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Biomarker of Malnutrition in Terms of Total Salivary Protein in Stunting Children (Literature Review)

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ABSTRACT

The prevalence of children under five (or Balita) with stunting in Indonesia is relatively high, it is 29.6% above the limit set by WHO (20%). Stunting is a condition where children fail to grow due to long-term malnutrition. Parents regrettably often underestimate such conditions. In case it is not detected prior to 24 months old, the consequences will be permanent. Oftentimes, malnutrition is detected at a later time, make it occurs even more frequently. Malnutrition affects general and oral health. In malnourished children, salivary gland hypofunction ensues which cause a decrease in flow rate, buffer capacity, and salivary secretion, both in quantity and composition, especially protein. The condition where increased severity of malnutrition followed by a decrease in salivary protein concentration is expected to be a biomarker of malnutrition. The purpose of this study is to analyze the potential of total salivary protein as a malnutrition biomarker.

Keywords: children; protein energy malnutrition; saliva; stunting; total protein

INTRODUCTION

Nutrition is the science of food and its relationship to health, while malnutrition is a cellular imbalance between nutrient and energy intake and the body's needs for growth, maintenance, and specific functions. Malnutrition refers to deficiency, excess, or imbalance in energy and/or nutrient intake. The term malnutrition is divided into 2 conditions, namely undernutrition and overnutrition/overweight. Undernutrition can occur for various reasons, and is classified into wasting, stunting, underweight, and vitamin and mineral deficiencies. While the term overnutrition / overweight is when a person is too heavy for his height. Overnutrition occurs due to an imbalance between energy consumed (too much) and energy expended (too little). [1] Malnutrition affects general health, as well as the health of the oral cavity. The abnormalities that occur depend on the time in which a person is malnourished. Deficiency of minerals and vitamins during conception affects the development of tooth organogenesis in the embryo, maxillary growth and skull/facial development. The occurrence of early nutritional imbalance will greatly affect the malformation. Imbalance of nutrients during the period of active growth will result in more extensive damage. Diet also affects oral health, conditions caries development, enamel development, tooth erosion, periodontal health conditions, characteristics of saliva and oral mucus in general.[2]

Protein Energy Malnutrition (PEM) will cause hypofunction of the salivary glands, which results in decreased salivary flow rate, buffering capacity, and decreased salivary constituents, especially protein. PEM and vitamin A deficiency are associated with atrophy of the salivary glands, which in turn reduces the ability of the oral cavity to fight infection.[3]

Serum albumin, globulin, transferrin, total protein is used as indicators of nutritional status, and salivary gland function.[4]

The most commonly used test specimen is blood. On the other hand, saliva can be termed as a non-invasive test sample which is easier to collect and painless compared to a blood sample. In contrast to blood, saliva does not contain cellular components, such as red blood cells, white blood cells, and platelets, and there is no clotting, so the collected samples are easier to measure.[5]

It is very important to be able to detect malnutrition through laboratory tests because with appropriate and supportive tests it can be used to detect malnutrition as early as possible before the deficiency can be seen through symptoms or clinical examination and clinical parameters are quite objective, so that if laboratory tests are carried out as a supporting examination can help to establish a proper diagnosis. The severity of PEM increases followed by a decrease in salivary protein concentration, therefore saliva with protein content can be used as an index of malnutrition. The severity of PEM increases followed by a decrease in salivary protein concentration, therefore saliva with protein content can be used as an index of malnutrition. [4]

METHOD

Literature study and theoretical approach with data sources from Sci-Direct, Google Scholar and PubMed using the following keywords either alone or in combination: “Stunting”, “Protein Energy Malnutrition”, “Total Protein”, “Saliva”, “Children”. Exclusion criteria were all other articles which did not have one of these topics as their primary endpoint.

