Hearing Research 252 (2009) 56–60

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research paper

The effect of sex hormones on bone metabolism of the otic capsule – an overview

Kathleen C. Horner *

Dept Physiologie Neurovégétative, CRN2M-UMR 6231, Université Paul Cézanne, Faculté des Sciences et Techniques, Boulevard Normandie Niémen, 13397 Marseille Cedex 20, France

ARTICLE INFO

Article history:
Received 16 September 2008
Received in revised form 28 November 2008
Accepted 4 December 2008
Available online 24 December 2008

Keywords:
Cochlea
Hormones
Bone
Prolactin
Estrogen
Osteoprotegerin
RANK

ABSTRACT

Bone resorption, which can occur after the menopause, has long been considered to due to the decrease of estrogen and so estrogen and estrogen/progestin treatment in women has been employed with the aim of slowing down the process. Other important factors have recently been considered, including follicle-stimulating hormone. The hormonal control of bone metabolism has taken on a new dimension since the description, within the last decade, of a major osteoclast inhibiting control system. The receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL) produced by osteoblastic lineage cells, must bind with its receptor RANK, located on osteoclasts, in order to allow the maturation and activation of osteoclasts. The potential continuous bone loss is controlled by the decoy receptor osteoprotegerin (OPG) which competitively binds to RANKL and hence blocks the interaction of RANKL–RANK. Estrogen contributes to bone protection since it decreases the response of osteoclasts to RANKL and induces osteoclast apoptosis. But estrogen, alone and especially in synergy with progesterone, is a potent stimulator of prolactin release. Prolactin affects calcium metabolism and hyperprolactinemia associated with pregnancy, lactation, antipsychotic drug treatment, or aging is reflected in decreased bone mineral density. Long-term estrogen treatment in guinea pig results in hyperprolactinemia and has been shown to lead to hearing loss as well as bone dysmorphology of the otic capsule. Recent data show that prolactin decreases OPG and increases RANKL. OPG has been shown to be expressed at high levels in the cochlea and OPG knock-out mice have indeed abnormal remodeling of the otic capsule and resorption of the auditory ossicles. So estrogen-induced hyperprolactinemia could oppose estrogen protection by the knock-down of the OPG bone protection system. This might explain why oral contraception treatment and hormone replacement therapies, involving estrogen together with progestin, increases the risk of otosclerosis and vestibular disorders. Hyperprolactinemia associated with pregnancy and lactation might also underlie the association of increased risk of otosclerosis with multiple pregnancies.

1. Introduction

The aim of the present contribution is not to review the literature on bone metabolism of the otic capsule. The aim is rather to bring together seeming disparate reports – old, new, forgotten or ignored – which in isolation have little impact but when taken together they consolidate todays interest in the influence of sex hormones on the inner ear. In particular, It is hoped that this overview will open the way to further interest in other interacting hormones and, in particular, prolactin which might affect the inner ear.

2. Sex hormones affect the inner ear

When interested in the effects of hormones and the inner ear, a rapid browse of some recent literature reveals that estrogen and more particularly receptor B is involved in the protection against acoustic trauma (Meltser et al., 2008) while hormone therapy, including progestin together with estrogen, can damage hearing (Guimaraes et al., 2006). These seemingly conflicting data come years after case reports of irreversible (Okulicz, 1978) or reversible hearing loss (Hanna, 1986), tinnitus (Mitre et al., 2006) as well as vestibular dysfunction (Mitre et al., 2006; Rybak, 1995) following the use of the contraceptive pill or hormone therapy (Strachan, 1996). On the other hand, a large cohort study found no statistical evidence for potentiating effect of oral contraceptives on ear disease (Vessey and Painter, 2001) and estrogen therapy was reported to slow down hearing loss in post-menopausal women (Kilicdag et al., 2004). Changes in otoacoustic emissions and auditory evoked potentials in women using oral contraceptives suggest that the auditory system may become more masculine (McFadden, 2000). Hormone level variations that occur in pregnancy can provoke the feeling of fullness of the ear (Tsunoda et al., 1999) and low frequency hearing loss (Sennaroglu and Belgin, 2001) which resolves after delivery (Tsunoda et al., 1999). Also, the menstrual cycle seems to be reflected in changes in postural stability (Darlington et al., 2001) or brainstem evoked auditory responses (Caruso et al., 2003; Elkind-Hirsch et al., 1992a, b; Serra et al., 2003) or

* Tel.: +4 91 28 83 83; fax: +4 91 28 88 85.
E-mail address: kathleen.horner@univ-cezanne.fr

0378-5955/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.heares.2008.12.004

hearing thresholds (Swanson and Dengerink, 1988). Gender does play a role in age-related hearing loss. Longitudinal studies of aging has shown that hearing declines more rapidly in males than females (Pearson et al., 1995) starting between 20 and 30 yr in men and above 50 yr in women (Gordon-Salant, 2005) and while women hear better at high frequencies before menopause they hear worse at lower frequencies after menopause (Murphy and Gates, 1997). In addition, better hearing has been reported to be correlated with higher serum estradiol levels in post-menopausal women (Kim et al., 2002). While the effects of different sex hormones, alone or together with the hypothalamus pituitary adrenal axis (HPA), on the ear is not fully understood it is quite clear that hormones do affect labyrinthine function (reviews) (Al-Mana et al., 2008; Horner, 2003; Hultcrantz et al., 2006; Seemungal et al., 2001).

