



Osteoporosis and periodontitis: a bidirectional relationship

Osteoporose e periodontite: uma relação bidirecional

Paramjit Kaur KHINDA¹

1 – Department of Periodontology – Genesis Institute of Dental sciences and Research – Punjab – India.

ABSTRACT

Osteoporosis is a condition of compromised bone strength that predisposes an individual to increased risk of fracture and is a major cause of morbidity in older susceptible individuals. Osteoporosis is related to various endocrinal abnormalities, metabolic and nutritional factors, postmenopausal hormonal changes and consumption of certain drugs such as cortisone. Emerging clinical and molecular evidence suggests that inflammation also exerts significant influence on osteoporotic bone changes. Numerous pro-inflammatory cytokines have been shown to be associated with regulation of osteoblast and osteoclast differentiation. Chronic inflammatory conditions causing immune system remodeling may serve as pathological risk factors for osteoporosis. The present article reviews the current perspective on the interaction between bone morphology and immune system in the inflammatory condition (periodontitis), unleashing the link between two chronic conditions.

KEYWORDS

Osteoporosis; Periodontitis; Inflammation; Bone remodelling.

RESUMO

A osteoporose é uma condição de resistência óssea comprometida que predispõe um indivíduo ao risco aumentado de fratura e é uma das principais causas de morbidade em indivíduos susceptíveis mais velhos. A osteoporose está relacionada a várias anomalias endócrinas, fatores metabólicos e nutricionais, alterações hormonais pós-menopausa e consumo de certos medicamentos como a cortisona. Evidências clínicas e moleculares emergentes sugerem que a inflamação também exerce uma influência significativa sobre as alterações ósseas osteoporóticas. Numerosas citocinas pró-inflamatórias demonstraram estar associadas à regulação da osteoblastos e da diferenciação osteoclástica. As condições inflamatórias crônicas, que provocam a remodelação do sistema imunitário, podem servir como fatores de risco patológicos para a osteoporose. O presente artigo apresenta uma revisão da perspectiva atual sobre a interação entre a morfologia óssea e o sistema imunológico na condição inflamatória (periodontite), desencadeando a ligação entre duas condições crônicas.

PALAVRAS-CHAVE

Osteoporose; Periodontite; Inflamação; Remodelação óssea.

INTRODUCTION

Periodontitis, an inflammatory disease characterized by resorption of alveolar bone as well as loss of soft tissue attachment of the tooth, is a major cause of tooth loss in adult population. Advances in science and technology over the last century have greatly expanded our knowledge on the pathogenesis of

periodontal disease. Though periodontal disease has essentially bacterial etiology, periodontal pathogens do not invariably cause disease by their presence alone. Several environmental and various host factors may affect and modify disease expression. [1-5]

Current concept states that host response varies among different individuals and that an insufficient host immune response or an

exaggerated immune response to bacterial pathogens may lead to more severe forms of periodontal disease. [6] Certain systemic disorders and conditions are known to alter host tissue physiology, which may impair host barrier integrity and immune response to bacterial pathogens, resulting in more destructive periodontal disease. [1,2] Various mediators involved in inflammation are linked with those critical for normal bone physiology and remodelling, suggesting the role of inflammatory conditions in the aetiopathogenesis of certain chronic bone disorders like osteoporosis. [7]

Osteoporosis is a systemic skeletal disorder; characterized by low bone mass density and micro-architectural deterioration of bone tissue without any change in its chemical composition and subsequent increase in bone fragility and susceptibility to fracture [8]. It may also be defined as a state of disequilibrium between structural demand for calcium and phosphate and their biologic demand during metabolically active states such as inflammation [9]. According to National Osteoporosis Foundation, osteoporosis is a major public threat for an estimated 44 million of the US population (55% of people > 50 years of age) [10] and almost twice that number have low bone mass and osteopenia (a condition of compromised bone strength that predisposes an individual to an increased risk of fracture and usually asymptomatic, becoming symptomatic when functional demand exceeds the structural viability of the skeleton). [11]

The incidence of osteoporosis is much higher in women (80%) than in men (20%). [12] This may be attributed to the fact that women attain less bone mineral content than males and levels of estrogen further decline post-menopause.

