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AN OVERVIEW ON TREATMENT OF PERIODONTAL DISEASE

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ABSTRACT:

Periodontal disease is a localized inflammatory response due to infection of periodontal pocket arising from accumulation of sub gingival plaque. It also affect the supporting structure of teeth leading to the formation of pocket due to which tooth loss occurs, for which site specific drug delivery system is gaining importance. Dental implant is a pharmaceutical device in the form of strip with very small drug loading and small size. Dental strips are the devices, containing one or more actives such as antimicrobial, antifungal, etc which are implanted into the periodontal pocket. The drug(s) with excellent activity against anaerobes, aerobes, gram negative or gram positive pathogens which are the major factor contributing periodontal disease formation are used. These strips can be prepared by using polymers, co-polymers, plasticizers, etc and then can be evaluated for their physicochemical parameters like thickness, weight variation, content uniformity and release characteristics, folding endurance, etc.

KEYWORDS: Periodontal disease, Dental implant, Dental strips.

Introduction:

1. Periodontal Disease:

Oral health is an important aspect of overall health status of an individual. Teeth and their supporting (periodontal) structures are of main importance to oral health[1-3]. Dental diseases are among the widest spread chronic disorder affecting mankind.

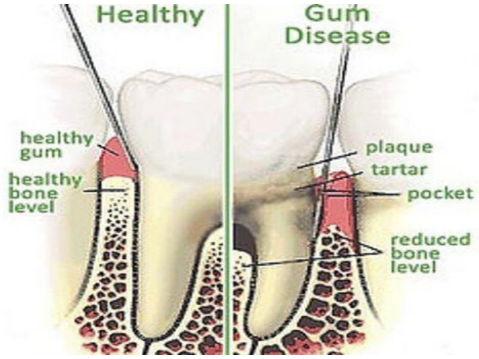

Figure 1: Healthy V/S Gum Disease.

The word “Perio" means around, and "dontal" refers to teeth. Periodontal Diseases are group of conditions, including Gingivitis and Periodontitis, which affect the supporting structures of the teeth such as gums, periodontal ligaments, alveolar bone and dental cementum. Periodontal disease is a localized inflammatory response due to infection of periodontal pocket arising from accumulation of sub gingival plaque (Haffajee et al., 1986) [4]. Gingivitis, the mildest form of periodontal disease, is highly prevalent and readily reversible by simple, effective oral hygiene. Gingivitis affects 50–90% of adults worldwide. Inflammation that extends deep into the tissues and causes loss of supporting connective tissue and alveolar bone is known as Periodontitis. Periodontitis results in the formation of soft tissue pockets or deepened crevices between the gingiva and tooth root. Severe Periodontitis can result in loosening of teeth, occasional pain and discomfort, impaired mastication, and eventual tooth loss [5-7]. Disease occurs at individual periodontal sites and leaves an historical record of the damage to the periodontium in the form of periodontal attachment or bone loss [8].It is initiated by bacteria that colonize the teeth and infect their surrounding soft tissues [9].

Periodontal disease, if not treated, results in the destruction of the bone and soft tissue supporting the tooth leading to tooth loss. The treatment of Periodontitis is directed at slowing down or arresting the progression of the disease by regenerating the alveolar bone, periodontal ligaments, and root cementum and preventing recurrence of the disease. Conventional therapy, based on scaling, surgery and the use of antibiotics or antimicrobials has been proposed. But due to bacterial resistance and toxic side effects of the administered antibiotics local delivery system are designed to maintain the antibiotic, in the gingival crevicular fluid at a concentration higher than that achieved by systemic administration [10-12].In the early stage of Periodontitis, scaling and root planning is usually effective in removing calculus and plaque, thereby, reducing bacterial count and probing depth. As the probing depth increases, the effectiveness of scaling and root planning decreases. Therefore, in recent years, many antibiotics are either topically or systematically used in the treatment. Systemic antibiotic therapy has certain advantages. However, long-term use of systemic antibiotics is associated with several side effects such as development of resistance, hypersensitivity, and unwanted side effects [13].

