Nutrition – the crusade against the ‘devilish’ carb

The carbohydrate-insulin model (CIM) gives the reason for overeating a shift of energy into the fat tissue, leaving non-adipose tissues ‘hungry’ and increases the urge to eat more ‘carb’. However, the results of a meticulous study with the latest advanced technology oppose the core of the hypothesis.

Avoid discussing two topics on a long flight with a friendly fellow passenger in the seat next to you: Politics and diets. Few other issues are so emotionally overloaded. Achieving a consensus in case of contradictory political views is illusory. To agree on differences in dietary restriction might be possible for good willing opponents by at least approving that the overall problem is to balance energy intake to energy expenditure. Dietary control for certain diseases and unhealthy conditions is necessary. The issue here is the need to discuss the fight against ‘carb’ critically and to adopt a balanced view on the topic (1).

The carbohydrate-insulin model (CIM)

A typical diet low in carbohydrates restricts grains, legumes, fruits, bread, pasta, and starchy vegetables, and, of course, sweet food and drinks. This means all that is tasty, and you like to consume ‘will condemn you to hell’. Still allowed are appealing certain types of protein food, like fish. The recommendation to follow such a dietary regime is based on the ‘carbohydrate-insulin model (CIM) (2). The model tries to explain why one cannot resist the urge to have another very delicious-looking cake after an already voluptuous dinner while wanting to reduce weight seriously.

The phenomenon of gaining weight by overeating contradicts metabolic adjustments. The ‘normal’ physiological mechanism as a response to overeating should be feeling full, and energy expenditure should increase (3). Unfortunately, the mechanism doesn’t work very well. Nutritional encouragement with the slogan ‘eat less’ and ‘move more’ failed to curtail worldwide overnutrition and obesity (4). Lifestyle factors and dietary intake play a role in the worldwide obesity pandemic. Conventional wisdom is that fat and carbohydrate intake is the main culprit for overnutrition and obesity. ‘Palatable, energy-dense food’ increase energy intake, while a ‘sedentary’ lifestyle decreases energy expenditure. The excess in calory then is metabolized and stored as fat resulting in obesity (5).

The role of insulin in CIM

A key factor of CIM is the hormone insulin. Insulin accelerates glucose uptake and promotes fat and glycogen accumulation. It also inhibits the release of fatty acids from the adipose tissue. The result is a decrease in glucose and lipids in the blood. The basal metabolism and physical activity are downregulated. Postprandial insulin lowers the concentration of glucose in the blood and prompts us to feel hungry. Thus, longing for food shortly after we just finished eating. The type of carbohydrate plays a significant role. Carbohydrates with a high glycemic index (GI) elevate blood glucose and consequently insulin after consumption. A high GI is dangerous for health and increases the risk of developing type 2 diabetes mellitus and cardiovascular diseases (6). The GI is moderately high for rice. The effect is worse in glutenous rice. Despite the ‘nutritional transition’, white rice and glutenous rice are the primary source of carbohydrates in Thailand and the latter, especially in the Northeast (7). Thais might be attempted to follow CIM. They should think twice.

Dietary recommendations for CIM

The recommended list of types of food based on CIM is long (2). It forbids potato products, warns about sugar and certain tropical fruits (which may annoy those living in tropical countries). The suggestions give way to replacing carbohydrates with dietary fat (8). (*As a husband, don't try to suggest that to a health-conscious, loving wife, who plainly tells you to cook by yourself*). Following a particular dietary regime needs a strong will and some fighting slogan, such as 'processed carbs are problem carbs'. The word 'carb' sounds like a really, really evil topic with an American English intonation. (*One might experience this discussing with USA college students' nutritional problems*).

Evidence supporting CIM

Circumstantial evidence suggests that the CIM might hold, as indicated in the review paper of Ludwig and Ebbeling (2). Supporting the model are animal research results, genetic models, behavioral trials, and the clinical implications. It is said that those criticizing CIM might misunderstand the physiological mechanism or misinterpreted metabolic studies. Yet, the authors admit that evidence for the effects in humans 'remains inconclusive'.

Testing the CIM theory in humans failed

To test the theory in humans is difficult. Dietary surveys cause ethical problems. To assure participation in a specific regime for months is problematic. Testing CIM with a small group and only for a short time barely verifies the model. Indeed, several attempts to test the model, seeking the cooperation of volunteers to participate in some studies, failed to uphold the theory.