Osteoporosis can be categorized into primary and secondary. Primary osteoporosis is associated with increased age and/or decreased sex hormones whereas secondary implies an underlying systemic cause which may include

usage of certain medications, systemic factors affecting bone turnover such as endocrine disorders (Cushing's syndrome, thyrotoxicosis), rheumatologic disorders (rheumatoid arthritis) and certain inherited diseases like multiple myeloma and low calcium intake.

Osteoporosis and Periodontal disease:

Osteoporosis is characterized by imbalance in normal bone turnover physiology with net decrease in bone mineral density, probably also alter oral bone turnover unfavourably. So, it is essential for proper clinical management of dentate and edentulous patients suffering from both osteopenia and osteoporosis. A rational dental treatment plan in patients with altered bone physiology would include periodontal therapy along with proper management of systemic bone loss.

Co-Risk factors for osteoporosis and periodontal disease:

Osteoporosis and periodontal disease are chronic multifactorial diseases and share several common risk factors illustrated in table below. (Table 1).

Estrogen deficiency is dominant pathogenic factor for osteoporosis in postmenopausal women. Estrogen either directly or indirectly,

Table 1 - Risk factors common to periodontal disease and osteoporosis

RISK FACTOR	MODIFIABLE	PREVENTION
Age	No	
Early menopause (Estrogen deficiency)	No	
Race	No	
Nutritional factors (Lack of Calcium, several vitamins)	Yes	Diet high in calcium and vitamins
Smoking	Yes	Smoking cessation
Alcohol	Yes	Decreased alcohol consumption
Heredity	No	
Diseases (e.g. Hyperparathyroidism)	To some extent	Treatment

modulates the production of cytokines and growth factors which in turn act as local regulators of the remodelling process. Cytokines under estrogen control with direct effects on bone cells include OPG, RANKL/RANK, IL-1 alpha, IL-1 beta, TNF-alpha, and granulocyte-macrophage colony-stimulating factor (M-CSF) secreted by monocytes and IL-6 secreted by osteoblasts. IL-1 induces the synthesis of IL-6, which increases bone resorption through osteoclast recruitment. Colony-stimulating factor plays a role in the maturation of osteoclasts. IL-1 and TNF-alpha stimulate mature osteoclasts, modulate bone cell proliferation, and induce bone resorption in vivo. Thus, estrogen deficiency causes an increase in the number of osteoclasts, driven by the higher levels of same cytokines that down-regulate osteoblast generation in normal physiological conditions. This creates imbalance in normal physiological metabolism, favouring bone resorption.

In addition, estrogen may affect bone turnover indirectly by acting as an antagonist

to PTH. But, the bone sparing effect of estrogen may be explained by its fundamental ability to interact with bone cells and alter the cytokine circuitry [13].

Norderyd and colleagues [14] reported lower, although not statistically significant, levels of clinical attachment loss and gingival bleeding in postmenopausal women receiving estrogen supplementation compared with estrogen-deficient postmenopausal women. A 5-year longitudinal study conducted on 69 women (with menopause receiving hormone replacement therapy) compared lumbar spine BMD with mandibular bone mass. A statistically significant but moderate correlation was observed between mandibular and lumbar spine bone mass and that estrogen replacement therapy after menopause had a positive effect on both lumbar and mandibular bone mineral density [16]. Payne and colleagues depicted, [15] in a 1-year longitudinal study of 24 postmenopausal women, that estrogen-deficient women displayed a mean net loss in alveolar bone density whereas estrogen sufficient

