© Med Sci Monit, 2011; 17(4): PH23-27
PMID: 21455116

www.MedSciMonit.com
Public Health

Received: 2010.03.05
Accepted: 2011.01.03
Published: 2011.04.01

Effect of hormone replacement therapy (HRT) on periodontal status of postmenopausal women

Giuseppe Pizzo[1ABCDEFG], Rosario Guiglia[1BCEF], Maria E. Licata[1BCEF], Ignazio Pizzo[1BEF], Joan M. Davis[2DEF], Giovanna Giuliana[1AD]

[1] Section of Oral Sciences, University of Palermo, Palermo, Italy
[2] Department of Dental Hygiene, College of Applied Sciences and Arts, Southern Illinois University, Carbondale, IL, U.S.A.

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Source of support: This study was supported in part by the University of Palermo (ex-60% Ministry of Education, University and Research [MIUR] grant to G.P.)

This work was published despite the drastic reduction of public funding for universities and research pursued by the Italian government (see the article "Cut-throat savings", Nature 455, October 2008, *http://www.nature.com/nature/journal/v455/n7215/full/455835b.html)*

Summary

Background: The risks/benefits balance of hormone replacement therapy (HRT) is controversial. The aim of this study was to assess the periodontal status of a postmenopausal women group receiving HRT and to determine the effects of HRT on clinical measures of periodontal disease.

Material/Methods: Ninety-one postmenopausal women, 52 taking HRT (HRT+) and 39 not taking HRT (HRT–), completed the study. Clinical parameters measured included visible supragingival plaque, probing pocket depth (PD) and clinical attachment level (CAL). Gingival status was recorded as gingival bleeding on probing (BOP). Previous oral contraceptive use and current and past smoking status were also assessed.

Results: Data indicated that PD and CAL were not significantly different between HRT+ patients and HRT– patients (P=0.8067 and P=0.1627, respectively). The HRT+ group exhibited significantly lower visible plaque levels compared to the control group (P<0.0001). The percentage of gingival sites with positive BOP was significantly lower in the HRT+ group compared to the HRT– group (34.85% *vs.* 65.15%; P=0.0007). Plaque accumulation was also tested in ANCOVA as a possible explanatory variable for the differences observed in gingival bleeding. The ANCOVA showed no significant differences in gingival bleeding between HRT+ and HRT– women (P=0.4677). No significant differences in past smoking status and oral contraceptive use were detected between HRT+ and HRT– women (P=0.9999 and P=0.0845, respectively).

Conclusions: These findings indicated that long-term HRT was not associated with relevant effects on periodontal status and clinical measures of periodontal disease, thus suggesting that HRT may not confer protection against periodontitis in postmenopausal women.

key words: **hormone replacement therapy • postmenopause • periodontitis • gingivitis • female**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=881700
Word count: 2411
Tables: 1
Figures: –
References: 61

Author's address: Giuseppe Pizzo, Section of Oral Sciences, Università di Palermo, Via del Vespro 129, 90127 Palermo, Italy, e-mail: giuseppepizzo@unipa.it

Background

Chronic periodontitis is an inflammatory disease initiated by microbial pathogens that elicit a host immune response with subsequent loss of connective tissue attachment and supporting alveolar bone [1]. Although bacteria are the causal agents of periodontitis, individual susceptibility to disease may be influenced by systemic factors [2]. Recently, estrogen deficiency has received increasing attention in relation to susceptibility to chronic periodontitis in postmenopausal women [3,4]. The production of estrogens changes drastically at menopause, leading to osteoporosis in skeletal bones, characterized by the loss of bone mass and reduction of bone density, and with a consequent increase in bone fragility and susceptibility to fracture [5]. Total skeletal mass reduction in postmenopausal women may include jawbones, particularly the mandible [6–9].

A number of studies have shown that bone changes in osteoporosis are associated with loss of periodontal attachment, loss of teeth, and height of residual ridge [10–15]. Based on these findings, it has been hypothesized that osteoporosis may be a risk factor for the progression of periodontitis. Both osteoporosis and periodontitis, in fact, are bone resorptive diseases sharing common etiologic agents/risk factor (e.g., sex, cigarette smoking, alcohol consumption, systemic diseases, heredity) that may either affect or modulate the process of both diseases [3,5].