LITERATURE REVIEW

Malnutrition

Malnutrition is a common and widespread condition that usually occurs as a deficiency in the intake of energy, protein, or micronutrients. Malnutrition is one of the main causes of the death of children under the age of 5 years and is one of the most common causes of the decline in the health and life of children, which results in decreased learnability, inefficiency, and inability to acquire skills.[6]

The indicators stunting, wasting, overweight and underweight are used to measure nutritional imbalance; such imbalance results in either undernutrition (assessed from stunting, wasting and underweight) or overweight. Child growth is internationally recognized as an important indicator of nutritional status and health in populations. [7] Stunting refers to a situation whereby children have a lower than normal height-for-age. Stunting predisposes to poor child performance in school and also to delayed developmental milestones and decreased intellectual development in terms of capacity. Wasting refers to lower than normal weight-for-height, while underweight refers to lower than normal weight-for-age. Childhood wasting also predisposes to immunosuppression, subsequently leading to increased susceptibility to infections. Micronutrient deficiency refers to inadequate intake of vitamins and minerals. Overnutrition comprises obesity and overweight. overweight and obesity (especially in adolescence and childhood) increase the risk of developing short- or long-term health problems, notably cardiovascular disorders and diabetes mellitus.[8]

Factories that can cause malnutrition are broad and different. The immediate causes of child undernutrition are inadequate dietary intake and disease. Dietary sufficiency in terms of energy and essential nutrients is critical for the normal growth and development of infants and young children. Undernutrition does not only refer to a child's lack of protein and energy, also micronutrients play a major role. Infection has the effect of increasing the body's requirements for nutrients, reducing appetite and reducing the absorption of nutrients from the intestine. Undernutrition and infection often occur at the same time. Undernutrition can increase the risk of infection while infection can cause undernutrition leading to a vicious cycle of undernutrition and infection. Malnutrition caused improper growth and development, weakness and different kind of abnormalities and deformities among the children. The author further classified the malnutrition adversely affect the health problems. These problems may be classified or categorized as Short-term implications: In early childhood the child, grow so fast. Nutrient deficiencies can have short-term implications such as improper functioning of immune system and improper growth of the body. Long-term implications: The short-term implications of malnutrition eventually give way to long-term complications, such as Slow body growth and Slow cognitive development [9]

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Protein-energy malnutrition (PEM) appears to have multiple effects on the oral tissues and subsequent oral disease development. During childhood, malnutrition may restrict organ development as salivary glands leading to a diminished metabolic capacity involving concomitant deficiencies of antioxidant nutrients. This may explain the finding of present study as a lower mean values of salivary vitamins (A, C and E) and total protein were recorded among malnourished children compared to well-nourished with highly significant differences.[10]

The teeth which are in a pre-eruptive phase are influenced by the nutritional status of the body. The deficiencies of vitamin D, vitamin C, vitamin B and vitamin A and Protein Energy Malnutrition (PEM) have been associated with the disturbances in the oral structures. Enamel hypoplasia is a lesion which is characterized by hypoplastic grooves and/or pits in the enamel, which are often horizontal or linear in appearance. Some hypoplasia and pits on the surface of the enamel correlate to a lack of vitamin A. More diffused hypoplastic forms of the enamel have been reported with a vitamin D deficiency as well. The structural damage can testify the period in which the lack of nutrition has occurred.[3]

Deficient Nutrient	Effect on oral structures
Vitamin B1 (Thiamine)	Cracked lips, Angular cheilosis
Vitamin B2 (Riboflavin) Vitamin B3 (Niacin)	Inflammation of the tongue, Angular cheilosis Ulcerative gingivitis
Vitamin B6	Periodontal disease, Anemia Sore tongue Burning sensation in the oral cavity.
Vitamin B12	Angular cheilosis, Halitosis Bone loss, Hemorrhagic gingivitis Detachment of periodontal fibers Painful ulcers in the mouth
Iron	Salivary gland dysfunction Very red, painful tongue with a burning sensation, Dysphagia, Angular cheilosis
Protein/calorie malnutrition	Delayed tooth eruption, Reduced tooth size Decreased enamel solubility, Salivary gland dysfunction.
Vitamin A	Decreased epithelial tissue development, Impaired tooth formation, Enamel hypoplasia.
Vitamin D/Calcium phosphorus	Lowered plasma calcium, Hypomineralization Compromised tooth integrity, Delayed eruption pattern Absence of lamina dura, Abnormal alveolar bone patterns.
Vitamin C	Irregular dentin formation, Dental pulpal alterations Bleeding gums, Delayed wound healing, Defective collagen formation.

