SALIVARY FERRITIN – A CONCISE UPDATE ON CURRENT CONCEPTS

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ABSTRACT

Ferritin is a ubiquitous and highly conserved iron-binding protein. Increasingly, perturbations in cellular iron and Ferritin are emerging as an important element in the pathogenesis of disease. Ferritin levels seem to reflect the magnitude of iron stores in the body and decreased or increased serum Ferritin levels are used as a marker for anaemia and iron overload disorders. Serum Ferritin was discovered in the 1930s, and was developed as a clinical test in the 1970s. However, the presence of Ferritin in saliva was not documented until 1984. The salivary Ferritin values are usually higher than the iron stores present in the body and these values are subject to change in iron deficiency anaemia, iron overload disorders and protein malnutrition. The biological system maintains the salivary Ferritin levels at a higher level, probably for the iron dependent enzymatic functions of the saliva, thus conserving the iron through saliva. This paper gives an update of Ferritin and its presence in saliva and various mechanisms which cause a rise in Ferritin.

Key Words: saliva, Ferritin, iron deficiency, anaemia, malnutrition

INTRODUCTION

Although essential for most forms of life, too much iron is harmful. To cope with these antagonistic phenomena an iron-storage molecule, Ferritin, has evolved. Ferritin evolved as the only protein able to solve the problem of iron/oxygen chemistry and metabolism¹. Aquated, ferrous iron is oxidized with oxygen to concentrate as many as 4000 iron atoms as a solid oxo-mineral in the centre of the Ferritin protein².

Ferritin is a highly specialized ubiquitous iron storage protein and has generally been thought to function as a “housekeeper” storage protein which can release iron required for cellular proliferation and metabolic renewal³. It stores iron and releases it in a controlled fashion. Ferritin levels seem to reflect the magnitude of iron stores in the body and decreased or increased Ferritin levels are used as a marker for anaemia and iron overload disorders⁴. Ferritins are part of the extensive ‘Ferritin-like superfamily’ of proteins within which all members are believed to share the characteristic four-helical bundle structural motif⁵. Ferritin is found mainly in the cytoplasm of the reticuloendothelial cells, liver cells, and to a lesser extent in the developing red cell precursors in the bone marrow⁶.

Historical Perspective:

Ferritin, an iron storage protein was initially discovered by Laufberger and
colleagues in 1937, who isolated a new protein from horse spleen which contained up to 23% by dry weight of iron. Discovered early in the 20th century, Ferritin began yielding its secrets at the century’s end\textsuperscript{3}. Pauline, in 1952 was the first to introduce Ferritin crystals in the laboratory of Nobel laureate Dorothy Hodgkins, and he isolated Ferritin from horse spleen in 1957 in the old Scala Cinema in Sheffield, UK. The appearance of Ferritin in human serum was documented several years thereafter\textsuperscript{8}. Since 1972, when the first sensitive immunoassay for Ferritin was described, there have been an impressive number of studies on serum Ferritin concentration in normal and disease states, and the clinical usefulness of the serum Ferritin assay in evaluating body iron status is now well established\textsuperscript{5}. Serum Ferritin continues to be a useful and convenient method of assessing the iron storage, although it is now known that many additional factors, including inflammation, infection and malignancy may elevate serum Ferritin and complicate the interpretation of this value\textsuperscript{10}. The presence of Ferritin in Saliva has been documented by Agarwal and co-workers in 1984\textsuperscript{11}.

**Structural Aspects of Ferritin**

As early as 1944, Granick and Hahn claimed that the iron-cores were particulate 'micellar' in form\textsuperscript{12}. Farant in 1954 demonstrated the structure of Ferritin electron microscopically and considered it to be a tetrad with four subunits, the iron being deposited at the four corners of a cube with a diameter of about 55 Å\textsuperscript{13}. In 1960, Kerr and Muir described the iron-core of Ferritin as consisting of six subunits arranged at the apices of a regular octahedron\textsuperscript{14}. The growth of three-dimensional structure of Ferritin suggested that tetragonal crystals were grown for apoFerritin and Ferritin co-crystallized with apoFerritin in an orthorhombic form\textsuperscript{15}. Human Ferritin is a globular protein complex and a high molecular weight iron compound keeping iron in a soluble and non-toxic form. The protein shell consists of a component named apoFerritin with a molecular weight of approximately 4,50,000 Daltons. It is composed of 20-24 subunits which forms a hollow sphere of internal diameter about 70Å and is made up of heart (H) and liver (L) subunits, with molecular masses of 21 kDa and 19 kDa, respectively\textsuperscript{16, 17}. In the centre core of this shell, these is presence of variable number of iron atoms up to about 4500 , accommodated as a microcrystalline core, or micelle, of hydrated ferric phosphate(FeOOH)\textsubscript{8} (FeO:PO\textsubscript{4}H\textsubscript{2}). It consisting of 24 protein subunits and is the primary intracellular iron-storage protein\textsuperscript{18, 19}. Iron may compromise upto 20% of the molecule which may have a molecular weight as high as 9,00,000\textsuperscript{20}.