3. Hormones underlie osteoporosis – does prolactin play a role?

Osteoporosis in post-menopausal women has long been associated with the fall in estrogen levels – thus contributing to justification for the continued use of hormone replacement therapy in women. Bone loss in post-menopausal women typically occurs in two phases – a rapid phase, related to the lack of estrogen on bone metabolism, which can last several years, and a slow phase, related to the calcium homeostasis, of indefinite duration (Riggs, 2002). While estrogen is probably a major actor, other hormones come into play. Indeed some debate has been sparked off by the recent report concluding that follicle-stimulating hormone, independently of estrogen, directly regulates bone mass (Sun et al., 2006). Others argue that both could be involved (Baron, 2006). But osteoporosis also occurs in association with normal pregnancy and indeed parity could have an inverse effect on bone mineral density (Allali et al., 2007). During pregnancy, estrogen and progesterone levels increase continuously and FSH is suppressed. So, change in bone metabolism might rather be related to high prolactin levels which increases throughout pregnancy. Prolactin is an important regulator of intestinal calcium transport in pregnant as well as non-pregnant rats (Charoenphandhu and Krishnamra, 2007). Interestingly, prolactin has recently been shown to be linked to bone metabolism (Charoenphandhu et al., 2008; Seriwatanachai et al., 2008a, b). Long-term breast-feeding is a period associated with hyperprolactinemia and low estrogen and also clearly associated with osteoporosis (Kovacs, 2005). Hyperprolactinemia can occur with aging (Baranowska et al., 2007; Blackman et al., 1986; Metka et al., 1994). Hyperprolactinemia has been detected in menopausal women and hormone replacement therapy can increase prolactin levels (Metka et al., 1994). Of particular significance is that osteoporosis in people with mental illness, is clearly related to antipsychotic drug-induced hyperprolactinemia (Peveler et al., 2008).

4. Hormones and otosclerosis

Otosclerosis is a chronic inflammatory infection of the otic capsule resulting in bone resorption. The pathology has a complex etiology and the state of the art has been reviewed recently (Arnold, 2007). The measles virus has been pin-pointed as one crucial contributing factor. The virus was first detected by immunohistochemistry in otosclerotic lesions and measle virus specific antibodies have been detected in perilymph (Arnold et al., 1996). While only 1% of the population may develop clinical otosclerosis with hearing loss, histological evidence from autopsy suggests rather 8% or 11%. Otosclerosis becomes manifest between the ages of 20 and 50 yr and is usually bilateral. It affects twice as many females as males (Chole and McKenna, 2001). While otosclerosis is reported to worsen during periods of intense hormonal activity (Sellari-Franceschini et al., 1998), a possible link between aggravation of otosclerosis and pregnancy is still debated. A retrospective study on a sample of 479 women with otosclerosis showed that the risk of subjective hearing deterioration with bilateral otosclerosis increased from 33% after one pregnancy to 63% after six pregnancies (Gristwood and Venables, 1983). On the other hand, a retrospective study on women, who had undergone stapedectomy, found no significant correlation between number of children and hearing loss (Lippy et al., 2005). Several reports have suggested that oral contraceptives may increase the risk of hearing loss and in particular otosclerosis, although no clear conclusion has been drawn (Vessey and Painter, 2001). As discussed above, some recent data show that hormone replacement therapy, including estrogen together with progestin, can worsen hearing (Guimaraes et al., 2006). However that study did not consider the possibility that the hormone treatment might influence bone and indeed the women presenting middle ear pathologies were actually excluded from the analysis.

Although otosclerosis is a bone pathology of the otic capsule there have been several studies relating age-related decrease in bone mineral density to otosclerosis. Bone mineral density of the lower hip or heel was found to be moderately associated with hearing loss in men but not women aged between 70 and 79 years (Helzner et al., 2005). There was a consistent inverse association between femoral neck bone mass and hearing loss in women aged between 60 and 85 years (Clark et al., 1995). These two studies assumed that decrease in bone mineral density would reflect demineralisation of the temporal bone which would be related to hearing loss as earlier described (Huizing and de Groot, 1987). In contrast, in a retrospective study of female patients aged between 50 and 75 years who had undergone a stapedectomy for otosclerosis, 15 of 100 women had otosclerosis concomitant with osteoporosis as compared with 4 of 100 women with presbyacusis. The data yielded a significant clinical association between diagnosed osteoporosis and confirmed otosclerosis (Clayton et al., 2004). Interestingly, a significantly high association has been reported between otosclerosis or osteoporosis and polymorphic markers within the COLIA1 (collagen 1A1) gene, suggesting a shared genetic etiology between otosclerosis and osteoporosis (McKenna et al., 2004).

