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## Chapter

# Gender-Associated Oral and Periodontal Health Based on Retrospective Panoramic Radiographic Analysis of Alveolar Bone Loss

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## Abstract

Gender-based heterogeneity in periodontal disease has been witnessed in the recent past with huge mounting evidence. The composite effect of sex-based genetic structure and the sex steroid hormones runs in line with the corresponding gender-related differences in risk for chronic periodontitis. Since estrogens, the predominant sex hormones in women, show immune protective and anti-inflammatory effects in hormonally active premenopausal women, they show better periodontal status compared to age-matched men. Conversely, after menopause with a weakening estrogen signal, women may show an equal or even more serious periodontal status compared to men. Periodontal status of postmenopausal women may be improved by menopausal hormone therapy. Alveolar bone loss, an irreversible sign of past periodontal disease activity can be easily observed on radiographs in an objective manner. Orthopantomographs provide a fairly accurate assessment of the status of alveolar bone in the whole mouth. A cross-sectional retrospective panoramic radiographic analysis has been carried out in a north Indian dental institute to decipher the gender-based distribution of periodontal bone loss. The current chapter shall provide an update on gender-based differences in oral health, underlying mechanisms, differences in patterns and distribution of alveolar bone loss (case study), and potential gender-specific disease protection and management strategies.

**Keywords:** oral health, periodontal, gender, alveolar bone loss, radiography, panoramic

## 1. Introduction

Many human diseases, specifically chronic immune-mediated diseases, present differentially in males and females [1]. Differential gene expression and immune system in the human body guided by sex steroid hormones are responsible for the differential physiologic constitution of the two genders [2]. Chronic periodontal disease is an immune-inflammatory disorder affecting teeth and

supporting tissues, inducing the destruction of alveolar bone, and ultimately leading to loss of teeth if it remains untreated. As evidence of periodontal infection's influence on overall chronic inflammatory disease states of human body continues to mount from last two decades, a whole new concept of the status of the oral cavity and its impact on systemic health and disease has evolved. Immense research efforts have been directed toward better understanding of the prevention and control of human periodontal diseases that have been warranted in the recent past [3].

Enhanced understanding regarding the causation mechanisms of human periodontal disease in the recent past and the identification and recognition of the potential significant susceptibility factors, which are a part of the causal chain for initiation and progression of periodontal disease, have led to focused research into specific risk factors for periodontal disease. Greater age [4–8], male sex [9, 10], bacterial plaque [4, 8], and smoking [8, 11–13] have been linked with an increased susceptibility to periodontal disease [14].

Epidemiological investigations have explored the role of these risk factors for periodontal disease causation and treatment needs of populations. A risk factor may be anything like environmental exposure, a behavioral aspect, or a constitutional feature which may enhance the chances of occurrence of disease. The term “determinant” is generally used interchangeably with risk factors, but it is more appropriate to limit its usage for the risk factors that cannot be modified, for example, age and sex. Readers are referred to go through many elaborate and exhaustive reviews on these particular aspects to enhance their understanding regarding differential risk and risk factors of periodontal diseases [15]. The current chapter shall provide an update specifically on gender-based differences in oral and periodontal health, underlying mechanisms, differences in patterns and distribution of alveolar bone loss (based on the case study), and potential gender-specific disease protection and management strategies.

## **2. Periodontal disease**

Periodontal diseases primarily comprise the two most common oral inflammatory disorders, that is, gingivitis and periodontitis, which are caused by microbes residing in the subgingival dental plaque. To name a few, primary pathogens like *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, and *Treponema denticola* trigger an immune reaction from the host, including innate, inflammatory, and adaptive components causing major part of the tissue destruction indirectly. Direct damage from the microbial products constitutes a minor part of the total tissue loss [16, 17]. Gingivitis is an inflammation of the gingiva, limited to soft-tissue compartment of the gingival epithelium and connective tissue only and the tooth does not suffer an attachment loss [18]. Periodontitis, on the other hand, is an inflammation of the supporting tissues of the teeth with progressive attachment loss and bone destruction [19, 20].

Many investigations have been conducted in diverse areas worldwide. A variable, yet significant prevalence of the periodontal disease has been noted, which amounts to an enormous disease burden in the domain of public health. The National Institute of Dental and Craniofacial Research refer to periodontal diseases as the leading cause of tooth loss in adults [21]. In 2013, Marcenes et al. ranked periodontitis as the sixth most prevalent condition while estimating the global burden of oral conditions from 1990 to 2010 [22]. Moreover, severe periodontitis is considered as the primary cause of disability-adjusted life years (DALYs) in the age-group of 35- to 59-year-old. Several studies have reported the prevalence of periodontitis in

the United States [23, 24]. The overall prevalence of periodontitis was 66% for all seniors 65 years of age or older with males being predominantly affected [25].

Prevalence of the periodontal disease varies in different regions of the world and a higher prevalence and severity of periodontal disease in Asian countries has been reported [26]. The authors looked into the geographic and economic risk factors, oral health distribution and practices in these vast groups of countries to enhance understanding regarding the oral health care needs and formulating health policy decisions [27]. A study from Pakistan revealed that 63.5% of the subjects had Community periodontal index score  $\leq 2$  while 34.5% had  $\geq 3$ . Age, gender, occupation, smoking, diabetes, arthritis, cardiovascular disease, kidney disease, stress, medications, and oral hygiene habits of using tooth powder or tooth brushing were significantly associated with periodontal status [28]. Multiple studies to understand the occurrence, prevalence, and all associated factors have been carried out in many states and across the country in India also [29–34]. A systematic review pointed out that due to lack of homogeneous studies, it is difficult to estimate an overall prevalence rate. A nationwide multicentric prevalence studies initiative is needed to obtain the true prevalence rate of periodontal disease in India so that interventions should be provided for the same to maintain the oral health and quality of life of the affected population [29–34].

## **2.1 Clinical features of periodontitis**

Generally speaking, periodontal disease is a chronic silent disease, which barely has any symptoms at an early stage. Most patients suffering from chronic periodontal disease seek treatment very late by the time the disease has progressed significantly. Redness or bleeding of gums with or without tooth brushing or flossing or biting into hard food, repeat episodes of gingival inflammation, oral malodor or bad breath, and a persistent metallic taste in the mouth. In progressed disease, gingival recession, resulting in loss of gums exposing the roots of teeth, deep pockets between the teeth and the gums mobile teeth, in the later stages, drifting and flaring of incisors, increased spacing between the teeth, tendency to dig between the teeth, packing of food in between teeth, itchy gums, sensitivity to hot and cold foods. Periodontal disease is generally regarded as painless. Patients generally consider only bleeding without pain from gums with or without brushing as an insignificant sign; however, this may be indicative of ongoing disease activity and progression of chronic periodontitis. Poor oral hygiene, soft sticky deposits, that is, dental plaque and hard mineralized subgingival as well as supragingival calculus are frequent findings of periodontal disease [35].

## **2.2 Periodontal pathogenesis**

Periodontitis is a chronic multifactorial disease causing inflammation of the supporting tissues of teeth mediated by the host, which is associated with an imbalance in the existing microbial flora in dental plaque and resulting in a continuous loss of tooth-supporting apparatus [36, 37]. The bacteria in the dental plaque are the essential initiators of the gingival inflammation; however, not all cases suffering from gingivitis progress into periodontitis. This transition is largely determined by the host immune response. Once gingival inflammation is set in, tissue microenvironment changes and causes an alteration in the microbial ecology and also in host response mechanisms against the residing bacteria. This leads to the stimulation of several key molecular and cellular signaling pathways, which ultimately activate host-derived collagenases [matrix metalloproteinases (MMPs)] which are responsible for tissue destruction. Such lytic process cause loss of principal fibers of the

periodontal ligament, apical migration of the gingival attachment, and allows apical extension of biofilm and subjacent inflammation along the root surface and further spreads the disease process [36]. It leads to loss of clinical attachment, pocket formation, sometimes gingival recession, and radiographically accompanied bone loss [37, 38]. Gingivitis is a completely reversible disease process and the essential first step to progression to periodontitis, suggests periodontitis can be prevented at its early stage, yet it remains one of the most common causes of tooth loss. Therefore, prevention and early detection of periodontal disease are essential to reduce the damages it implies to the oral and systemic health of the individual.

