Editorial

Does intake of sugarless carbonated water at physical activity cause type 2 diabetes?

Besides being middle-aged or older several other factors have been shown to be associated with the occurrence of type 2 diabetes mellitus (T2D), two of them include being overweight (Ohlson et al. 1988, Chan et al. 1994) and having hypertension (Wei et al. 2011). Additionally, the consumption of diet soda (Nettleton et al. 2009), sugar-sweetened beverages (Malik et al. 2010), low magnesium intake (Dong et al. 2011) and exposure to environmental pollution (Andersen et al. 2012) are external factors that have been found to more or less relate to the incidence of T2D. In the last decades, certain molecular genetic characteristics have been discovered to have a role, and various opinions on their significance for the risk of T2D have been put forward (Lyssenko et al. 2008, McCarthy 2010, Ahlqvist et al. 2011). In accordance with results of some groups of researchers, one more idea is proposed and considered here to try to indicate a causal origin of cases of T2D.

Early observations

After having found the local CO$_2$ tension to affect the degree of the bronchiolar dilatation, an action of CO$_2$ that is one of the halves of the ventilation–perfusion coupling (Nisell 1950, 1951, 2011a,b), the idea occurred that other physiological functions of the body may react to changes in the regional concentration of CO$_2$. Pure CO$_2$ gas administered into a duodenal tube inserted through the nose to the stomach increased the ventilation magnitude, heart rate and oxygen uptake of the subjects (Landin et al. 1966).

An intriguing question was whether the CO$_2$ tension had a bearing on carbohydrate metabolism. In the 1950s and 1960s, personal observations were made of a number of middle-aged and older persons and patients afflicted with diabetes mellitus. Most of them were in the habit of drinking carbonated mineral water often, something they had done earlier, too, before showing symptoms of diabetes and having been diagnosed with the disease. Might drinking the carbonated water, heightening the CO$_2$ concentration of the portal vein blood, have been of importance to the appearance of their diabetes? Administering CO$_2$ gas to the stomach increases the CO$_2$ tension of the pulmonary artery blood (Landin et al. 1966, fig. 4). This increase comes from the blood flowing through the hepatic veins, indicating a still higher rise of the CO$_2$ tension of the blood of the portal vein and the liver.

Longmore et al. (1969) found in the isolated rat liver an elevated CO$_2$ concentration to increase the synthesis of glycogen from glucose. If CO$_2$ has a similar effect in the human liver, an elevated CO$_2$ tension of the portal vein blood might lower the sugar levels of a glucose tolerance test below the levels they otherwise would have. When performing oral glucose tolerance tests with and without CO$_2$ gas administered to the stomach, no uniform effect could be ascribed to CO$_2$ (Nisell 1957), although in some reproduced curves of the study, the blood sugar levels are lower with CO$_2$ gas administered than without that gas. During the tests, the subjects’ recumbent position and the gas volumes administered appeared to affect the gastroenteral absorption of glucose, which possibly disguised a glycaemic effect of CO$_2$. An imaginable influence of the elevated hepatic CO$_2$ tension on the glucose levels of a test might perhaps have been revealed if the intravenous tolerance test had been used, or if the subjects had been sitting during the oral test.

Blood sugar reactions at an elevated hepatic CO$_2$ tension

The results of Longmore et al. (1969) regarding the effects of CO$_2$ on the carbohydrate metabolism of the isolated rat liver suggest that CO$_2$ may hinder glyco- genolysis. According to their results, an elevated CO$_2$ concentration of the blood perfusing the rat liver increased the conversion of glucose and glycerol to glycogen. Consequently, this means, if applicable at appropriate tension levels, that a higher tension of CO$_2$ will make the reverse biochemical reaction, a hepatic breakdown of glycogen to glucose, more difficult to occur than a lower tension will do. Such an effect of CO$_2$ is included in a personal hypothesis arrived at in the middle of the 1960s, indicating a possible origin of the appearance of cases of T2D.

The need to supply the muscles with glucose increases at physical activity. Part of or most of this glucose supply is normally obtained from a breakdown of liver glycogen, and the blood sugar concentration will, with the help of this process, be kept at an ordinary level. If only little glucose would be formed from the glycogen of the liver, because the breakdown of glycogen would be hindered and glucose generated too slowly, an increased glucose
absorption of the muscles is likely to cause the blood sugar level to become abnormally low. This might happen at physical activity when an elevated local tension of CO\textsubscript{2} obstructs a glucose production from the glycogen of the liver as the hypothesis proposes and also is concluded from the observations of Longmore et al. (1969). If this is the case, the resulting hypoglycaemia should stimulate glucosensors, including one localized to the portal vein existing in the rat and dog and suggestively in man (Hevener et al. 1997, 2001). The glucosensors will initiate a homeostatic response and increase the low blood sugar concentration to a higher level.