In the early phase of the disease, the gingiva is inflamed and extended to deeper tissues in Periodontitis, leading to gingival swelling, changes in the morphology of gingival tissues, bleeding upon probing and bad breath. In the late phase of the disease, the supporting collagen of the periodontium degenerates, alveolar bone began to resorbs and the gingival epithelium along the tooth surface migrated to “periodontal pocket” formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria [14]. However, the periodontal pocket remains to harbor the bacteria associated with the disease, potentiate for a further destructive phase exist in which the teeth may be lost.

Periodontitis develops in specific site manner; it does not occur in everyone with uncontrolled dental plaque, on all the teeth of susceptible or on all the surfaces of these teeth [15].Different sites within an individual may be infected with different numbers and different species of pathogens as well as different protective species [16].

2. Classification of Periodontal Disease [17]

The American Academy of Periodontology classification system identifies distinct types of periodontal diseases, by taking into consideration factors such as age of onset, clinical appearance, rate of disease progression, pathogenic microbial flora and systemic influences. The two major categories are Gingivitis and Periodontitis.

2.1 Gingivitis [18]:-

The mouth posses numerous cracks and crevices, where the pathological bacteria harbor. These bacteria excrete toxins as waste products in the pockets and provoke an immune response which leads to inflammation. Gingivitis does not cause loss of attachment fibers or bone supporting structures.

2.1.1 Types of gingivitis:-

a) Plaque-Associated Gingivitis:-

Gingival redness, edema, bleeding upon probing, enlargement and tenderness. Radiographic evaluation shows no signs of bone loss.

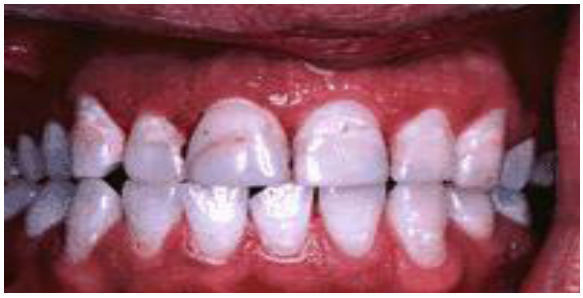

Figure 3: Plaque Associated Gingivitis.

b) Chronic Gingivitis:-

Inflammation of the gingival, resulting in loss of clinical attachment due to periodontal ligament destruction and loss of the adjacent supporting bone.

c) Acute Necrotizing Ulcerative Gingivitis:-

Patients diagnosed with Acute Necrotizing Ulcerative Gingivitis may present with the following clinical findings: Papillary necrosis, bleeding, pain and fetor oris (odor).

d) Gingivitis Associated with Systemic Conditions or Medications:-

- Hormone-Induced Gingival Inflammation:-

  Changes in the levels of circulating estrogen and progesterone can cause gingival hyperplasia, this can occur at puberty or during pregnancy. Clinical findings of patients diagnosed with Hormone-Induced Gingival Inflammation may include the following: Gingival redness, bleeding upon probing, edema and gingival enlargement associated with proliferation of blood vessels.

- Drug-Influenced Gingivitis:-

Patients that take medications such as Dilantin, Cyclosporin or Procardia often present with gingival overgrowth. This case illustrates a patient who is taking the medication Cyclosporin for treatment of a kidney transplant. Clinical findings include: Fibrotic gingival response, pseudo pockets and bleeding upon probing.

- Linear Gingival Erythema (LGE):-

  Patients that are HIV+ may exhibit this type of gingival response.

e) Gingival Manifestations of Systemic Diseases and Mucocutaneous Lesions:-

- Bacterial, Viral or Fungal:-

Two examples of cases in this gingivitis category include patients with Acute Herpetic Gingivostomatitis or Candida Albicans.

- Blood Dyscrasias (for example Acute Monocytic Leukemia) :-

Patients with a history of blood disorders, such as Acute Monocytic Leukemia, commonly leads to a compromised or reduction of the host immune response. Clinical Findings often include; spontaneous bleeding upon probing or by simply touching the gingival tissues.