5. Molecular basis of bone metabolism – and the otic capsule

Healthy bone metabolism involves the coupling between bone formation and bone resorption via osteoblasts and osteoclasts respectively. Loss of function of osteoclasts is known as osteopetrosis, gain of function of osteoblasts as osteoclerosis and relative increase of bone resorption over bone formation as osteoporosis. Our present understanding of bone metabolism largely considers the role of three members of the tumor necrosis factor (TNF) and TNF receptor families of proteins (Boyle et al., 2003), described within the last decade. These include a major osteoclast stimulating factor – receptor activator of NF-κB ligand (RANKL), which is produced by osteoblastic lineage cells, its receptor RANK located on osteoclast precursors and osteoprotegerin (OPG) – a soluble TNF-related protein which acts as a decoy receptor. The efficiency of OPG lies in its capacity to inhibit the maturation and activation of osteoclasts and to promote their apoptosis. Osteopetrosis occurs where there is overexpression of OPG in transgenic mice (Simonet et al., 1997), or in RANKL deficient (Kong et al., 1999) or in RANK knock-out mice (Dougall et al., 1999; Li et al., 2000). Furthermore osteopetrosis also occurs in mice NF-κB knock-out mice (Iotsova et al., 1997). On the other hand OPG-deficient mice develop osteoporosis (Bucay et al., 1998; Mizuno et al., 1998).

The molecular biology of otosclerosis is likely to be similar to that described above and the current state of knowledge has been reviewed recently (McKenna and Kristiansen, 2007). Osteoprotegerin is expressed in the spiral ligament and secreted into the perilymph (Zehnder et al., 2005). Interestingly, there is abnormal bone remodeling of the otic capsule in OPG knock-out mice (Kanzaki et al., 2006; Zehnder et al., 2006). Indeed, OPG expression is decreased in measles-related otosclerosis (Karosi et al., 2006) giving support to the theory that persistent measles virus can contribute to otosclerosis (Niedermeyer and Arnold, 2008).

6. Hormones affect the molecular control of bone metabolism – estrogen versus prolactin

While the RANKL–RANK–OPG system now appears to be determinant in the control of bone metabolism, the system is regulated by hormones. Estrogen has its protective effect on bone because it can inhibit bone resorption by inducing apoptosis of osteoclasts (Kameda et al., 1997) and blocking the maturation of osteoclasts (Pacifici, 1996). Estrogen has now been found to stimulate OPG in osteoblastic cells (Hofbauer et al., 1999) and to decrease the response of osteoclasts to RANKL (Srivastava et al., 2001). On the other hand, estrogen is a potent activator of prolactin release (Raymond et al., 1978) and recent exciting data show that prolactin also has a major influence on bone metabolism. Prolactin is an important regulator of intestinal calcium transport (Charoenphandhu and Krishnamra, 2007) and has a direct inhibitory effect on osteoblast function (Charoenphandhu et al., 2008; Coss et al., 2000). Prolactin enhances bone resorption by increasing RANKL/OPG ratio expression by osteoblasts derived from adult humans (Seriwatanachai et al., 2008b) or by proportional decrease in expression of both RANKL and OPG from adult rats (Charoenphandhu et al., 2008). In contrast in fetal osteoblast cells, prolactin was found to decrease the expression ratio of RANKL/OPG (Seriwatanachai et al., 2008a). Raloxifene, a selective estrogen receptor modulator, used in the management of osteoporosis in women stimulates prolactin secretion in ovariectomized rats (Pinilla et al., 2001). Estrogen as well as progesterone promote prolactin (Caligaris et al., 1974) release by reducing dopaminergic inhibition of prolactin secretion from the pituitary (Arbogast and Ben-Jonathan, 1990). Indeed synergic interaction between estrogen and progesterone induces hyperprolactinemia in monkeys (Pecins-Thompson and Bethea, 1997; Williams et al., 1985). Hyperprolactinemia, which results from antipsychotic drug treatment has been more or less ignored for years. Fortunately, it has recently been recognized as underlying the decrease in bone mineral density of mentally-ill patients and new clinical recommendations have been put forward (Peveler et al., 2008). From the above, it seems quite plausible that hyperprolactinemia could result from some hormone therapies with consequent adverse effects on bone metabolism and the otic capsule but this possibility has never been considered in the literature.

7. Prolactin is linked to other labyrinthine pathologies

As discussed above pregnancy, lactation, contraceptive pills, and hormone replacement therapy, are conditions affecting bone structure and have, only loosely, been related to different types of labyrinthine dysfunctions. While estrogen is accepted as a possible actor, the same cannot be said for the role of prolactin. However, further supporting evidence for this hypothesis comes from other pathologies.

Ménière's disease is characterized by hearing loss, tinnitus and vestibular dysfunction. It is thought that endolymph malabsorption is the underlying cause of the swelling of the endolymphatic spaces (hydrops) – a morpho-pathological feature. A subset of Ménière's patients can also present otosclerosis (Paparella et al., 1984; Shea et al., 1994; Sismanis et al., 1986; Yoon et al., 1990). While hyperprolactinemia has been reported in some patients (Falkenius-Schmidt et al., 2005; Horner et al., 2002), there is no data to link hyperprolactinemia in some Ménière-like patients to otosclerosis in those patients. One clue is provided by estrogen-induced hyperprolactinemia which was reported to provoke hearing loss and otic capsule dysmorphology in guinea pigs (Horner et al., 2007).

