Literature Review: Use of Xylitol for Prevention of Acute Otitis Media

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SUMMARY

Introduction: Xylitol is a sugar naturally found in various vegetables and fruits. Studies have demonstrated that the xylitol can be used as new preventive method for acute otitis media (AOM).

Objective: To clarify the possible mechanisms of xylitol actions to inhibit the growth of otopathogenic bacteria and to describe researches that contribute for the discussion about the feasibility of the use of this sugar in the prevention of AOM.

Method: Literature review based on scientific articles selected by means of the medical databases: MEDLINE, Cochrane, PubMed (MeSH) and Web of Science.

Results: Studies have demonstrated the efficacy of xylitol to prevent the AOM, when it is administered five times a day in chewing gum. However, this sugar is not so effective in the prevention of AOM during upper airways infections.

Final Comments: Xylitol seems to be an effective strategy in prevention of acute otitis media. However, new studies are necessary to establish ideal doses, frequencies and vehicles for the correct administration of the sugar, which allows for its utilization in the public health system.

Keywords: otitis media, child, xylitol, *Streptococcus pneumoniae*.

Introduction

Otitis media is one of the most common pediatric diseases with the high morbidity, mainly in children aged less than three years (1,2). The disease prevalence is also high in children who are beginning school life, about six years of age. There is a great concern as for the episodes and recurrences of otitis media in this age range, since it's a period in which the auditory integrity is essential for the suitable development of oral and written language (1,3).

Antibiotic therapy is the most common treatment in cases of otitis media. However, there are many discussions as for the prescription of this type of medication since the individual may undergo several episodes of the disease during childhood. Therefore, the antibiotics are extensively used, which may cause an increase of the resistance of pathogenic bacteria (2,4,5). The development of preventive strategies, able to limit the use of antibiotics and avoid the development of more severe after-effects arising out of the disease, have been encouraged, amongst which, the use of xylitol (6,7,8).

The xylitol is a polysaccharide carbohydrate that is present in many fruits and vegetables, and it's used as a sweetener in some industrial products, specially chewing gums (9). Studies report the xylitol may have several medical applications, such as in the prevention of dental caries and acute otitis media (AOM) (10).

The discovery of the xylitol benefit in the prevention of acute otitis media occurred as from comparative studies in the dental area. The results obtained about the anticariogenic effects produced by this sugar encouraged the development of researches aiming at verifying the carbohydrate action on other oral bacteria, such as, otopathogenic ones (10).

This literature review is aimed at carrying out a literature review, clarifying the possible action mechanisms of xylitol on the otopathogenic bacteria growth inhibition and describing studies that contribute for the discussion on the feasibility of use of such carbohydrate for prevention of AOM.

Xylitol

The xylitol is a carbohydrate naturally found in several fruits and vegetables. It has a sweetening power similar to sucrose containing 40% less calories. It's extracted mainly from Birch and special trees typical in Scandinavian countries (11). It may also be produced industrially from corncob, sugarcane, seeds peels and nuts (10,12). Today, the worldwide production of xylitol overtakes 10.000 tons per year and is forwarded to food, pharmaceutical and cosmetic industries. The addition of xylitol in diet products may replace totally or partially the various types of sugar contained in candies, sweets and chewing gums (14).

The name xylitol relates xylose, the sugar from wood, from which xylitol was obtained for the first time (10). In the chemical nomenclature, xylitol is classified similarly to sorbitol and mannitol, that is, as an alcohol-sugar or a polyol.

Xylitol has a large application potential in medical and dental areas. It has proved to be efficient for the treatment of diabetes, lipids metabolism disorder, renal and parenteral lesions, dental caries prevention, pulmonary infections, otitis and osteoporosis (10,15).

Xylitol in dental caries prevention

Xylitol was discovered in 1890 by the German chemist Emil Herman Fischer and his assistant Rudolf Stahel. Although Dr. Fischer received the Noble Prize for his accomplishments in the chemical sciences area, xylitol didn't received much attention during this period (10).

Studies relating to the use of xylitol and dental caries only started in the 1970's, in Turku, Finland. Initially, xylitol capacity to reduce the growth and the production of acids of Streptococcus mutans, the main bacterium responsible for the development of dental caries, was observed (16,17).

The dental caries are a multifactor diet-dependent infectious disease, ascribed primarily to the presence of oral bacteria and fermentable sugars. The bacterial adherence seems to be a pre-requirement for the dental caries progression (15,18).

The mechanism by which xylitol inhibits the growth and metabolism of cariogenic bacteria is not yet fully clarified (17,19,20). However, it may be partially explained by the consumption of phosphoenolpyruvate (PEP), once the xylitol is transported via fructose phosphotransferase system (21,22,23), which results in an intracellular accumulation of xylitol-5-phosphate. This intermediate metabolite is dephosphorilated and excreted as xylitol, without generating the ATP production. This "useless cycle" consumes energy and results in the bacterial growth and metabolism inhibition, and reduces the incidence of dental caries (24,25,26).

