

Features of diseases differ for women and men

Obesity, apple and pear, and the risk for heart diseases

Fat distribution and genomics are different for sexes

With a face of disgust, the girl shouted ‘carb’ as if a highly toxic nourishment was threatening her. She answered as one of a group of college students visiting Thailand, the host lecturer's question about important nutritional problems in the US. She did refer to one of the three macronutrients, carbohydrates, which provide most of the calories in food.

‘Carb’ and the carbohydrate-insulin model

Obesity is feared because of its hazard for type 2 diabetes mellitus, cardiovascular diseases, hypertension, and stroke (1). In the US, with the battle cry ‘processed carbs are problem carbs,’ low-fat and low-carb diets are heavily promoted in the fight against the worldwide problem (2). The initiative goes back to the carbohydrate-insulin model (CIM) (3). Basically, after a carbohydrate-rich meal, insulin decreases the glucose and lipids in the blood, and immediately after dinner or supper, one feels hungry again, continuing to eat and enhancing the already high-calorie intake even more.

A typical anti-carb diet is based on certain types of protein food, such as fish. Almost everything tasty, especially sweet food and drinks, is forbidden, together with bread and pasta (4). The college girl from the US learned with delight that carbohydrates with a high glycemic index (GI) are those that should be condemned, including sticky rice, the staple food of the Northeast of Thailand. For her, another telling example of her crusade against ‘carb’ is in connection with the high rate of overnutrition and obesity in Thailand. Conversely, the pros and cons of the CIM theory are extensively discussed, concluding that the diet is not without health risks and is not supported by recently advanced technology (5).

How it all started

Unfortunately, neither diets based on the CIM theory nor other forceful efforts helped to hamper the worldwide obesity pandemic (1). Assessing the history over time of overnutrition and related diseases, it all started after World War II (6). The Framingham Heart Study was one of the first attempts to evaluate the risk for the suddenly emerging high death rate for cardiovascular diseases (7), followed by renaming the Quetelet Index into Body Mass Index, and frustrating millions of overnourished and obese individuals with the ‘Weight Paradigm,’ because even achieving some weight reduction was only temporally successful. A revolting movement emerged with the slogan ‘You are not fat, you are beautiful’ and created the motion of ‘Health at Every Size’ to finally advocating ‘Metabolic Healthy Obesity’ (6). The magnitude of the problem can be universally elucidated as well as demonstrated in single countries such as Thailand.

Obesity, a burden for women

It was estimated globally that at the change of the century, 300 million adults were obese, while generally, males were more overweight and women suffered more from obesity (1). More recent estimation for Thailand found an overall age-standardized BMI of >30 for 15.4% among adults, with 6.5 % for males and 18.3% for females, supporting the notably higher risk for obesity in women (8). Contrary to adults, 27% of Thai children up to 17 years old are overweight or obese and boys are more affected than girls (9). Still, the sex ratio in children is reversed in a randomly selected study of 6,477 Thai elderly from 77 provinces nationwide. For both sexes together, almost 40% were obese, while the majority of women, with 43%, outnumbered the males, at 33.6% (10).

There are various reasons for the high prevalence of overnutrition and obesity. For instance, a logistic regression analysis of the Thai elderly study revealed that those most affected were aged 60 to 69, owned cable TV and mobile phones, lived in urban areas, and suffered from chronic diseases. The overall sedentary lifestyle poses a risk not only for the elderly. Although obesity is generally thought to be unhealthy, and those overnourished often feel or are discredited.

Losing weight and remaining slim is difficult

Body dissatisfaction with their weight is also common for those with normal weight. Yet, comparing normal-weight individuals with those who are obese, especially obese females, are unhappy about their appearance (11). Conscious of the slim contemporary beauty standards, young ladies fear not returning to their desired shape after pregnancy. It is well known that it is difficult to lose weight again. This problem is not limited to pregnancy. After succeeding in reducing weight, epigenetic mechanisms are at work to keep fat cells remembering their obesity status, working against the efforts to remain slim by easily starting to accumulate fat again (12).

Men follow females in gaining weight

The prevalence of overnutrition and obesity increases for females from middle age onwards into the time after menopause. Men might be indirectly affected. Their weight gain within the age range between twenty to thirty is due to 'one important influencing factor'... in reduction of exercise (13). A typical scenario might be that a freshly married husband cuts his formerly three to four visits a week to the sports club to keep the family atmosphere pleasant. Besides, the environmental factors mentioned above cannot be blamed as the only culprit for obesity.

Definitions and genomics

A very scholarly definition reads that 'human obesity is a heritable neurobehavioral disorder that is highly sensitive to environmental conditions (14).' A simpler all-encompassing expression refers to the nutritional status as an interaction of genes and environment. Advanced technical development in genomics laid open the increase of polygenetic influences in nutrition and metabolism, which by no means are easy to interpret (15).

BMI independent risk factor

For instance, after the initially conducted cohort studies, like the Framingham Study, concentrating on several biochemical indicators, which found their way as ‘metabolic syndrome’ into the literature, BMI was determined as an independent risk factor for heart failure (16, 17). There are twenty genes known to influence BMI (18, 19). Due to the polymorphism of the non-coding region, it is difficult to establish the action and precise mechanism of the phenotype (20, 21). Body weight, among other factors, depends on genetic variants regulating appetite and energy balance (22, 23). Variation most probably differs between sexes, which is not sufficiently clarified yet. Still, it has been found that variation exists between different geographical regions dependent on age groups as well (24, 25).

