Did The Captain only have gout?

Intake of fructose, but not glucose, stimulates purine metabolism and the production of uric acid, and increases production of lipids in the liver. The uric acid level may have a larger effect on the development of cardiovascular disease than previously assumed. The use of fructose as a sweetener in processed foods has increased strongly.

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The comic strip «The Katzenjammer Kids», featuring «The Captain» among other characters, was created by the American artist Rudolph Dirks (1877–1968). The strip was launched in the Sunday magazine The New York Journal in 1897, and is the oldest comic strip still in circulation.

Why was The Captain overweight and suffering from gout? In the 19th century, prominent physicians claimed that gout was associated with uric acid in the blood (1), and that uric acid could be one of several causes of hypertension (2). Could this knowledge be at the basis of the portrayal of The Captain? This notwithstanding, international therapeutic guidelines do not describe uric acid as a risk factor of causal importance for cardiovascular disease (3).

Uric acid – in retrospect

The correlation between high levels of uric acid and cardiovascular disease, especially in the context of hypertension and metabolic syndrome, has been known for many years, but high concentrations of uric acid have been regarded as a secondary phenomenon with no causal effect. Many who have high, but asymptomatic, levels of uric acid also have hypertension, overweight, metabolic syndrome, renal disease and cardiovascular disease. More than 70% of those who suffer from gout are overweight, more than 50% have hypertension, nearly all have renal failure and approximately 90% of them develop cardiovascular disease, of which this proves fatal for 20% (4, 5).

Approximately 15 million years ago, one of our ancestors developed a mutation in the gene for urokinase, an enzyme in the liver that splits uric acid to allantoin as an end product. Humans and the large primates, such as chimpanzees and gorillas, have a higher level of uric acid in their blood than less highly developed mammals. Humans have a reduced ability to regulate the concentration of uric acid apart from by renal excretion (6, 7).

Glucose and fructose – in retrospect

The cultivation of sugarcane for production of cane sugar first started in New Guinea and India. Cane sugar came to Venice and other European ports in the Middle Ages. Christopher Columbus took sugar to Haiti and the New World in 1493. Through the 18th century, the production of sugar from sugar beets increased strongly. From both these plants we can extract sucrose, a disaccharide consisting of equal parts glucose and fructose, which is used as table sugar in ordinary households. Later, when a method was found to process starch into glucose (corn syrup), the consumption of sugar from sugar beets increased strongly. From both these plants we can extract sucrose, a disaccharide consisting of equal parts glucose and fructose, which is used as table sugar in ordinary households. Later, when a method was found to process starch into glucose (corn syrup), the consumption of sugar from sugar beets increased strongly. From both these plants we can extract sucrose, a disaccharide consisting of equal parts glucose and fructose, which is used as table sugar in ordinary households.

In 1870, a Japanese research team succeeded in turning starch into glucose and more than 50% fructose (high fructose corn syrup, HFCS) (8). This represented a breakthrough for the addition of sugar to processed foods, and accounts for most of the daily intake of fructose in the US (9). Compared to glucose, fructose is sweeter, cheaper, more soluble at low temperatures and more stable. Fruit sugar is currently the most frequently used natural sweetener in foods and beverages, and accounts for more than 40% of all caloric sweeteners added to processed foods and beverages. In the period from 1970 to 1990, the consumption of HFCS increased by more than one thousand per cent, which is considerably more than the change in the intake of other foods (10). In industrialized countries there is a correlation between an increased intake of fruit sugar and increased prevalence of hypertension, obesity, metabolic syndrome, diabetes, renal failure and cardiovascular disease (9). Fruits, and especially vegetables, account for a very minor proportion of the daily intake of fruit sugar.

Metabolizing fructose

In Norway, fructose as a foodstuff has not been examined by The Norwegian Food Safety Authority. The amount of fructose in Norwegian foodstuffs is not declared, nor is there any obligation to do so. Some nutritionists have recommended that glucose should be replaced by fructose, since fructose is considered not to stimulate the production of insulin and has a lower «glycemic index», leading to less obesity.

Fructose is absorbed unchanged in the small intestine, 50% is metabolized in the liver, and the rest is absorbed by the kidneys and adipose tissue. Its intracellular transport takes place via the transport proteins GLUT-2 and GLUT-5. Both of these proteins are found in endothelial cells and renal tubular cells, especially in the proximal tubular cells. Fructose can be phosphorylated via hexokinase, but is displaced by glucose, which has preference. Phosphorylation is therefore effected via ketohexokinase (fructokinase). Fructose bypasses all the glycolytic control points. The passage via ketohexokinase has no negative feedback mechanism, and fructose is phosphorylated until all adenosine triphosphate (ATP) has been used up. As a reserve solution, the enzymes in purine metabolism (xanthine oxidoreductase) are activated, resulting in an increased production of the end product, uric acid (11).

Uric acid is an intracellular oxidant, it inhibits the production of nitric oxide and stimulates the monocyte chemotactic protein (MCP-1), a proinflammatory protein that causes development of renal fibrosis (12). In other words, the metabolization of fructose is not restricted by available ATP. Fructose affects proteins (protein-1c) that are involved in the regulation of the genetic expression of hepatic lipogenesis (13). It has also been proved that fructose stimulates endothelial inflammatory processes via an intercellular adhesion molecule.
(ICAM-1) and inhibits the production of endothelial nitric oxide synthase (14).