FIGURE 1: Effect of Malnutrition on oral structures and Its development.[3]

The conditions like recurrent aphthous stomatitis, atrophic glossitis or a painful, burning tongue which is characterized by inflammation and defoliation of the tongue, are possibly caused by nutritional deficiencies such as vitamin B and iron deficiencies.[3] PEM can be correlated with the host factors which are associated with the development of caries, especially tooth defects and the salivary system. The tooth defects of interest are the external structural defects (hypoplasia) that can provide a more cariogenic environmental niche and less protective enamel and defects that include hypomineralization, which might increase the susceptibility to demineralization.[3]

Effect of Protein Deficiency on Salivary Gland Function

Protein deficiency causes changes in the structure and function of the salivary glands. The effects of protein deficiency depend on the time in which the deficiency occurs. In the early stages, protein deficiency can lead to a reduction in the size of the submandibular gland. Studies in children have shown that the severity of PEM is associated with a reduction in stimulated salivary secretion. PEM also results in decreased calcium, chloride and salivary protein secretion and decreased salivary immunological factors and agglutination.[3]

The decrease in salivary flow rate can affect the cleaning of the oral cavity and the dilution of saliva. In addition, each defense mechanism requires an adequate supply of protein.

These antimicrobial factors are regulated by salivary flowrate. Glycoproteins that produce bacterial aggregation arise from the salivary glands. Immunoglobulins and cellular immunity also require protein to produce. In previous studies, it was found that protein deficiency causes a lower salivary flowrate, changes in protein content, and is prone to caries.[11]

Saliva as a Biomarker

Saliva is often referred to as the "window of health status" or the "mirror of the body". Saliva consists of water (99%), the remaining 1% consists of various inorganic compounds, organic compounds and proteins/polypeptide compounds. Salivary samples have been used several times in nutritional studies, because they are considered the least invasive of biological samples. Biomarkers in saliva have the potential to be used for screening purposes in epidemiological studies. The biological possibility of using saliva as a sample is that the salivary glands are surrounded by capillaries that allow the exchange of blood-based molecules into saliva, either by active transport, diffusion through cell membranes or passive diffusion, allowing blood biomarker constituents to enter the salivary acini and eventually into the salivary secretions. Biomarkers are defined as objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions.[12]

Biomarkers can be proteins, carbohydrates, lipids or microorganisms. These changes in the constitution of biological molecules can reflect the status of the underlying disease process and can assist in the diagnosis, management, evaluation of prognosis, and monitoring of outcomes of the condition. Saliva is considered a credible means to evaluate health status. This may be because saliva collection is considered easier, because less training is required and it can be collected in practice and in the community, the procedure is non-invasive, saliva samples are safer to handle, easier to transport, store, and more economical than blood samples collected. may clot [12]

Salivary Total Protein as a Marker of Malnutrition

The salivary profile of total protein varies depending on the presence or absence of PEM and this suggests that saliva can be a useful tool in the assessment of PEM. Significantly lower levels of total protein were found in malnourished children. Total protein levels also decrease in serum as the severity of PEM increases. The reason for lower total protein levels may be due to reduced food intake, while PEM may lead to reduced action of adrenergic mediators involved in salivary secretion. Of the 11 studies reporting total protein levels in malnourished individuals, seven showed a significant association. The study found that total protein was significantly lower in malnourished children compared to controls. Some reported significantly lower total protein levels in children, which was significantly correlated with serum protein.[13]