Pendred's syndrome is caused by a mutation of a gene which codes for pendrin (SlC26A4) – a transporter of chloride, bicarbonate and iodide. The clinical hallmarks are sensorineural hearing loss together with goiter. There is also bone malformation of the inner ear which includes enlargement of the vestibular aqueduct and in some cases there is a reduction in the number of cochlear turns (Kopp et al., 2008). Pendrin is expressed in the spiral prominence and outer sulcus cells, the transitional cells of vestibular organs and the endolymphatic sac. Since these all areas concerned with endolymph absorption, absence of pendrin results in endolymphatic hydrops (Royaux et al., 2003). Pendred's syndrome is typically associated with hypothyroidism, and so prolactin levels could be expected to be elevated (Sato et al., 1984), but this has not been an issue of discussion in the literature. On the other hand, there may yet be some uncovered role of prolactin given the fact that, in the mammary gland, prolactin actually stimulates the pendrin-iodide transporter which is essential for iodide uptake into milk (Rillema and Hill, 2003).

Turner's syndrome is characterized by gonadal dysgenesis, low estrogen levels, retarded growth as well as decreased bone mineral density and conductive and/or sensorineural hearing loss (Hultcrantz et al., 2006). Interestingly, in a group of 43 patients with Turner's Syndrome the mean basal prolactin level was reported to be significantly higher than a group of 192 female controls (Amendt et al., 1992). One recent study investigated OPG and RANKL concentrations in children with different pathologies. They found that serum OPG levels in children with Turner's syndrome was significantly lower than age-matched controls (Buzi et al., 2004). It should be recalled that prolactin enhances bone resorption in part by increasing RANKL and decreasing OPG expressions by osteoblasts (Seriwatanachai et al., 2008b). However, the possible contribution of prolactin to the bone manifestations has not been reported.

8. Future in molecular bone therapy of the otic capsule

Fundamental studies on molecular mechanisms of bone resorption in the past ten years have given way to therapeutical approaches aimed at inhibiting RANKL and protecting bones (Schwarz and Ritchlin, 2007). For example a single dose of OPG in post-menopausal women was reported to substantially reduce bone turnover and for a sustained period (Bekker et al., 2001). These and other data provide encouraging basis for the development of clinical anti-RANKL therapy for bone diseases (Hofbauer and Schoppet, 2001; Schwarz and Ritchlin, 2007) although the precise role of OPG in different disease states is not always clear (Hofbauer and Schoppet, 2001).

Evidence that the otic capsule may similarly be affected by RANKL–RANK–OPG is now emerging. There is renewed interest in the effect of hormones on hearing/vestibular function. Emphasis on the role of estrogen has given way to investigation on possible contribution of other hormones and especially that of prolactin. These new insights into bone metabolism should allow significant advances in the management and perhaps the prevention of labyrinthine bone disorders in the future.

References

Allali, F., Maaroufi, H., Aichaoui, S.E., Khazani, H., Saoud, B., Benyahya, B., Abouqal, R., Hajjaj-Hassouni, N., 2007. Influence of parity on bone mineral density and peripheral fracture risk in Moroccan postmenopausal women. Maturitas 57, 392–398.

Al-Mana, D., Ceranic, B., Djahanbakhch, O., Luxon, L.M., 2008. Hormones and the auditory system: a review of physiology and pathophysiology. Neuroscience 153, 881–900.

Amendt, P., Hesse, V., Rohde, W., 1992. Somatomedin-C/IGF-I, insulin and prolactin levels in Ullrich-Turner's syndrome. Exp. Clin. Endocrinol. 99, 73–76.

Arbogast, L.A., Ben-Jonathan, N., 1990. The preovulatory prolactin surge is prolonged by a progesterone-dependent dopaminergic mechanism. Endocrinology 126, 246–252.

Arnold, W. (Ed.), 2007. Advances in Oto-Rhino-Laryngology, vol. 65. Otosclerosis and Stapes Surgery, Karger, Basel.

Arnold, W., Niedermeyer, H.P., Altermatt, H.J., Neubert, W.J., 1996. Pathogenesis of otosclerosis. "State of the art". Hno 44, 121–129.

Baranowska, B., Wolinska-Witort, E., Bik, W., Baranowska-Bik, A., Martynska, L., Chmielowska, M., Broczek, K., Mossakowska, M., 2007. Evaluation of neuroendocrine status in longevity. Neurobiol. Aging 28, 774–783.

Baron, R., 2006. FSH versus estrogen: who's guilty of breaking bones? Cell Metab. 3, 302–305.

Bekker, P.J., Holloway, D., Nakanishi, A., Arrighi, M., Leese, P.T., Dunstan, C.R., 2001. The effect of a single dose of osteoprotegerin in postmenopausal women. J. Bone Miner. Res. 16, 348–360.