In the past decade HRT was recognized as an effective treatment of menopausal signs and symptoms [16–19]. This therapy leads to a reduction of bone mass loss, and therefore has a significant role in the primary and secondary prevention of postmenopausal osteoporosis [20–22]. It has also been suggested that HRT may be beneficial in optimizing periodontal status in postmenopausal women [23,24]. Some clinical studies showed that HRT had a positive effect on alveolar bone density and tooth retention [11,25–29]. Similarly, estrogen administration in rats was found to prevent alveolar bone loss resulting from an estrogen-deficient state [30,31]. Periodontal health in postmenopausal women taking HRT, however, has been addressed only in a limited number of studies [23,32,33]. It has been reported that women treated with HRT exhibited lower gingival bleeding than estrogen deficient women [23,32], but conflicting results were found when the effects of HRT on attachment level and pocket depth were determined [23,32,33].

The aims of this cross-sectional study were to assess the periodontal status of a group of postmenopausal women receiving HRT, and to evaluate the association between HRT and clinical measures of periodontal disease including attachment level, pocket depth and gingival bleeding.

Material and Methods

Study population

A total of 91 Caucasian postmenopausal women, being at least 5 years past their last menstrual period (age range 50 to 62 years; mean age±SD: 55.12±3.81), volunteered to participate in this clinical study. The women enrolled in the study were selected from a pool of 195 subjects attending the Obstetrics and Gynecology Unit of the University of Palermo Medical Center (Palermo, Italy) on the basis of the following criteria: being dentate with at least 9 natural teeth in the posterior sites (with the exclusion of third molars); having no history of early menopause (ie, occurring before age 45 years); having no cancer or active or chronic parathyroid diseases; and having no pharmacological history of steroidal or non-steroidal anti-inflammatory drug use or use of immunosuppressants. Subjects who were current smokers and those who had a surgically- or chemically-induced menopause were not enrolled in the study. Moreover, no woman included in the study had received periodontal therapy and/or used antimicrobial mouthrinses in the preceding 6 months.

Previous oral contraceptive use and past smoking status were recorded. Screening and selection of volunteers were carried out by a single investigator who explained the study and obtained witnessed and signed consent to participate. The study was performed between October 2005 and September 2008 at the Department of Oral Sciences, University of Palermo. The study design was approved by the local Ethics Committee and was found to conform to the requirements of the "Declaration of Helsinki" as adopted by the 18th World Medical Assembly in 1964 and subsequently revised [34].

The subjects were divided into 2 groups on the basis of HRT use. Women who reported current HRT supplementation (n=52) for at least 5 years were assigned to the HRT + group. The control group (HRT–) (n=39) consisted of the remaining women.

The mean age for both groups was similar, 55.67±3.36 (range 50–62 years) for HRT+ group, and 54.38±4.26 (range 50–62 years) for the control group. No significant differences in age were found between groups (P=0.1107).

Oral examination

Volunteers were given an oral examination performed by a single investigator. The following oral health variables were measured: Plaque Index (PI), recorded on 4 sites in each tooth (mesio-buccal, mid-buccal, disto-buccal, mid-lingual) [35]; Bleeding on Probing (BOP), recorded on 4 sites in each tooth (mesio-buccal, mid-buccal, disto-buccal, mid-lingual) [36]; Probing Depth (PD) and Clinical Attachment Level (CAL) recorded on 6 sites in each tooth (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual and distolingual). PD was measured from the free gingival margin (MG) to the base of the pocket. For CAL assessment, according to Ramfjord's technique, probing depth from the free gingival margin to the base of the pocket was measured; the distance from the gingival margin and the cemento-enamel junction (CEJ) was also recorded. The difference between the 2 obtained values indicated CAL [37]. The following considerations were observed when measuring CAL: 1) calculus that obscured the CEJ or interfered with the correct placement of the probe was removed with a curette; 2) when the margin of restoration was apical to the CEJ, the position of CEJ was estimated using adjacent landmarks and dental anatomy; 3) when the CEJ could not be estimated, the examiner excluded the site; 4) when the natural tooth was missing, the site was excluded; 5) partially erupted teeth and root tips were excluded.