Studying twenty adults participating in a low carbohydrate-high fat diet against a low fat but high carbohydrate diet, less food was consumed on the high-carbohydrate diet. The participants didn't complain about hunger or fullness. Contrary to expectation, the high-carbohydrate diet resulted in body fat loss (9). Several long-term surveys didn't validate CIM as well. Ten to fifteen weeks of a high-carbohydrate diet increased satiety and a one-year study with free-living volunteers, while comparing a high- against a low-carbohydrate diet, found no difference between both dietary regimes in energy intake, and postprandial insulin secretion didn't influence variation in weight (10-12).

Following the reasoning of CIM, a low carbohydrate diet should reduce insulin secretion, fat trapped in the adipose tissue should be set free, and energy expenditure should increase. Such a dietary regime is supposed to work against 'internal starvation' Two studies with overnourished and obese participants exposed to carbohydrate low diets for one to two months lowered their post-prandial insulin secretion. Still, body fat loss was the same as for the isocaloric control group. In one study, energy expenditure decreased instead of increasing as expected. Participants of a second study increased energy expenditure but only for a few weeks (13, 14).

The popularity of 'low carb'

The 'low-carb' diet is one of several popular diets in the USA. Several books promote the diet, with catching titles, such as 'Dr. Atkins' diet revolution' (Atkins, R.C. 1973, London:

Bantham Press), or 'The big fat surprise: why butter, meat, and cheese belong in a healthy diet' (Teichholz, N. 2014, New York: Simon and Schuster) and 'Always hungry, Conquer cravings, retrain your fat cells, and lose weight permanently' (Ludwig, D.S. 2016, New York: Grand Central Publishing).

Risks following 'low carb' too strictly

Lowering carbohydrate intake can reduce weight, but how low is low? To lower carbohydrate-rich food but don't increase protein and saturated fat intake, weight reduction might be achieved, without diametral health effects. To the suggestions of 'carb' reduction to avoid certain vegetables, some grains, beans, and legumes are added. Strictly following the recommendations, vitamin and mineral deficiencies might appear. Lack of fibers might increase the risk of colon cancer. If meat and saturated fat substitute carbohydrates to a greater extent, the risk for cardiovascular diseases and cancer is enhanced. Because of the potential hazards, the diet is probably not in accordance with dietary guidelines for the USA and is still controversially discussed (15, 16).

The mice experiment to verify CIM - methodology

To shed light on the controversial views on CIM, the results of a carefully planned and conducted experiment was published recently (17). Four hundred eighty male mice were fed with 4 series of diets with various carbohydrate- but fixed protein content. Each series comprised of 6 different diets, and altogether 24 different diets were tested. The fat level was set to 20% or 60% and that of protein to 10% or 25%. (In a subsequent publication, the variations were mentioned to be 10% to 80% fat and carbohydrate, and 5% to 30% protein (18)). Twenty mice were exposed to each of the 24 different diets. The trial used C57BL/6 mice. The inbred strain is suitable for research in human diseases, and each strain is genetically identical. The intention was to match the diets to westernized diets with 15% calories from protein, 35% calories from fat, and 50% carbohydrates.

Additionally, wide variations in macronutrient compositions were considered (18). Mice were kept in a clean and stress-free environment. Access to food and water was ad libitum. The animals were 'euthanized' with carbon dioxide after 12 weeks on the experimental diet and dissected.

Variables evaluated

Numerous variables were measured, including fasting blood glucose to determine the 'starvation state', and post-prandial serum insulin. The latter could be related to fat tissue metabolism in relation not only to circulating insulin levels but also to the carbohydrate content of the diet. Besides food intake, the body composition, particularly fat mass and lean mass, was evaluated by an EchoMRI Body Composition Analyzer. Physical activity was taken, and energy expenditure was measured for two days after ten weeks by transferring the mice into a TSE PhenoMaster/LabMaster system. The de novo lipogenesis was estimated by relating the respiratory exchange ratio (RER) to the food quotient (FQ) (details see page 28 (17)). A genetic exploration was performed in sampling hypothalamic and subcutaneous white adipose tissue (sWAT), and the total RNA in the hypothalamic and sWAT samples was extracted using an RNeasy Mini Kit.

Results obtained

The results are given by testing the prediction of the model.

CIM predicts that post-prandial insulin levels increase following dietary levels of carbohydrate intake, and fasting glucose will decrease, resulting in some sort of 'starvation state'. Increasing carbohydrate intake resulted in increased post-prandial insulin levels, but post-prandial glucose levels didn't change, and fasting glucose and fasting insulin levels decreased too.

According to the CI model, elevated insulin alters fat tissue metabolism, increases lipogenesis, and decreases lipolysis. The phenomenon is directly related to circulating insulin levels and dietary carbohydrate content. This is common knowledge and not particularly associated with the model. Consequently, lipolysis is inhibited, but there is no clue that this alters the lipogenesis pathway.