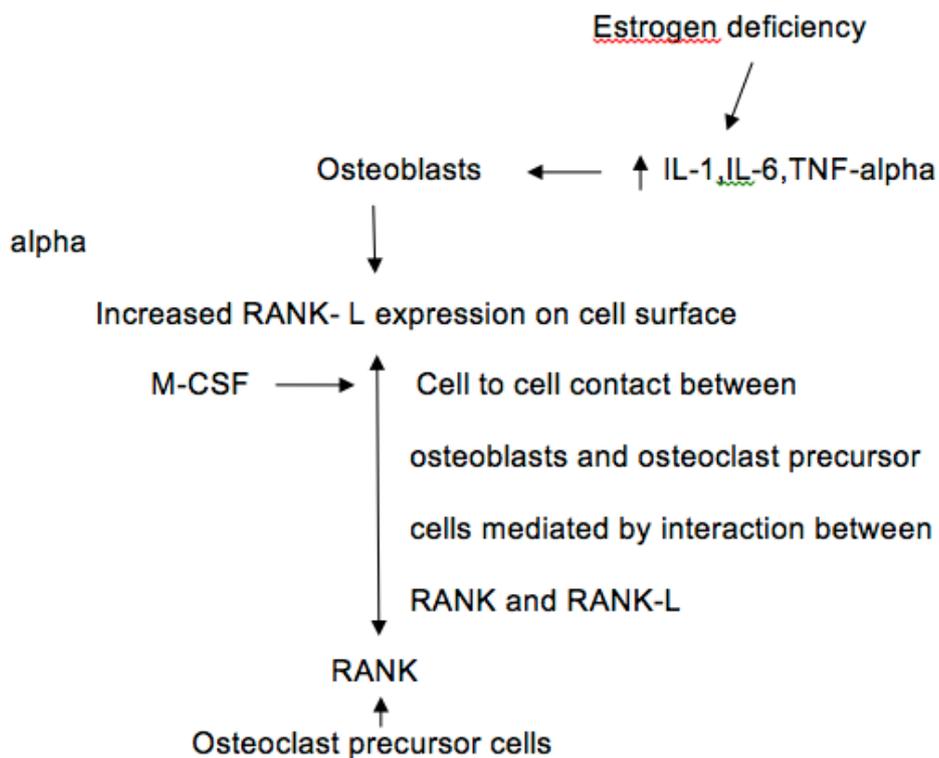


Figure 1 - Role of Estrogen in osteoclast differentiation.

women, displayed a mean net gain in alveolar bone density. (Table 2)

Smoking

Smoking interferes with efficient calcium absorption resulting in accelerated bone loss. A meta-analysis of 29 studies including 2,156 smokers and 9,750 non-smokers examined the effect of cigarette smoking on skeletal bone mineral density. While bone density in premenopausal women was comparable in smokers and non-smokers, in postmenopausal women bone loss was greater in current smokers compared with non-smokers, [17] suggesting that the effect of smoking on skeletal BMD is modulated by estrogen.

A meta-analysis of available literature indicates that smokers have 2.5 times the risk for severe periodontal disease compared with non-smokers, independent of the effects of age, socioeconomic factors, diabetes mellitus, or dental plaque. Furthermore, the risk is cumulative and dose dependent in that the severity of periodontal disease is related to the duration and frequency of smoking.

Dietary Factors

Adequate dietary calcium is essential for the growth and development of a normal skeleton. Insufficient calcium intake during childhood and adolescence can reduce peak bone mass attainment and enhance post-menopausal and age-related osteoporosis [18]. Individuals with diet deficient in calcium had statistically higher levels of periodontal disease compared with those with calcium sufficient diets [19].

Therefore, a diet rich in vitamins and minerals is essential not only for normal physiological skeletal development, but also protects against the destruction of connective tissue and alveolar bone resulting from periodontal infection.

Genetics Factors

Osteoporosis is a multifactorial, polygenic condition involving multiple genes regulating the control of bone turnover.

The vitamin D receptor (VDR) is required for normal calcium absorption from the gut. Common allelic variants in the gene encoding the vitamin D receptor has direct effect on bone density. Other polymorphisms imparting susceptibility to osteoporosis include the binding site in collagen type I alpha 1 (COL1A 1) gene, [20] transforming growth factor-beta (TGF- β) gene, [21] the estrogen receptor [22] as well as genes regulating cytokines involved in bone turnover. Periodontal disease is a multifactorial disease with genetic predisposition being critical factor in disease development [23]. Candidate genes for susceptibility to periodontal disease include genes defining the FcyRII receptor genes regulating immunoglobulin synthesis, especially IgG2, and genes regulating cytokine synthesis.

Role of inflammation in osteoporosis

Clinical observations reveal co-incidence of systemic osteoporosis with period of systemic inflammation as well as co-localization of regional osteoporosis with areas of regional inflammation [24]. Different epidemiological studies reported an increase in the risk of developing osteoporosis in various inflammatory conditions.