Statistical analysis

Assuming a=0.05, the present design ensured a 93.6% chance of detecting a difference of 0.5 at a standard deviation of 0.67.

The data were analyzed for normality of distribution through the use of the Kolmogorov-Smirnov test. Since the data were normally distributed, an unpaired t-test was performed to determine differences in PI, PD and CAL between the HRT+ group and the HRT– (control) group. BOP data were analyzed using the Pearson's chi-square test. The Fisher exact test was used when the number observed was quite small. The significance level was set at P<0.05.

Analysis of covariance (ANCOVA) was performed to further assess differences in BOP while adjusting for relationship detected by the initial analyses. Data management and analysis were performed using StatView 5.0.1 (SAS Institute, Inc. Cary, NC).

Results

Mean PI, PD and CAL for both HRT+ and HRT– groups are shown in Table 1. Mean PI were significantly lower in HRT+ women than in HRT- women (P<0.0001). Conversely, no significant differences were found for PD and CAL between groups (P=0.8067 and P=0.1627, respectively). The percentage of gingival sites with positive BOP was significantly lower in the HRT+ group compared to the control group (34.85% *vs.* 65.15%; P=0.0007) (Table 1).

Plaque accumulation was tested in ANCOVA as a possible explanatory variable for the differences observed in gingival bleeding. The ANCOVA showed that this covariate was significantly different between groups (P<0.0001) (data not shown). After the effect adjustments, no significant differences in gingival bleeding were found between HRT+ and HRT– women (P=0.4677) (data not shown).

No significant differences in women who smoked and those who used oral contraceptives were detected between HRT+ and HRT– subjects (P=0.9999 and P=0.0845, respectively) (data not shown).

Discussion

The physiological changes associated with menopause can cause some women to experience uncomfortable symptoms such as hot flashes and night sweats, vaginal dryness and dyspareunia, disturbed sleep and irritability/depression [5,38]. Moreover, estrogen deficiency arising from menopause, in association with age-related factors, has been shown to increase the risk of developing cardiovascular disease, including coronary heart disease and stroke, colorectal cancer and osteoporosis [5]. Until recently, HRT was considered the single most effective treatment of menopausal symptoms and its use was recommended for the prevention of diseases associated with estrogen deficiency [5,21,39]. After the publication of the Women's Health Initiative (WHI) findings in 2002 and 2004 [40,41], the use of HRT at menopause has become a matter of debate and its utility has been questioned [19,20,38]. Recent analyses of the WHI data and other randomized controlled trials,

Table 1. Clinical Measurement in HRT+ and HRT– women.

	HRT+	HRT–
PI*	1.37±0.36 (0.7–1.9)	1.74±0.35 (1.2–2.41)
PD**	2.05±0.4 (1.33–2.9)	2.07±0.46 (1.24–2.87)
CAL***	1.94±0.69 (0.67–3.43)	1.76±0.47 (0.73–2.52)
BOP****	34.85	65.15

PI, PD and CAL data are expressed as mean ± SD (range). BOP data are expressed as percentage of positive sites (BOP+). * Significant (P<0.0001); **, *** Not significant (*P*>0.1); **** Significant (*P*<0.001).

however, have suggested that the potential risks involved in taking HRT (increased risk of breast cancer, cardiovascular outcomes and stroke) may largely depend on the estrogen and progesterone/progestin formulation, dosage, mode of administration, patient's age, associated diseases, and duration of treatment [16–18,42–46]. Therefore, based on the current evidence, the intention, dose and regimen of HRT need to be individualized, based on the principle of choosing the lowest appropriate dose in relation to the severity of symptoms and age at onset of menopause [38]. For early postmenopausal women, HRT may be the most effective treatment available for vasomotor and urinary/genital symptoms [46], and may be still considered a good therapeutic choice to prevent osteoporosis and cardiovascular risk [16–18,20,46,47]. Moreover, the current evidence supports the use of HRT in women at the beginning of menopause and suffering from heard-to-bear vasomotor symptoms and disturbed sleep [38,46].