Blackman, M.R., Kowatch, M.A., Wehmann, R.E., Harman, S.M., 1986. Basal serum prolactin levels and prolactin responses to constant infusions of thyrotropin releasing hormone in healthy aging men. J. Gerontol. 41, 699–705.

Boyle, W.J., Simonet, W.S., Lacey, D.L., 2003. Osteoclast differentiation and activation. Nature 423, 337–342.

Bucay, N., Sarosi, I., Dunstan, C.R., Morony, S., Tarpley, J., Capparelli, C., Scully, S., Tan, H.L., Xu, W., Lacey, D.L., Boyle, W.J., Simonet, W.S., 1998. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev. 12, 1260–1268.

Buzi, F., Maccarinelli, G., Guaragni, B., Ruggeri, F., Radetti, G., Meini, A., Mazzolari, E., Cocchi, D., 2004. Serum osteoprotegerin and receptor activator of nuclear factors kB (RANKL) concentrations in normal children and in children with pubertal precocity, Turner's syndrome and rheumatoid arthritis. Clin. Endocrinol. (Oxf) 60, 87–91.

Caligaris, L., Astrada, J.J., Taleisnik, S., 1974. Oestrogen and progesterone influence on the release of prolactin in ovariectomized rats. J. Endocrinol. 60, 205–215.

Caruso, S., Maiolino, L., Rugolo, S., Intelisano, G., Farina, M., Cocuzza, S., Serra, A., 2003. Auditory brainstem response in premenopausal women taking oral contraceptives. Hum. Reprod. 18, 85–89.

Charoenphandhu, N., Krishnamra, N., 2007. Prolactin is an important regulator of intestinal calcium transport. Can. J. Physiol. Pharmacol. 85, 569–581.

Charoenphandhu, N., Teerapornpuntakit, J., Methawasin, M., Wongdee, K., Thongchote, K., Krishnamra, N., 2008. Prolactin decreases expression of Runx2, osteoprotegerin, and RANKL in primary osteoblasts derived from tibiae of adult female rats. Can. J. Physiol. Pharmacol. 86, 240–248.

Chole, R.A., McKenna, M., 2001. Pathophysiology of otosclerosis. Otol. Neurotol. 22, 249–257.

Clark, K., Sowers, M.R., Wallace, R.B., Jannausch, M.L., Lemke, J., Anderson, C.V., 1995. Age-related hearing loss and bone mass in a population of rural women aged 60 to 85 years. Ann. Epidemiol. 5, 8–14.

Clayton, A.E., Mikulec, A.A., Mikulec, K.H., Merchant, S.N., McKenna, M.J., 2004. Association between osteoporosis and otosclerosis in women. J. Laryngol. Otol. 118, 617–621.

Coss, D., Yang, L., Kuo, C.B., Xu, X., Luben, R.A., Walker, A.M., 2000. Effects of prolactin on osteoblast alkaline phosphatase and bone formation in the developing rat. Am. J. Physiol. Endocrinol. Metab. 279, E1216–E1225.

Darlington, C.L., Ross, A., King, J., Smith, P.F., 2001. Menstrual cycle effects on postural stability but not optokinetic function. Neurosci. Lett. 307, 147–150.

Dougall, W.C., Glaccum, M., Charrier, K., Rohrbach, K., Brasel, K., De Smedt, T., Daro, E., Smith, J., Tometsko, M.E., Maliszewski, C.R., Armstrong, A., Shen, V., Bain, S., Cosman, D., Anderson, D., Morrissey, P.J., Peschon, J.J., Schuh, J., 1999. RANK is essential for osteoclast and lymph node development. Genes Dev. 13, 2412–2424.

Elkind-Hirsch, K.E., Stoner, W.R., Stach, B.A., Jerger, J.F., 1992a. Estrogen influences auditory brainstem responses during the normal menstrual cycle. Hear. Res. 60, 143–148.

Elkind-Hirsch, K.E., Wallace, E., Stach, B.A., Jerger, J.F., 1992b. Cyclic steroid replacement alters auditory brainstem responses in young women with premature ovarian failure. Hear. Res. 64, 93–98.

Falkenius-Schmidt, K., Rydmarker, S., Horner, K.C., 2005. Hyperprolactinemia in some Meniere patients even in the absence of incapacitating vertigo. Hear. Res. 203, 154–158.

Gordon-Salant, S., 2005. Hearing loss and aging: new research findings and clinical implications. J. Rehabil. Res. Dev. 42, 9–24.

Gristwood, R.E., Venables, W.N., 1983. Pregnancy and otosclerosis. Clin. Otolaryngol. Allied Sci. 8, 205–210.

Guimaraes, P., Frisina, S.T., Mapes, F., Tadros, S.F., Frisina, D.R., Frisina, R.D., 2006. Progestin negatively affects hearing in aged women. Proc. Natl. Acad. Sci. USA 103, 14246–14249.

Hanna, G.S., 1986. Sudden deafness and the contraceptive pill. J. Laryngol. Otol. 100, 701–706.

Helzner, E.P., Cauley, J.A., Pratt, S.R., Wisniewski, S.R., Talbott, E.O., Zmuda, J.M., Harris, T.B., Rubin, S.M., Taaffe, D.R., Tylavsky, F.A., Newman, A.B., 2005. Hearing sensitivity and bone mineral density in older adults: the health, aging and body composition study. Osteoporos. Int. 16, 1675–1682.

Hofbauer, L.C., Khosla, S., Dunstan, C.R., Lacey, D.L., Spelsberg, T.C., Riggs, B.L., 1999. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. Endocrinology 140, 4367–4370.

Hofbauer, L.C., Schoppet, M., 2001. Serum measurement of osteoprotegerin–clinical relevance and potential applications. Eur. J. Endocrinol. 145, 681–683.

Horner, K.C., 2003. The emotional ear in stress. Neurosci. Biobehav. Rev. 27, 437–446.

Horner, K.C., Cazals, Y., Guieu, R., Lenoir, M., Sauze, N., 2007. Experimental estrogen-induced hyperprolactinemia results in bone-related hearing loss in the guinea pig. Am. J. Physiol. Endocrinol. Metab. 293, E1224–E1232.

Horner, K.C., Guieu, R., Magnan, J., Chays, A., Cazals, Y., 2002. Prolactinoma in some Meniere's patients–is stress involved? Neuropsychopharmacology 26, 135–138.

Huizing, E.H., de Groot, J.A., 1987. Densitometry of the cochlear capsule and correlation between bone density loss and bone conduction hearing loss in otosclerosis. Acta Otolaryngol. 103, 464–468.

Hultcrantz, M., Simonoska, R., Stenberg, A.E., 2006. Estrogen and hearing: a summary of recent investigations. Acta Otolaryngol. 126, 10–14.

Iotsova, V., Caamano, J., Loy, J., Yang, Y., Lewin, A., Bravo, R., 1997. Osteopetrosis in mice lacking NF-kappaB1 and NF-kappaB2. Nat. Med. 3, 1285–1289.

Kameda, T., Mano, H., Yuasa, T., Mori, Y., Miyazawa, K., Shiokawa, M., Nakamaru, Y., Hiroi, E., Hiura, K., Kameda, A., Yang, N.N., Hakeda, Y., Kumegawa, M., 1997. Estrogen inhibits bone resorption by directly inducing apoptosis of the bone-resorbing osteoclasts. J. Exp. Med. 186, 489–495.

Kanzaki, S., Ito, M., Takada, Y., Ogawa, K., Matsuo, K., 2006. Resorption of auditory ossicles and hearing loss in mice lacking osteoprotegerin. Bone 39, 414–419.

Karosi, T., Jokay, I., Konya, J., Szabo, L.Z., Pytel, J., Jori, J., Szalmas, A., Sziklai, I., 2006. Detection of osteoprotegerin and TNF-alpha mRNA in ankylotic stapes footplates in connection with measles virus positivity. Laryngoscope 116, 1427–1433.

Kilicdag, E.B., Yavuz, H., Bagis, T., Tarim, E., Erkan, A.N., Kazanci, F., 2004. Effects of estrogen therapy on hearing in postmenopausal women. Am. J. Obstet. Gynecol. 190, 77–82.

Kim, S.H., Kang, B.M., Chae, H.D., Kim, C.H., 2002. The association between serum estradiol level and hearing sensitivity in postmenopausal women. Obstet. Gynecol. 99, 726–730.

Kong, Y.Y., Yoshida, H., Sarosi, I., Tan, H.L., Timms, E., Capparelli, C., Morony, S., Oliveira-dos-Santos, A.J., Van, G., Itie, A., Khoo, W., Wakeham, A., Dunstan, C.R., Lacey, D.L., Mak, T.W., Boyle, W.J., Penninger, J.M., 1999. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature 397, 315–323.

Kopp, P., Pesce, L., Solis, S.J., 2008. Pendred syndrome and iodide transport in the thyroid. Trends Endocrinol. Metab. 19, 260–268.

Kovacs, C.S., 2005. Calcium and bone metabolism during pregnancy and lactation. J. Mammary Gland Biol. Neoplasia 10, 105–118.

Li, J., Sarosi, I., Yan, X.Q., Morony, S., Capparelli, C., Tan, H.L., McCabe, S., Elliott, R., Scully, S., Van, G., Kaufman, S., Juan, S.C., Sun, Y., Tarpley, J., Martin, L., Christensen, K., McCabe, J., Kostenuik, P., Hsu, H., Fletcher, F., Dunstan, C.R., Lacey, D.L., Boyle, W.J., 2000. RANK is the intrinsic hematopoietic cell surface receptor that controls osteoclastogenesis and regulation of bone mass and calcium metabolism. Proc. Natl. Acad. Sci. USA 97, 1566–1571.

Lippy, W.H., Berenholz, L.P., Schuring, A.G., Burkey, J.M., 2005. Does pregnancy affect otosclerosis? Laryngoscope 115, 1833–1836.

McFadden, D., 2000. Masculinizing effects on otoacoustic emissions and auditory evoked potentials in women using oral contraceptives. Hear. Res. 142, 23–33.