Comparison of Salivary Protein with Plasma Protein

From a recent experimental study, a total of 2290 protein catalogs were found in saliva. This saliva protein list was compared with 2698 proteins found in plasma. Approximately 27% of salivary protein is found in plasma. However, despite this degree of overlap, the distributions found across the categories of Ontological Genes, such as molecular functions, biological processes, and cellular components, show significant similarities. In addition, nearly 40% of the proteins that have been proposed to be markers of diseases such as cancer, cardiovascular disease, and stroke can be found in whole saliva. These comparisons and correlations should encourage researchers to consider using saliva to discover novel disease protein markers and as a diagnostic fluid for detecting early signs of disease throughout the body.[14]

DISSCUSION

Malnutrition is a global health problem and a major contributor to child morbidity and mortality. Malnutrition is estimated to contribute to more than a third of all child deaths, although it is rarely the direct cause. There are reports on the influence of diet and nutrition on the morphology and function of the salivary glands in humans and animals. [3]

As a diagnostic fluid, saliva has advantages over serum. Saliva is more cost-effective for screening large populations. Specific salivary glands can be used for the diagnosis of specific pathology in one of the major salivary glands. [3] The secretion of salivary gland fluids and proteins is controlled by autonomic nerves and inhibition of these nerves has been shown to cause cessation of secretion. Parasympathetic nerve-mediated stimulation and release of acetylcholine play a major role in activating acinar cells in salivary fluid secretion. [14]

Simultaneously, glandular blood flow is increased through cholinergic, peptidergic and nitric oxide-mediated vasodilation. The release of noradrenaline from the sympathetic nerves plays an important role in increasing protein secretion. Neuropeptide co-transmitters present in autonomic nerves also modulate secretion through the salivary glands. Activation of beta-adrenoceptors on salivary acinar cells increases the intracellular cyclic denosine monophosphate which causes the secretion of stored protein. Parasympathetic stimulation activates muscarinic cholinergic receptors associated with the formation of inositol triphosphate and diacylglycerol and will cause an increase in intracellular calcium which opens membrane ion channels, especially apical chloride channels, leading to fluid secretion.[15]

A secondary factor that also affects the secretion of saliva is the blood supply to the glands because the secretions always require adequate nutrition. The supply of the parasympathetic nerves to the salivary glands will induce saliva in large quantities which causes dilation of blood vessels, resulting in an increase in nutritional needs. Part of this additional vasodilator is caused by kallikrein secreted by activated salivary cells, which in turn act as enzymes to break down one of the blood proteins, an α2-globulin to form bradykinin, a potent vasodilator.[16]

The salivary glands in the malnourished group showed acinar cell atrophy, cytoplasmic vacuolization with pleomorphism, and periductal fibrosis. Acinar cell atrophy in the salivary glands of malnourished mice can be thought to be the result of decreased cell proliferation or increased apoptosis. Similar to the findings of this study, histological analysis of the submandibular gland in the protein energy malnutrition group has shown replacement of parenchymal cells by fibrous tissue and inflammatory cells leading to a reduction in acinar cell volume. Acinar cell atrophy can also be a pathological process related to malnutrition which results in degeneration and damage to the salivary glands.[17]

The acinar cells are removed by the process of apoptosis in the gland. Apoptosis is an important factor in the loss of acinar cells, especially in the early stages of glandular atrophy.[18] In addition to the apoptotic loss of acinar cells, necrotic acinar cells and structures representing the transition from acinus to ducts, were observed in later atrophic stages. This, similar to previous reports, suggests that necrosis and transition are involved in the loss of acinar cells. Most acinar cells are lost in salivary glands, which suggests that necrosis and transition participate in acinar cell loss in addition to apoptosis in salivary gland atrophy.[18]

During salivary gland atrophy, the number of ducts increases. The increase in the number of ducts is due to degranulation of the acinar cells at the resting stage. However, it was later shown that the increase in the number of ducts was due to the proliferation of ductal cells. In salivary gland atrophy, Bhasker et al. used light microscopy and reported that there were degranulated acini that were indistinguishable from newly formed ducts and from existing ducts. This suggests that mitotic proliferation and transition contribute to an increase in the number of ducts during salivary gland atrophy and that mitotic proliferation is important in the early phases of atrophy and transition in later phases.[18] It was concluded that acinar cell apoptosis and ductal cell mitosis play important roles in salivary gland atrophy and the acinar to ductal transition and acinar cell necrosis are important additional factors.[18]