**Fructose and metabolic syndrome, hypertension and renal disease**

In animal studies, an intake of fructose over four weeks as compared with intake of glucose, results in heightened levels of uric acid in the blood, reduced urinary excretion of uric acid, heightened levels of triglycerides, heightened fasting insulin levels, increased production of insulin after a glucose tolerance test and a lowered insulin sensitivity index. All these differences even out after intake of the xanthine oxidase inhibitor allopurinol (15). Intake of fructose results in a significantly accelerated progression of chronic renal failure, enlarged kidneys, glomerular hypertrophy with focal segmental sclerosis and increased interstitial fibrosis when compared with glucose (16).

Increased peripheral insulin resistance can be explained as an effect of uric acid and/or fructose inhibiting the production of nitric oxide, thereby causing reduced peripheral circulation. Stimulation of the production of MCP-1 and ICAM-1 can explain the renal effect.

Glucose tolerance tests undertaken on adult, overweight persons following nine weeks of treatment with equivalent quantities of glucose or fructose show significantly higher values of glucose and insulin after preceding intake of fructose compared with glucose. The same applies to de novo lipogenesis in the liver and visceral adiposity (13).

In a follow-up study of 46 000 men over 12 years, with self-reported nutritional case history, it was found that intake of sugared beverages and fructose, including fruits and fruit juices with a high fructose content, was strongly associated with an increased risk of gout (17). A cross sectional study from the US showed that a daily intake of ≥ 75 grams of fructose is independently associated with elevated blood pressure in adults (18). In a controlled intervention study, adult men were given 200 grams of fructose for 14 days, with or without added allopurinol. Both groups developed findings that were consistent with metabolic syndrome, and allopurinol was shown to have a clear effect in reducing blood pressure (19).

**Uric acid and cardiovascular risk**

In animal experiments there is a linear association between the concentration of uric acid and acetylcholine-induced vasodilation (15). The same can be seen in healthy adults who have normal levels of uric acid (20). In adults who have untreated, uncomplicated hypertension, the concentration of uric acid is independently and more strongly associated with endothelial dysfunction than what is the case for systolic blood pressure and hyperlipidemia (21).

Several studies have been undertaken to reveal causal correlations of clinical importance between uric acid, endothelial function and disease (22–24). In a study of 78 children aged 8–13, those who had a birthweight < 2 500 grams also had elevated levels of uric acid, poorer endothelial function and higher systolic blood pressure than those with a birthweight > 3 000 grams (24). In a retrospective analysis of 125 persons aged 6–18 who had been referred for hypertension, the children with essential hypertension had a lower birthweight. A linear association was found between blood pressure levels and uric acid levels in persons with a normal as well as an elevated blood pressure (23).

A reduction of the uric acid level with the aid of allopurinol resulted in lowered blood pressure. The hypothesis of the effect of a low number of nephrons in the context of low birthweight was discussed.
A cross sectional study of 1,370 boys and girls aged 12–17 discovered a linear association between quartiles of uric acid levels and metabolic syndrome, and between uric acid levels and the number of components of metabolic syndrome (25). Two recent studies revealed that, after nine months, allopurinol reduced left-ventricle hypertrophy and endothelial dysfunction in patients with chronic renal failure (Kao and associates, European Renal Association-European Dialysis and Transplant Association Congress, 27 June 2010), and improved coronary hypoxia after six weeks, assessed on the basis of electrocardiography and the occurrence of chest pain (26).

## Uric acid and renal risk

In several large follow-up studies involving thousands of participants, the initial concentration of uric acid constituted an independent risk factor for newly acquired renal failure (27, 28). In a controlled intervention study over 12 months, the progression of renal failure among persons with hyperuricaemia was significantly slower compared with the control group when allopurinol was administered (29).

### Intake of fructose

Animal experiments and clinical studies send a warning that fructose has negative effects on cardiovascular health. The clinical significance of this finding has not been clarified. Intake of > 74 grams of fructose has been shown to be independently associated with higher blood pressure (18). A meta-analysis of 14 randomized and non-randomized studies, in which fructose replaced sucrose, glucose and starch, showed uncertain differences in fasting HbA1c and triglyceride values (30). The authors concluded that compared with starch, a daily intake of > 100 grams of fructose is unfortunate (daily fructose intake among adult US citizens can reach 150 grams). The studies differ, and the results are hard to interpret.

### Conclusion

Scientific studies indicate that we should intensify the public scrutiny of nutritionally unfortunate consequences of a high intake of fructose, especially when used as a sweeter in processed foods and beverages. Compared to glucose, fructose is «a double-edged sword», which stimulates the production of lipids as well as uric acid. Children and adolescents are most at risk.

The Captain in «The Katzenjammer Kids» suffered from gout, a clinical consequence of elevated uric acid levels and an indication for intervention. Furthermore, the Captain was also at a considerably higher risk of developing metabolic syndrome, cardiovascular disease and chronic renal failure, for which uric acid may have a causal effect. Preventive treatment seeking to reduce his levels of uric acid should have been initiated.

### Reported conflicts of interest: None

## References


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