In past years, various studies have been conducted to evaluate the effect of HRT in modifying the periodontal conditions in postmenopausal women due to a possible connection between osteoporosis and the progression or severity of periodontitis [23–25,27,32,33]. However, the clinical significance of HRT in periodontal health is not well established. HRT was associated with a reduction of alveolar bone loss [6,25,27,28], but a number of studies failed to find an inverse correlation between alveolar bone density and severity of periodontal disease [48–51]. Furthermore, some authors failed to demonstrate any beneficial effect of HRT on alveolar bone density/height [52,53].

HRT has also been associated with decreased levels of gingival bleeding [23,32]. It has been suggested that estrogen may have an inhibitory effect on gingival inflammation by inhibiting mediators (IL-1, TNF-α, IL-6, IL-1β, IL-8) and cellular mechanism of inflammation (PMN recruitment, lymphocyte activation) [54–57]. Similarly, estrogen supplementation may modulate the rate of breakdown of periodontal tissue through a mechanism involving down-regulation of matrix metalloproteinases (MMP-8 and MMP-13) and cytokines involved in bone resorption [4,57–59]. Conflicting results exist on the effects of HRT on probing pocket depth and attachment level [23,32,33]. Furthermore, the risk of tooth loss was found to be lower in women who used HRT

than those who did not [26,29,52,60,61]. Tooth loss, however, could not be used as a surrogate evaluation for periodontal disease, since reasons for tooth loss could include caries or trauma. Moreover, the extent of periodontal destruction around the remaining teeth was not taken into account in this analysis.

The aim of this study was to evaluate the periodontal status of postmenopausal women and to determine the effect of HRT on standard clinical measurements of periodontal disease. In the present study, HRT+ women had lower inflammatory gingival scores than HRT- women, as indicated by the lower percentage of bleeding sites (P=0.0007). The level of supragingival plaque accumulation was found to be significantly lower in HRT+ women than in HRT– women (P<0.0001). To account for factors that are known to be associated with gingivitis, it was of great importance to adjust for the difference in plaque level in the final analysis between groups. The findings of initial statistical analysis were not confirmed after correcting for plaque accumulation by those women on HRT having less gingival bleeding (ANCOVA, P=0.4677). Women taking HRT had fewer bleeding sites than did HRT- women, but this finding may be related to the lower level of supragingival plaque than to the effect of HRT. These results are in contrast with previous reports linking the use of HRT with the reduction of bleeding sites [23,32]. In those studies, the percent of gingival sites with bleeding was significantly lower in HRT+ women compared to HRT– women, despite the levels of plaque accumulation.

The results of the present study showed no detectable differences in CAL between groups. CAL is an important measure of periodontitis progression because of its relationship with alveolar bone loss. Due to the known beneficial effects of HRT on osteoporosis, it may be expected to significantly lower values for CAL in the HRT+ group. Ronderos et al. [24] found the mean CAL differences observed between postmenopausal females who reported the use of estrogen supplementation for more than 5 years and those who never used estrogens were significant, although quite small (1.74 *vs.* 1.56) [24]. Other previous studies reported lower values of CAL in women using HRT, but the difference found between HRT+ and HRT– patients was not significant [23,32].

In the present study, no significant difference was detected in the mean PD between the 2 groups of women. This finding is in agreement with previous studies [23,32], with the exception of the study by Lopez Marcos et al. [33], who evaluated the differences in PD values between HRT+ and HRT– groups at the beginning of the therapy and then revaluated over 6 months to 1 year after the beginning of the HRT. Lopez Marcos et al. [33] reported the PD variable for patients not receiving HRT evolved to worse stages, whereas patients receiving HRT showed a significant improvement in PD. It must be noted, however, that these results cannot be compared with those of the present study because of the different study designs. Moreover, in the study of Lopez Marcos et al. [33], CAL was not assessed and other clinical measures of periodontitis (dental pain of periodontal origin, gingival recessions) did not show significant improvement in the HRT+ group. Thus, the decrease of PD values in patients receiving HRT could be related to the reduction of gingival inflammation due to the estrogen action rather than to an effective gain of attachment [33].