Table 2 - Relationship between estrogen status and periodontal disease

Author	Periodontal parameter	Osteoporosis assessment	Study design	Results
Norderyd et al, 1993 [14]	CAL, gingival bleeding and levels of plaque	234 postmenopausal women (57 ERT; 177 non-ERT)	Cross-sectional	ERT associated with less gingival inflammation in postmenopausal women
Payne et al, 1997 [15]	Alveolar bone density	24 postmenopausal women (10 estrogen sufficient; 14 estrogen deficient)	Longitudinal	Estrogen status may influence alveolar bone density status
Jacobs et al, 1996 [16]	BMC; mandible	BMC; lumbar spine	Longitudinal	Estrogen status directly related to mandibular bone mass

Immunological dysfunction, autoimmune and various inflammatory conditions, [25] hyper IgE syndrome, [26] rheumatoid arthritis, [27] haematological disorders, particularly myeloma [28] and inflammatory bowel diseases [29] are associated with osteoporosis.

C-reactive protein (CRP), a pentameric protein found in blood plasma is elevated during conditions of active inflammation. C- Reactive protein production in liver is upregulated by various pro-inflammatory cytokines like IL-1, IL-6 and TNF-alpha and is regarded as sensitive marker of systemic inflammation [30,31]. An association between circulating levels of high sensitive (hs) CRP and bone mineral density has been observed in several immune and inflammatory conditions, suggesting an association between subclinical systemic inflammation and osteoporosis. [32]

An intriguing aspect of immunosenescence is the increased production of pro-inflammatory cytokines with aging (inflamm-ageing) [32]. As age advances, continuous exposure to chronic antigenic load and oxidative stress may impair the normal physiological counter-regulatory mechanism; which inhibits bone resorption following T-cell activation. This would contribute, together with low grade systemic inflammation, to increasing incidence of osteoporosis during senescence.

Excessive osteoclastic resorption is a common feature of chronic inflammatory processes such as periodontal disease. The underlying mechanism of increased bone resorption may be directed by increased systemic/local osteoclastic activity, or by elevated local cellular or cytokine profile. In physiological bone remodelling, the cell-to-cell contact between receptor activator of nuclear factor- κ B ligand (RANK-L) expressed by osteoclasts and RANK expressed by monocyte/osteoclast precursor cells is crucial. (Figure 1) In inflammatory processes activated T lymphocytes express higher levels of RANK-L, increasing the possibility of osteoclast differentiation and synthesis. RANK-L is inhibited by osteoprotegerin

(OPG) released by stromal cells and osteoblasts. B lymphocytes may also participate in osteoclast formation, either by expressing RANK-L or by serving as osteoclast progenitor cells themselves. [33] RANK-L mRNA is upregulated in the gingiva of patients with advanced periodontitis [34] whereas osteoprotegerin (OPG) mRNA is downregulated. [35] The hypothesis linking osteoprotegerin and periodontal disease is strengthened by studies involving many gram-negative bacteria. Bacterial infection by these pathogens may trigger RANK-L activation and subsequent osteoclast proliferation, inducing osteoporotic bone changes in patients with periodontal infection. RANK-L, RANK and OPG are considered as interesting molecular links between bone remodelling, immunity and inflammation.

Another factor, NO is an important element of the host defence mechanism against *P. gingivalis*. [36] Activation of the inducible nitric oxide synthesis pathway by cytokines, such as IL-1 and TNF-alpha, inhibits osteoblast function in vitro and stimulates osteoblast apoptosis shifting bone physiology towards resorption. [37] But the role of NO is controversial as its low levels are known to maintain homeostasis, whereas high levels of NO induce bone resorption as seen in many inflammatory conditions. [38]

Recently, some studies have reported an association between osteoporosis and oral bone loss in periodontal disease, first attempt for which was made as early as 1960. [39] Most of the research carried out on mandibular bone revealed a relationship between systemic and oral bone loss evaluated by means of radiography, histology (microradiography), single-photon absorptiometry (SPA), dual-photon absorptiometry (DPA), quantitative CT (QCT) and more recently, dual-energy X-ray absorptiometry (DXA). [40-42]

Relationship of skeletal bone mass to mandibular bone density

It has been postulated that mandibular bone density may be indicative of systemic

Table 3 - Studies performed to determine relationship between mandibular bone density and osteoporosis