Body fat and adipocytes

The BMI as a measure of weight, to a great extent, depends on muscle mass and body fat depositions. In a healthy situation, the range of body fat for men is approximately 18-24%, which is higher for females at 25-31% (26). The difference in the location of fat deposition in the body contributes to women's attraction to men and men to women. More important for health and diseases is the active role of fat tissue in the overall control of homeostasis. The regulation of homeostasis is different between the sexes, and so are the risks for the health.

Body fat is stored as a tissue of fat cells, in histology named adipocytes. Generally, fat tissue for men is located in front of the stomach, addressed as visceral-, and for women, on the hips as subcutaneous fat. Because of the sex difference in the location of fat, the male apple and female pear shapes are known as android and gynoid fat distribution. White fatty tissue stores surplus energy. Fat tissue described as beige consists of small brown clusters of tissue mixed into white adipocytes. The brown adipose tissue generates heat and mobilizes lipids and glucose together with other metabolites. Visceral fat is stored in the abdomen and subcutaneous fat in things, arms, and the backside in the gynoid fat distribution (27-29). The survival of mankind throughout the often occurring periods of severe food shortage was possible because of the female's ability to store energy as fat, which is different from that of men (30).

Fat deposition in men and women

Males used to store energy within the visceral fat tissue in the abdomen, while in females, starting with the menarche, the pelvis widens and fat shifts from the abdomen to the ‘gluteofemoral’ regions of the buttocks, hips, and thighs (31). Compared with women of the same age and BMI, high visceral adipose tissue is more dangerous for men for metabolic cardiovascular risk factors. The fat in the lower extremities is more beneficial for females (32).

Mediterranean diet

Attention to the importance of fat as such and fat deposition was drawn by having a closer look on the Mediterranean diet (i.e. nutrition in the European countries such as Spain and Greece). The diet is rich in vegetables and fruits and contains unsaturated fat as ‘extra virgin olive oil’ combined often with a gynoid body shape (33, 34). The attention on fat increased in the field of genomics and science after it was determined that fat is an important player in the body's metabolism.

Females and the protective effect of estrogen

For communication with the organism, the adipocytes secrete extracellular vesicles (EV) containing signaling proteins, such as lipids, mRNA, and miRNAs, connecting to obesity-related diseases such as type 2 diabetes mellitus, cardiovascular diseases, and cancer (35). Females are spared from cardiovascular diseases to a certain extent through the protective role of estrogen (E2) and the receptors. ER α , ER β , and a G-protein-coupled ER (GPR30) (36), however, the total fat and body adiposity increase during menopause (37).

After menopause, females might also display visceral fat deposit

Obese women, particularly those in menopause, also tend to accumulate vascular adipose tissue (VAT), which poses a higher risk for cardiovascular diseases than for men, who are more in danger because of intramyocellular lipids (32). Menopausal lean women seem to have some advantage of protection by polymorphism in special immunogenetic systems related to systemic inflammation. For instance, lean women had a genotype FAM13A (rs1903003) that seemed beneficial to lean women. At the same time, the co-existence of other genetic variants (PPAR- γ 2 C1431C) occurred together with a higher BMI and higher systolic and diastolic blood pressure (38).

As mentioned previously concerning the genetic loci adiponectin, fat accumulated in overnutrition and obesity does not automatically mean one is at risk for cardiovascular diseases (6). The adiponectin system finds its 'exosome' way to the heart and skeletal muscle, where, together with another system called T-cadherin, it protects the vascular system against certain fat accumulations (39). For pharmaceuticals, such a system might be of interest for therapeutic protection against atherosclerosis.

Outline

Women assured mankind's survival over thousands of years in a hostile environment. Probably one of the oldest specimens of art, 30.000 years ago, 'symbolized an adult and faceless female with exaggerated genitalia, pronounced haunches, protruding belly, and heavy breasts, 'the well-known Venus of Willendorf (40). By emphasizing the female's shape, it seems our forefathers were quite sure which of the two specimens of mankind had to be worshiped. Still, about 6.000 years ago, female idols showed protruding fat accumulation around the hips (41). The ancient Greek and Roman female statues 'modernized' our understanding of female beauty (42).

Genomics now remind us about the importance of fat, through the adipocyte-derived EV signal system, and the role of the fat tissue in the metabolism of females, which is different from that of men due to the evolutionary forced task for females to assure the existence of humans. A short glimpse into the complex situation of how the metabolism of females is ruled by the genetic setting illustrates that genomics should not be neglected by curative medicine and public health in research and deciding for preventive measures.

The focus on the whole spectrum of diseases must consider the two sexes equally and be more aware of the particular female's situation. For instance, the research and work against the risk for heart disease concentrated on men with the misperception that women largely are not pursued by cardiovascular diseases. The truth is that these diseases develop seven to 10 years later compared to men and are a significant cause of death for women (43). In a following entry, relevant issues related to the diseases of the heart for curative medicine will be explored. As a first step of public health, working on a differentiated risk profile in the population, using anthropometric and biochemical parameters would be of benefit, particularly in combining the findings with those achieved in genomics. This would allow meaningful strategies for prevention instead of merely raising through taxes the price for sugar and salt to curb consumption.

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For comments and questions, please contact <awuso11@gmail.com>.