Fitting CIM, increased carbohydrate intake should increase food intake as a whole and dimmish energy expenditure. However, there was no indication of such a metabolic mechanism.

Following CIM, the 'insulin-generated state of cellular starvation' initiates neurological pathways in the brain related to food intake and a decrease in the periphery energy expenditure by turning white adipose tissue (WAT) into brown adipose tissue. Indeed, elevated fasting insulin correlated with the 'inhibition of pathways regulating food intake in the brain and adipose tissue browning was inhibited', but this did not change the overall daily energy expenditure.

In conclusion, only changes in the post-prandial insulin and fasting glucose go along with CIM, but not fasting insulin, energy intake, energy expenditure, and body fat mass in mice. Therefore, an increase in carbohydrate intake might be the cause of overnutrition but don't trigger a dangerous metabolic reaction leading to overeating. It is not uncommon that for some diets, the fat and not the carbohydrate content is the culprit for gaining weight. As reported in a separate publication, the experiments in mice disclosed that as well, namely that dietary fat and not protein or carbohydrate caused adiposity in mice (19).

Objecting the results of the mice experiment

The experiment and the results obtained were challenged by those in favor of CIM, and both sides plaid hardball making their point. The experiment was conducted by scientists in mainland China with the cooperation of colleagues from the UK. Since CIM is very popular in the USA and obviously, the American group supporting CIM was not happy about the publication. The most senior adversaries of both parties are listed as the first author in the exchange of 'pros and cons' (while conventionally, the senior ones appear at the end of the list of authors).

Objections from the USA

The main criticism by Ludwig et al. (20) centers around the composition of the dietary regimes: Firstly, neither rodents nor a general human population will eat a regime of diets as used in the study. Secondly, comparing carbohydrates with a high GI in the low carbohydrate diets with carbohydrates with a low GI in the high intake group confounds the result. Thirdly

it is not possible to test CIM in feeding mice with a diet high in fat since that causes obesity and insulin resistance. Finally, the Chinese- UK group is advised to keep their hands off criticizing diets, which help work against the obesity epidemic. (In the publication, it reads as follows: In light of the striking failure of conventional obesity prevention and treatment on a population basis, all sides of this debate would do well to avoid categorical conclusions about the validity of the CIM in any species at this time).

Response from China and the UK

Speakman et al. (18) noted that the wide range in the composition of the dietary regimes included fairly well also those in the general human population. The notion that the regimes were not suitable for mice was refuted in quoting that wild house mice and rats show very brought dietary intake patterns, and one and the same species have different diets in locations only 15 km apart. In addition, the metabolic outlay of the laboratory mice strains used respond to the GI content differently than humans, so that the allocation of the carbohydrates with different GI meets the intention in comparing different GI regimes, and there is no confounding effect to be expected. Further on, the mice had no indication of neuroinflammation according to the 'RNAseq' explorations. It remained unclear on what grounds Ludwig et al. concluded that the experiment was hampered by such a condition. Finally, the main point of CIM is that not high fat causes obesity but high levels of high GI carbohydrates. So, the assertion that one cannot test CIM using a high fat diet disproves the theory Ludwig et al. stands for. The response of Speakman et al. to their opponents ends with the remark that the criticism is 'completely unfounded' and CIM does not explain the 'impacts of different macronutrients on the body weight and adiposity in mice.

How valid are research results for humans obtained with mice experiments?

A valid point made by Speakman et al. with the remark in his response is that 'the jury remains out on whether this refutation of the model is unique to mice or also pertains to humans'. The remark has far-reaching implications. Is it meaningful to conclude that research results obtained with animals are also valid for humans? In a previous entry to this blog, the topic was discussed in reviewing advancements in immunology. In immunology, the trend for research in humans instead of mice will increase in the future. For instance, side effects experienced after vaccination in humans are challenging to detect in animal studies. Maybe individual variations in immunological reactions are much more frequent than individual deviations from general metabolic pathways in nutrition. With advanced methods, it is now possible to study immunological responses in humans as well. As mentioned above, long-time surveys into the dietary intake of humans are complex. Hopefully, metabolic mechanisms in mammals are more unified along with the species than the more delicate immunological reactions. Therefore, metabolic exploration in animals might still give beneficial valid results.

Conclusion - changing from CIM to the energy balance model

Further research into bodyweight regulations might divert from the carbohydrate-insulin model to a more advanced energy balance model, as suggested by Speakman and Hall (1). They point out that insulin has a pleiotropic effect on multiple organs. Thus, the metabolic regulation of body fat is best understood as a 'dynamic network of factors' of our metabolism causing 'energy imbalance'.