Author	Oral measure	Osteoporosis assessment	Study Design	Results
Kribbs et al. [43]	Mandibular bone density	Total body calcium	Cross-sectional	Positive
Kribbs et al. [41]	Mandibular bone mass	Total body calcium, bone mass at radius and bone density at spine	Cross-sectional	Positive
Kribbs et al. [44]	Mandibular bone density	Bone mass at wrist and spine	Cross-sectional	Positive Osteoporotic group had less mandibular bone mass and density
Horner et al. [45]	BMD mandibular body, ramus, symphysis	BMD lumbar spine, femoral neck, forearm		Positive
Melescanu-Imre et al. [46]	Alveolar bone mass	Skeletal BMD		Negative
Melescanu-Imre et al. [46]	Mandibular angular cortex density	Estrogen use		Positive
B Cakur et al. [47]	Mandibular cortical index	Skeletal BMD		Negative
Ducnea et al. [48]	Panoromic mandibular index	BMD hip, femoral neck		Positive

Table 4 - Studies determining the relationship between osteoporotic condition and alveolar crestal height

Author	Oral Measure	Osteoporosis Assessment	Epidemiological Design	Results
Humphries et al. [49]	Residual ridge resorption	Gender, age	Cross sectional	Positive
Elders et al. [50]	Alveolar bone height	BMD spine, Metacarpal cortical thickness	Cross sectional	Negative
Klemetti et al. [51]	Crestal alveolar bone loss	Cortical or trabecular density		Negative
Hirai et al. [52]	Residual ridge resorption	Osteoporosis	Cross sectional	Positive
Wactawski-Wende et al. [53]	Alveolar crestal height	BMD spine, hip	Cross sectional	Positive
Payne et al. [54]	Alveolar crestal height	BMD spine	Prospective	Positive
Tezal et al. [55]	Alveolar crestal height	BMD spine, hip	Cross sectional	Positive

bone mineral density. Kribbs and colleagues addressed this relationship in both normal and osteoporotic women. Non-osteoporotic women revealed positive co-relation between total bodycalcium and mandibular bone density [43] and mandibular bone mass was significantly associated with skeletal bone mass at the spine and wrist [44]. (Table 3) A study conducted by Melescanu-Imre et al. revealed no relationship between alveolar bone mass and skeletal BMD but mandibular cortical thickness was influenced by estrogen levels. [46]

Alveolar crestal height and Osteoporosis:

Several studies were conducted to determine the relationship between crestal bone level and skeletal BMD. Elders et al. [50] and Kalmetti et al. [51] failed to determine any positive co-relation between alveolar bone and skeletal bone mass. Wactawski-Wende et al, in

a study of 70 postmenopausal women found a significant relationship between alveolar crestal bone height as a measure of periodontitis and skeletal osteopenia (femur and lumbar spine) measured by DXA. [53] Payne et al. [54] and Tezal et al. [55] suggested positive co-relation between alveolar bone height and BMD spine and hip. (Table 4)

Tooth loss and Osteoporosis:

Several studies have demonstrated a relationship between tooth loss and systemic osteoporosis in both dentate and edentulous individuals. Daniell and colleagues suggested that systemic bone loss was a risk factor for edentulism. [56] Women with severe osteoporosis, defined as extreme thinning of the metacarpal cortical area, were three times more likely (44% versus 15%) to have no teeth compared with healthy, age-matched controls. In

a study of 329 healthy postmenopausal women, for each additional tooth present, spinal BMD increased 0.003 g per cm². [59] Collectively, this evidence indicates that osteoporotic women have lost significantly more teeth, and more are edentulous compared with non-osteoporotic women. (Table 5)

Periodontal disease and Osteopenia/Osteoporosis:

Payne and his colleagues [54] demonstrated in a prospective study, positive

co-relation between periodontal destruction and BMD at spine and hip. Yoshihara and colleagues also demonstrated similar results in another prospective study. [65] von Wowern and colleagues in a case-control study comparing 12 female patients with osteoporotic fractures and 14 normal women, reported significantly greater periodontal attachment loss in the osteoporotic women compared with the normal women. They found that the osteoporotic women had less mandibular bone mineral content than the 14 normal women. [67,68] (Table 6)

Table 5 - Studies on relationship between osteoporosis and number of teeth present