- Mucocutaneous Diseases (Lichen Planus, Cicatricial Pemphigoid) :-

Examples of gingival diseases in this category include; Lichen Planus, Pemphigus Vulgaris and Desquamative Gingivitis.

2.2. Periodontitis:-

It is a set of inflammatory diseases affecting the periodontium, i.e., the tissues that surround and support the teeth. Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth. Periodontitis is caused by microorganisms that adhere to and grow on the tooth's surfaces, along with an overly aggressive immune response against these microorganisms. A diagnosis of Periodontitis is established by inspecting the soft gum tissues around the teeth with a probe (i.e. a *clinical exam*) and by evaluating the patient's x-ray films (i.e. a radiographic exam), to determine the amount of bone loss around the teeth.

2.2.1 Types of periodontitis:-

a) Plaque-Associated Periodontitis:-

Adult Periodontitis is the most common chronic form of periodontitis. The presence of local factors such as plaque is usually comparable with the disease progression.

b) Early-Onset Periodontitis:-

- Prepubertal:-A rare periodontal disease, onset is often during or immediately following eruption of the deciduous dentition. Clinical findings include generalized severe and rapid destruction of bone. Other medical conditions are usually present.
- Juvenile Periodontitis:- In these patients, local factors are minimal, there is rapid loss of attachment, bilateral symmetry is common, destruction of bone is often localized to first permanent molars, permanent incisors but can be generalized destruction, and mild to moderate inflammatory response.
- Rapidly Progressive:- This case is a young female diagnosed with Rapidly Progressive Periodontitis. In these type of cases, clinical manifestations of inflammation may be present, local factors are minimal, generalized severe and rapid bone destruction occurs.

c) Periodontitis Associated with Systemic Diseases:- With certain systemic conditions the inflammatory response is altered in the presence of local irritants thereby, accelerating the progression of periodontal disease. The patient in this case has a history of Diabetes

d) Necrotizing Ulcerative Periodontitis:- Necrotizing Ulcerative Periodontitis can be described similar to Acute Necrotizing Ulcerative Gingivitis. Findings may include erythema, ulceration and necrosis of the gingival margin, with destruction of the supporting bone. The deep interdental osseous craters are distinctive when compared to other types of bony defects found in periodontal diseases.

e) Refractory:- These types of cases normally do not respond to "well-executed" periodontal therapy.

f) Peri-implantitis:- This is a new category established by the AAP. Patients in this category have implants that exhibit a "periodontitis-like-process" similar to natural teeth.

3. Causes of periodontal diseases:

The search for the etiological agents for destructive periodontal disease has been in progress for over 100 years. However, until recently, there were few consensus periodontal pathogens. Some of the reasons for the uncertainty in defining periodontal pathogens were determined by the following circumstances (Haffajee and Socransky 1994; Socransky et al. 1987):

- The complexity of the subgingival microbiota:

Over 30–1,000 species may be recovered from a single site.

- *Sample taking*:

The physical constrains of a pocket make it difficult to obtain a representative sample from that pocket.

- Difficulties *in cultivation, characterization and identification of micro-organisms of plaque*:

No single medium or environment is capable of recovering all of the organisms, which currently can be isolated from subgingivalplaque.

- *Mixed infections*:

Not only single species are responsiblefor disease. If disease is caused by a combinationof two or more microbial species, the complexity increases enormously.

- *Opportunistic microbial species*:

The opportunistic species may grow as a result of the disease, taking advantages of the conditions produced by the true pathogen. Changes in the environment such as the release of required substrates from damaged tissues or deepening of the periodontal pocket could be selected by certain opportunistic species. Their levels may increase concomitant with or after those of the true pathogens and they may thus be difficult to distinguish experimentally.

- *Disease activity*:

Periodontal disease appears to progress with periods of exacerbation and remission.

- *The carrier state*:

Pathogens may be carried in low numbers in mouths that are free of destructive periodontal diseases (the so-called carrier state), making their role in disease more difficult to evaluate.

- *Virulent factors*:

Strains of putative pathogens may differ in virulence. A virulent clonal type might be detected in periodontally healthy subjects, whereas virulent clonal types might be present in subjects with periodontal disease [19-20].

