Editorial

Obesity, Fructose, and Uricemia

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The World Health Organization (WHO) has raised the alarm of "Globesity" due to the vertiginous worldwide growth of obesity, recognized as the number one health problem and defined as a chronic, progressive, and relapsing disease, often accompanied by underestimation, stigma, and blame, associated with more than 200 complications, including type 2 diabetes, cardiovascular diseases, cancers, and chronic liver and respiratory diseases. Italy, the first country in the world to do so, on October 1st, 2025, officially recognized obesity as a disease and established a national program for the prevention, treatment, and social inclusion of these very numerous patients. Indeed, according to the *Obesity and overweight* report of May 7th, 2025 by the WHO, in 2022 one in eight people worldwide lived with obesity; since 1990 obese adults have more than doubled and obese adolescents have quadrupled; 2.5 billion adults over 18 were overweight (43%) and 890 million (16%) obese; over 390 million children and adolescents aged 5–19 were overweight, and among these, 160 million were obese. These alarming figures are confirmed by the 2025 UNICEF report: worldwide, obesity affects 188 million children and adolescents; since 2000, obesity rates in children aged 5–19 have increased from 3% to 9.4%; one in five children and adolescents (391 million) is overweight; in Italy, 27% of those aged 5–19 are overweight and 10% are obese. Finally, according to ISTAT, in 2023 Italians aged 3–17 who are overweight or obese account for 26.7% (males 29.3%, females 24%); those aged 3–5 are 33.8% (continuously increasing over the last 6 years), those aged 6–10 are 32.5%, those aged 11–13 are 24.6%, and those aged 14–17 are 17.4%, with a modest but progressive reduction of overweight with increasing age, which would also show that the problem is not insurmountable. Obesity is a condition specific to *Homo sapiens* and to animals living alongside humans and therefore conditioned by them, but unknown in all wild animals living freely in nature. Excess weight is influenced by many factors, such as DNA, gut microbiome, some medications, poor sleep, stress, affordable healthy food, safe places for physical activity, and access to healthcare. For this reason, lifestyle changes are not always sufficient to produce lasting results that improve long-term health. Moreover, when a person reduces caloric intake to lose weight, the body may increase the production of hormones that regulate hunger and food cravings, triggering a vicious cycle. New drugs for type 2 diabetes, which inhibit appetite and are therefore also used for obesity, show that in 2024 there was an additional major increase in their use; according to the National Observatory on the Use of Medicines (OsMed 2025), total public expenditure reached 1.642 billion euros, an increase of 13.2% compared to 2023 due to both consumption (+4.3%) and the average cost per dose (+8.3%); in particular, for GLP-1 analogues, including semaglutide, an 11.5% increase in spending and a 13.3% increase in consumption were recorded, with semaglutide alone rising by 58.4% and 59.8%, respectively. According to the most accepted hypothesis to date, proposed in 1962 by geneticist James V. Neel, obesity is rooted in the so-called "thrifty genes," which were selected in Paleolithic hunter-gatherers to help them survive: the chances of hunting and returning to camp with the carcass of a large animal (bison, deer, etc.) were very slim, given that the only weapon available was the so-called javelin, a stick with a chipped stone tied to one end. Thus, two pillars: high daily physical activity with great energy expenditure, and frequent food scarcity, as even the gathering of wild plants by women provided low-calorie food; days of fasting or semi-fasting were far more common than days of abundant food, characterized by a single large meat feast, since it was not possible to preserve the meat for the following days. Thrifty genes would have favored the development of adipose tissue to store excess calories from the feast, providing a competitive advantage during periods of fasting. Today, however, these genes are useless or even harmful, since in our affluent industrialized society food is abundant and hypercaloric, and sedentary behavior is widespread (1). Until the development of agriculture, about 10–12 thousand years ago, meat and the proteins it contained were, in the collective unconscious, the fundamental food, a conviction that remained deeply rooted even among scholars, so much so that, as Tannahill R. reports in *Food in History* (Rizzoli 1987), Galen, one of the fathers of medicine, claimed that his father lived to be 100 years old because he had never eaten fruit. The *Rapporto Italia 2025* by Eurispes reveals that 52% of Italians have significantly increased their consumption of