Xylitol in the prevention of acute otitis media

The anticariogenic effect produced by the xylitol has encouraged the accomplishment of researches able to clarify the carbohydrate action on other oral bacteria, such as the otopathogenic ones (6,7,8).

The first research aiming at verifying the xylitol influence on the growth of microorganisms causing AOM was performed in 1995 by Kontiokari et al (6). The authors supposed the possible capacity of the sugar to cause damages to other bacterial types present in the nasopharynx flora, mainly those responsible for respiratory infections. The study demonstrated the growth inhibition of the Streptococcus pneumoniae cultivated in vitro 35% and 72% at the presence of 1% and 5% of xylitol respectively. The sugar influence in the samples growth of Haemophilus influenzae and Moraxella catarrhalis was also studied. However, no significant differences were observed after the use of sugar.

The xylitol action mechanism in the otopathogenic bacteria is not justified only by the bacterial growth inhibition. The literature describes the carbohydrate has features that diminish the adherence of the pneumococcus to the nasopharynx cells, which makes their migration difficult up to the middle ear, an important acute otitis media pathophysiology stage (27,28).

Kontiokari et al (28) confirmed the xylitol influence on the adhesiveness of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis to epithelial cells, after the exposure of epithelial bacteria and cells, associated or not to a concentration of 5% of xylitol. Before any type of sugar exposure, the Streptococcus pneumoniae adehesiveness was of 32 to 47 bacteria per cell. When only the bacterium was exposed, the adhesiveness reduced to 25 bacteria per epithelial cell, but no statistically significant differences were observed. When bacteria and cells were simultaneously exposed to xylitol, the adhesiveness was significantly reduced to 13 bacteria per cell. The adhesiveness of the Haemophilus influenziae not exposed to xylitol ranged between 17 to 54 bacteria per cell, while only 16 bacteria were adhered to each epithelial cell when both were exposed to 5% of sugar. The Haemophilus influenziae and Moraxella catarrhalis isolated exposure to xylitol didn't either result in a significant reduction of the bacterial adherence to the epithelial cell, as previously observed in the S. pneumoniae group.

After observing that the xylitol may inhibit the growth and adhesiveness of pneumococcuses, a study was accomplished that evaluated the xylitol effect at the presence of fructose and sorbitol on the S. pneumoniae growth (Tapiainen et al) (29). A remarkable growth inhibition was detected in this bacterial type in a basic means with 0.2% of glucose and 5% of xylitol. When xylitol was used associated with fructose in different concentrations (1%, 2.5% and 5%), no bacterial growth inhibition was observed. The addition of 1% of glucose, 1% of galactose or 1% of sucrose didn't change the xylitol inhibitory effect. The sorbitol in the concentrations of 1%, 2.5% and 5% didn't inhibit nor stimulate the pneumococcuses growth. The xylitol in the concentration of 2.5%, associated or not to sorbitol, was effective for the bacterial growth inhibition. For the authors, the xylitol action mechanism in the pneumococcuses growth inhibition seemed to be similar to that of the Streptococcus mutans, that is, formation of xylitol-5-phosphate, dephosphorilated metabolite and excreted without energy generation.

With the confirmation of the hypothesis the xylitol may interfere with the main otopathogenic bacterium, the Streptococcus pneumoniae, four randomized clinical studies were carried out aiming at proving the efficacy of the carbohydrate in the prevention of AOM.

Uhari et al (7) enrolled 306 children, with average age of 5 years, from public baby nursery in the city of Oulu, Finland. The children were divided into two groups and monitored for the period of two months. To group 1, chewing gums containing only sucrose were administrated daily (control group), while group 2 was given chewing gum containing only xylitol (8.4 g/day). The results demonstrated a lower number of AOM cases of children who consumed chewing gum containing xylitol (n=19), when compared with the number of AOM cases in children who consumed chewing gums containing only sucrose (n=31). These data were sufficient to confirm that xylitol seems to have a preventive effect on the acute otitis media.

Another clinical study performed involved 857 healthy children enrolled in baby nurseries in the city of Oulu/Finland (8). The children were divided into five groups at random: (1) 165 children used syrup without xylitol (control), (2) 159 children used syrups containing xylitol, (3) 178 children consumed chewing gum without xylitol (control), (4) 179 children consumed chewing gums containing xylitol and (5) 176 children consumed pastille containing xylitol. The daily dose of xylitol was of 8.4 g (in the chewing gums) and 10 g (in the syrups). After three months of daily follow-up, the authors could observe that 68 (41%) children of group 1 developed at least one case of otitis media and only 46 (29%) children of group 2 developed the disease during the period studied. In children of group 3, only 49 (28%) developed AOM, while 29 (16%) children belonging to group 4 were affected with at least one AOM episode. In group 5 the disease incidence was verified in 39 (22%) children. The

research showed that xylitol is efficient in the AOM prevention, reduces its occurrences significantly and decreases the need for antibiotics prescription.