TGF-β signaling is critical for wound healing, the main purpose of which is to regain original tissue composition and function. In most cases, injury, infection, and systemic disease can impair regeneration, resulting in the need for repair. Repair is accomplished by cessation of inflammation and replacement of the injured tissue through fibrosis, which consists of excessive Extracellular Matrix (ECM) accumulation and remodeling. Inflammation has the potential to activate the latent form of TGF-β1 which is concentrated in the ECM, inducing a pro-fibrotic response. Fibrosis is used for regeneration, but uncontrolled fibrosis results in scar tissue and organ dysfunction which can sometimes be fatal.[19] TGF-β isoforms, in particular TGF-β1, are critical for the pathogenesis of fibrosis, as evidenced by preclinical evidence: (1) Exogenous TGF-β introduced in healthy animal models exhibits increased fibrosis, (2) TGF-β is overexpressed in transgenic models showed increased, often diffuse fibrosis, and (3) inhibition of TGF- reduced experimental fibrosis. TGF-β produces fibrosis by increasing ECM synthesis, fibroblast activation, acquisition of myofibroblast phenotype.[19] TGF-β1 induces fibroblast activation resulting in myofibroblast differentiation has been reported as an important source of collagen, glycoproteins, proteoglycans, and matrix metallopeptidases (MMPs) in wound healing and fibrosis. The acquired myofibroblasts are then lost via apoptosis during the transition from granulation tissue to scar tissue in wound healing.[19]

Periductal fibrosis can cause duct stiffness and cause impaired secretion. The results of this study suggest that the histological changes observed in the salivary glands of malnourished rats may be related to functional and biochemical changes in secretion. These changes may contribute to the pathophysiology of the impaired oral function associated with PEM. Cytoplasmic vacuolization with pleomorphism is often observed when the cell is under stress such as impaired cellular nutrition. This may be a form of cellular adaptive processes to stress due to malnutrition. In addition, atrophy of acinar cells in the glands can lead to reduced secretion of salivary mucin which can lead to impaired salivary function.[17]

Changes and nutritional deficiencies can also affect salivary function. A simple reduction in daily food intake can result in a decrease in salivary protein, whereas severe calorie restriction tends to reduce salivary flow, cell count, and saliva composition.[20] Salivary total protein levels increase through -sympathetic activity in the salivary glands, because salivary secretion is mainly influenced by the action of adrenergic mediators. PEM will interfere with the action of adrenergic mediators and cause a decrease in the protein content in saliva.[4]

Saliva has hundreds of components that provide biomarkers of health and disease status. Saliva has an important role in ensuring adequate nutrition, salivary gland function and providing protection from oral diseases. Poor nutrition can lead to decreased salivary gland activity and a further decrease in salivary flow. At the same time, nutritional deficiencies impair salivary gland function, thereby increasing susceptibility to dental caries and oral infections and reducing quality of life (Danielle, Logan. 2020). Studies have reported a decrease in salivary flow rate in malnourished children. Decreased salivary flow rate is associated with stunted growth in malnourished children with salivary gland involvement. In a previous study, the flow rate was significantly lower in malnourished rats compared to the control group, indicating that PEM is associated with salivary gland hypofunction in rats [20]

Due to the increasing severity of PEM followed by a decrease in the total salivary protein concentration, saliva with salivary protein content in the early stages of malnutrition can be used as a PEM index.[4] Hypofunction of the salivary glands will also reduce the buffering capacity of saliva, so that saliva cannot return the pH to its normal value, as a result, teeth will be susceptible to caries. By knowing PEM early through detection in saliva, so that preventive measures can be sought to prevent the occurrence of abnormalities that can arise in the oral cavity. [4]

CONCLUSION

The increasing severity of malnutrition is followed by a decrease in the total salivary protein concentration, thus the salivary protein content can be used to diagnose malnutrition.

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REFFERENCE

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