Conclusions

The findings of the present study indicate that, in postmenopausal women, long-term HRT was not associated with significant effects on periodontal status and clinical measures of periodontitis, thus suggesting that HRT may not confer protection against periodontitis. Periodontitis may be primarily related to the presence of plaque and to a lesser extent to hormonal changes such as estrogen deficiency. However, the possibility exists that the decreased estrogen levels associated with the postmenopausal period may contribute to the progression of periodontal disease by affecting the oral bone mass [3,10–12,15,23,28,50]. Thus, postmenopausal women with periodontal disease should undergo periodical screening examinations in order to detect changes in their periodontal status and support them with periodontal treatment.

References:

1. Flemming TF: Periodontitis. Ann Periodontol, 1999; 4: 32–37
2. Reddy MS: Reaching a better understanding of non-oral disease and the implication of periodontal infections. Periodontol 2000, 2007; 44: 9–14
3. Geurs NC: Osteoporosis and periodontal disease. Periodontol 2000, 2007; 44: 29–43
4. Lerner UH: Inflammation-induced bone remodelling in periodontal disease and the influence of post-menopausal osteoporosis. J Dent Res, 2006; 85: 596–607
5. Friedlander AH: The physiology, medical management and oral implication of menopause. J Am Dent Assoc, 2002; 133: 73–81
6. Jacobs R, Ghyselen J, Koninckx P, van Steenberghe D: Long-term bone mass evaluation of mandible and lumbar spine in a group of women receiving hormone replacement therapy. Eur J Oral Sci, 1996; 104: 10–16
7. Jeffcoat MK, Lewis CE, Reddy MS et al: Post-menopausal bone loss and its relationship to oral bone loss. Periodontol 2000, 2000; 23: 94–102
8. Southard KA, Southard DE, Schlechte JA, Meis PA: The relationship between the density of the alveolar processes and that of post-cranial bone. J Dent Res, 2000; 79: 964–69
9. Shrout MK, Hildebolt CF, Potter BJ et al: Comparison of morphological measurements extracted from digitized dental radiographs with lumbar and femoral bone mineral density measurements in postmenopausal women. J Periodontol, 2000; 71: 335–40
10. Yoshihara A, Seida Y, Hanada N, Miyazaki H: A longitudinal study of the relationship between periodontal disease and bone mineral density in community-dwelling older adults. J Clin Periodontol, 2004; 31: 680–84
11. Payne JB, Reinhardt RA, Nummikoski PV, Patil KD: Longitudinal alveolar bone loss in postmenopausal osteoporotic/osteopenic women. Osteoporos Int, 1999; 10: 34–40
12. Persson RE, Hollender LG, Powell LV et al: Assessment of periodontal conditions and systemic disease in older subjects. I. Focus on osteoporosis. J Clin Periodontol, 2002; 29: 796–802
13. Wactawski-Wende J, Hausmann E, Hovey K et al: The association between osteoporosis and alveolar crestal height in postmenopausal women. J Periodontol, 2005; 76: 2116–24
14. Inagaki K, Kurosu Y, Yoshinari N et al: Efficacy of periodontal disease and tooth loss to screen for low bone mineral density in Japanese women. Calcif Tissue Int, 2005; 77: 9–14
15. Brennan RM, Genco RJ, Hovey KM et al: Clinical attachment loss, systemic bone density, and subgingival calculus in postmenopausal women. J Periodontol, 2007; 78: 2104–11
16. Caufriez A: Hormonal replacement therapy (HRT) in postmenopause: a reappraisal. Ann Endocrinol (Paris), 2007; 68: 241–45
17. Harman SM: Estrogen replacement in menopausal women: recent and current prospective studies, the WHI and the KEEPS. Gend Med, 2006; 3: 254–69
18. MacLennan AH: HRT: a reappraisal of the risks and benefits. Med J Aust, 2007; 186: 643–46