Author	Oral Measure	Osteoporosis Assessment	Epidemiological Design	Results
Daniell et al. [56]	Edentulism	Metacarpal index	Cross sectional	Positive
Kribbs et al. [44]	Edentulism	Osteoporosis	Cross sectional	Positive
Astrom et al. [57]	Tooth loss	Hip fracture	Prospective	Positive
Krall et al. [58]	Number of Teeth	BMD spine/ forearm	Cross sectional	Positive
Taguchi et al. [59]	Number of Teeth	Fracture spine	Cross sectional	Positive
Krall et al. [60]	Number of Teeth	Estrogen use	Cross sectional	Positive
Mohammad et al. [61]	Tooth loss	BMD spine	Cross sectional	Negative
Hildebolt et al. [62]	Number of Teeth	BMD spine, hip	Cross sectional	Negative
Earnshaw et al. [63]	Number of Teeth	BMD	Cross sectional	Negative

Table 6 - Studies demonstrating relationship between osteoporosis and periodontal tissue loss

Author	Periodontal Parameters evaluated	Osteoporosis Assessment	Epidemiological Design	Results
Yoshihara et al. [64]	CAL	BMD	Prospective	Positive
Payne et al. [54]	Bleeding on probing, plaque	BMD spine, hip, wrist	Prospective	Positive
Tezal et al. [55]	CAL	Osteoporosis	Cross sectional	Positive
Richardt et al. [65]	CAL	Serum Estradiol levels	Prospective	Negative
Mohammad et al. [61]	CAL, Gingival recession	BMD spine	Cross sectional	Positive
Hildebolt et al. [62]	CAL	BMD spine, hip	Cross sectional	Negative
Mohammad et al. [66]	CAL	BMD spine	Cross sectional	Positive
von Wowern et al. [67]	CAL	Fracture	Cross sectional	Positive
von Wowern et al. [68]	CAL	BMC	Prospective	Negative
Kribbs et al. [41]	PD	BMD	Cross sectional	Positive
Kribbs et al. [44]	PD/CAL	Osteoporosis	Cross sectional	Negative
Ward and Manson [69]	PD	Metacarpal index	Cross sectional	Negative
Phillips and Ashey [70]	PD	Metacarpal index	Cross sectional	Positive
Groen et al. [71]	CAL	Osteoporosis X-ray		Positive

Hence, though limited, the evidence from various studies suggest an association between osteopenia, osteoporosis, and periodontal disease.

DISCUSSION

Although number of studies have found that the density of the alveolar bone in the mandible correlated with the density of the bone in the rest of the skeleton and that systemic bone loss may accelerate oral bone loss, but still controversial results exist. Thus, further studies should be attempted to clarify this correlation with different study design. Large population based prospective and interventional studies need to be practiced.

Identification of inflammatory mediators; RANKL-OPG has significantly contributed to the emergence of new branch of immunology -- osteoimmunity, helping us in examination of the interplay between active immunity and maintenance of bone homeostasis. Detailed knowledge of the molecular mechanisms involved in RANKL-RANK-OPG axis activation and downstream signalling could generate new pharmacological principles for the inhibition of excessive bone resorption in various periodontal pathological conditions. Though modulating the immune system is a delicate work, alteration in molecular biology may form the basis for rational drug therapy in treating periodontal infection effectively.

Hormone replacement therapy has future prospects in treatment of periodontal disease in elderly women. Evidence suggests that hormone replacement therapy improves bone density in postmenopausal women. In a 3-year randomized trial in postmenopausal women with moderate to advanced periodontal destruction, estrogen therapy significantly improved alveolar bone density compared with placebo ($p = 0.04$), along with increase in bone mineral density of the femur but not in the lumbar spine [72]. Furthermore, women

receiving hormonal therapy had significantly less gingival inflammation, lower plaque scores, and lesser loss of attachment.

CONCLUSION

As stated earlier periodontal disease is multifactorial disease with primarily bacterial etiology but is influenced by several systemic diseases and conditions. Periodontal disease itself an inflammatory condition, could alter the course of several chronic conditions like osteoporosis due to generation of activated immune profile. Hormonal Replacement Therapies found beneficial in preventing the progression of periodontal disease in postmenopausal women indicate that osteoporosis is definitely a risk indicator for periodontal destruction.

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Paramjit Kaur Khinda
(Corresponding address)

Genesis Institute of Dental Sciences &
Research. (Dental College & Hospital)
Ferozpur – Moga Road,
Ferozpur – 152 002

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