- Periodontal pathogens:

About 500 bacterial species have been identified within human oral cavity [21].*Porphyromonas gingivalis*, *Bacteroides forsythus*, and *Treponema denticola* were identified from multiple subjects. *Actinobacillas actinomycetemcomitans* (for juvenile periodontitis), *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Fusobacterium nucleatum, Prevotella intermedia, Eikenella corrodens, Eubacterium nodatum, Campylobacter rectus* and additionally, facultative anaerobes such as *Staphylococcus aureus, Staphylococcus epidermidis* have synergistic effects [22-25].

Microbes must be able to attach to periodontal tissues,Multiply,Compete with other microbes in their habitat anddefend them from host defense mechanisms.

- Genetics, Stress, Malnutrition, Diabetes, Smoking/Use of Tobacco, Pregnancy and Puberty, Medications.

4. Treatment for periodontal disease :

Once periodontal disease has been diagnosed, scaling and root planning is effective. But as the periodontal pocket increases, effectiveness of this therapy decreases.Other treatments includes: (1) surgical pocket elimination or reduction, (2) modified Widman flap surgery, (3) sub gingival curettage [32]. Antimicrobial therapy may be a useful supplement to scaling and root planning, particularly in moderate-to-deep pockets where bacterial control is unpredictable (Waerhaug 1978) [33, 34]. Moreover antimicrobial resistance, surfacing of untoward reactions owing to systemic consumption of antibiotics has further advocated the use of local delivery of physiologically active substances into the periodontal pocket. While antimicrobials polymerized into acrylic strips, incorporated into biodegradable collagen and hollow permeable cellulose acetate fibers, multiparticulate systems, bio-absorbable dental materials, biodegradable gels/ointments, injectables, mucoadhesive microcapsules and nanospheres will be more amenable for direct placement into the periodontal pockets.

The systemic drug administration has been used in conventional treatments but the disadvantage is that the drug is diluted several thousand folds before it reaches the site and exposes the rest of the body to potential side effects [35].To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to administer this type of drug delivery systems several times a day. This results in a fluctuated drug level. Hence, Local antimicrobial therapy has been considered for use in the treatment of chronic periodontal disease, resulting in a lower dose of drug [36].

Further, it is necessary to achieve the controlled drug delivery which maintains the therapeutic concentration of drug for a prolonged period of time and sustains the drug action. This factor and repetitive dosing and unpredictable absorption lead to the concept of Controlled Drug Delivery System.

Site-specific therapy has three potential advantages: decreased drug doses, increased drug concentration at the site of infection, and reduced systemic side effects such as gastrointestinal distress [37]. Periodontal disease treatment with a localized drug delivery system aims at delivering a therapeutic agent at a sufficient level inside the periodontal pocket and at the same time minimizes the side effects associated with systemic drug administration. Hence, drug delivery systems containing antimicrobial agents are used for delivery to the periodontal pocket. The use of a topical antimicrobial agent for treatment of periodontitis is generally preferred as it allows direct access of high local concentration of antimicrobial agents [38].

Periodontal disease can be treated by 2 ways:-

4.1. Surgery:

Insertion of Dental Implants [39]

A dental implant is an artificial tooth root that a periodontics places int replacemen ooth or bridge. It requires surgery and are made up of inert material like titanium, ceramics, silica, etc

- Advantages:-

1) Dental implants will preserve bone and significantly reduce bone resorption and deterioration that results in loss of jaw bone height.

2) Dental implants have been shown to reduce the need for subsequent restorative intervention of adjacent teeth.

3) Long term data on implants suggests that implants last for a much longer time than conventional restoration on teeth.

4) Implant over dentures may allow you to chew your food better and speak more clearly. Many studies have shown that over dentures contribute to improved chewing efficiency and speaking, compared to full dentures.

- Disadvantages [40]:-

1) Cost: As compared to the other alternatives for replacing a missing tooth or teeth, cost is quite high.
2) Surgery: Dental implant requires surgery. As the implant have to be placed into your bone and surgery is not without risk. Risk such as infection, prolonged bleeding, damage to other teeth, nerve damage, delayed bone healing, jaw fracture, etc.

