset of obesity, a new model is needed.

The energy-rush and insulin model

Here, I propose the energy-rush and insulin model (ERIM) to explain that obesity can emerge only when both energy-rush and insulin secretion increase concurrently (Fig. 1a).

Excessive energy intake is crucial for the onset of obesity (Hall et al. 2022). The term "energy-rush" in the ERIM, however, does not refer to the total amount of energy consumed, but rather to the total amount of energy in the blood, which is determined by how quickly the energy is absorbed and exhausted. This means that various physiological processes, such as food ingestion, digestion, absorption, basic metabolism, and physical activity, have an impact on the energy-rush. Therefore, energy-rush is not solely determined by energy intake and expenditure, but also by the food composition and digestibility. Due to differences in food digestibility, which determines how easily the food is digested and how quickly the energy is absorbed into the blood, two meals with the same calorie and food composition may lead to quite different energy-rush. For example, the energy-rush of easily digested white bread is much higher than that of spaghetti, as the energy-rush mentioned here is mainly contributed by the increased blood glucose (Ludwig 2002).

Insulin also plays a critical role in obesity development. Reducing insulin secretion can lead to weight loss while injecting additional insulin can cause weight gain (Ludwig and Ebbeling 2018, Ludwig et al. 2021). Insulin has been reported to lower blood glucose, facilitate fat deposition, promote glycogen and protein synthesis, inhibit the lysis of glycogen and fat, and suppress gluconeogenesis (Dimitriadis et al. 2021). In addition to these reported features, the ERIM claims that the major function of insulin is to enhance the processing of high energy-rush caused by food digestion and absorption, since insulin not only promotes the elimination of glucose and amino acids in the blood but also enhances free fatty acids reduction and fat deposition during the postprandial stage. By facilitating fat storage and

inhibiting lipolysis, insulin could contribute to the additional fat storage and the onset of obesity.

Thus, the ERIM claims that any diet, which can increase both the energy-rush and insulin secretion, will drive additional fat deposition and obesity development (Fig. 1a). For example, the most fattening Western diet (Kopp 2019), which is typically full of easily digested carbohydrates and fats, rich in sugar, and low in fiber (Ludwig and Ebbeling 2018, Ludwig et al. 2021, Ludwig et al. 2022, Hall et al. 2022), induces a dramatic increase in both the energy-rush and insulin secretion to drive the additional fat storage (Fig. 1b).

After consuming an easily digested low-fat diet (Fig. 1b), the carbohydrates, fats, and proteins in food are rapidly absorbed in the intestine, inducing a rapid rise in postprandial insulin secretion which further leads to a significant decrease in circulatory free fatty acids within half an hour, as well as the inhibition of fat lysis and enhanced glucose and fat storage (Dimitriadis et al. 2021, Hall et al. 2021). Such rapid digestion and processing of food will lead to an increased likelihood of hunger, prompting individuals to consume more food to prevent hunger from reoccurring, which can ultimately contribute to the onset of obesity (Ludwig and Ebbeling 2018, Ludwig et al. 2021, Ludwig et al. 2022, Hall et al. 2022).

In contrast, consuming a low-sugar, high-fiber, low-fat, and indigestible high-carbohydrate diet leads to slow nutrient digestion and absorption (Fig. 1b), resulting in a less intense energy-rush and reduced insulin secretion. As a result, hunger onset is delayed and total energy intake is not increased in the long term. This slow digestion and absorption of food lead to a smoother rise and fall of energy in the blood, reducing the likelihood of excessive fat storage and the onset of obesity.

On the other hand, a high-fat and low-carbohydrate ketogenic diet does not stimulate massive insulin secretion due to slow digestion and a lack of glucose and amino acids (Fig. 1b). Although the intake of high-fat food will result in a high energy-rush, there is no insulin to drive excessive fat accumulation in the adipose tissues and can prevent obesity development or even help with weight loss (Ludwig and Ebbeling 2018, Ludwig et al. 2021, Hall et al. 2021).

Unlike the EBM supports low-fat diets and the CIM advocates low-carbohydrate diets (Ludwig and Ebbeling 2018, Ludwig et al. 2021, Ludwig et al. 2022, Hall et al. 2022), the ERIM supports any diet that can delay or prevent additional fat accumulation by limiting either or both the energy-rush and insulin secretion. This is also consistent with the existing studies that find both low-fat and low-carbohydrate diets can help with weight loss (Chawla et al. 2020, Ge et al. 2020). Therefore the ERIM provides a more comprehensive and evidence-based explanation of the onset of obesity than that of the EBM and CIM.