Occurrences of this kind would happen when an individual during bodily activity drinks carbonated water with no sugar, increasing the CO\textsubscript{2} tension of the upper gastro-intestinal tract and that of the portal vein blood. The elevated CO\textsubscript{2} tension then coming to pass in the liver supposedly impedes glycogen from breaking down to glucose which together with a physical activity will induce hypoglycaemia. The difficulty in this case to satisfy the supply of glucose to the muscles is no hinder for exercise or its usefulness other times.

The glucosensor counterregulation of the low blood sugar will increase glucose production. But the blood sugar increase needed cannot take place in the ordinary manner, as the occurrent elevated CO\textsubscript{2} tension opposes the normal breakdown of glycogen to glucose in the liver. The blood sugar increase must therefore be accomplished in another and abnormal way. These reactions come probably to pass in the liver and will have the characteristic of being able to function at the elevated CO\textsubscript{2} tension. The glucosensor response will thus initiate an abnormal kind of glucose production, perhaps hard to regulate. That may lead to a hyperglycaemia which, if the reaction happens often, may be lasting as T2D.

This clinical result of the hypothesis corresponds with that of the study of Nettleton et al. (2009) based on 6814 adults, followed during a period of seven years. In that piece of work daily consumers of ‘diet soft drinks, unsweetened mineral water’ (diet soda), containing CO\textsubscript{2} but no sugar, were found to have a significantly elevated risk of T2D compared with non-consumers.

**Sugar intake counteracts risk of T2D at an elevated hepatic CO\textsubscript{2} tension**

If the carbonated water ingested contains sugar, the risk of T2D should vanish. The absorbed glucose increases the sugar concentration of the portal vein blood, and this happens despite a physical activity and despite the absorbed CO\textsubscript{2} hindering hepatic glycogenolysis. Local hypoglycaemia does not occur, and the portal vein glucosensor (Hevener et al. 1997, 2001) is not stimulated to raise the blood sugar level. The sugar intake will provide with the glucose that the working muscles utilize when the CO\textsubscript{2} from the carbonated water hinders the glycogenolysis of the liver. Hypoglycaemia is not brought about, nor a glucosensor response and an abnormal glucose production with T2D will not follow. Although an increased local CO\textsubscript{2} tension impedes the hepatic breakdown of glycogen to glucose, the risk of T2D should disappear when enough sugar is an ingredient of carbonated drinks. Similarly, carbohydrates in food ingested with or not long before the carbonated water should protect from the risk of T2D.

The work of Nettleton et al. (2009) confirms a preventive effect of a sugar intake. Their data had no significant association between sugar-sweetened soda consumption and risk of T2D. Sugar-sweetened soda included ‘regular soft drinks, soda, sweetened mineral water (not diet) and nonalcoholic beer’. Paynter et al. (2006), too, found the incidence of T2D to show no consistent association with a sweetened beverage (sugar-sweetened soft drinks) consumption.

Some consumers change between diet soda and sugar-sweetened soda. They should be excluded as subjects if the relation of the risk of T2D to a sugar-sweetened soda intake is to be investigated. An intake of diet soda of such consumers could cause cases of T2D, making the result of a study ambiguous. There may be studies of the risk of T2D at a consumption of sugar-sweetened beverages when diet soda also happened to be consumed that caused cases of T2D, confounding the outcome of the study.

As described above, Nettleton et al. (2009) found the intake of diet soda but not that of sugar-sweetened beverages to be associated with an elevated risk of T2D, but the causes behind were difficult to explain. The hypothesis put forward here offers plausible reasons for the different effects of the two kinds of liquid intake. The power of the hypothesis to do this sustains its validity.

**Conclusions**

The idea presented suggests that a carbonated water intake elevating the CO\textsubscript{2} tension of the portal vein blood hinders the glycogenolysis of the liver. This together with simultaneous physical activity would cause a hypoglycaemia, supposedly bringing about a glucosensor response that leads to an abnormal glucose production and risk of T2D. A concurrent sugar intake will prevent from a hypoglycaemia and a glucosensor response with the consequence that hyperglycaemia and T2D do not follow. At least four studies agree with parts of the propositions. In that of Long-
more et al. (1969), a CO2 increase of the portal vein blood of the isolated perfused rat liver raised the conversion of glucose to glycogen. The work of Hevener et al. (1997, 2001) demonstrated a portal vein glucosensor locus responsive to hypoglycaemia in the rat and dog. Nettleton et al. (2009) noted consumers of diet soda to have a significantly elevated risk of T2D compared with nonconsumers. They did not find the risk of T2D to differ between nonconsumers and consumers of sugar-sweetened soda, confirming a corresponding observation by Paynter et al. (2006).

An answer to the title question calls for research, resulting in relevant information. Studies ought to either reject or corroborate and complete the hypothesis. The idea might be tested in animals, fed once or either reject or corroborate and complete the hypothesis. Studies ought to respond by Paynter et al. (2006).

Conflict of interest
There is no conflict of interest.

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References