3) Loss of Bone: over many years, slight bone loss is normal around the dental implant, if the loss is more; whole implants have to be replaced.
4) Biocompatibility: Of the Implant material used.
5) Time: It's the most common disadvantage. Length of time required from initial dental implant placement to implant restoration. Treatment time varies from approximately 3-6 months and this depends on the area where the implant is placed and the quality of the bone.
6) Damage to the sinus cavities: the sinus cavity which is connected to the sinuses is also directly linked to the bone where the Dental Implant is secured.
7) Restoration replacement: dental implants have to be replaced some day.

4.2. Drug delivery system:-

a) Systemic Route [41]:-

Antibiotics by systemic routes play a synergistic role with scaling and root canalling. The systemic drug administration has been useful in treating periodontitis but the disadvantage is that, drug is diluted several thousand folds before it reaches the site and exposes the rest of the body to potential side effects. This problem can be overcome by administering the drug directly to the intended site of action with lesser dose [42].

b) Local Drug Delivery System [43]:-

Localized drug delivery to the mouth is used for the treatment of conditions of the oral cavity, principally aphthous ulcers, fungal conditions and periodontal disease.

Local drug delivery devices are of two types:-

- In the first type, the drug delivery system is designed to deliver agent locally in the periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time. Such devices generally exhibit exponential increase and decrease in drug concentration at the site.
- Second type is the controlled release local drug delivery devices which may secure antimicrobial effect for a prolonged period of time at the diseased site, than that can be achieved by systemic or local topical applications and also by passes the systemic complications.

Types of local antimicrobial agent therapy include:

A. Personally applied (in-patient home care system)
a) Non-sustained subgingival drug delivery (home oral irrigation).
b) Sustained subgingival drug delivery (yet to be developed).\
B. Professionally applied (in dental clinics)
a) Non-sustained subgingival drug delivery (Professional pocket irrigation).
b) Sustained subgingival drug delivery (Controlled drug release devices).

Controlled drug delivery is designed to release the drug slowly for prolonged period of time sustaining the drug action. These drug delivery systems are commonly referred as sustained release, prolonged release, controlled release, timed release and slow release.

These drug delivery systems ensure therapeutic concentrations of drug release in the gingival area for atleast 3 days following single application [44]. These systems are mostly polymer based with diffusion of drug across a rate controlling membrane. These devices are categorized as:

1. Reservoir Devices/ Membrane Diffusion Systems [45]:

These drug delivery systems include dialysis tubing 3-5 mm long, 0.2 mm wide containing a core of drug solution which is left in the pocket for a week. Reservoir devices that lack rate control include hollow fibres, gels and dialysis tubing. These systems tend to release drug very quickly and only marginally qualify as sustained release devices. The problems associated with these devices are irritation of the pocket, premature loss from the pocket and rapid drug release.

2. Monolithic Devices [46]:

Bioabsorbable, biodegradable materials can be left in situ. This eliminates the risk of disturbing a site after therapy. The controlled release local delivery devices (monolithic) are usually polymers (films/fibres) containing homogeneously dissolved or dispersed drug.In these devices, the drug is dispersed in a solid polymer matrix. Examples include acrylic strips and ethylene vinyl acetate (EVA) fibres. Acrylic strips are typically 0-2 mm thick. Treatment is carried out over 2 - 4 weeks, with a replacement of new strips inserted each week. Drug release occurs over a period of 10 - 14 days. Strips tend to be lost from the pocket. This can be avoided by applying periodontal dressing. Other monolithic devices include strips made of ethyl cellulose (EC), poly ethylene glycol (PEG), Hydroxy propylmethyl cellulose (HPMC) and cross linked collagen films

3. Gels:

Gels include poly (ethylene oxide) and white petrolatum. This provides advantage of syringeability and therefore eases placement. But this type of drug delivery systems have disadvantage of rapid release of drug.

4. Hybrids:

Hybrids combine features of more than one class of devices mentioned above. One example is the microencapsulated drug polymer spheres (monolithic device), approximately 0.2 mm in diameter. These spheres are carried in a thermosetting gel which becomes more viscous at body temperature. This aids retention and placement as the device is syringeable.