protein-rich foods, especially among those under 25 and those aged 25–34. However, the team of H. Pontzer, using the doubly labelled water method (deuterium and oxygen-18) and counting steps via a GPS device, measured daily energy expenditure and showed that the Hadza, who still live today as hunter-gatherers in Tanzania, walk more, explore more territory, follow more paths, with much greater physical activity, yet with daily energy expenditure almost equal to that of the average sedentary American, because at the same time the body reduces other energy costs, especially thermoregulation (2-5). After Pontzer reduced the importance of high energy expenditure, other research reevaluated the relevance of fasting and meat proteins. Indeed, fats were a vital component of hunter-gatherer diets, especially in winter months when animals were lean and meat alone was insufficient for sustenance. Neanderthals, hominins of the Upper Pleistocene, were already extracting fat from bones 125,000 years ago, and *Homo sapiens* at least 28,000 years ago, since marrow fat was a highly caloric nutrient source: bones were broken into small segments using stone hammers and boiled to extract the fat, which floated and could be collected after cooling. Moreover, Neanderthals probably ate fermented meat with a side of maggots, and the high $\delta^{15}N$ nitrogen levels found in them may have been inflated by the year-round consumption of maggots enriched in ^{15}N found in dried, frozen, or preserved animal foods; they were therefore able to preserve meat for subsequent days, avoiding alternation between feasts and fasting. Finally, our ancestors had learned to light and use fire to cook food and also consumed starchy foods based on roots and tubers, which clearly formed part of their diet from 120,000 to 65,000 years ago, in line with genetic studies showing modification of the human genome due to duplication of the AMY1 gene, coding for amylase, the enzyme needed for starch digestion. At a Middle Eastern hunter-gatherer site, ancient remains of bread dating to about 14,000 years ago—before the spread of agriculture—have been found (6-8). Thus, to understand the dietary habits of our ancestors, we must go much further back in time, about 26 million years ago, when the first apes evolved, probably in East Africa: they had large bodies, no tail, larger skulls and brains, walked on four limbs, lived in trees, and fed on fruit in the tropical African rainforests. About 21 million years ago, Africa merged with Eurasia, and apes, along with giraffes, elephants, and antelopes, left Africa; however, about 16.5 million years ago, because of global climate cooling, they began to suffer winter hunger due to fruit scarcity and turned to tubers and roots. About 7 million years ago, some apes migrated to Asia, becoming the ancestors of gibbons and orangutans, while others returned to Africa, evolving into the African great apes (gorillas, chimpanzees, and bonobos) and later into *Homo sapiens*. *Homo sapiens*, chimpanzees, and gorillas share a mutation that improves alcohol dehydrogenase (ADH4), crucial for ethanol metabolism, linked to the long-standing habit, over 10 million years old, of some primates feeding on fallen fermented fruit containing ethanol. Gorillas and chimpanzees still eat fallen fruit today, in 25–62% of fruit-feeding episodes, whereas orangutans do not and lack the genetic mutation for efficient alcohol metabolism. But in the African species, another, even more significant genetic mutation occurred: the loss of uricase, the enzyme that converts uric acid into allantoin, leading to increased uric acid levels in the blood. Uric acid is a natural antioxidant present in our blood, along with vitamins C and E, and the mutation may have compensated for the loss of vitamin C synthesis. The rise in uricemia was accentuated by the consumption of honey and bee larvae, which provided significant amounts of energy, complementing meat and plants, for brain development (9). Honey is a substance produced by bees from flower nectar, composed of 20% water and 76% sugars (fructose 41%, glucose 33%, sucrose 1.1%, maltose 1.1%, isomaltose 1.1%); it provides 2.85 Kcal/g and has a sweetening power of 1.73; it also contains enzymes and, in small amounts, vitamins and minerals. A prehistoric cave painting from 8,000–10,000 years ago, found in the Cuevas de la Araña (Spider Cave) in Valencia, depicts the earliest known evidence of honey gathering, showing a brave individual, naked, climbing a cliff with a rope ladder to gather honey from a hive despite the danger of furious bee stings. The Sumerians already recognized its value as a natural remedy, the Egyptians used it for food preservation, and the Greeks and Romans appreciated it as a sweetener. Today, honey continues to hold an important place not only in nutrition but also as a home remedy ("grandmother's remedies") for upper respiratory tract symptoms