**Salivary Ferritin:**

Saliva is a complex fluid composed of a wide variety of organic and inorganic substances in the form of protein, various enzymes, sodium, potassium, thiocyanates and some minerals such as iron, copper and chromium. These minerals are present in saliva at a gradient which is comparable with serum. They collectively act to modulate the oral environment\textsuperscript{21}.

**a. Salivary Ferritin in Iron deficiency anaemia**

Agarwal and coworkers observed that saliva contains Ferritin and changes in Ferritin levels have been observed in iron deficiency and its levels in saliva were much higher than the normal\textsuperscript{11}. Lagunoff and Benditt in 1963 first observed Ferritin-like particles in occasional mast-cell granules and suggested that Ferritin may be taken up as such by the granules and then transformed into another form. This was the first step in the discovery of salivary Ferritin\textsuperscript{22}.
The exact mechanism by which anaemia caused a rise in salivary Ferritin is not exactly known. The levels of salivary Ferritin in normal subjects is 95-105 µg/ dl whereas the levels increases up to 130 – 170 µg/ dl in iron deficiency anaemia\(^{23}\). However, it may be speculated that the iron dependent enzymatic functions of the saliva also help in the conservation of iron through saliva of iron deficient patients \(^{23}\). Changes in Salivary Ferritin occur even before the hematological changes and hence these measurements are clinically significant in monitoring the iron status\(^{24}\). Other possibilities include endocytosis of Ferritin by the ducts of salivary glands and its excretion into the saliva and presence of high molecular weight iron binding properties of saliva\(^{22,25}\). Internalization of Ferritin in the intercalated ducts in the form of lysosomes in the parotid duct could serve as a possible mechanism for the increased salivary levels. This mechanism hitherto has been established in rats, but evidence is not conclusive in human beings. This may also be the mechanism for alterations in the proteins in saliva before it reaches the oral cavity \(^{25}\). Furthermore saliva possesses a marked iron binding ability and the high molecular weight iron binding substance in saliva might have a function in health and disease, both because of its molecular weight and its resistance to acid peptic digestion\(^{26}\). Another possible mechanism may also be attributed to the increased salivary manganese levels which inhibit the salivary Ferritin transport leading to its retention thereby raising the salivary Ferritin in iron deficiency anaemia. However, the scanty literature on this aspect does not allow us to draw an exact pathogenesis for the rise of Ferritin\(^{27}\). Activity of the enzyme arginase, in human saliva has been found to be more in serum. It is possible that iron and manganese share a common cellular transport mechanism and thus excesses of one element inhibit transport of the other \(^{26}\). Ferritin is usually present in the saliva of all men with iron deficient anaemia and in 73% of iron deficient women. In normal individuals, salivary Fe\(^{3+}\) are met only in 50% of men and 32% of women\(^{27}\).

b. Salivary Ferritin in Iron Overload disorders:
The salivary ferritin shows a considerable rise in iron overload disorders. However the ratio of serum and salivary ferritin remains constant, demonstrating that there is a proportional rise in salivary ferritin and serum ferritin maintaining a constant value\(^ {23}\).

c. Salivary Ferritin in Protein Energy Malnutrition:
The salivary Ferritin is remarkably reduced in grade I PEM and shows a mild decrease in grade III PEM. Whether the change is basically related to protein deficiency or is due to low iron stores in these patients is difficult to say\(^ {11}\).

CONCLUSION
The role of saliva as a diagnostic tool has been a topic of interest in the recent years. Salivary Ferritin would add as a monitoring tool in diagnosis of iron deficiency anaemia and will aid to improve the quality of life of iron deficient individuals. Thus the presence of Ferritin in saliva could serve as a diagnostic tool in various field works and epidemiological surveys.

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Structure of ferritin: