

PAPERS AND ORIGINALS

Osteoporosis after Oophorectomy for Non-malignant Disease in Premenopausal Women

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Summary

The role of oophorectomy in the development of osteoporosis was assessed retrospectively in 258 women who had been hysterectomized premenopausally for non-malignant disease. Bone density was assessed using the radiographic density of the third metacarpal. Oophorectomy before the age of 45 years was found to be associated with a significantly increased prevalence of osteoporosis within three to six years of operation. The bone density of women oophorectomized after the age of 45 years was indistinguishable three to six years after operation from that found in healthy women with intact ovaries. These findings confirm the major part played by loss of ovarian function in the development of postmenopausal osteoporosis.

Introduction

Albright *et al.* (1941) suggested that there was an aetiological association between the menopause and osteoporosis in women. Since then much evidence has accumulated in support of this hypothesis (Meema *et al.*, 1963, 1966; Jasani *et al.*, 1965; Nordin *et al.*, 1966; Garn *et al.*, 1967; Smith *et al.*, 1969), and both Meema *et al.* (1965) and Nordin *et al.* (1968) tried to show that loss of ovarian function was the most important single factor responsible for the development of postmenopausal osteo-

porosis. The researches of Meema *et al.* (1965) using the proximal radius, and Nordin *et al.* (1968) using the spine, established that oophorectomy was followed within a variable period of time by excessive loss of bone mineral from the proximal radius and the lumbar spine respectively, although Donaldson and Nassim (1954) had previously been unable to find any association between oophorectomy and spinal osteoporosis. Unfortunately, neither Meema *et al.* (1965) nor Nordin *et al.* (1968) compared their oophorectomized patients with unselected women who had undergone hysterectomy alone, and in many respects the documentation of both their controls and their oophorectomized patients was inadequate. Since both studies were retrospective, and neither group of workers actually measured a change in bone mineral content after oophorectomy, it was essential that the controls used for comparative purposes should have differed from the oophorectomized patients only with respect to the presence or absence of ovaries. Furthermore, neither group of workers attempted to determine whether the age at the time of oophorectomy was an important factor. This was of particular importance since it has already been shown that bone mineral loss from the female skeleton starts at about the age of 35 years (Smith *et al.*, 1969). It can be seen that if it were shown, with regard to the development of osteoporosis, that the age of a premenopausal woman at the time of oophorectomy was more important than the fact that she was still menstruating, this would greatly simplify the gynaecological approach towards oophorectomy.

It was thought desirable, therefore, to re-examine the association between oophorectomy and osteoporosis, paying special attention to the comparability of the controls, in order to determine the influence of the patient's age at oophorectomy on the development of osteoporosis.

Patients and Methods

Altogether, 258 Glasgow women were reviewed either three or six years after hysterectomy which had been performed when they were still menstruating. Of these, 95 had undergone hysterectomy alone and 163 had undergone hysterectomy and bilateral salpingo-oophorectomy. All patients with malignant disease or benign ovarian tumours were excluded. Women with

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a past or present history of conditions which might have contributed to bone mineral loss—for example, intestinal malabsorption, renal insufficiency, rheumatoid arthritis and other conditions associated with skeletal immobilization, endocrine diseases, including diabetes mellitus, thyrotoxicosis, adrenal hyperfunction or hypofunction, acromegaly or hypopituitarism, and hyperparathyroidism or hypoparathyroidism—were excluded. None of the women studied had taken hormone therapy after hysterectomy, and all the women with intact ovaries were found to have oestrogenized squames on vaginal smear and did not admit to menopausal symptoms such as excessive flushing or sweating when they were reviewed. All the women reviewed had agreed to attend on a purely voluntary basis.

A radiograph was taken of the right hand using an aluminium stepwedge as a density standard. The aluminium equivalent (A.E.) at the midpoint of the third metacarpal was measured on the x-ray film (Anderson *et al.*, 1966), and from this the whole bone density (W.B.D.) at the middle of the metacarpal was calculated (Shimmins *et al.*, 1972). Whole bone density, in g ash/cm³, is effectively independent of metacarpal size and therefore makes allowance for people of different sizes. The normal Glasgow female population data described by Smith *et al.* (1969), from which percentile values for W.B.D. measurements had been derived according to the subject's age, was used to convert each W.B.D. measurement to a W.B.D. percentile value, thus making it possible to allow for the patients' age when assessing their bone mineral status. This procedure was necessary since the mineral content of the skeleton is known to vary with age. Osteoporosis was considered to be present where the W.B.D. was less than 0.79 g ash/cm³, since values below this level are associated with a significant incidence of spinal biconcavity and crush fractures (Smith *et al.*, 1968).

INDICATIONS FOR HYSTERECTOMY

The indications for operation are shown in table I. Most of the women came to hysterectomy on account of menorrhagia, and the commonest cause for this was uterine fibroids. No specific pathological cause for the menorrhagia was found in 28% of the women who underwent hysterectomy alone or in 16% of those who underwent hysterectomy and bilateral salpingo-oophorectomy. In these women the indication for operation was described as dysfunctional uterine bleeding. With the exception of hyster-

ectomy alone for uterine prolapse, performed vaginally, the pathological findings at operation did not appear to influence the decision as to whether or not to remove or conserve the ovaries.

The ovaries were conserved in only 22% of the women coming to hysterectomy after the age of 45 years, whereas 93% of the women hysterectomized before the age of 40 years retained their ovaries. It was only in the age range 41-45 years that oophorectomy appeared to be a relatively arbitrary decision with 49% of the women retaining their ovaries and 51% having their ovaries removed.

Results

OOPHORECTOMY IN OLDER WOMEN

The detailed results from the women hysterectomized after the age of 45 years are shown in table II. The mean age at which the operation was performed was similar in each of the four groups. The mean age at review of the women who underwent hysterectomy alone three years previously was the same as the mean age of the three-year oophorectomy group, and hence both the A.E. and W.B.D. measurements were directly comparable without having to make an allowance for age. Neither the A.E. nor the W.B.D. were significantly different, but the small number of women with intact ovaries makes such comparisons difficult to interpret. Similarly, no significant difference was found between the results in the oophorectomized and the non-oophorectomized women who underwent operation six years before review.

In table III the results from table II have been condensed so that all the women who underwent hysterectomy alone could be compared with all the oophorectomized women irrespective of the time interval since the operation. The mean ages of the two groups and the mean ages at operation were almost identical as were the A.E., W.B.D., and W.B.D. percentile values. The prevalence of osteoporosis was almost the same in both groups irrespective of the presence or the absence of the ovaries.

OOPHORECTOMY IN YOUNGER WOMEN

The detailed results obtained relating to the women hysterectomized at or before the age of 45 years are shown in table

TABLE I—Indications for Operation in Women Studied

	Hysterectomy Only				Hysterectomy and Oophorectomy			
	Age at Operation (Years)			Total	Age at Operation (Years)			Total
	35-40	41-45	46-54		35-40	41-45	46-54	
Adenomyosis	1	0	1	2	0	2	1	3
Pelvic inflammation	3	2	0	5	0	1	3	4
Dysfunctional bleeding	13	9	5	27	2	9	19	30
Endometriosis	2	1	0	3	1	4	1	6
Fibroids	15	18	9	42	2	37	68	107
Carcinoma in situ cervix	7	2	0	9	1	6	3	10
Uterine prolapse	3	2	1	6	0	0	0	0
Metropathia haemorrhagica	0	0	0	0	0	1	2	3
Postpartum haemorrhage	1	0	0	1	0	0	0	0
Total	45	34	16	95	6	60	97	163

TABLE II—Effect of Oophorectomy on Metacarpal Mineral Content in Women aged 49-58 Years who had been Hysterectomized three or six Years before Review. Aluminium Equivalent (A.E.) and Whole Bone Density (W.B.D.) Used to Assess Metacarpal Mineral. Figures are Means \pm S.E. of Mean

	No. of Women	Age (Years)	Age at Operation (Years)	A.E. (mm A1)	W.B.D. (g Ash/cm ³)	W.B.D. Percentile
Three years after hysterectomy alone	9	52.1 (\pm 0.99)	49.1 *	2.66 (\pm 0.09) †	0.91 (\pm 0.036) §	55.9 (\pm 8.54) ¶
Six years after hysterectomy alone	7	54.3 (\pm 0.81)	48.3 *	2.44 (\pm 0.15) ‡	0.82 (\pm 0.054) §	39.1 (\pm 12.2) ¶
Three years after oophorectomy	57	51.7 (\pm 0.30)	48.7 *	2.49 (\pm 0.04) ‡	0.88 (\pm 0.014) §	46.2 (\pm 3.44) ¶
Six years after oophorectomy	40	54.8 (\pm 0.36)	48.8 *	2.55 (\pm 0.07) ‡	0.87 (\pm 0.026) §	52.1 (\pm 5.36) ¶

* N.S. † $t = 0.96$; N.S.
 ‡ $t = 1.60$; N.S. § $t = 1.05$; N.S.
 ¶ $t = 1.26$; N.S. ** $t = 0.94$; N.S.
 † $t = 0.88$; N.S.
 N.S. = Not significant.

TABLE III—Effect of Oophorectomy on Metacarpal Mineral Content in Women aged 49-58 Years who had been Hysterectomized Three or Six Years before review. Aluminium Equivalent (A.E.) and Whole Bone Density (W.B.D.) Used to Assess Metacarpal Mineral. Figures are Means \pm S.E. of Mean

	No. of Women	Age (Years)	Age at Operation (Years)	A.E. (mm Al)	W.B.D. (g Ash/cm ³)	W.B.D. Percentile	No. with W.B.D. <0.79 g Ash/cm ³	Percentage Osteoporotic
Three and six years after hysterectomy alone	16	53.1 (\pm 0.70)	48.8	2.56 (\pm 0.08)	0.87 (\pm 0.033)	48.6 (\pm 7.23)	4	25
Three and six years after oophorectomy	97	53.0 (\pm 0.28)	48.7	2.51 (\pm 0.03)	0.88 (\pm 0.013)	48.6 (\pm 2.99)	21	22
				N.S.	N.S.	N.S.		N.S.

N.S. = Not significant.

TABLE IV—Effect of Oophorectomy on Metacarpal Mineral Content in Women aged 38-51 Years who had been Hysterectomized Three or Six Years before Review. Aluminium Equivalent (A.E.) and Whole Bone Density (W.B.D.) used to Assess Metacarpal Mineral. Figures are Means \pm S.E. of Mean

	No. of Women	Age (Years)	Age at Operation (Years)	A.E. (mm Al)	W.B.D. (g Ash/cm ³)	W.B.D. Percentile
Three years after hysterectomy alone	52	42.5 (\pm 0.40) *	39.5	2.77 (\pm 0.03) †	0.95 (\pm 0.015) §	45.9 (\pm 3.62) *
Six years after hysterectomy alone	27	45.8 (\pm 0.60) *	39.8	2.87 (\pm 0.06) ‡	0.97 (\pm 0.028) §	57.7 (\pm 5.04) *
Three years after oophorectomy	44	46.3 (\pm 0.26) *	43.3	2.53 (\pm 0.05) ‡	0.88 (\pm 0.017) §	35.3 (\pm 4.00) *
Six years after oophorectomy	22	48.3 (\pm 0.54) *	42.3	2.34 (\pm 0.06) ‡	0.81 (\pm 0.024) §	24.0 (\pm 4.30) *

* $P < 0.001$. † $t = 4.64$; $P < 0.001$.‡ $t = 4.39$; $P < 0.001$. § $t = 1.97$; N.S.‡ $t = 6.27$; $P < 0.001$. ** $t = 4.95$; $P < 0.001$.§ $t = 3.12$; $P < 0.01$.TABLE V—Effect of Oophorectomy on Metacarpal Mineral Content in Women aged 38-51 Years who had been Hysterectomized Three or Six Years before Review. Aluminium Equivalent (A.E.) and Whole Bone Density (W.B.D.) Used to Assess Metacarpal Mineral. Figures are Means \pm S.E. of Mean

	No. of Women	Age (Years)	Age at Operation (Years)	A.E. (mm Al)	W.B.D. (g Ash/cm ³)	W.B.D. Percentile	No. with W.B.D. <0.79 g Ash/cm ³	Percentage Osteoporotic
Three and six years after hysterectomy alone	79	43.6 (\pm 0.37)	39.6	2.80 (\pm 0.03)	0.96 (\pm 0.014)	49.9 (\pm 2.99)	2	2.5
Three and six years after oophorectomy	66	47.0 (\pm 0.28)	43.0	2.47 (\pm 0.04)	0.86 (\pm 0.015)	31.5 (\pm 3.08)	17	26
		$t = 7.02$; $P < 0.001$		$t = 7.14$; $P < 0.001$	$t = 5.27$; $P < 0.001$	$t = 4.26$; $P < 0.001$	$\chi^2 = 17.04$; $P < 0.001$	

TABLE VI—Effect of Oophorectomy on Metacarpal Mineral Content in Women aged 38-51 Years who had been Hysterectomized Three or Six Years before Review. Aluminium Equivalent (A.E.) and Whole Bone Density (W.B.D.) used to Assess Metacarpal Mineral. Figures are Means \pm S.E. of Mean

	No. of Women	Age (Years)	Age of Operation (Years)	A.E. (mm Al)	W.B.D. (g Ash/cm ³)	W.B.D. Percentile
Hysterectomy alone at age 35-40 years	45	41.3 (\pm 0.29)	37.4	2.81 (\pm 0.04) *	0.95 (\pm 0.019) †	46.3 (\pm 3.97) *
Hysterectomy alone at age 41-45 years	34	46.3 (\pm 0.38)	42.4	2.80 (\pm 0.05) ‡	0.96 (\pm 0.021) §	54.7 (\pm 4.47) *
Oophorectomy at age 35-40 years	6	42.7 (\pm 1.20)	37.7	2.55 (\pm 0.07) ‡	0.85 (\pm 0.026) §	20.7 (\pm 6.23) *
Oophorectomy at age 41-45 years	60	47.3 (\pm 0.22)	43.5	2.46 (\pm 0.04) ‡	0.86 (\pm 0.016) §	32.6 (\pm 3.31) *

* $t = 2.27$; $P < 0.05$. † $t = 4.41$; $P < 0.001$.‡ $t = 5.37$; $P < 0.001$. § $t = 2.29$; $P < 0.05$.‡ $t = 2.04$; $P < 0.05$. § $t = 3.99$; $P < 0.001$.

IV. At the time of review the oophorectomized women were on average about three to four years older than the women who underwent hysterectomy alone, and it was not surprising therefore that the mean A.E. and W.B.D. values were significantly lower in the women who had been oophorectomized than they were in those who had undergone hysterectomy alone, because W.B.D. falls progressively after the age of 35 years in normal women (Smith *et al.*, 1969). When using the W.B.D. percentile values, which are independent of age, it can be seen that the three-year post-oophorectomy group had a mean value which was 10.6% lower than that found in the women with intact ovaries but this difference was not statistically significant. The difference between the mean percentile values of the six-year post-oophorectomy group and the six-year group with intact ovaries was 33.7% with the oophorectomized women having the lower mean value and the difference being highly significant ($P < 0.001$). The mean W.B.D. percentile value of the six-year post-oophorectomy group at 24.0% was not significantly lower than that found in the three-year oophorectomy group where the corresponding figure was 35.3%.

All the women who underwent hysterectomy alone before the age of 45 years have been compared in table V with all the women who were oophorectomized before the age of 45 years, irrespective of the time interval between operation and review.

The oophorectomy group was still significantly older than the group with intact ovaries ($P < 0.001$), and only the age independent W.B.D. percentile values can be compared meaningfully. The mean W.B.D. percentile was 18.4% lower in the oophorectomized women than it was in the women who underwent hysterectomy alone, and the difference was highly significant ($P < 0.001$). Just over 1 in 4 of the oophorectomized women were osteoporotic whereas only 1 in 40 of the hysterectomized women with intact ovaries were osteoporotic. The mean W.B.D. of the women with intact ovaries was about 11% higher than that found in the older women with intact ovaries who were almost 10 years their senior (table III).

The women operated on at or before the age of 45 years have been divided at the age of 40 years into two sub-groups (table VI). By splitting these women in this way, the mean ages of the two oophorectomized sub-groups have become more comparable with the mean ages of the two sub-groups with intact ovaries. Furthermore, the mean A.E., W.B.D., and W.B.D. percentile values were significantly lower in both oophorectomized sub-groups than they were in both the sub-groups with intact ovaries, whether the operation had been performed between the ages of 35 and 40 years or between the ages of 41 and 45 years. The mean W.B.D. percentile value of the oophorectomized women in the younger subgroup was 11.9% lower than

that found in the older oophorectomy sub-group but the difference was not statistically significant.

