EFFECT OF FLUORIDE INTAKE ON CARBOHYDRATE METABOLISM, GLUCOSE TOLERANCE, AND INSULIN SIGNALING

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SUMMARY: Fluoride is known to cause both local and systemic alterations in animals and humans, such as dental fluorosis and disturbances in glucose homeostasis. The effects of fluoride are dose dependent and can produce decreased insulin secretion, inhibition of glycolysis, glycogen depletion, hyperglycemia, and insulin resistance. Because excessive ingestion of fluoride during tooth brushing can lead to deterioration in health, the use of low-fluoride dentifrices is recommended for young children with diabetes.

Keywords: Childhood diabetes; Diabetes mellitus; Glucose homeostasis; Hyperglycemia; Insulin resistance; Low-fluoride dentifrices.

INTRODUCTION

In the USA and elsewhere, the incidence of diabetes mellitus (DM) has reached epidemic proportions with further increase continuing.[1] Micro- and macrovascular complications of diabetes are a major threat to health worldwide, with huge economic and social costs.[2,3] In diabetes, the main cause of microcirculatory damage is the consequence of non-enzymatic glycosylation of proteins, which is the consequence of high extracellular glucose levels. This damage may be reversible with restoration of normoglycemia, or may be irreversible due to cumulative changes in long-lived molecules.[4] Hyperglycemia may occur during acute or prolonged treatment with high doses of NaF.[5-9] This finding indicates that glucose homeostasis is affected by fluoride (F). Moreover, the observed changes in glucose levels are similar to those seen in DM. Since F has been used in various ways to prevent dental caries and, in the form of fluoridated dentifrices in combination with fluoridation of public water supplies, it has been widely credited for observed declines in dental caries incidence.[10] However, the use of fluoridated dentifrices alone exposes some children to F levels above the recommended safe dose limit.[11,12] Moreover, F is present in significant amounts in foods that are greatly enjoyed by children, such as chocolate bars, cookies,[13] breakfast cereals, and snacks.[14]

This review presents a brief discussion of DM and analyzes the effects of F intake on carbohydrate metabolism, glucose tolerance, and insulin signaling.

DIABETES MELLITUS AND PUBLIC HEALTH

Diabetes mellitus is a growing public health problem that is also very costly in economic terms, while it also has recognized potential for prevention.[3] Diabetes is a chronic disease that is caused by a deficiency of the pancreas to produce insulin or by an inability of insulin to exercise its functions.[15] There are two main types of diabetes: type 1 diabetes (DM1) and type 2 diabetes (DM2). In DM1, the pancreas

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does not produce the amount of insulin essential for survival. This type of diabetes occurs most often in children and adolescents, but can also occur in older people.[15] In contrast, DM2 results from the inability of the body to respond adequately to insulin produced by the pancreas. This type of diabetes occurs more frequently in adults, but is being seen increasingly in children and adolescents.[15] Insulin resistance in the tissues and elevated levels of fasting plasma insulin are alterations that are quite frequent in persons who are obese and are often the first signs of the development of DM2. This type of diabetes contributes to >30% of new cases of DM, a finding that indicates a possible relationship between the increasing prevalence of childhood obesity and the development of DM2.[16] In childhood, insulin resistance associated with hyperinsulinemia is a major risk factor for the development of decreased glucose tolerance in obese children.[17] Since diabetes causes changes in the metabolism of lipids and carbohydrates, it is important to consider environmental factors such as F that can interfere with the metabolism of lipids and carbohydrates.[5-9,18-20]

CONSUMPTION OF FLUORIDE

F is readily absorbed through the lining of the stomach and small intestine and is absorbed faster on an empty stomach than with the intake of food containing elements like calcium and magnesium, and also aluminum, which, as polyvalent cations, can reduce F absorption through their high affinity for F.[21,22] However, when the ratio of F to Al is high, absorption of Al is increased, as seen in a study in rats.[23] When ingested, F enters the bloodstream by diffusion (intestinal absorption) and in the form of hydrogen fluoride (HF) by passive diffusion (gastrointestinal absorption).[24] Although there are reports that support the theory that gastrointestinal absorption of F is a passive process, there is also evidence that it involves active diffusion, especially at high doses.[25] Most of the absorbed F is taken up by calcified tissues or is excreted in urine.[26] The percentage of F excreted relative to the amount ingested or absorbed depends on the age of the individual, with children absorbing more F than adults.[27]

Along with the widespread use of F-containing dental care products in recent decades, the prevalence of dental caries has generally decreased in industrialized and developing countries.[10] However, an increased prevalence of dental fluorosis has been concurrently reported owing to excess F intake from various sources during the critical period of permanent tooth formation (11 months to 7 years of life).[28,29] Dentifrices are an important source of exposure to F,[30] and F intake from fluoridated dentifrices can vary from 14% to 98% (in children aged 2–3 years) and from 0% to 76% (in children aged 4–7 years) of the amount applied onto the toothbrush.[11,12] Increased fluoridation of public water supply and widespread use of fluoridated dentifrices help explain the increasing prevalence of dental fluorosis.[31] Thus, it is important to know the appropriate dosage of F that will be associated with a maximum reduction of caries with minimal risk of dental fluorosis.[30] Currently, the recommended limit of F intake to avoid dental fluorosis is approximately 0.05 to 0.07 mg F/kg bw/ day.[32] Studies performed in children aged 20 to 30 months showed that F in toothpastes contributes approximately 55%

of the total daily exposure to F. According to these studies, children are exposed to an average of 0.052 mg F/kg bw/day through dentifrice, thus approaching the recommended dosage limit. However, some children are exposed to excessively high doses of F (0.185 mg F/kg bw/day), resulting from ingestion of up to 90% of the dentifrice placed on the toothbrush.[12] Pessan et al.[11] observed that, in children aged 4 to 7 years, the dentifrice is the main source of F intake, which reaches as high as 57% of the total daily F ingested or an average of 0.037 mg F/kg bw/day. In some cases, F intake reached 0.155 mg F/kg bw/day, just through toothbrushing with a fluoridated dentifrice.

FLUORIDE AND GLUCOSE HOMEOSTASIS

Various studies have shown that excessive consumption of F causes hyperglycemia by different mechanisms.[5-9,33-35]A study of 25 patients with endemic fluorosis showed that 40% of them had impaired glucose tolerance that was reversed when excess F from the water was eliminated.[36] De la Sota et al.[37] observed through glucose tolerance tests that residents in an endemic fluorosis area exhibited plasma insulin levels that were inversely correlated with fluoremia. Xie et al.[38] reported higher plasma glucose levels and a delay in the peak plasma insulin after a glucose tolerance test in people with high F intake. Rigalli et al.[5] observed a decrease in insulin secretion in humans and rats after intake of 0.84 and 16.8 mg/kg of NaF, respectively. Owing to the need to reach similar peak plasma levels in both models, the dose of NaF given to the rats was 20 times more than was given to human volunteers; this difference in the dose is probably due to the large difference in the rate of turnover of the bone. In further studies in rats, Rigalli et al.[8] showed that NaF diffused into the plasma affected glucose homeostasis when F levels exceeded 5 μmol/L. In addition, F causes inhibition of glycolysis[19], hyperglycemia,[5-9,33-35] and depletion of liver, muscle, and spleen glycogen.[18-20] According to Allmann and Kleiner,[34] the mechanism by which NaF induces hyperglycemia may be due to one or more factors, such as increased glycogenolysis due to increased cAMP, increased release of epinephrine, and activation or inhibition of certain enzymes.

Behaving similarly to epinephrine or glucagon, F may stimulate adenylyl cyclase and, because of its stimulation, the conversion of ATP to cAMP. The latter activates cAMP-dependent protein kinase, which is responsible for activation of cascade phosphorylations leading to activation of the key enzyme of glycogenolysis—glycogen phosphorylase. As the result of phosphorylation, the enzyme undergoes activation to its active phospho- form and catalyzes glycogen breakdown, what leads to the release of glucose into the bloodstream and hyperglycemia.[39] Menoyo et al.[40] showed that NaF at 5–20 μmol/L inhibited insulin secretion by isolated Langerhans islets stimulated with glucose. Their results suggested that fluoride affects some stage of insulin secretion situated below the cascade of events that include the participation of calmodulin, protein-kinase C, and cyclic AMP. McGown and Suttie[33] proposed that NaF-induced hyperglycemia is due to the positive effect of NaF on epinephrine release, which could increase glycogenolysis.

Insulin resistance has also been correlated with decreased tyrosine phosphorylation of the insulin receptor and its substrates.[41] Research performed by Viñals et al.[42,43] on insulin receptors from rat muscle tissue and human placenta showed that fluoride, in concentrations 100–1000 times higher than those *in vivo*, can cause a decrease in insulin-induced tyrosine autophosphorylation and phosphorylation of the exogenous substrates used. Menoyo et al.[44] demonstrated that acute treatment of rats with F from a single dose of NaF (16.8 mg /kg bw) induced insulin resistance. Recently, Chiba et al. [45,46] observed that, in castrated rats, chronic NaF treatment (4.0 mg F/kg bw/day) promoted a decrease in the pp185 tyrosine phosphorylation status in muscle tissue and in white adipose tissue, resulting in decreased insulin signaling. Moreover, NaF caused insulin resistance, as demonstrated by an increase in the HOMA-IR (homeostasis model assessment of insulin resistance) index, which was calculated from the values of insulinemia and glycemia of the animals.[45] On the other hand, Chehoud et al.[47] found that acute treatment of rats with a single dose of NaF (1.0 mg F/kg bw) by gavage did not promote changes in insulin sensitivity or pp185 tyrosine phosphorylation status in the muscle or in white adipose tissues. This divergence in results may be due to differences in F dosage or manner of administration.

In addition to the public water supply and fluoridated toothpaste, F is also consumed through beverages and foods. Significant concentrations of fluoride are found in black tea and tea-based drinks, with a potential to expose children at approximately 0.07 mg/kg bw/day.[48] Buzalaf et al.[29] showed that milk powder could be a risk factor for dental fluorosis, especially in fluoridated areas, due to the use of fluoridated water to reconstitute the formula for feeding. Lupo et al.[49] evaluated the effect of the intake of fluoridated water supply on glucose metabolism in rats with normal and deficient renal function. These researchers concluded that the consumption of fluoridated water did not affect plasma glucose levels, even in animals with renal disease. In both groups, however, plasma insulin levels increased with increasing F concentration in drinking water.

In vitro studies using a more acidified toothpaste with fluoride concentrations of 550 µg/g (pH 4.5)[50] and 550 µg/g (pH 5.5)[51] indicated that these acidified toothpastes had the same anticariogenic effectiveness as neutral toothpastes (pH 7.0) with 1100 µg/g of F. In a study performed on 4-year-old schoolchildren living in a fluoridated area, Vilhena et al.[52] showed that a low-F acidified liquid dentifrice with 550 µg/g (pH 4.5) of F seems to lead to similar rates of caries progression as conventional toothpaste with 1100 µg/g (pH 7.0) of fluoride. Given that F can alter carbohydrate metabolism, glucose tolerance, and insulin signaling, there is clearly a need to control the consumption of fluoridated products or even to recommend the use of dentifrices with low concentrations of F. These measures could prevent F intake above the threshold dose. Such approaches would particularly benefit children and adolescents with DM for whom excessive F intake might exacerbate effects of the disease.

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