linked to colds, sore throats, and coughs, especially during colder months, thanks to its flavonoids (quercetin, luteolin, chrysin, rutin, catechin, apigenin, kaempferol) and phenolic acids (caffeic, ferulic, cinnamic, gallic acids, anthocyanins, carotenoids, tannins, and many others) derived from plants, varying according to botanical and geographical origin, climatic conditions, and even storage methods. However, its high fructose content also promotes increased fasting blood glucose, triglycerides, LDL cholesterol, and reduced HDL cholesterol. Moreover, excess uric acid may precipitate in tissues, forming crystals that cause gout or kidney stones (10-17). Humans and African apes had only a moderate increase in uricemia, because on one hand they could excrete uric acid in urine rather quickly, and on the other, their ancestral lifestyle did not promote excessive increases, as is still the case today in African apes and in human ethnic groups that have maintained these traditional behaviors. In contrast, in societies with Western diets and sedentary habits, uricemia levels are rising sharply: at pH 7.4 and 37°C, hyperuricemia is commonly defined as ≥7 mg/dL in men and ≥6.0 mg/dL in women; the prevalence of gout in Italy increased from 8.5% in 2005 to 11.9% in 2009 (18). This increase predisposes to obesity, diabetes, dyslipidemia, metabolic syndrome, cardiovascular risk (MI and stroke), cancers, and nephropathy in type 2 diabetes, making it absolutely necessary to limit fructose consumption. One of the main contributors to rising uricemia is the consumption of soft drinks, typical of modern societies. Also because, according to the Higher Institute of Health, only 17% of Italians can identify sugar sources on labels. A NutriNet-Santé study involving 101,257 French adults (79% women), who over about a decade answered questionnaires on their dietary habits, found that sugary drink consumption is positively associated with the risk of all cancers and in particular breast cancer (19). Moreover, uric acid, thanks to its antioxidant action, plays an endogenous neuroprotective role against neurological diseases, such as Parkinson's disease, cognitive decline, and Alzheimer's, and a highly significant positive correlation has been demonstrated between IQ and uricemia. Emotional aspects, impulsivity, and curiosity are associated with higher uricemia levels: even genetically modified mice with high uricemia become more exploratory and enterprising. Higher uricemia levels have been recorded in individuals in the superior and gifted categories compared with normal or borderline IQ subjects; members of MENSA, the association of individuals reaching or exceeding the 98th percentile of global IQ distribution, have a high prevalence of hyperuricemia and gout. Many illustrious historical figures suffered from gout, including military leaders and rulers such as Alexander the Great, Caesar, Augustus, Charlemagne, Lorenzo the Magnificent and the Medici, Henry VIII, Andrea Doria, the Bourbons, Luther, Cromwell, Horatio Nelson, Napoleon. Popes such as Pius III, Julius II, Clement VII. Artists and intellectuals such as Horace, Ovid, Martial, Michelangelo, Leonardo, Rubens, Vittorio Alfieri, Goethe, Kant, and Calvin. Scientists such as Newton, Franklin, Linnaeus, and Darwin (20-31). The apparent paradox of a simultaneously positive and negative effect is explained by the fact that antioxidant compounds can become pro-oxidants under certain conditions and especially at levels above normal. Therefore, it is absolutely necessary to reduce the daily amount of fructose consumed through carbonated and/or sweetened beverages, sweet or salty snacks (32). To this end, an analysis of 58 studies including over one million adults, adolescents, and children, lasting about one year, conducted in schools, shops, or restaurants, found "moderately certain" to "weak" evidence supporting a series of measures to adopt. Among these: easy-to-understand labels classifying how healthy beverages are, restrictions on the availability of sugary drinks in schools, price increases for sugary carbonated drinks in restaurants, shops, and leisure centers, the availability of healthier beverages on children's menus, and the promotion of healthier drinks in supermarkets (33). A study on the Amoris Cohort conducted on 800,000 Swedes over 35 years found that the 1,224 individuals who became centenarians had higher blood levels of cholesterol and iron and lower levels of uric acid, glucose, creatinine, and liver enzymes (34). Therefore, it is no surprise that I do not agree with the conclusions of the American Heart Association, which excluded uricemia from the important factors for maintaining cardiovascular health across the lifetime, considering only physical activity, diet, body weight, cholesterol, blood sugar, blood pressure, and smoking habits (*Life's Simple 7*) (35).

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