Discussion

The present study has shown that oophorectomy in women under the age of 45 years was associated with premature loss of bone from the skeleton and the development of osteoporosis at an earlier age than would have occurred had the ovaries been left intact. These findings support the original views of Albright *et al.* (1941) and are consistent with the overall findings of Meema *et al.* (1965) and Nordin *et al.* (1968) that the menopause was the major factor in the aetiology of osteoporosis in women. The failure of Donaldson and Nassim (1954) to find similar changes was almost certainly caused by the insensitivity of their method for quantitating the bone mineral content of the spine.

The retrospective nature of the present study and those of Meema *et al.* (1965) and Nordin *et al.* (1968) imposes certain restrictions on the interpretation of the data and in particular makes it important to recognize that the information relates only to differences between groups and not to the actual bone mineral changes which have occurred after oophorectomy. In this context it is of great importance that the control subjects used for comparison with the oophorectomized women should differ in respect to only one variable—namely, the presence or absence of the ovaries. The controls used by both Meema *et al.* (1965) and Nordin *et al.* (1968) were not well categorized, most of them had intact uteri, and little information was furnished about the methods used to “select” both the controls and the oophorectomized women. Furthermore, the mean age at oophorectomy of the women in the study of Meema *et al.* (1965) was 37 years, whereas Nordin *et al.* (1968) gave no details about their patients’ ages, the age at oophorectomy, or the interval between oophorectomy and review.

In the present study the mean age at oophorectomy was 46.4 years—that is, these women were on average almost 10 years older at oophorectomy than those studied by Meema *et al.* (1965). In the absence of further information on their indications for oophorectomy, one is left in some doubt as to whether the health of their oophorectomized patients before operation was comparable to that of their controls.

Ideally, investigations of this kind should be conducted using women in whom the ovaries had been either conserved or removed in a random manner at the time of hysterectomy, but this would be difficult for ethical reasons. However, in spite of this it was clear in the present study that for women hysterectomized in the first half of the fifth decade of life, the decision as to whether or not the ovaries should have been conserved or removed appeared to have been relatively arbitrary. Nonetheless, the women oophorectomized in this short age interval still had significantly less bone mineral than the controls with intact ovaries. There is little doubt that most surgeons remove the ovaries from premenopausal middle-aged women because of a subconscious fear that an ill-defined proportion of these women would otherwise subsequently die of ovarian malignancy. A much longer study would be required in order to decide whether the cumulative hazards of the mortality and associated morbidity from future skeletal fracture would outweigh the risk of death from ovarian malignancy. Most surgeons

routinely remove the ovaries at the time of hysterectomy from women who are over the age of 45 years. This policy clearly applied in the present study, and in spite of the fact that all the women had been menstruating up to the time of hysterectomy, the oophorectomized women fared no worse than the women in whom the ovaries had been left intact, in so far as no appreciable difference in metacarpal density was detectable about four years later. This point was overlooked by Meema *et al.* (1965) and Nordin *et al.* (1968) who gave the impression that oophorectomy in a premenopausal woman carried the same risk of the development of osteoporosis irrespective of the age of the patient at the time of oophorectomy.

It should be noted that in this study there was an apparent fall in metacarpal density of about 11% in almost 10 years in the women with intact ovaries, although these women had oestrogenized vaginal smears and lacked menopausal symptoms when reviewed, and had been menstruating up to the time of hysterectomy. Smith *et al.* (1969) showed that there was a similar fall in metacarpal density of about 1% a year in normal women after the age of 35 years. The presence of menstruation and a normal vaginal smear and the absence of menopausal symptoms therefore give little help in diagnosing intact ovarian osteotrophic activity.

Oophorectomy in women before the age of 45 years was associated with the premature loss of bone from the skeleton, whereas oophorectomy after this age, when ovarian endocrine function was probably already declining, had little if any effect on subsequent bone mineral loss or the ultimate development of osteoporosis. Loss of ovarian function and loss of bone mineral would not appear to be independent phenomena individually related to ageing, but rather lack of ovarian function appeared to be the major determinant in relation to the loss of bone mineral with age.

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