McKenna, M.J., Kristiansen, A.G., 2007. Molecular biology of otosclerosis. Adv. Otorhinolaryngol. 65, 68–74.

McKenna, M.J., Nguyen-Huynh, A.T., Kristiansen, A.G., 2004. Association of otosclerosis with Sp1 binding site polymorphism in COL1A1 gene: evidence for a shared genetic etiology with osteoporosis. Otol. Neurotol. 25, 447–450.

Meltser, I., Tahera, Y., Simpson, E., Hultcrantz, M., Charitidi, K., Gustafsson, J.A., Canlon, B., 2008. Estrogen receptor beta protects against acoustic trauma in mice. J. Clin. Invest. 118, 1563–1570.

Metka, M., Holzer, G., Raimann, H., Heytmanek, G., Hartmann, B., Kurz, C., 1994. The role of prolactin in the menopause. Maturitas 20, 151–154.

Mitre, E.I., Figueira, A.S., Rocha, A.B., Alves, S.M., 2006. Audiometric and vestibular evaluation in women using the hormonal contraceptive method. Rev. Bras. Otorrinolaringol. (Engl. Ed.) 72, 350–354.

Mizuno, A., Amizuka, N., Irie, K., Murakami, A., Fujise, N., Kanno, T., Sato, Y., Nakagawa, N., Yasuda, H., Mochizuki, S., Gomibuchi, T., Yano, K., Shima, N., Washida, N., Tsuda, E., Morinaga, T., Higashio, K., Ozawa, H., 1998. Severe osteoporosis in mice lacking osteoclastogenesis inhibitory factor/osteoprotegerin. Biochem. Biophys. Res. Commun. 247, 610–615.

Murphy, M.P., Gates, G.A., 1997. Hearing loss: does gender play a role? Med. Womens Health 2, 2.

Niedermeyer, H.P., Arnold, W., 2008. Otosclerosis and measles virus – association or causation? ORL J. Otorhinolaryngol. Relat. Spec. 70, 63–69 (discussion 69–70).

Okulicz, G., 1978. Inner ear disturbance following long-term usage of hormonal contraceptives (author's transl). Hno 26, 330–334.

Pacifici, R., 1996. Estrogen, cytokines, and pathogenesis of postmenopausal osteoporosis. J. Bone Miner. Res. 11, 1043–1051.

