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Invited review

Iron metabolism in obesity: How interaction between homoeostatic mechanisms can interfere with their original purpose. Part II: Epidemiological and historic aspects of the iron/obesity interaction

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ABSTRACT

The change from a mainly vegetarian fare to meat consumption went along with brain growth and increased insulin resistance to improve brain's glucose supply. Meat consumption increased iron bioavailability and, thus, physical and mental fitness. The "predation-release-hypothesis" proposes that group coordination, arms and fire abolished the survival advantage of lean individuals from predation. The "thrifty gene-hypothesis", in contrast, proposes that surviving repeated episodes of starvation increased efficiency of food utilization in the offspring; they learned to utilize every available calorie. As a consequence of either mechanism, improved food security will increase prevalence of obesity along with that of its fatal consequences, such as diabetes, hypertension, heart diseases, and cancer. Thus, improved food security collides with the biologically evolved mechanisms to store excessive calories in preparation for a famine that never came. The crash between homoeostatic mechanisms and human intervention caused the presently observed pandemia of obesity and explains why it is so difficult to avoid, in spite of its well known and often fatal consequences.

Contents

Abbreviations: AT, adipose tissue; BMI, body mass index; BMP-6, bone morphogenetic protein 6; BMPR-II, bone morphogenetic protein receptor type II; CRP, C-reactive protein; DALY, disability-adjusted life year; DMT1, divalent metal transporter 1; ER, endoplasmic reticulum; HIF2-α, hypoxia-inducible factor 1, alpha subunit; H-ferritin, human ferritin; ICAM-1, intercellular adhesion molecule 1; IL-1, interleukin 1; IL-6, interleukin 6; IRP, iron regulatory protein; IRE, iron-responsive element; IRP/IRE system, iron regulatory protein/iron-responsive element system; Jak2/STAT3, Janus kinase 2/signal transducer and activator of transcription 3; L-ferritin, ferritin light chain; MCP-1, monocyte chemotactic protein 1; mRNA, messenger RNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; RES, reticulo-endothelial system; SMAD proteins, Sma and Mad related proteins; STAT3, signal transducer and activator of transcription 3; TfR1, transferrin receptor protein 1; TLR-4, toll-like receptor 4; TMPRSS6, transmembrane protease, serine 6; TNF-R1, tumor necrosis factor receptor superfamily, member 1A; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion protein 1.

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In the attempt to link the physiological interactions summed up in the first part of this review to public health observations we searched the literature for data (1) on the changing perception of obesity from prehistoric times to the present, (2) on the involvement of obesity and iron-deficiency in human evolution, and (3) on the emerging pandemic dimension of obesity.

Views on obesity from prehistoric times to the present: Small idols of obese women were carved from the dawn of mankind onward. The oldest artifacts found so far date back to our ancestor *Homo erectus* and were found in present-day Morocco (Venus of Tan-Tan) and in the Golan Heights (Venus of Berekhat Ram). They are estimated to date from 230,000–500,000 years ago. The "Hohle Fels Venus" (estimated age: 35,000 years) and the "Willendorf Venus" (22,000 years) were unearthed in Southern Germany. These two figurines carved in mammoth ivory still show the same features of excessive obesity as those from several 100,000 years earlier. Hunter-gatherer skeletons of corresponding age, in contrast, state good health and dietary status. These individuals died of accidents and trauma in early or middle adulthood. The interpretation has been given, therefore, that these obese figurines represent idealized symbols of high fertility and wealth rather than portraying a realistic account of contemporary nutritional status [1,2]. They may present the oldest reflection of the "obesity survival paradox", i.e. of higher survival chances in obese as compared to lean persons when confronted by life-threatening diseases, as demonstrated for pneumonia in a recent meta-analysis [3]. These figurines may present the personified ideal of abundant food supply, wealth and security. Such survival advantage was termed a "paradox", because obesity increases cardiovascular risk, and is related to a higher prevalence of premature death. Increased survival rates of obese individuals in severe diseases are attributable to larger metabolic reserves, which provide an edge to survive severe maladies. Accordingly, Hippocrates stated: "In severe maladies those who are fat do best" [4–6].

In traditional cultures, even at present days, "plumpness" is still considered an ideal of feminine beauty and a symbol of prestige [7]. In industrialized countries, in contrast, socio-economics state is negatively correlated with obesity [8]. Such negative connotations of obesity seem to be a very recent development related to a high degree of food security and to a perspective of a much longer routine average life expectance.

The evolution of obesity: The roots of the present-day pandemia of obesity reach back to a change in climate some 2 million years ago. The altered conditions forced our early ancestors to add more fish and meat to their mainly vegetarian fare. This, in turn, is assumed to have served as a supply bases for "encephalisation", i.e. for a "great leap forward" in brain growth. Proteins and long-chain polyunsaturated fatty acids serve as essential building blocks of neuronal tissue [9]. However, brain metabolism is fueled almost exclusively by glucose. Thus, the reduced dietary carbohydrate supply fostered the development of insulin-resistance to reduce the glucose drain from the circulation into tissue. This avoids hypoglycaemia and permits a steady supply of carbohydrates to the brain, the metabolic requirements of which are high. Human brains consume approx. 20% of total resting energy expenditure. In turn, increased brain capacity permitted to use fire for cooking, which increased food energy yield considerably [10].

Along with socially coordinated defense-strategies and with the development of tools and arms, the use of fire helped to keep predators at bay. The "predation-release-hypothesis" builds on such considerations [11]. It assumes genetic controls that keep bodyweight low to reduce the risk of predation, as fat individuals are an easier and more attractive pray. The use of arms and fire abolished the predator-related survival advantage of lean individuals. As a point in case, the bodyweight of "field voles" showed to be negatively correlated with the population density of weasels, which are their main predators. When the voles sense less predator feces in the area, they build up larger fat stores, which give them a survival advantage in winter [11].

The "thrifty-gene-hypothesis" [12], in contrast, assumes that a "founder generation" survived one or several episodes of starvation by exceptional efficiency in absorbing and utilizing food. The related genes are supposed to give their offspring an edge, if food supply should be compromised again. Low food security is likely to have been frequent in areas with seasonal variation in food availability. Neolithic agricultural revolution 10,000–12,000 years ago was a socio-economic landslide with carbohydrates becoming the predominant macronutrient again. It increased food security and allowed to balance seasonal variations by stocking food for the winter [13].

Under conditions of food security, the "thrifty" genes selected under condition of food scarcity no longer offer a survival advantage. In this situation, the affected population stores fat to prepare for a famine that never comes. The Nauru Islanders in the tropical Pacific seem a fit example to support the "thrifty-gene-hypothesis". This population shows the highest prevalence of type II diabetes world-wide (35–50%) [14]. This may be related to the survival of episodes of extreme famine that reduced the founder population during the long voyages across the Pacific. The survivors could utilize every available calorie, and there was rare mixing with other populations in the centuries thereafter. This genotype did not lead to manifest obesity and diabetes as long as calorie supply obtained by fishing and local agriculture was low. However, after 1954, when Nauru Islanders became affluent by selling the ample phosphate resources found on the island on the world fertilizer market, they could afford to consume an average of more that one pound of sugar per person per day and soon presented with a high prevalence of type II diabetes. Subsequently, the disease affected one-quarter of individuals in the age-group over 20 years, one third in those over 35 years of age, and up to 70% at an age over 70 years. These observations suggest a "thrifty gene" as underlying cause, leading to detrimental effects when meeting respective environmental conditions [14].

Impact of life style: Regarding type II diabetes some populations are more affected than others (Table 1) [14]. The lowest prevalence is found in rural Third World populations, and the highest in Nauru Islanders as mentioned above [15,16]. Another example is that of the Pima tribe of Amerindians in Arizona, USA, who also went through repeated episodes of famine, and evolved without admixture tribes outside of the Sonora desert [17]. The type II diabetes prevalence is also high on the South-Asian countries and among the Chinese, whereas it is comparably lower in Europeans. So, there seems to be a genetic component in the manifestation of type II diabetes that is superimposed upon lifestyle risk factors, such as high calorie intake and low exercise levels.

The prevalence of type II diabetes is 5–10 times higher in obese than in lean individuals, and symptoms can be reversed by exercise and dieting. Evidence for the impact of lifestyle comes from observations in a homogeneous Italian-American community in Pennsylvania, USA, known as "Rosetta Study". Examination of 3859 death certificates between 1935 and 1985 showed a significantly lower mortality from myocardial infarction than in a neighboring community with a typical American life-style during the first 30 years of that interval, i.e. up to 1965, although both communities had a common water supply and access to the same physicians and hospitals. Between 1955 and 1965 the traditional Italian cohesive family and community life with its typical social character, group dynamics and food attitudes eroded, death statistics increased and no longer showed any differences between both communities [18].

Another example for the impact of lifestyle comes from a drastic intervention-trial in 10 male middle-aged Australian aborigines with obesity and type II diabetes. These volunteers lived under