19. Gambacciani M, Ciaponi M, Genazzani AR: The HRT misuse and osteoporosis epidemic: a possible future scenario. Climacteric, 2007; 10: 273–75
20. U.S. Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendation statement. Ann Intern Med, 2005; 142: 855–60
21. Humphries KH, Gill S: Risks and benefits of hormone replacement therapy: the evidence speaks. CMAJ, 2003; 168: 1001–10
22. Cauley JA, Robbins J, Chen Z et al: Effects of estrogen plus progestin on risk fracture and bone mineral density: the Women's Health Initiative randomized trial. J Am Med Assoc, 2003; 290: 1729–38
23. Reinhardt RA, Payne JB, Maze CA et al: Influence of estrogen and osteopenia/osteoporosis on clinical periodontitis in postmenopausal women. J Periodontol, 1999; 70: 823–28
24. Ronderos M, Jacobs DR, Himes JH, Pihlstrom BL: Associations of periodontal disease with femoral bone mineral density and estrogen replacement therapy: cross-sectional evaluation of US adults from NHANES III. J Clin Periodontol, 2000; 27: 778–86
25. Civitelli R, Pilgram TK, Dotson M et al: Alveolar and postcranial bone density in postmenopausal women receiving hormone/estrogen replacement therapy. Arch Intern Med, 2002; 162: 1409–15
26. Krall EA, Dawson-Hughes B, Hannan MT et al: Postmenopausal estrogen replacement and tooth retention. Am J Med, 1997; 102: 536–42
27. Payne BJ, Zachs NR, Reinhardt RA et al: The association between estrogen status and alveolar bone density in postmenopausal women with a history of periodontitis. J Periodontol, 1997; 68: 24–31
28. Hildebolt CH, Pilgram TK, Yokoama-Crothers N et al: The pattern of alveolar crest height change in healthy postmenopausal women after 3 years of hormone/estrogen replacement therapy. J Periodontol, 2002; 73: 1279–84
29. Meisel P, Reifenberger J, Haase R et al: Women are periodontally healthier than men, but why don't they have more teeth than men? Menopause, 2008; 15: 270–75
30. Duarte PM, Goncalves PF, Sallum AW et al: Effect of an estrogen-deficient state and its therapy on bone loss resulting from an experimental periodontitis in rats. J Periodontal Res, 2004; 39: 107–10
31. Kawamoto S, Ejiri S, Nagaoka E, Ozawa H: Effects of oestrogen deficiency on osteoclastogenesis in the rat periodontium. Arch Oral Biol, 2002; 47: 67–73
32. Norderyd OM, Grossi SG, Machtei EE et al: Periodontal status of women taking postmenopausal estrogen supplementation. J Periodontol, 1993; 64: 957–62
33. Lopez Marcos JF, Garcia Valle S, Garcia Iglesias AA: Periodontal aspects in menopausal women undergoing hormone replacement therapy. Med Oral Patol Oral Cir Bucal, 2005; 10: 132–41
34. The World Medical Association Policy: World Medical Association Declaration of Helsinki. 2008. Available from: *http://www.wma.net/en/30publications/10policies/b3/index.html*
35. Silness J, Löe H: Periodontal disease in pregnancy (II). Correlation between oral hygiene and periodontal conditions. Acta Odontol Scand, 1964; 22: 121–35
36. Löe H: The gingival index, the plaque index and the retention index system. J Periodontol, 1967; 38: 610–16
37. Burt BA, Eklund SA: Dentistry, Dental practice, and the Community. 6th ed. St Louis: Elsevier Saunders, 2005
38. Mosconi P, Donati S, Colombo C et al: Informing women about hormone replacement therapy: the consensus conference statement. BMC Women's Health, 2009; 9: 14
39. Rymer J, Wilson R, Ballard K: Making decisions about hormone replacement therapy. Br Med J, 2003; 326: 322–26
40. Rossouw JU, Anderson GL, Prentice RL et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. J Am Med Assoc, 2002; 288: 321–33