Factors affecting energy-rush and insulin secretion

We are currently following an easily digested high-carbohydrate diet with both the high energy-rush and insulin secretion, which can accelerate the development of obesity.

Studies have found that excessive salt intake, alcohol consumption and lack of sleep all lead to overeating and increased energy intake (Cappuccio et al. 2008, Moosavian et al. 2017, Covassin et al. 2022), which will further lead to high energy-rush and insulin secretion. High salt intake not only increases total energy intake but also promotes a preference for foods with high fat (Bolhuis et al. 2016a, Bolhuis et al. 2016b). Physical inactivity is also associated with the obesity epidemic (Safaei et al. 2021), as it leads to a increase in energy expenditure (Fig. 1a), which in turn will increase the energy-rush and more energy will be stored as fat to promote obesity development.

Food composition is another important factor that determines insulin secretion and the energy-rush. When consumed alone, carbohydrates induce the strongest insulin secretion, followed by proteins, while fat ingestion barely affects insulin secretion (Holt et al. 1997, Bao et al. 2009, Ludwig and Ebbeling 2018). Therefore carbohydrates typically have the highest IL, followed by proteins, and then fat (Holt et al. 1997, Bao et al. 2009, Nimptsch et al. 2011). The ERIM emphasizes the importance of carbohydrates because of their strong insulin secretion effect. Meanwhile, the increase in fat will raise the energy-rush, which is also crucial for the development of obesity (Hall et al. 2022). In the context of a high-carbohydrate diet, increasing fat ingestion not only significantly increases the energy-rush but also promotes insulin secretion (Jones et al. 1989, Bao et al. 2009), which will further inhibit lipolysis and increase fat deposition. Therefore, the ERIM acknowledges the contribution of both fat and carbohydrates in the development of obesity.

Food digestibility also affects insulin secretion and the energy-rush, especially for high-carbohydrate foods. Easily digested foods, such as white bread, induce much higher levels of blood glucose and insulin than slow-digesting foods like spaghetti with the same calorie (Ludwig 2002). Moreover, when the same amount of glucose is infused into the intestine, the faster glucose enters the intestine, the higher blood glucose and insulin secretion it triggers (Ma et al. 2012). Thus, easily digested foods tend to be more fattening, while slow-digesting foods can help with weight loss. What's more, food digestibility can also help resolve the paradox of why both low-fat and low-carbohydrate diets can either induce obesity or help with weight loss (Chawla et al. 2020, Ge et al. 2020).

Slowing food digestion and absorption aids in weight loss

The speed of food digestion and absorption, which determines the energy-rush and insulin secretion, is influenced by various factors, such as gastric emptying and medications. Gastric emptying is regulated by the enteric nervous system, the vagus nerve system, and numerous endocrine hormones (Kuo et al. 2007). It is reported that gastric emptying accounts for more than 30% of the postprandial variance in blood glucose (Dimitriadis et al. 2021).

Glucagon-like peptide-1 (GLP-1) is a hormone that has been extensively studied for its ability to delay gastric emptying (Nauck et al. 1997). GLP-1 is secreted from L-cells present in the distal ileum and colon of the intestinal tract (Baggio and Drucker 2007, Dimitriadis et al. 2021). When there are too many nutrients for the small intestine to absorb, the extra

glucose, amino acids, or fatty acids can reach the distal ileum and stimulate the secretion of GLP-1, which in turn helps to inhibit gastric emptying and slow down food digestion and absorption (Nauck et al. 1997).

Several weight-loss approaches and medications work by increasing GLP-1 secretion or enhancing its effectiveness (Drucker 2022). GLP-1 receptor agonists such as liraglutide, dulaglutide, semaglutide, and tirzepatide are currently very effective drugs for treating obesity, semaglutide and tirzepatide can help lose 14.9% and 20.9% of body weight, respectively (Wilding et al. 2021, Drucker 2022, Jastreboff et al. 2022). Metformin has also been reported to increase GLP-1 secretion and help with weight loss in the long term (Bauer et al. 2018).

Bariatric surgeries, such as Sleeve Gastrectomy (SG), robotic Roux-en-Y Gastric Bypass (RYGB), and Gastric banding, are widely used for weight loss and can increase GLP-1 secretion (Meek et al. 2016). The bariatric effect is stronger in RYGB than in SG, and the GLP-1 is more upregulated in RYGB than in SG (Pucci and Batterham 2019). Those who lose more weight after RYGB surgery also have higher levels of GLP-1 secretion (Dirksen et al. 2013). GLP-1 receptor agonists have also been shown to reduce total insulin secretion in the long run (Rosenstock et al. 2014, van Can et al. 2014). In addition to GLP-1, bariatric surgery increases the secretion of many hormones that inhibit gastric emptying, such as cholecystokinin (CCK) and peptide-tyrosine-tyrosine (PYY), while decreasing the secretion of ghrelin, which promotes gastric emptying (Meek et al. 2016, Pucci and Batterham 2019).

In summary, GLP-1 and other hormones can delay gastric emptying to slow food digestion and absorption, which decreases both the energy-rush and insulin secretion, can reduce total energy intake in the long term and further aid in weight loss.

As previously mentioned, both the EBM and CIM advocate for non-refined foods that are rich in fiber and low in sugar, which can help slow down food digestion and absorption (Reynolds et al. 2019). Additionally, protein and fat-rich foods have longer gastric emptying times and solid foods also have longer gastric emptying times than liquid foods (Phillips et al. 2015, Goyal et al. 2019). This explains why nuts are helpful for weight loss and obesity prevention (Nishi et al. 2021).

Direct inhibition of food digestion and nutrient absorption can also help with weight loss. A combination of orlistat, which inhibits fat absorption, and acarbose, which inhibits carbohydrate digestion, has also been shown to facilitate weight loss (Holmback et al. 2020).

Current studies support the claims of the ERIM that limiting food digestion and absorption through diet, medication, and surgery can aid in weight loss by reducing the energy rush and insulin secretion.

Conclusions

The ERIM introduces a novel theoretical framework, which claims that an easily digested energy-dense diet with both high energy-rush and high insulin secretion is the leading cause of obesity, to explain the onset of obesity. The ERIM not only resolves the conflicts between the EBM and CIM but also provides insights to control obesity by slowing down food digestion and absorption. In the future, the ERIM may assist in the prevention of obesity and reverse the obesity pandemic.

Conflicts of interest

The authors have declared that no competing interests exist.

References

- Baggio LL, Drucker DJ (2007) Biology of incretins: GLP-1 and GIP. Gastroenterology 132 (6): 2131-57. https://doi.org/10.1053/j.gastro.2007.03.054
- Bao J, de Jong V, Atkinson F, Petocz P, Brand-Miller JC (2009) Food insulin index: physiologic basis for predicting insulin demand evoked by composite meals. Am J Clin Nutr 90 (4): 986-92. https://doi.org/10.3945/ajcn.2009.27720
- Bauer PV, Duca FA, Waise TMZ, Rasmussen BA, Abraham MA, Dranse HJ, Puri A, O'Brien CA, Lam TKT (2018) Metformin Alters Upper Small Intestinal Microbiota that Impact a Glucose-SGLT1-Sensing Glucoregulatory Pathway. Cell Metab 27 (1): 101-117. https://doi.org/10.1016/j.cmet.2017.09.019
- Blüher M (2019) Obesity: global epidemiology and pathogenesis. Nature Reviews Endocrinology 15 (5): 288-298. https://doi.org/10.1038/s41574-019-0176-8
- Bolhuis DP, Newman LP, Keast RS (2016a) Effects of Salt and Fat Combinations on Taste Preference and Perception. Chem Senses 41 (3): 189-95. https://doi.org/10.1093/chemse/bjv079
- Bolhuis DP, Costanzo A, Newman LP, Keast RS (2016b) Salt Promotes Passive Overconsumption of Dietary Fat in Humans. J Nutr 146 (4): 838-45. https://doi.org/10.3945/jn.115.226365
- Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, Miller MA (2008) Meta-analysis of short sleep duration and obesity in children and adults. Sleep 31 (5): 619-26. https://doi.org/10.1093/sleep/31.5.619
- Chawla S, Tessarolo Silva F, Amaral Medeiros S, Mekary RA, Radenkovic D (2020) The Effect of Low-Fat and Low-Carbohydrate Diets on Weight Loss and Lipid Levels: A Systematic Review and Meta-Analysis. Nutrients 12 (12). https://doi.org/10.3390/nu12123774
- Covassin N, Singh P, McCrady-Spitzer SK, St Louis EK, Calvin AD, Levine JA, Somers VK (2022) Effects of Experimental Sleep Restriction on Energy Intake, Energy Expenditure, and Visceral Obesity. J Am Coll Cardiol 79 (13): 1254-1265. https://doi.org/10.1016/j.jacc.2022.01.038

- Dimitriadis GD, Maratou E, Kountouri A, Board M, Lambadiari V (2021) Regulation of Postabsorptive and Postprandial Glucose Metabolism by Insulin-Dependent and Insulin-Independent Mechanisms: An Integrative Approach. Nutrients 13 (1). https://doi.org/10.3390/nu13010159
- Dirksen C, Jorgensen NB, Bojsen-Moller KN, Kielgast U, Jacobsen SH, Clausen TR, Worm D, Hartmann B, Rehfeld JF, Damgaard M, Madsen JL, Madsbad S, Holst JJ, Hansen DL (2013) Gut hormones, early dumping and resting energy expenditure in patients with good and poor weight loss response after Roux-en-Y gastric bypass. Int J Obes (Lond) 37 (11): 1452-9. https://doi.org/10.1038/ijo.2013.15
- Drucker DJ (2022) GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab 57 https://doi.org/10.1016/j.molmet.2021.101351
- Ge L, Sadeghirad B, Ball GDC, da Costa BR, Hitchcock CL, Svendrovski A, Kiflen R, Quadri K, Kwon HY, Karamouzian M, Adams-Webber T, Ahmed W, Damanhoury S, Zeraatkar D, Nikolakopoulou A, Tsuyuki RT, Tian J, Yang K, Guyatt GH, Johnston BC (2020) Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. BMJ 369 https://doi.org/10.1136/bmj.m696
- Ghaus S, Ahsan T, Sohail E, Erum U, Aijaz W (2021) Burden of Elevated Body Mass Index and Its Association With Non-Communicable Diseases in Patients Presenting to an Endocrinology Clinic. Cureus 13 (2). https://doi.org/10.7759/cureus.13471
- Goyal RK, Guo Y, Mashimo H (2019) Advances in the physiology of gastric emptying. Neurogastroenterol Motil 31 (4). https://doi.org/10.1111/nmo.13546
- Hall KD, Guo J, Courville AB, Boring J, Brychta R, Chen KY, Darcey V, Forde CG, Gharib AM, Gallagher I, Howard R, Joseph PV, Milley L, Ouwerkerk R, Raisinger K, Rozga I, Schick A, Stagliano M, Torres S, Walter M, Walter P, Yang S, Chung ST (2021) Effect of a plant-based, low-fat diet versus an animal-based, ketogenic diet on ad libitum energy intake. Nat Med 27 (2): 344-353. https://doi.org/10.1038/s41591-020-01209-1
- Hall KD, Farooqi IS, Friedman JM, Klein S, Loos RJF, Mangelsdorf DJ, O'Rahilly S, Ravussin E, Redman LM, Ryan DH, Speakman JR, Tobias DK (2022) The energy balance model of obesity: beyond calories in, calories out. Am J Clin Nutr 115 (5): 1243-1254. https://doi.org/10.1093/ajcn/nqac031
- Holmback U, Forslund A, Gruden S, Alderborn G, Soderhall A, Hellstrom PM, Lennernas H (2020) Effects of a novel combination of orlistat and acarbose on tolerability, appetite, and glucose metabolism in persons with obesity. Obes Sci Pract 6 (3): 313-323. https://doi.org/10.1002/osp4.405
- Holt SH, Miller JC, Petocz P (1997) An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. Am J Clin Nutr 66 (5): 1264-76. https://doi.org/10.1093/ajcn/66.5.1264
- Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A, Investigators S (2022) Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med 387 (3): 205-216. https://doi.org/10.1056/NEJMoa2206038
- Jones IR, Owens DR, Luzio S, Williams S, Hayes TM (1989) The glucose dependent insulinotropic polypeptide response to oral glucose and mixed meals is increased in

patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 32 (9):
668-77. https://doi.org/10.1007/BF00274255