Tapiainen et al (9) carried out a study to measure the maximal concentration and duration of salivary detection of xylitol in children who swallowed chewing gums and syrup containing the sugar. The 65 children aged from 1 to 6 years were divided into two groups: G1 (consumed chewing gums containing 1.68 g of xylitol) and G2 (consumed 5 ml of syrup containing 400 mg/l of the sugar). Non-stimulated saliva samples were collected in different periods and analyzed. The results confirmed that the children who consumed chewing gums maintained salivary concentrations of the carbohydrate above 1% for longer periods when compared to the children who received xylitol in syrup. However, a minimum salivary concentration of 1% of xylitol, required for the obtainment of the antimicrobial effect, was detected up to the maximum of 15 minutes after its consumption, no matter the form used. After obtaining such results, the authors proposed researches that could develop the sugar administration methods that used stronger concentrations and less frequency, which would make the use of xylitol more attractive for the prevention of acute otitis media and other diseases.

Aiming at verifying whether the prescription of xylitol could reduce the AOM occurrence in children with upper airways infection picture, 1277 healthy children were enrolled from baby nursery of Oulu/Finland (Tapiainen et al) (13). The children were followed-up weekly during four months. The UAI episodes were confirmed by the researchers, who administrated five times a day: syrup containing xylitol (n=212), syrup without xylitol (n=212), chewing gum with xylitol (n=286), chewing gum without xylitol (n=280) or pastilles with xylitol (n=287) for the children. The authors confirmed that the AOM occurrence in the children who didn't use xylitol was similar to the groups that received the sugar and concluded that the administration of xylitol during UAI cases was not effective to prevent acute otitis media. A more recent study also demonstrated the inefficacy in the prevention of acute otitis media when chewing gums and pastilles containing the sugar were used three times a day by children during episodes of upper airways infection (Hautalahti et al, 2007) (30).

Tapiainen et al. (31) carried out a study aiming at analyzing the Streptococcus pneumoniae cellular ultrastructure after exposure to xylitol. Different samples of pneumococcus were exposed to concentrations of 0.5% and 5% of xylitol, 5% of glucose, 5% of fructose or 5% of sorbitol, during 30 min and 2 h. The bacterial ultrastructure was examined by means of transmission electronic microscopy. The results showed that the bacterial cell exposed to xylitol for 30 min didn't have significant changes in its morphology. However, after 2 h of exposure to the same sugar, a polysaccharide capsule of minor diameter could be observed, as well as a more irregular, diffuse and disperse cellular wall. Such changes were not observed after the S. pneumoniae exposure to other kinds of sugars. The authors suggested the changes noted after xylitol exposure may affect the pneumococcus adherence and virulence, which would also explain the xylitol clinical efficacy in the acute otitis media prevention.

Disadvantages of xylitol

In spite it's found naturally in many fruits and vegetables, the xylitol has collateral effects associated to its consumption. For it's absorbed very slowly by the gastrointestinal tract, osmotic diarrhea and abdominal discomfort may occur due to the ingestion of large quantities of this sugar (31).

Xylitol ingestion limits have not yet been precisely defined. Some studies report that adult individuals may stand the ingestion of up to 200 g of xylitol/day, without the presence of any type of gastrointestinal alteration, while children tolerate lower quantities, up to 45 g/day of the sugar (6,32,33). However, Bastos et al (34) state the maximum recommendable daily dosage so that undesirable effects don't occur in humans is equal to 20 g/day, which don't represent significant hazard to the people's health.

Tapiainen et al (13) confirmed the xylitol administration difficulties for AOM prevention. The use of chewing gums containing xylitol five times a day is able to prevent acute otitis media cases. However, such application protocols are not acceptable, since they submit the patient to the chewing process for a long period of the day, which could cause other kinds of problems relating to functional stress, such as strong dental wear and temporo-mandibular dysfunction. In addition, such form of administration does not include young children, when the highest indexes of acute otitis media are observed.

The regular distribution of chewing gums containing xylitol by the public health system may also be deemed to be one of the strongest difficulties for the adoption of this preventive action. Patients belonging to groups of risk of development of AOM and UAI should ingest large daily quantities of chewing gum (10 tablets containing 0.84 g of the sugar) for long periods of time. Such periods would become longer and longer, the highest the number of diseases to be prevented were, such as pulmonary infections, osteoporosis and dental caries.

Final Considerations

The acute otitis media pathogenesis is multifactorial. The bacterial infectious agents are among the most critical etiologic factors of the disease. The AOM recurrence is common during childhood, and its incidences are normally treated with the use of antibiotic therapy.

The development of preventive methods is prevalent for the control of the appearing of new pictures of any kind of disease. In this case, to prevent means to avoid the recurrent use of antibiotics able to select resistant bacteria, which makes the disease more and more aggressive and difficult to treat.

Xylitol seems to be an efficient method for the prevention of acute otitis media. However, for the obtainment of satisfactory results, the availing of the sugar must occur for longer periods of time and in suitable concentrations in the bucal cavity.

There are not many randomized clinical studies, so far, concerned with testing the xylitol use effectiveness in the acute otitis media prevention, which require the verification of scientific evidences on the theme. Studies must be intended for the determination of concepts on dose-response, bioavailability, action mechanisms and a potential generating this sugar microbial resistance.

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