It seems that our evolutionary past as hunter-gatherers makes us prone to a positive energy balance (21). Let's consider homo sapiens evolved about 200.000 years ago. The 'Neolithic'- or 'First Agricultural Revolution' goes back just only about ten to seven thousand years. Up to that time, living conditions were extremely harsh and food availability by no means assured. Even after man learned to harvest grains and raise livestock, hunger and starvation remained a common thread. Through evolution, our survival depended on our metabolic ability to accumulate and store energy and reuse it in times of need. Unfortunately, our metabolism hasn't adjusted to the current lifestyle, with abundant food availability and reduced physical activity. A more advanced model contrasting the one-sided carbohydrate-insulin model is necessary to explore the essence of the complex metabolic setup for the energy balance.

Literature

1. Speakman JR, Hall KD. Carbohydrates, insulin, and obesity. Science. 2021;372(6542):577-8.
2. Ludwig DS, Ebbeling CB. The Carbohydrate-Insulin Model of Obesity: Beyond "Calories In, Calories Out". JAMA Intern Med. 2018;178(8):1098-103.
3. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332(10):621-8.
4. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, et al. Obesity Pathogenesis: An Endocrine Society Scientific Statement. Endocr Rev. 2017;38(4):267-96.
5. Ludwig DS, Friedman MI. Increasing adiposity: consequence or cause of overeating? JAMA. 2014;311(21):2167-8.
6. Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health--a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. Am J Clin Nutr. 2008;87(1):258S-68S.
7. Chupanit P, Muktabhant B, Schelp FP. Dietary patterns and their association with the components of metabolic syndrome: A cross-sectional study of adults from northeast Thailand. F1000Res. 2018;7:905.
8. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 2015;31(1):1-13.
9. Hall KD, Guo J, Courville AB, Boring J, Brychta R, Chen KY, et al. Effect of a plant-based, low-fat diet versus an animal-based, ketogenic diet on ad libitum energy intake. Nat Med. 2021;27(2):344-53.
10. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, et al. Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial. JAMA. 2018;319(7):667-79.
11. Guo J, Robinson JL, Gardner CD, Hall KD. Objective versus Self-Reported Energy Intake Changes During Low-Carbohydrate and Low-Fat Diets. Obesity (Silver Spring). 2019;27(3):420-6.
12. Shimy KJ, Feldman HA, Klein GL, Bielak L, Ebbeling CB, Ludwig DS. Effects of Dietary Carbohydrate Content on Circulating Metabolic Fuel Availability in the Postprandial State. J Endocr Soc. 2020;4(7):bvaa062.

13. Hall KD, Bemis T, Brychta R, Chen KY, Courville A, Crayner EJ, et al. Calorie for Calorie, Dietary Fat Restriction Results in More Body Fat Loss than Carbohydrate Restriction in People with Obesity. Cell Metab. 2015;22(3):427-36.
14. Hall KD, Chen KY, Guo J, Lam YY, Leibel RL, Mayer LE, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. Am J Clin Nutr. 2016;104(2):324-33.
15. Hall KD, Guyenet SJ, Leibel RL. The Carbohydrate-Insulin Model of Obesity Is Difficult to Reconcile With Current Evidence. JAMA Intern Med. 2018;178(8):1103-5.
16. Howell S, Kones R. "Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories. Am J Physiol Endocrinol Metab. 2017;313(5):E608-E12.
17. Hu S, Wang L, Togo J, Yang D, Xu Y, Wu Y, et al. The carbohydrate-insulin model does not explain the impact of varying dietary macronutrients on the body weight and adiposity of mice. Mol Metab. 2020;32:27-43.
18. Speakman JR, Hu S, Togo J. Testing the carbohydrate insulin model in mice: Erroneous critique does not alter previous conclusion. Mol Metab. 2020;35:100961.
19. Hu S, Wang L, Yang D, Li L, Togo J, Wu Y, et al. Dietary Fat, but Not Protein or Carbohydrate, Regulates Energy Intake and Causes Adiposity in Mice. Cell Metab. 2018;28(3):415-31 e4.
20. Ludwig DS, Ebbeling CB, Bikman BT, Johnson JD. Testing the carbohydrate-insulin model in mice: The importance of distinguishing primary hyperinsulinemia from insulin resistance and metabolic dysfunction. Mol Metab. 2020;35:100960.
21. Pontzer H, Raichlen DA, Wood BM, Mabulla AZ, Racette SB, Marlowe FW. Hunter-gatherer energetics and human obesity. PLoS One. 2012;7(7):e40503.

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