- Kivimaki M, Strandberg T, Pentti J, Nyberg ST, Frank P, Jokela M, Ervasti J, Suominen
  SB, Vahtera J, Sipila PN, Lindbohm JV, Ferrie JE (2022) Body-mass index and risk of
  obesity-related complex multimorbidity: an observational multicohort study. Lancet
  Diabetes Endocrinol 10 (4): 253-263. https://doi.org/10.1016/S2213-8587(22)00033-X

- Kopp W (2019) How Western Diet And Lifestyle Drive The Pandemic Of Obesity And
  Civilization Diseases. Diabetes Metab Syndr Obes 12: 2221-2236. https://doi.org/
  10.2147/DMSO.S216791

- Kuo P, Rayner CK, Horowitz M (2007) Gastric emptying, diabetes, and aging. Clin
  Geriatr Med 23 (4): 785-808. https://doi.org/10.1016/j.cger.2007.06.009

- Ludwig DS (2002) The glycemic index: physiological mechanisms relating to obesity,
  diabetes, and cardiovascular disease. JAMA 287 (18): 2414-23. https://doi.org/10.1001/
  jama.287.18.2414

- Ludwig DS, Ebbeling CB (2018) The Carbohydrate-Insulin Model of Obesity: Beyond
  "Calories In, Calories Out". JAMA Intern Med 178 (8): 1098-1103. https://doi.org/
  10.1001/jamainternmed.2018.2933

- Ludwig DS, Aronne LJ, Astrup A, de Cabo R, Cantley LC, Friedman MI, Heymsfield SB,
  Johnson JD, King JC, Krauss RM, Lieberman DE, Taubes G, Volek JS, Westman EC,
  Willett WC, Yancy WS, Ebbeling CB (2021) The carbohydrate-insulin model: a
  physiological perspective on the obesity pandemic. Am J Clin Nutr 114 (6): 1873-1885.
  https://doi.org/10.1093/ajcn/nqab270

- Ludwig DS, Apovian CM, Aronne LJ, Astrup A, Cantley LC, Ebbeling CB, Heymsfield
  SB, Johnson JD, King JC, Krauss RM, Taubes G, Volek JS, Westman EC, Willett WC,
  Yancy WSJ, Friedman MI (2022) Competing paradigms of obesity pathogenesis: energy
  balance versus carbohydrate-insulin models. Eur J Clin Nutr 76 (9): 1209-1221. https://
  doi.org/10.1038/s41430-022-01179-2

- Ma J, Pilichiewicz AN, Feinle-Bisset C, Wishart JM, Jones KL, Horowitz M, Rayner CK
  (2012) Effects of variations in duodenal glucose load on glycaemic, insulin, and incretin
  responses in type 2 diabetes. Diabet Med 29 (5): 604-8. https://doi.org/10.1111/j.
  1464-5491.2011.03496.x

- Meek CL, Lewis HB, Reimann F, Gribble FM, Park AJ (2016) The effect of bariatric
  surgery on gastrointestinal and pancreatic peptide hormones. Peptides 77: 28-37.
  https://doi.org/10.1016/j.peptides.2015.08.013

- Moosavian SP, Haghighatdoost F, Surkan PJ, Azadbakht L (2017) Salt and obesity: a
  systematic review and meta-analysis of observational studies. Int J Food Sci Nutr 68
  (3): 265-277. https://doi.org/10.1080/09637486.2016.1239700

- Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Orskov C, Ritzel R, Schmiegel WH
  (1997) Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic
  effects in healthy humans. Am J Physiol 273 (5): 981-8. https://doi.org/10.1152/ajpendo.
  1997.273.5.E981

- Nimptsch K, Brand-Miller JC, Franz M, Sampson L, Willett WC, Giovannucci E (2011)
  Dietary insulin index and insulin load in relation to biomarkers of glycemic control,
  plasma lipids, and inflammation markers. Am J Clin Nutr 94 (1): 182-90. https://doi.org/
  10.3945/ajcn.110.009555

- Nishi SK, Viguiliouk E, Blanco Mejia S, Kendall CWC, Bazinet RP, Hanley AJ, Comelli
  EM, Salas Salvado J, Jenkins DJA, Sievenpiper JL (2021) Are fatty nuts a weighty

concern? A systematic review and meta-analysis and dose-response meta-regression of prospective cohorts and randomized controlled trials. Obes Rev 22 (11). https://doi.org/10.1111/obr.13330