### **2.3 Alveolar bone loss in periodontal disease**

Alveolar bone loss is a characteristic sign of advanced periodontitis and ongoing bone loss is characteristic of the progression of periodontitis. The prevention of periodontal disease progression and bone loss is a key clinical challenge in periodontal therapy. Bone destruction is an eventual outcome of the host immune and inflammatory response and the dental plaque microbial challenge interplay. However, the underlying mechanism of disruption of the homeostatic balance of bone formation and resorption in favor of bone loss in these clinical situations remains to be understood.

#### *2.3.1 Immunopathogenesis of periodontal bone loss*

In chronic periodontal disease, many bioactive microbial molecules from dental plaque incite an immunological response from the resident and immune cells present in gingiva and periodontal tissues [39]. This leads to an influx of multiple cytokines that mediate the biochemical pathways of inflammation, for example, PGE<sub>2</sub>, IL-1, TNF-alpha and RANK-L, etc., which are responsible for osteoclastogenesis, the primary bone-resorbing process. Thus, the pathologic inflammatory process disrupts the fine balance between protective and destructive processes and leads to initiation of osteoclastic activity [40–45]. “Osteoimmunology” is the science which is dealing with the understanding of the intricacies of this immune-mediated bone destruction [46, 47]. The cellular inflammatory infiltrates of periodontal immunity cells such as T cells, B cells, macrophages, and neutrophils are increased within the gingival connective tissue and a concurrent increase in the inflammatory mediators’ production is also evident [48, 49]. RANKL-mediated osteoclastogenesis is the prime mechanism underlying the inflammatory bone resorption in periodontal tissues [43, 50]. Activated T and B lymphocytes in inflamed periodontal tissues are the prime producers of RANKL- [43, 44, 51, 52]. An increase in osteoclast numbers on the alveolar bone crest has been observed in animal studies where antigen-specific lymphocytes are present and which can be suppressed by OPG [51, 53, 54].

Heterogenous populations of gingival fibroblasts are involved in dual actions in the inflammatory process. They are documented to have a protective role to suppress osteoclast formation as they produce OPG in response to LPS and IL-1; however, they may also augment chronic inflammatory processes through IL-6 and IFN production. The known periopathogens *Aggregatibacter actinomycetemcomitans* (*Aa*) and *Porphyromonas gingivalis* (*Pg*) induce the production of RANKL from the resident cells of periodontium viz. osteoblasts and gingival fibroblasts. Recently, it has been shown that an increased RANKL/OPG ratio is associated with periods of tissue destruction and ongoing disease activity. This ratio is further upregulated in patients in the presence of other known risk factors, for example, smokers and diabetics [55]. It has also been reported that the molecular mechanisms of T cell-mediated regulation of osteoclast formation occurs through cross talk signaling between RANKL and IFN-gamma [56].

### 2.3.2 Patterns and trends of alveolar bone loss

Periodontitis is usually asymptomatic chronic inflammatory condition caused by bacterial aggregation which affects the crest of the alveolar process by reducing the normal height in a vertical and/or a horizontal manner; furthermore, bone loss might be presented in a localized or a generalized form [35]. Bone destruction can be detected using several radiographical techniques that evaluate the quantity of the remaining bone and subsequently estimating the amount of bone loss on a radiograph. Panoramic radiography has a little diagnostic value in the identification of periodontal disease. It is useful to obtain the overall generalized status of bone, rather than very fine or precise details. However, it can be used as a valuable adjunct to conventional diagnostic procedures. It can be recommended as a part of routine dental and periodontal assessment which captures the entire maxilla-mandibular radiographic image on a single film. However, a panoramic radiograph should not be used to replace other intraoral radiographic techniques. Semenoff et al. assessed variations between different dental radiographs for assessment of the interseptal bone crest loss on conventional and digitized periapical, bitewing, and panoramic radiographs. Comparison among them showed that a small reduction in height of the interseptal bone crest observed in panoramic radiographs should be carefully evaluated for overestimation. Moreover, several studies proposed that panoramic radiography might serve as a diagnostic aid in dental health evaluation programs [57].

### 2.3.3 Bone destruction patterns in periodontal disease

Periodontal disease may affect the bone, altering its morphologic features in addition to reducing the vertical level of the bone height. An understanding of tissue mechanisms causing these alterations is important for effective diagnosis and effective treatment modalities.

I. Goldman and Cohen 1958 [58]: Classified infrabony defects based on the location and number of osseous walls remaining about the pocket as.

- Three osseous walls:
  - Proximal, buccal, and lingual walls
  - Buccal, mesial, and distal walls
  - Lingual, mesial, and distal walls

These trough-like defects are mostly seen in the interdental areas. These may exist as either shallow and wide lesions or deep and narrow ones.

- Two osseous walls:
  - Buccal and lingual walls (crater)
  - Buccal and proximal walls
  - Lingual and proximal walls

Two wall infrabony pockets may also occur in the interdental areas. With the buccal and lingual walls intact, but lost proximal wall, the lesion is termed as an intraosseous interproximal crater.

- One osseous wall:
  - Proximal wall (hemiseptum)
  - Buccal wall
  - Lingual wall

Generally in these lesions, a proximal wall is present with both buccal and lingual walls' resorbed.

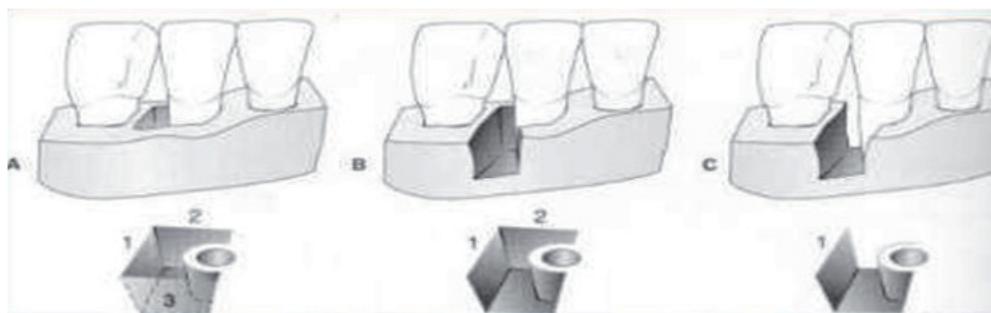
- Combination:
  - 3 walls +2 walls
  - 3 walls +2 walls +1 wall
  - 3 walls +1 wall
  - 2 walls +1 wall

They may be seen in a variety of combination forms and can be located on a single or multiple surface of a tooth (**Figure 1**).

II. Karn KW et al. 1983 [59]:

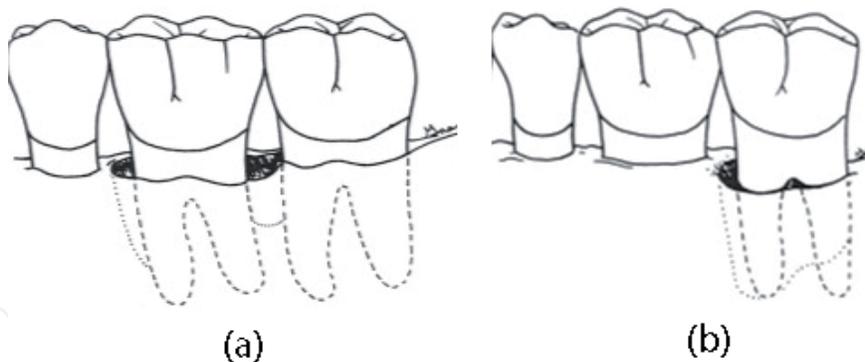
1. When the original topography of the alveolar process is altered by uniform loss of bone from around the teeth and the plan of bone remains perpendicular to the long axis of the tooth: Horizontal bone loss
2. Deformities created by nonuniform loss of bone are based on the following basic terms:

- a. Crater: A crater is formed as a result of loss of alveolar bone and a portion of the contiguous supporting alveolar bone from only one surface of a tooth. They are identified by the mesial, distal, facial, or lingual tooth surface involved. Craters may be confluent if they occur on adjacent proximal surfaces, and termed as two-surface craters (affecting two tooth surfaces), named with two teeth involved.

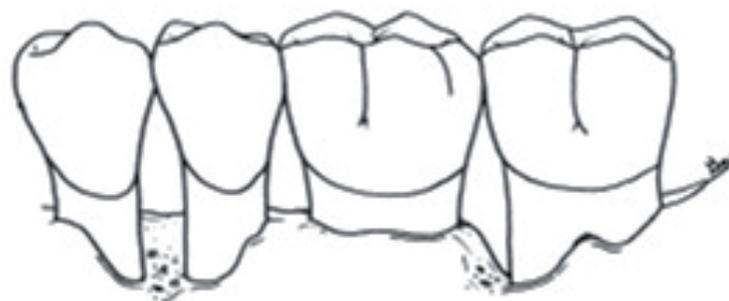


**Figure 1.**  
*Showing wall defects.*

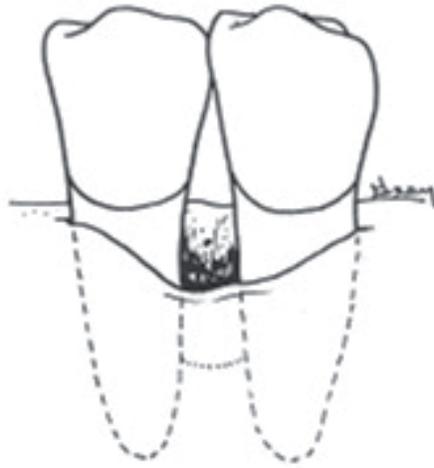
- b. Trench: When bone loss as mentioned for crater affects two or three confluent surfaces of the same tooth, it is known as a trench. Trenches can be similarly identified by the tooth surfaces involved (e.g., mesiofacial and mesio-lingual- distal). There are eight possible types of trenches (MF, ML, DF, DL, MFD, MLD, FML, and FDL).
- c. Moat: When bone deformities involves all four surfaces of a tooth. Only the tooth number is necessary to identify it (**Figure 2**).
- d. Ramp: When both alveolar bone and its supporting bone are lost to the same degree but that the margins of the deformity are at different levels, it is known as Ramp. These are named for the tooth surface aspect from which the greatest bone loss has occurred and the teeth involved.
- e. Plane: It is similar to ramp but the margins of the deformity remain at the same level. It can be considered horizontal bone loss about one tooth or portion of a tooth (**Figure 3**).
- f. Cratered ramp: If only the most coronal rim of the deformity were considered, it would represent a ramp. However, a crater is presenting apical to the entire extent of the ramp and hence the term “cratered ramp.” It is basically a crater with a portion of its facial and/or lingual wall missing. Cratered ramps are named for the teeth involved, the aspect of the alveolar process from which bone has been lost in the ramp portion and the tooth surfaces involved with the crater (or trench) (**Figure 4**).



**Figure 2.**  
*Showing a moat type of bone defect.*



**Figure 3.**  
*Showing a plane type of bone defect.*



**Figure 4.**  
*Showing cratered ramp type of bone defect.*

g. Ramp into A Crater or Trench: Its salient characteristic is that it is a ramp in the coronal aspect, but distinctly a crater or trench in the apical portion (**Figure 5**).

h. Furcation invasions: It refers to the involvement of the furcation area of the teeth by any kind of bone loss patterns described above.

III. Prichard JF 1983 [60]: Classified the bone defects as follows:

a. Intrabony defect: It is surrounded by bony walls on three sides and the root of tooth forming the fourth wall. The walls may be at different levels coronally forming combinations with other defects, but only the “inside” of the defect, the part that is apical to all three bony walls, is “within” bone or intrabony. They are also found in the apical region where the base of the arch is usually wider than the crest.

b. Hemiseptum: Periodontitis may affect one tooth and destroy septal bone adjacent to that tooth without affecting the contiguous tooth, thus leaving a hemiseptum of interalveolar bone.



**Figure 5.**  
*Showing ramp into a crater type of bone defect.*

- c. Inconsistent margins: Destruction of marginal bone usually creates what Schluger called an inconsistent margin and on the tooth root the marginal defect may expose a furca. Across the interproximal space, the inconsistent margin may be associated with a crater or a hemiseptum.
- d. Crater: A crater is a wide-mouthed cup or bowl-shaped defect in the interalveolar bone, with bone destruction about equal on the roots of the contiguous teeth; the sidewalls of the crater are formed by marginal bone on the vestibular and lingual surfaces.
- e. Furca involvement: In the maxilla, defects in the interalveolar bone may be complicated by exposure of a furca and there may be bone destruction in the interradicular area.

### *2.3.3.1 Progression of periodontal disease*

The earlier viewpoint regarding the progression of periodontal disease was that bacterial plaque accumulation universally leads to gingivitis, with subsequent progressive destruction of the supporting tissues of periodontium, with continuous irreversible attachment loss and bone resorption over time. Such conclusions have mostly come from observing cross-sectional populations over long periods of time. Later in order to determine the rate, pattern, and course of bone loss, researchers longitudinally studied subjects with repeated clinical and radiological measurements of patients suffering from periodontitis. Papapanou and coworkers [61] studied over 200 subjects with full-mouth radiographic surveys taken 10 years apart. The findings revealed that the mean annual rate of bone level resorption varied by age. Subjects between the ages of 25 and 65 years exhibited between 0.07 and 0.14 mm/year; whereas subjects over 70 years of age had a significantly higher rate of bone loss (0.28 mm). This particular investigation gave an insight into the trend of alveolar bone loss that it was continuous, slowly progressive, but with a great deal of the variable rate of progression among teeth and subjects. A similar 6-year long study in elderly Chinese subjects also revealed the individual range of bone loss varied dramatically from 0 to 0.53 mm/year [62]. Similar observations had been seen from the previous classically cited study by L oe and coworkers in Sri Lankan tea workers [63], which also reported huge differences in the rate of periodontal destruction among individuals.

Goodson and coworkers [64] challenged the prevalent belief system at that time that oral bone loss proceeded in a gradual fashion. In a series of studies, they examined the individual tooth site for progressive bone loss [65–68]. Among 22 untreated subjects with existing chronic periodontitis and pockets due to bone loss, only 15 subjects witnessed significantly deeper pockets over a time span of 1 year, whereas the other tooth sites rather showed a gain in attachment and reduction in the existing pocket depths. This investigation provided the evidence that alveolar bone destruction associated with periodontal disease was a dynamic condition and exhibited exacerbations and remissions of the disease activity over a period of time. This led to the emergence of “burst model” for periodontal disease progression pattern which had irregular bouts of the disease activity as opposed to continuous slow bone destruction over time. These classic studies utilized conventional manual probing to measure clinical attachment-levels to identify specific sites exhibiting more than 2 mm of progressive attachment loss and merely 5% of tooth sites exhibited progressive attachment loss. Another study [69] revealed 29% of the tooth sites showing progression over a 6-month period in adult patients previously diagnosed

with periodontitis, by utilizing a more sensitive electronic probe to measure attachment loss. Modeling of the data over time showed that 76% of tooth sites lost attachment consistent with linear patterns, 12% of tooth sites showed exacerbations and remissions, and 12% revealed bursts of disease activity. Since then, a lot of periodontal disease progression models have come into being based on diverse studies, for example, Socransky, Goodson 1984 [70]. (1) Continuous Models: Slow and continuous, constantly progressive rate of destruction throughout the duration of the disease. (2) Random or episodic burst model: Short bursts of destruction followed by periods of no destruction, random pattern of disease w.r.t. the tooth sites affected. (3) Asynchronous, multiple burst model: periodontal destruction occurs in bursts, around affected teeth during defined periods of life. The chronology of these bursts of disease is asynchronous for individual teeth or groups of teeth. The natural history and progression patterns of intraoral bone loss are yet not clearly and completely understood at this time [71].

### **3. Risk factors for periodontal disease**

Several studies' results indicated that the tooth loss associated with periodontitis was much higher than the number of persons who suffer such tooth loss [72, 73]. Although a large proportion of the population is susceptible to periodontitis, yet a very small segment of the population witnesses severe forms of periodontitis. Such observations about the differential disease susceptibility led to the emergence of the concept of risk factors impacting the periodontal disease expression [74]. A risk factor is defined as an environmental, behavioral, or biologic factor confirmed by temporal sequence, usually in longitudinal studies, which if present, directly increases the likelihood of a disease occurring, and if absent or removed, reduces the probability of the disease event. Risk factors are considered as a part of the causal chain or expose the host to the causal chain. The most salient feature of a risk factor is its temporal presence before the emergence of the disease itself. Risk factors can be both modifiable and non-modifiable. Once a disease occurs, the removal of a risk factor may not result in a cure [75–77]. Based on whether they can be modified or not and documentation of their strength of association with the consequent disease, these have been classified as different categories as risk factors per se as defined, risk determinants, risk indicators, and risk predictors. Risk indicators are probable or putative risk factors that have been identified in cross-sectional studies but not confirmed through longitudinal studies. Risk predictors/markers, although associated with increased risk for disease, however, have not been clearly known to cause the disease. Risk determinants or background factors are those which are seen to be associated with the disease, but are not modifiable.

The contemporary concept that the rate of progression, age at onset, and severity of periodontal disease in an individual are often determined by systemic risk factors in the host is a recent one, supported by epidemiologic investigations of periodontal disease and the role of an associated multitude of genetic, epigenetic and environmental risk factors.

#### **3.1 Age and gender as a risk determinant for periodontal disease**

##### *3.1.1 Age*

Epidemiological studies have revealed a higher prevalence of the periodontal disease in elderly people compared to younger age-groups. The evidence demonstrates that both the extent and severity of periodontal disease increase in older

individuals. Whether the increased prevalence and the severity in older persons are the outcomes of the lifetime accumulation of local factors such as dental plaque and microbial deposits or an inherent greater chance of susceptibility to periodontal deterioration exists in them remains largely debatable. Aging is associated with an increased incidence of periodontal disease [5, 6]. In a cross-sectional investigation of 1426 individuals aged 25–74 years, age was the most strongly associated risk factor with clinical attachment level with an odds ratio of 1.2 for persons aged 35–44 years and 9.01 for subjects aged 65–74. A stronger association between age and alveolar bone loss was seen in the same body with odds being 2.6 for people aged 35–44 years and 24.08 for age-group 67–74 years. Similar associations were reported in a large military population from the United States (1783 subjects) with an odds ratio of 5.03. Brown et al. reported contradictory findings and found age as not related to attachment loss in older individuals. Ismail et al. found that average attachment loss was greater in older individuals over a period of 28 years, though statistically not significant association, but significant in a multivariate model. Abdellatif and Bart [4] evaluated the relative significance of age and oral hygiene status as determinants of periodontitis and reported the rate of increase of periodontitis with increasing age across all age-groups was much higher for those with poor oral hygiene than those with excellent oral hygiene. They concluded that the effect of the age as a risk factor on periodontal disease progression is minimal when coupled with good oral hygiene [78]. Several studies show that the prevalence and severity of periodontal disease increase with age [79–86]. Papapanou et al. demonstrated that the mean annual rate of bone loss among the initially 70-year-old subjects was 0.28 mm compared to 0.07 on the 25-year-old individuals [86]. The increased severity of periodontal disease and bone loss with age was attributed to the time period, for how long the etiologic factors have been present in contact with the periodontal and is considered to reflect an individual's cumulative risk contact history [87]. More studies carried out in some of the developed countries show changing patterns of periodontal disease progression. These studies have shown that advanced periodontal destruction and bone loss are seldom seen in individuals under the age of 40 [83, 88]. A similar finding has been observed even in the elderly population. Studies among the elderly have shown that advanced periodontal disease affects only a small fraction of this age-group [82, 88]. However, among those with advanced disease, further breakdown does occur with increasing age [89].

Thus, the increased level of periodontal destruction observed with aging is now considered as the result of cumulative destruction rather than a result of increased rates of destruction. Thus aging is not a risk factor per se [76, 79] but enhances the susceptibility of greater incidence, prevalence, extent, and severity of periodontal disease owing to cumulative damage caused by local and other contributing etiologic factors over a period of time.

### *3.1.2 Gender*

Gender has been associated with the diverse occurrence of periodontal disease in population studies and generally, males are known to suffer greater from gum disease than females of comparable age. Males usually exhibit poorer oral hygiene compared to females also. However, when oral hygiene, socioeconomic status, age, is correlated with gender, males are found to be associated with more severe periodontal disease. Females are more hygiene and esthetics conscious and seek dental treatment more often when compared to males. In their life span, there are gingival inflammatory conditions consistent with the physiologic reproductive hormonal fluctuations at different stages, such as puberty, pregnancy, and menopause [78]. Most of the data regarding the effect of female gender on gingival and periodontal

tissues come from the clinical manifestations of inflammatory responses during specific periods of reproductive life such as puberty, pregnancy, and menopause, periods of immense alterations of female sex hormones. More gingival inflammatory diseases have been documented in association with sex steroid hormone levels, even without any alteration in the oral hygiene level of the individual. There is recent mounting evidence suggesting alterations in the male periodontium commiserating with androgen level fluctuations, in addition to most studies conducted in premenstrual females [90]. There is largely inconclusive evidence for the role of gender as a discriminating factor, in prevalence, progression, and severity of periodontal disease [3].

Numerous studies reported higher periodontal destruction among males compared to the female population. A high prevalence of periodontal disease of 73.9% was found among Chinese pre-conception women. Self-reported frequent bleeding during tooth brushing and the increased rate of periodontal disease revealed statistically significant association [91, 92]. Shaizu et al. in a systematic review and meta-analyses estimated sex-related differences in the prevalence of periodontitis. They found that sex exhibited a significant association with prevalence, reflecting a 9% difference between males and females (37.4 vs. 28.1%, respectively), although the overall effect of sex in the meta-analysis was comparatively small ( $d = 0.19$ ; 95% confidence interval, 0.16 and 0.22). They calculated the mean difference in prevalence between males and females to be the same regardless of the severity of disease threshold and after adjustment for other risk factors. They concluded that men appeared at greater risk for destructive periodontal disease than women; however, men do not appear at higher risk for more rapid periodontal destruction than women. Recently, Hass et al. [93] reported almost two-fold higher susceptibility to suffering from periodontitis but similar periodontal status in postmenopausal women not on hormone replacement therapy (HRT) as compared to premenopausal women [94]. The reasons for these sex differences are not clear but can be related to multiple aspects, for example, as a demographic, biological, genetic, or epigenetic [95, 96]. However, the relationship observed between sex and the disease is not apparent and is not considered as strong and consistent [89].

### *3.1.2.1 Periodontium as a target tissue for sex steroid hormones*

Sex steroid hormone receptors are not uniformly distributed but are found concentrated in certain hormone-sensitive tissues known as target tissues. Preferential accumulation and retention of hormones may occur depending upon the number of cytoplasmic and nuclear receptors that bind to particular hormones within the tissue. Many investigations have reported the preferential localization and retention of sex steroids, for example, estrogens [97, 98], androgens [98] and progestins [99] in periodontal tissues as well [90, 100]. The presence of specific hormonal receptors determines the response and regulates gene expression regarding the specific hormone ligand [101].

There are two kinds of estrogen receptors (a and b) which are genetically distinct forms and have differential distribution and functions [102]. Upon binding to a receptor, the activated receptor-steroid hormone complex binds with specific nuclear sites with a strong affinity. The intracytoplasmic or intranuclear activation step, followed by gene activation and transcription of mRNA finally guides the cellular protein synthesis. All sex steroids have effects on cell membranes and thus affect the second messenger systems in addition to regulation of gene transcription [103]. These activities affect neural transmission [104], modify the transport

of calcium ions into cells [105], and stimulate the intracellular concentration of polyamines [106]. The periodontium of humans and animals is equipped with all the necessary enzymatic machinery to metabolize sex steroid hormones by common metabolic pathways and increased metabolic activity has been reported in inflamed periodontal tissues [3, 100, 101, 107, 108].

### *3.1.2.2 Proposed mechanisms for sex-specific hormones effecting periodontal disease pathogenesis*

#### *3.1.2.2.1 Periodontal microbiota*

The majority of scientific investigations have not been able to identify any remarkable differences in periodontopathogenic bacteria between males and females [109–111]. Kumar et al. (2013) reviewed the effects of gonadal hormones on oral microbiota and documented only a transient alteration in the number and proportions of specific microorganisms during puberty or pregnancy [112]. So, there is not enough support that such minor and transitory relationships can bear a significant effect on susceptibility for periodontal breakdown [113, 114].

#### *3.1.2.2.2 Vasculature*

Similar to reproductive system vasculature, the blood vessels of gingiva is also responsive to sex steroid hormones. Many scientific investigations have correlated the increased flow of GCF, coinciding with the periods of fluctuation of sex steroid hormones. A comparison of the amount of gingival crevicular fluid in pregnant women versus postpartum controls has revealed approx. 54% elevation in pregnant females [115]. In a few animal studies, exogenous estrogen and/or progesterone administration has shown a significant increase in the amount of crevicular fluid irrespective of the inflammatory status of the status [116–118]. Both estrogen receptors a and b have effects on blood vascular functions [119].

Several mechanisms have been put forth to explain how the hormone may control the tonicity of the blood vessels by:

1. Inhibiting the calcium ions through the voltage-sensitive calcium channels [120].
2. Influencing the sympathetic transmitters [121, 122], or affecting alpha-adrenoceptor number or affinity [123, 124].
3. Increasing capillary permeability by stimulating the release of various mediators (e.g., adenosine, bradykinin, vasoactive intestinal polypeptide, neurotensin, substance P, various prostaglandins, AMP, ADP, ATP, cAMP, guanosine, thymidine, histamine, cytidine, uridine, acetylcholine, isoproterenol, and glycosaminoglycans) [125]. Some evidence regarding nitric oxide-induced vasodilation, re-endothelialization angiogenesis have also been accounted for such alterations through activation of the estrogen receptor-a [119, 126]. However, progesterone has been known to oppose the actions of estrogen, presumably by reducing estrogen receptor numbers, rather than having any individual effects on vasculature [90, 125].

Resident Cells Estrogen is known to regulate periodontal ligament cell proliferation including fibroblasts, keratinocytes, and promote osteoblastic cell differentiation [127, 128].

#### *3.1.2.2.3 Epithelial cells*

Several investigators perceived that estrogens increased epithelial keratinization and stimulated proliferation [129, 130]. Trott noticed a reduction in keratinization of the marginal gingival epithelium in postmenopausal women when plasma estrogens levels were declining [131]. Androgens were perceived to stimulate an increase in epithelial cell number [132, 133].

#### *3.1.2.2.4 Connective tissue cells*

The cellular effects of estrogen on collagen synthesis may largely be organ or site-specific [134]. In contrast to testosterone and progesterone, estrogens appear to be stimulatory in gingival fibroblasts derived from either feline or human drug enlarged gingiva [135]. Mariotti reported increased cell proliferation in fibroblasts derived from clinically healthy human gingiva of premenopausal women, with physiological concentrations of estradiol *in vitro*. They reported a characteristic estrogen-sensitive cellular subpopulation within the whole parent cell population of fibroblasts from premenopausal women [136]. Estradiol also induces a dose-dependent increase in interleukin-6, interleukin-8, and vascular endothelial growth factor in gingival fibroblasts [137]. In periodontal ligament cells, estrogens caused downregulation of lipopolysaccharide-induced cytokines while enhancing the production of osteoprotegerin [138, 139]. Natoli et al. demonstrated the expression of matrix proteins including collagen, elastin, and fibrillin-1, and their regulators as impacted by estrogen [140].

#### *3.1.2.2.5 Bone cells*

Sex steroids play a critical role for skeletal development and for the maintenance of bone health throughout adult life [141]. The deficiency of estrogen increases osteoclast precursor cells. Estrogen increases osteoprotegerin, upregulates transforming growth factor-beta, an inhibitor of bone resorption that acts directly on osteoclastogenic cells to decrease activity and increase apoptosis [142–144].

Specifically, increased T-cell production of tumor necrosis may be mediated by estrogen deficiency via a mechanism dependent upon regulatory cytokines, for example, *in vivo* bone destruction has been shown to involve interleukin-7, probably through its influence on T-cell development and homeostasis [141, 145].

#### *3.1.2.2.6 Immune cells*

Straub proposed that sex steroid hormones modulate the immune system via multiple ways: the immune stimulus and antigen-specific immune response; the target cells involved; the microenvironment of the tissue; hormone concentration; the variability of receptor isoforms; and the intracellular metabolism of hormones to either biologically active or inactive forms [146–148].

#### *3.1.2.2.7 Intracellular signaling*

Infectious challenge studies have revealed that males produce a significantly higher level of the inflammatory cytokine IL-6 and the acute phase protein LPS-binding protein (LBP) than females, after *in vivo* endotoxin exposure male-derived macrophages produce higher levels of IL 1b and lower levels of prostaglandin E2 than similarly treated female derived cells on exposure to LPS [147]. Estrogen and progesterone have antagonizing effects on neutrophil chemotaxis [149, 150]. Estrogen has

been shown to upregulate nitric oxide synthase expression in neutrophils ex-vivo, with nitric oxide production being the highest [151, 152].

#### *3.1.2.2.8 Adaptive immunity*

**B cells:** documented evidence suggests that estrogen acts as a polyclonal B cell activator and has been shown to alter B lymphocyte function. Estrogen inhibits CD8+ T- cell-mediated suppression of B cells, the accelerated maturation of B cells into plasma cells; or increased amounts of the antibody produced per cell [152]. Similar findings have been demonstrated in animal models [153]. Testosterone has been shown to inhibit immunoglobulin IgG and IgM production of peripheral blood mononuclear cells [154].

**T cells:** Estrogen displays a biphasic effect on the antigen-stimulated secretion of TNF- $\alpha$ , with inhibition at high concentrations and enhancement at low doses [155]. Pregnancy and periovulatory levels of estrogen enhance IL-10 and IFN- $\gamma$  response in CD4+ cells in humans and mice [156]. Estrogen inhibits IL-6 cytokine production in T cells. In healthy men and women, the polarization of immune response into Th1 or Th2 cytokines or cellular types is not absolute but the ratio of these components varies according to physiological demand and clinical conditions [157, 158]. Estrogen is known to be a potential physiological regulatory factor for the peripheral development of CD4 + CD25+ Treg cells [159]. Additionally, it was discovered that hormones peripherally activated prohormones and regulated the Th1/Th2 balance [160–163].

#### *3.1.2.2.9 Antigen-presenting cells*

(APCs) regulate Th cell differentiation and Th cell functioning under resting and activated conditions of the immune system in both the gender. IL6 pathways regulates the homeostasis of the Th cell network in women, while this homeostasis is regulated by IFN $\gamma$  pathways in men. Physiological homeostasis between Treg, Th17, and Th9 cells in the resting state in the transition to the activation phase and in the return to the resting state [157].

#### *3.1.2.2.10 Immunosenescence-Gender-specific effects*

Contemporary studies about the immune system functions have documented that there exists a differential effect on the activities and regulation of T helper (Th) cytokine pathways, which is affected by aging, but not to the same extent in both genders. Different cytokines regulate the development of immune response in humans at different phases, based on gender, for example, early evolution by the positive inter regulation of IFN $\gamma$ -IL10 and IL6-IL4 in males, and the negative interrelation of IL6-IL10 in females whereas, the late evolution by the positive inter regulation of IFN $\gamma$ -IL4 in males and by IL6-IFN $\gamma$  in females. Alterations in these gender-specific cytokines regulatory pathways during aging could adversely affect the success of the immune response [158].

## **4. Preliminary case study: a retrospective panoramic analysis of distribution patterns of alveolar bone loss in chronic periodontitis patients from North India**

A small preliminary investigation designed as a hospital based retrospective study of distribution patterns of alveolar bone loss on panoramic X-rays (OPG)

of chronic periodontitis patients from North India was planned to draw an insight regarding the differential role of gender in context of periodontal disease. The aim of this study was to conduct an orthopantomograph radiographic screening in order to determine the overall distribution of alveolar bone loss, patterns (horizontal/vertical), and extent (coronal, middle, and apical thirds of the tooth root) in population by digital measurement analysis based on age and gender of the study participants.

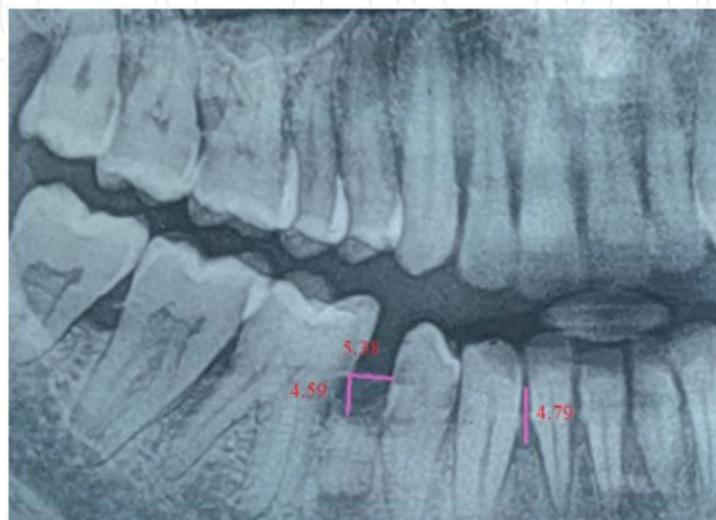
#### **4.1 Materials and methods**

Orthopantomographs (OPG X-rays) of a total of 64 patients who visited the Department of Periodontology in the month of February–March, 2020 were recruited from the records, in order to evaluate the interproximal alveolar bone loss and potential explanatory variables including age, gender and number of sites. Panoramic views were obtained using Planmeca 2002 CC Proline with Dimax 3, Panoramic digital X-ray unit (60 KV and 20 mA), 1.2 magnification ratios. The scanned version of OPG X-ray films were analyzed with the help of a publicly available free online image assessment tool viz. Image J. It is a Java-based image processing program developed at the National Institutes of Health and the Laboratory for Optical and Computational Instrumentation (LOCI, University of Wisconsin) [163, 164].

A digital method of estimating alveolar bone height on panoramic radiographs using 3X magnification was employed using constant anatomic landmarks as reference points - CEJ and alveolar crest as shown in **Figures 6** and 7.



**Figure 6.**  
*Digital OPG X-ray image.*



**Figure 7.**  
*Method of estimating alveolar bone height on panoramic radiographs using image analysis software.*

Bone loss was considered when the distance from the CEJ to the alveolar crest exceeded 2 mm. Radiographic images were interpreted by a single calibrated examiner in order to reduce variability in image assessment and recording of data. Distorted, overlapped, unclear images particularly at the maxillary and mandibular anterior region or patients with orthodontic appliances were excluded for evaluation. Bone loss was estimated digitally by measuring the distance between CEJ and alveolar crest at the interproximal areas minus 2 mm (physiologic high of interseptal alveolar crest) at sites with reduced normal level of interseptal bone. The data so collected was put to appropriate descriptive and inferential statistics. Student's T test and Mann Whitney test was used to intercept the differences in the mean of normal and skewed data parameters for different categories resp. Further, odds ratio was calculated to predict the future bone loss trends for patients with existing periodontal bone loss based on the no. of sites involved in bone loss.

## 4.2 Results

The collected OPG X-rays were categorized according to age and gender based on the accompanying clinical history recording and it was observed that there were OPGs from 30 females and 34 males and 11 subjects were below 30 years of age and 53 were above 30 years of age (**Table 1**).

**Table 2** demonstrates the mean age and the distribution of bone loss patterns in total study population based on different defined categories of the bone loss providing mean no. of bone loss sites, along with the observed range in each category. As the study population was chronic periodontitis patients, all radiographic images showed evidence of bone loss at one or more than one site. Overall, 17 sites of bone loss were observed as an average no. of bone loss sites in the total population. Similarly, a mean value of 9.69 and 7.50 was observed for horizontal and vertical kind of bone loss sites in all population. The no. of bone loss sites extended to coronal, middle third and apical third of the root surface revealed a mean score of 3.11, 11.45, and 2.52 per individual, respectively (**Table 1**).

**Tables 3 and 4** reveals comparative analysis of gender and age based distribution of total no. of bone loss sites in the total study population in current study. According to the gender, there was not observed any statistically significant difference in the total no. of bone loss sites, whereas there existed significant difference in the total no. of bone loss sites as per age.

**Tables 5 and 6** reveals genderwise distribution of no. of bone loss site based on categories and its comparative analysis, respectively. None of the categories revealed statistically significant difference in the no. of bone loss sites between males and females. Similarly, **Tables 7 and 8** reveals agewise distribution of no. of bone loss site based on categories and its comparative analysis, respectively. Statistically significant difference in the no. of bone loss sites between males and

No. of subjects	Category	Frequency	Percent	Valid percent	Cumulative percent
64	Females	30	46.9	46.9	46.9
	Males	34	53.1	53.1	100.0
	<=30 years	11	17.2	17.2	17.2
	>30 years	53	82.8	82.8	100.0

**Table 1.**  
*Distribution of study participants based on categories.*

S.No	Clinical Parameters	No. of subjects	Minimum	Maximum	Mean	Std. Deviation	Median	Inter quartile range
1	Age	64	17	84	41.67	11.982	—	—
2	Total No. of sites	64	4	29	17.03	5.768	—	—
3	No. of Sites with horizontal bone Loss	64	0	26	9.69	5.377	9.00	5–13.75
4	No. of Sites with vertical bone loss	64	0	22	7.50	5.507	7.00	3.25–10.00
5	Coronal 3rd	64	0	18	3.11	4.303	1.00	0.00–4.75
6	Middle 3rd	64	0	26	11.45	7.322	12.00	4.25–17.75
7	Apical 3rd	64	0	23	2.52	4.922	0.00	0.00–2.00

**Table 2.**  
*Distribution of study parameters in total study population based on different categories.*

Sex	Mean	N	Std. deviation	Std. error mean	Sig. (2-tailed)
M	17.03	34	5.060	.868	0.998
F	17.03	30	6.568	1.199	

**Table 3.**  
*Comparative analysis of gender based distribution of total No. of bone loss sites in study population.*

Age-groups	Mean	N	Std. deviation	Std. error mean	Sig. (2-tailed)
<=30 years	12.91	11	6.789	2.047	0.008**
>30 years	17.89	53	5.206	0.715	

**Table 4.**  
*Comparative analysis of age-based distribution of total No. of bone loss sites in study population.*

females in the category of subjects with bone loss extending to middle third of the root, whereas none of the categories revealed statistically significant difference in the no. of bone loss sites between subjects above and below 30 years of age.

Further, a risk estimate analysis based on both age and gender as risk factors was carried out for prediction of future susceptibility of bone loss by calculating Odds ratios, which revealed age of the individual as a significant risk determinant for the same (Tables 9 and 10).

### 4.3 Discussion

Gender has been implicated as a risk factor for many human diseases particularly rooted in chronic diseases, where disease pathogenesis is impacted significantly by immune mechanisms of the body including periodontal disease [165, 166]. The findings from the present case study revealed the presence of bone loss in all study participants which is indicative of the fact that periodontal bone loss is the hallmark of chronic periodontal disease. On average, 17 sites with bone loss were found to be

Category of patient		No. of patients	Median	Std. deviation	Interquartile range	
M	No. of sites with horizontal bone loss	34	9.00	5.132	5.00	13.25
	No. of sites with vertical bone loss	34	7.50	5.710	4.00	10.00
	Coronal 3rd	34	1.00	4.351	0.00	5.00
	Middle 3rd	34	12.00	6.881	6.25	16.00
	Apical 3rd	34	.00	4.931	0.00	2.25
	Sex	34	1.00	0.000	1.00	1.00
F	No. of sites with horizontal bone loss	30	9.50	5.637	5.00	14.00
	No. of sites with vertical bone loss	30	6.50	5.078	3.00	10.25
	Coronal 3rd	30	1.00	4.321	0.00	4.50
	Middle 3rd	30	11.67	7.906	4.00	18.25
	Apical 3rd	30	2.43	4.994	0.00	2.50

**Table 5.**  
 Genderwise distribution of No. of bone loss site based on categories.

	No. of sites with horizontal bone loss	No. of sites with vertical bone loss	Coronal 3rd	Middle 3rd	Apical 3rd
Mann-Whitney U	453.000	458.000	503.000	488.000	495.000
Wilcoxon W	1048.000	923.000	1098.000	1083.000	960.000
Z	-0.769	-0.702	-0.100	-0.297	-0.230
Asymp. Sig. (2-tailed)	0.442	0.483	0.920	0.767	0.818

a. Grouping variable: Sex

**Table 6.**  
 Comparative analysis of genderwise distribution of No. of bone loss site based on categories.

present across the study population. Horizontal bone loss was more prevalent than the vertical bone loss, which is again in sync with the existing knowledge regarding the periodontal bone loss patterns. Most patients suffered from moderate periodontitis in terms of the severity of bone loss as maximum sites in population revealed bone loss extending up to the middle third of the root surface. With the new 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Condition as a reference, the majority study population falls under the Stage III periodontitis category based on the residual bone level criteria for categorization [167]. Further, there was observed no statistically significant difference in the total number of bone loss sites based on gender, but there existed a significant difference in the total number of bone loss sites as per age in the study population. A statistically significant difference in the number of bone loss sites between males and females in the category of subjects with bone loss extending to the middle third of the root are also revealed, but neither of the other two categories based on age nor all categories based on gender witnessed any statistically significant differences in terms of the number of bone loss sites varied according to the severity of the bone loss.

Category of patient		No. of patients	Median	Std. deviation	Interquartile range	
<=30 years	No. of sites with horizontal bone loss	11	5.00	4.657	4.00	13.00
	No. of sites with vertical bone loss	11	4.00	6.496	0.00	8.00
	Coronal 3rd	11	5.00	3.828	.00	7.00
	Middle 3rd	11	4.00	8.201	0.00	14.00
	Apical 3rd	11	0.00	4.771	0.00	2.00
>30 years	No. of sites with horizontal bone loss	53	10.00	5.375	6.00	14.00
	No. of sites with vertical bone loss	53	7.00	5.170	4.00	10.00
	Coronal 3rd	53	0.00	4.383	0.00	4.00
	Middle 3rd	53	13.00	6.739	8.00	18.00
	Apical 3rd	53	0.00	4.984	0.00	3.50

**Table 7.**  
Age-wise distribution of No. of bone loss site based on categories.

	No. of sites with horizontal bone loss	No. of sites with vertical bone loss	Coronal 3rd	Middle 3rd	Apical 3rd
Mann-Whitney U	187.500	211.000	211.500	159.000	248.000
Wilcoxon W	253.500	277.000	1642.500	225.000	314.000
Z	-1.856	-1.437	-1.514	-2.362	-0.881
Asymp. Sig. (2-tailed)	0.064	0.151	0.130	0.018 <sup>a</sup>	0.378

a. Grouping variable: Age-groups

**Table 8.**  
Comparative analysis of age-wise distribution of No. of bone loss site based on categories.

Previous literature has also reported that there was no significant sex difference. Gender is inherently a very complex risk factor that may play a role through diverse mechanisms as discussed in earlier sections. Premenopausal women exhibit the lower prevalence of periodontitis as compared with men and on contrary, after menopause, with a weakening estrogen signal, women may show equal or even greater periodontal destruction as compared to age matched men [168]. Wulandari et al. reported no difference in periodontal severity between perimenopausal and postmenopausal women, however, emphasized the role of the bacterial plaque regarding periodontal disease severity in perimenopausal and postmenopausal women in a cross-sectional investigation in 63 subjects, aged 45–59 years, in East Jakarta [169]. Paramashivaiah et al. examined 104 postmenopausal women, age-group ranging from 35 to 60 years, and reported radiographic alveolar bone loss correlated with clinical indicators including attachment loss. Most females had periodontitis and low serum 17-β estradiol and calcium levels [170]. Lee et al. indicated an association between hormone replacement therapy (HRT) and periodontal disease, after adjusting for various potential confounders for periodontal diseases. The authors showed that the HRT+ group was less likely to develop periodontal diseases

		M	F	Asymp. Sig. (2-sided)		
Total sites 13	>13	Count	26	0.559	47	0.559
		% within Sex	76.50%	70.00%		
	<=13	Count	8	9	17	
		% within Sex	23.50%	30.00%	26.60%	
Total	Count	34	30	64		
	% within Sex	100.00%	100.00%	100.00%		
Risk Estimate		Value	95% Confidence interval			
			Lower	Upper		
Odds ratio for total sites 13 (>13 / <=13)		1.393	0.458	4.237		
For cohort SEX = M		1.176	0.668	2.07		
For cohort SEX = F		0.844	0.487	1.462		
No. of valid cases		64				

**Table 9.**  
 Risk estimate of bone loss based on gender as a risk determinant.

		Age-groups		Total	Asymp. Sig. (2-sided)	
		>30 years	<=30 years			
Total sites 13	>13	Count	42	5	47	0.021*
		% within age-groups	79.2%	45.5%	73.4%	
	<=13	Count	11	6	17	
		% within age-groups	20.8%	54.5%	26.6%	
Total	Count	53	11	64		
	% within age-groups	100.0%	100.0%	100.0%		
Risk estimate		Value	95% Confidence interval			
			Lower	Upper		
Odds ratio for total sites 13 (>13/<=13)		4.582	1.176	17.849		
For cohort age-groups = > 30 years		1.381	0.959	1.989		
For cohort age-groups = <= 30 years		0.301	0.106	0.861		
No. of valid cases		64				

**Table 10.**  
 Risk estimate of bone loss based on age as a risk determinant.

than the HRT- group upon analysis of 45 and 74 years old menopausal women [171]. Another study by Pizzo et al. in 91 Italian menopausal women (50 ~ 62 years) reported similar periodontal pocket depths between the group who underwent HRT

and who did not, but the group without HRT had a higher level of dental plaque [172]. López-Marcos et al. [173] studied in 210 Spanish menopausal women aged 40–58 years that the estrogen patch group showed a reduction in periodontal pocket depth. People with a longer menopausal period and lower bone mass more evidently witnessed the effects of estrogen deficiency [174, 175]. The authors recommend that the studies aimed at a clear delineation of the role of gender as a risk factor should rather be more meticulously designed in terms of studying the role of gender in differential age-groups, larger study samples, and well-designed investigations as females undergo specific periods of hormonal fluctuations according to the stage of their reproductive life cycle.

A study was conducted by Wouters et al. in 1989 in 733 randomly selected dentate individuals aged 20 years and above using periapical radiographs with interproximal intrabony periodontal defect depth and width of at least 5 and 10 mm, respectively, to determine the relationship between the prevalence of interproximal periodontal intrabony defect and age. It was reported that the prevalence increased with age and was higher in men than in women [168]. However, the significantly lower prevalence of interproximal periodontal intrabony defect in women than in men does not support the studies of Nielsen et al. [176], in which no significant sex differences were reported [177]. The present study findings still need to compare with caution as it differed in the X-ray images taken as reference was OPGs of the study subjects. So the differences in study settings, design and tools may also be responsible for the observed heterogeneity in study results.

A higher incidence of bone loss in adult patients (24–30 years old) is a fact, that periodontitis is an age dependent disease the incidence and severity of bone loss and attachment loss increase with age (16) as a result of longer exposure to local factors as age grows older. The present study revealed a nonsignificantly higher prevalence of bone loss among females than males, and the authors attributed these findings to a higher prevalence of aggressive periodontitis among females rather than males [178].

Khateeb et al. carried out an investigation in a total of 190 female patients (mean age,  $22.4 \pm 2.46$  years) and Patients' age was found to be a good predictor for alveolar bone loss and number of periapical lesions ( $P \leq 0.05$ ) [179]. Another study from China revealed that 40–59-year-old patients with chronic periodontitis had severe bone loss. And a lesser degree of alveolar bone loss was seen in males than females [179]. Menopause in females and smoking in both genders may have affected the level of bone loss. Male smokers experienced a greater degree of bone loss ( $41.67 \pm 5.76\%$ ) than male non-smokers ( $32.95 \pm 4.31\%$ ). A  $42.23 \pm 6.34\%$  bone loss was found in menopausal females versus  $31.35 \pm 3.62\%$  in non-menopausal females [180].

Bansal M et al. (2015) [181], in a cross-sectional prevalence study among hospital-based Indian population, assessed the prevalence of the periodontal disease. They stated that healthy periodontium was found in 19 (3.9%) subjects with the highest percentage in the 15–19 years age-groups and after 44 years no person had healthy teeth. Also, advanced stages were more prevalent in older age-groups, deep pockets occurring in 87 (17.90%) subjects that increased as the age advanced up to 45–54. According to them, males were more affected with moderate and severe periodontitis as compared to females. Bokhari et al. (2015) [28], reported that subjects aged 40 years and above were four times more likely to have periodontitis using Community Periodontal Index (CPI) methods. Marya, CM, et al. (2020) [182], in a cross sectional study assessed if there are any gender differences in oral health-related quality of life (OHRQoL) among the elderly population of Haryana. Genderwise, no significant association was found with different parameters of periodontitis. They found a significant association of OHRQoL with the main factor causing periodontal problems, that is, mobile teeth and no comparable difference

was observed in the OHRQoL among males and females. They suggested one needs to target the geriatric population as a whole for planning and implementing public oral health strategies.

## **5. Clinical relevance of understanding the specific effects of gender on periodontal disease**

Despite the extensive evidence from the recent past has recognized gender as an important factor in the regulation of immune responses, sex differences are still very much understudied and poorly understood in scientific research with females being under-represented in clinical disease trials. Specific exploration of sex-specific biomarkers should be considered for both the genders. Studies of multifactorial diseases demonstrate differential susceptibilities between genders encounter confounding variables, such as lifestyle, socioeconomic status, environmental exposures, and genetic polymorphisms. Hence, novel experimental models with gender differences shall be developed to understand disease pathogenesis based on gender [183, 184].

Effie Ioannidou in 2017 developed the methodological and analytical framework with the recognition of sex/gender as important determinants of disease pathogenesis. The authors aimed to present relevant sex biologic evidence to understand the plausibility of the epidemiologic data. In periodontitis pathogenesis, sex dimorphism has been implicated in the disease etiology. With the clear distinction between sex and gender, gender oral health disparities have been explained by socioeconomic factors, cultural attitudes as well as access to preventive and regular care. Economic inequality and hardship for women have resulted in limited access to oral care in some parts of the world. As a result, gender emerged as a complex socioeconomic and behavioral factor influencing oral health outcomes [185].

With the expanding knowledge regarding gender as a risk factor, we must intend to perform specific gender-based periodontal research to find better insight into the mechanisms of disease pathogenesis and mediators, so that specific gender-based tools for periodontal diagnosis, risk assessment, predictive medicine, and disease management strategies can be developed to provide optimized periodontal health care solutions to our patients.

## **6. Conclusion**

Our current knowledge and understanding of the specific role of gender in the context of periodontal health status remain limited and need further elucidation. The combined effect of sex-specific genetic architecture and the circulating levels of sex steroid hormones may account for variation in risk for chronic periodontitis, with men exhibiting greater susceptibility than women. The preliminary case study presented here revealed age as a significantly associated factor, with the total number of bone loss sites and with the bone loss site extended up to a middle third of tooth root (moderate to severe periodontitis cases), but could not delineate gender, the primary factor being explored as a clear-cut risk factor, owing to the lack of statistical strength and study limitations as the small-sized sample, retrospective study design. This shall not obviate the need to explore this factor as a cause of concern as contemporary models of periodontal pathogenesis; differences in susceptibility, and progression of destructive periodontal disease are attributed to the individual and collective biologic and modifiable risk factors. With this framework

of information, gender as a risk factor for periodontal disease needs to decipher in detail its underlying mechanisms by conducting longitudinal well-controlled, designed, and characterized studies. Such investigations to further explore the role of gender in the prevalence, progression, and severity of chronic periodontal disease are warranted in the future so that novel strategies for risk assessment, disease identification, and individualized therapeutic approaches can be developed for optimized patient care based on gender.

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