5. Methods of preparation [47]:

5.1. Solvent casting:-

In this method, film base is prepared by dissolving the polymer, excipient and active drug in suitable solvent and to form a viscous solution that is then spread on a flat, non-adhesive surface; then the solvent slowly evaporates. The resultant polymer film is then peeled from the surface.

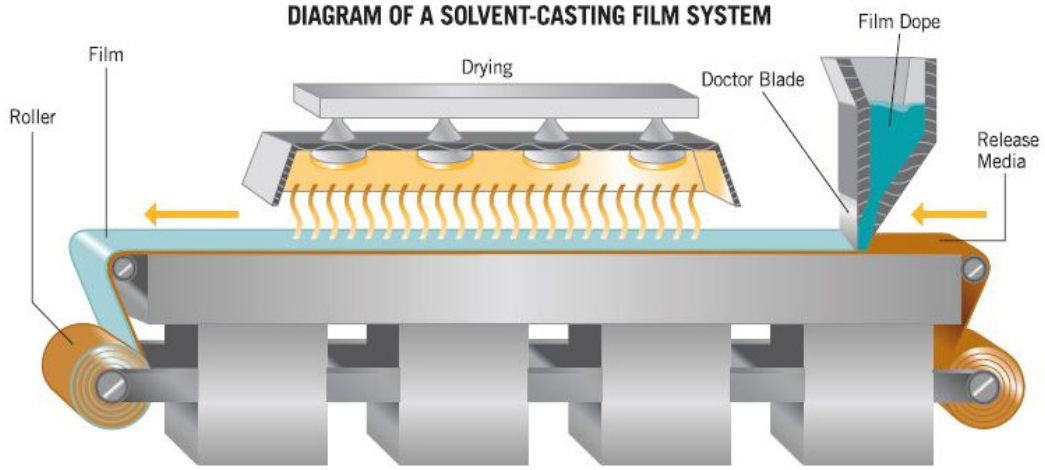

Figure 3: Solvent casting method

On laboratory scale, the thickness of the polymer is controlled with a "Gardener Knife" a device that allows micrometer adjustments of a blade height above the casting surface. Industrially, rotating metal drums or moving belt systems.

5.2. Hot melt extrusion:-

This technique involves shaping of the polymer into a film with the help of heating process. In this method the API and other excipient are mixed in dry state which are then subjected to heating and then extruded out in molten state. In this process solvent system is not used. The molten mass so formed is used to cast the films, which are then cooled and then cu to the desired size. The main disadvantage of this process is the use of high temperature which may degrade thermo-labile Active Pharmaceutical Ingredient.

5.3. Solid dispersion extrusion:-

This technique refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in presence of amorphous hydrophilic polymers and also it uses the method of melt extrusion. In this, the dug is first dissolved in a suitable solvent and then the solution is incorporated into the melt of suitable polymer, obtained below 70^0C without removing the liquid solvent.

5.4. Rolling method:-

The film is prepared by pre mixing of an active ingredient and excipient followed by addition of solvent. Then the film is formed on to the inert substrate and is carried away via the support roller. Then the wet film is dried using controlled bottom drying in absence of external air currents or heat on the top surface (exposed) of the film.

5.5. Polymerization in situ:-

This method is used for preparation of sheets of cross-linked polymer sheets in which drug can be incorporated. A liquid polymer or pre polymerized inside a suitable mould. The release from monolithic devices depends on diffusion of drug through matrix. By manipulating the system, selecting the ideal polymer, adjusting the cross-linking, fillers, and plasticizers and by using co-polymers, release of some low molecular drug can be achieved. For an antimicrobial agent to be successful the pathogen must be known, it must be susceptible to the drug. It should not readily develop resistance for an adequate period of time. Also the drug should have little or no side effects.

Conclusion:

Although a comparison of surgical and non-surgical periodontal therapies may provide an interesting academic discussion, the prudence of such a comparison is highly arguable. Decision making in periodontal therapy requires a thorough understanding of the long term outcomes of all available treatment modalities.

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