- OECD and WHO (2020) Overweight and obesity, in health at a glance: Asia/Pacific 2020: Measuring progress towards universal health coverage. Paris: OECD Publishing https://doi.org/10.1787/a47d0cd2-en

- Phillips LK, Deane AM, Jones KL, Rayner CK, Horowitz M (2015) Gastric emptying and glycaemia in health and diabetes mellitus. Nat Rev Endocrinol 11 (2): 112-28. https://doi.org/10.1038/nrendo.2014.202

- Pucci A, Batterham RL (2019) Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different. J Endocrinol Invest 42 (2): 117-128. https://doi.org/10.1007/s40618-018-0892-2

- Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L (2019) Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 393 (10170): 434-445. https://doi.org/10.1016/S0140-6736(18)31809-9

- Rosenstock J, Hanefeld M, Shamanna P, Min KW, Boka G, Miossec P, Zhou T, Muehlen-Bartmer I, Ratner RE (2014) Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). J Diabetes Complications 28 (3): 386-92. https://doi.org/10.1016/j.jdiacomp.2014.01.012

- Safaei M, Sundararajan EA, Driss M, Boulila W, Shapi'i A (2021) A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. Comput Biol Med 136 https://doi.org/10.1016/j.compbiomed.2021.104754

- Speakman JR, Hall KD (2021) Carbohydrates, insulin, and obesity. Science 372 (6542): 577-578. https://doi.org/10.1126/science.aav0448

- van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH (2014) Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond) 38 (6): 784-93. https://doi.org/10.1038/ijo.2013.162

- Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF, Group SS (2021) Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med 384 (11): 989-1002. https://doi.org/10.1056/NEJMoa2032183
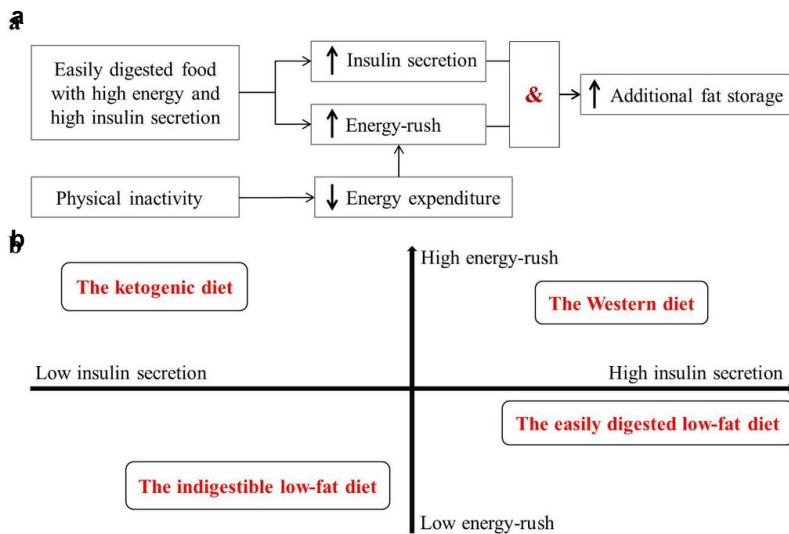
a

```
┌─────────────────────┐        ┌──────────────────────┐
│ Easily digested food │ ──────▶│ ↑ Insulin secretion  │──┐
│ with high energy and │        └──────────────────────┘  │  ┌───┐      ┌────────────────────────┐
│ high insulin secretion│ ─────▶│ ↑ Energy-rush        │──┤  │ & │ ──▶ │ ↑ Additional fat storage │
└─────────────────────┘        └──────────────────────┘  │  └───┘      └────────────────────────┘
```

```
┌─────────────────────┐        ┌──────────────────────┐
│ Physical inactivity │ ──────▶│ ↓ Energy expenditure │
└─────────────────────┘        └──────────────────────┘
```

b

High energy-rush

The ketogenic diet

The Western diet

Low insulin secretion ──────────────────────────────▶ High insulin secretion

The easily digested low-fat diet

The indigestible low-fat diet

Low energy-rush

Figure 1.

The energy-rush and insulin model of obesity.

a: The energy-rush and insulin model claims that easily digested food with high energy and high insulin secretion, which can lead to both high energy-rush and insulin secretion, is the leading cause of obesity.
b: Diets with varying food composition and digestibility result in different energy-rush and insulin secretion.