Paparella, M.M., Mancini, F., Liston, S.L., 1984. Otosclerosis and Meniere's syndrome: diagnosis and treatment. Laryngoscope 94, 1414–1417.
Pearson, J.D., Morrell, C.H., Gordon-Salant, S., Brant, L.J., Metter, E.J., Klein, L.L., Fozard, J.L., 1995. Gender differences in a longitudinal study of age-associated hearing loss. J. Acoust. Soc. Am. 97, 1196–1205.
Pecins-Thompson, M., Bethea, C.L., 1997. RU 486 blocks and fluoxetine augments progesterone-induced prolactin secretion in monkeys. Neuroendocrinology 65, 335–343.
Peveler, R.C., Branford, D., Citrome, L., Fitzgerald, P., Harvey, P.W., Holt, R.I., Howard, L., Kohen, D., Jones, I., O'Keane, V., Pariente, C.M., Pendlebury, J., Smith, S.M., Yeomans, D., 2008. Antipsychotics and hyperprolactinaemia: clinical recommendations. J. Psychopharmacol. 22, 98–103.
Pinilla, L., Gonzalez, L.C., Tena-Sempere, M., Aguilar, E., 2001. Evidence for an estrogen-like action of raloxifene upon the hypothalamic-pituitary unit: raloxifene inhibits luteinizing hormone secretion and stimulates prolactin secretion in ovariectomized female rats. Neurosci. Lett. 311, 149–152.
Raymond, V., Beaulieu, M., Labrie, F., Boissier, J., 1978. Potent antidopaminergic activity of estradiol at the pituitary level on prolactin release. Science 200, 1173–1175.
Riggs, B.L., 2002. Endocrine causes of age-related bone loss and osteoporosis. Novartis Found Symp. 242, 247–259 (discussion 260–4).
Rillema, J.A., Hill, M.A., 2003. Prolactin regulation of the pendrin-iodide transporter in the mammary gland. Am. J. Physiol. Endocrinol. Metab. 284, E25–E28.
Royaux, I.E., Belyantseva, I.A., Wu, T., Kachar, B., Everett, L.A., Marcus, D.C., Green, E.D., 2003. Localization and functional studies of pendrin in the mouse inner ear provide insight about the etiology of deafness in pendred syndrome. J. Assoc. Res. Otolaryngol. 4, 394–404.
Rybak, L.P., 1995. Metabolic disorders of the vestibular system. Otolaryngol. Head Neck Surg. 112, 128–132.
Sato, S., Hanew, K., Sasaki, A., Shimizu, Y., Murakami, O., Fukazawa, H., Sakurada, T., Saito, S., Yoshinaga, K., 1984. Enhanced prolactin secretion in patients with primary hypothyroidism during thyroid replacement. Tohoku J. Exp. Med. 144, 425–431.
Schwarz, E.M., Ritchlin, C.T., 2007. Clinical development of anti-RANKL therapy. Arthritis Res. Ther. 9 (Suppl. 1), S7.
Seemungal, B.M., Gresty, M.A., Bronstein, A.M., 2001. The endocrine system, vertigo and balance. Curr. Opin. Neurol. 14, 27–34.
Sellari-Franceschini, S., Ravecca, F., De Vito, A., Berrettini, S., 1998. Progressive sensorineural hearing loss in cochlear otosclerosis. Acta Otorhinolaryngol. Ital. 18, 59–65.
Sennaroglu, G., Belgin, E., 2001. Audiological findings in pregnancy. J. Laryngol. Otol. 115, 617–621.
Seriwatanachai, D., Charoenphandhu, N., Suthiphongchai, T., Krishnamra, N., 2008a. Prolactin decreases the expression ratio of receptor activator of nuclear factor kappaB ligand/osteoprotegerin in human fetal osteoblast cells. Cell Biol. Int. 32, 1126–1135.
Seriwatanachai, D., Thongchote, K., Charoenphandhu, N., Pandaranandaka, J., Tudpor, K., Teerapornpuntakit, J., Suthiphongchai, T., Krishnamra, N., 2008b. Prolactin directly enhances bone turnover by raising osteoblast-expressed receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio. Bone 42, 535–546.
Serra, A., Maiolino, L., Agnello, C., Messina, A., Caruso, S., 2003. Auditory brain stem response throughout the menstrual cycle. Ann. Otol. Rhinol. Laryngol. 112, 549–553.
Shea Jr., J.J., Ge, X., Orchik, D.J., 1994. Endolymphatic hydrops associated with otosclerosis. Am. J. Otol. 15, 348–357.
Simonet, W.S., Lacey, D.L., Dunstan, C.R., Kelley, M., Chang, M.S., Luthy, R., Nguyen, H.Q., Wooden, S., Bennett, L., Boone, T., Shimamoto, G., DeRose, M., Elliott, R., Colombero, A., Tan, H.L., Trail, G., Sullivan, J., Davy, E., Bucay, N., Renshaw-Gegg, L., Hughes, T.M., Hill, D., Pattison, W., Campbell, P., Sander, S., Van, G., Tarpley, J., Derby, P., Lee, R., Boyle, W.J., 1997. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 89, 309–319.
Sismanis, A., Hughes, G.B., Abedi, E., 1986. Coexisting otosclerosis and Meniere's disease: a diagnostic and therapeutic dilemma. Laryngoscope 96, 9–13.
Srivastava, S., Toraldo, G., Weitzmann, M.N., Cenci, S., Ross, F.P., Pacifici, R., 2001. Estrogen decreases osteoclast formation by down-regulating receptor activator of NF-kappa B ligand (RANKL)-induced JNK activation. J. Biol. Chem. 276, 8836–8840.
Strachan, D., 1996. Sudden sensorineural deafness and hormone replacement therapy. J. Laryngol. Otol. 110, 1148–1150.
Sun, L., Peng, Y., Sharrow, A.C., Iqbal, J., Zhang, Z., Papachristou, D.J., Zaidi, S., Zhu, L.L., Yaroslavskiy, B.B., Zhou, H., Zallone, A., Sairam, M.R., Kumar, T.R., Bo, W., Braun, J., Cardoso-Landa, L., Schaffler, M.B., Moonga, B.S., Blair, H.C., Zaidi, M., 2006. FSH directly regulates bone mass. Cell 125, 247–260.
Swanson, S.J., Dengerink, H.A., 1988. Changes in pure-tone thresholds and temporary threshold shifts as a function of menstrual cycle and oral contraceptives. J. Speech Hear. Res. 31, 569–574.
Tsunoda, K., Takahashi, S., Takanosawa, M., Shimoji, Y., 1999. The influence of pregnancy on sensation of ear problems–ear problems associated with healthy pregnancy. J. Laryngol. Otol. 113, 318–320.
Vessey, M., Painter, R., 2001. Oral contraception and ear disease: findings in a large cohort study. Contraception 63, 61–63.
Williams, R.F., Gianfortoni, J.G., Hodgen, G.D., 1985. Hyperprolactinemia induced by an estrogen–progesterone synergy: quantitative and temporal effects of estrogen priming in monkeys. J. Clin. Endocrinol. Metab. 60, 126–132.
Yoon, T.H., Paparella, M.M., Schachern, P.A., 1990. Otosclerosis involving the vestibular aqueduct and Meniere's disease. Otolaryngol. Head Neck Surg. 103, 107–112.
Zehnder, A.F., Kristiansen, A.G., Adams, J.C., Kujawa, S.G., Merchant, S.N., McKenna, M.J., 2006. Osteoprotegrin knockout mice demonstrate abnormal remodeling of the otic capsule and progressive hearing loss. Laryngoscope 116, 201–206.
Zehnder, A.F., Kristiansen, A.G., Adams, J.C., Merchant, S.N., McKenna, M.J., 2005. Osteoprotegerin in the inner ear may inhibit bone remodeling in the otic capsule. Laryngoscope 115, 172–177.