41. Anderson GL, Limacher M, Assaf AR et al: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. J Am Med Assoc, 2004; 291: 1701–12
42. Rosano GM, Vitale C, Fini M: Hormone replacement therapy and cardioprotection: what is good and what is bad for the cardiovascular system? Ann N Y Acad Sci, 2006; 1092: 341–48
43. Mastorakos G, Sakkas EG, Xydakis AM, Creatsas G: Pitfalls of the WHIs: Women's Health Initiative. Ann N Y Acad Sci, 2006; 1092: 331–40
44. Vickers MR, MacLennan AH, Lawton B et al: Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. Br Med J, 2007; 335: 239
45. Rossouw JE, Prentice RL, Manson JE et al: Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. J Am Med Assoc, 2007; 297: 1465–77
46. Santen R, Allred DC, Ardoin SP et al: Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab, 2010; 95(7 Suppl.1): s1–s66
47. Palacios S: Advances in hormone replacement therapy: making the menopause manageable. BMC Women's Health, 2008; 8: 22
48. Phipps KR, Chan BK, Madden TE et al: Longitudinal study of bone density and periodontal disease in men. J Dent Res, 2007; 86: 1110–14
49. Weyant RJ, Pearlstein ME, Churak AP et al: The association between osteopenia and periodontal attachment loss in older women. J Periodontol, 1999; 70: 982–91
50. Hildebolt CF, Pilgram TK, Dotson M et al: Attachment loss with postmenopausal age and smoking. J Periodontal Res, 1997; 32: 619–25
51. Pilgram TK, Hildebolt CF, Yokoyama-Crothers N et al: Relationships between longitudinal changes in radiographic alveolar bone height and probing depth measurements: data from postmenopausal women. J Periodontol, 1999; 70: 829–33
52. Taguchi A, Sanada M, Suei Y et al: Effect of estrogen use on tooth retention, oral bone height, and oral bone porosity in Japanese postmenopausal women. Menopause, 2004; 11: 556–62
53. Bollen AM, Taguchi A, Hujoel PP, Hollender LG: Number of teeth and residual ridge height in subject with a history of self reported osteoporotic fractures. Osteoporos Int, 2004; 15: 970–74
54. Miyagi M, Aoyama H, Morishita M, Iwamoto Y: Effects of sex hormones on chemotaxis of human peripheral polymorphonuclear leukocytes and monocytes. J Periodontol, 1992; 63: 28–32
55. Reinhardt RA, Payne JB, Maze C et al: Gingival fluid IL-1b in postmenopausal females on supportive periodontal therapy: a longitudinal 2-year study. J Clin Periodontol, 1998; 25: 1029–35
56. Ito I, Hayashi T, Yamada K et al: Physiological concentration of estradiol inhibits polymorphonuclear leukocyte chemotaxis via a receptor mediated system. Life Sci, 1995; 56: 2247–53
57. Weitzmann MN, Pacifici R: Estrogen deficiency and bone loss: an inflammatory tale. J Clin Invest, 2006; 116: 1186–94
58. Streckfus CF, Johnson RB, Nick T et al: Comparison of alveolar bone loss, alveolar bone density and second metacarpal bone density, salivary and gingival crevicular fluid interleukin-6 concentrations in healthy premenopausal and postmenopausal women on estrogen therapy. J Gerontol A Biol Sci Med Sci, 1997; 52: M343–51
59. Golub LM, Ramamurthy NS, Llavaneras A et al: A chemically modified nonantimicrobial tetracycline (CMT-8) inhibits gingival matrix metalloproteinases, periodontal breakdown, and extra-oral bone loss in ovariectomized rats. Ann N Y Acad Sci, 1999; 878: 290–310
60. Paganini-Hill A: The benefits of estrogen replacement therapy on oral health. Arch Intern Med, 1995; 155: 2325–29
61. Grodstein F, Colditz GA, Stampfer MJ: Post-menopausal hormone use and tooth loss: a prospective study. J Am Dent Assoc, 1996; 127: 370–77