HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis

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Summary

Background In-vitro research has suggested that bacterial vaginosis may increase the survival of HIV-1 in the genital tract. Therefore, we investigated the association of HIV-1 infection with vaginal flora abnormalities, including bacterial vaginosis and depletion of lactobacilli, after adjustment for sexual activity and the presence of other sexually transmitted diseases (STDs).

Methods During the initial survey round of our community-based trial of STD control for HIV-1 prevention in rural Rakai District, southwestern Uganda, we selected 4718 women aged 15–59 years. They provided interview information, blood for HIV-1 and syphilis serology, urine for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, and two self-administered vaginal swabs for culture of *Trichomonas vaginalis* and gram-stain detection of vaginal flora, classified by standardised, quantitative, morphological scoring. Scores 0–3 were normal vaginal flora (predominant lactobacilli). Higher scores suggested replacement of lactobacilli by gram-negative, anaerobic microorganisms (4–6 intermediate; 7–8 and 9–10 moderate and severe bacterial vaginosis).

Findings HIV-1 frequency was 14·2% among women with normal vaginal flora and 26·7% among those with severe bacterial vaginosis ($p<0·0001$). We found an association between bacterial vaginosis and increased HIV-1 infection among younger women, but not among women older than 40 years; the association could not be explained by differences in sexual activity or concurrent infection with other STDs. The frequency of bacterial vaginosis was similar among HIV-1-infected women with symptoms (55·0%) and without symptoms (55·7%). The adjusted odds ratio of HIV-1 infection associated with any vaginal flora abnormality (scores 4–10) was 1·52 (95% CI 1·22–1·90), for moderate bacterial vagniosis (scores 7–8) it was 1·50 (1·18–1·89), and for severe bacterial vaginosis (scores 9–10) it was 2·08 (1·48–2·94).

Interpretation This cross-sectional study cannot show whether disturbed vaginal flora increases susceptibility to HIV-1 infection. Nevertheless, the increased frequency of HIV-1 associated with abnormal flora among younger women, for whom HIV-1 acquisition is likely to be recent, but not among older women, in whom HIV-1 is likely to have been acquired earlier, suggests that loss of lactobacilli or presence of bacterial vaginosis may increase susceptibility to HIV-1 acquisition. If this inference is correct, control of bacterial vaginosis could reduce HIV-1 transmission.

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Introduction

In normal vaginal flora, peroxide-producing lactobacilli are predominant and maintain a low vaginal pH.[1] Studies also suggest that peroxide-generating *Lactobacillus acidophilus* have viricidal effects on HIV-1,[2] and that a low vaginal pH inhibits CD4 lymphocyte activation and may reduce the number of HIV-1 target cells in the vagina.[3] Bacterial vaginosis is a common disorder caused by an alteration in the vaginal flora in which the normally predominant lactobacilli are replaced by anaerobic bacteria, genital mycoplasms, and *Gardnerella* spp, with a consequent increase in vaginal pH.[1] Bacterial vaginosis has been implicated as a cause of adverse pregnancy outcomes[4,5] and is associated with upper-genital-tract infections.[6,7] One cross-sectional study of prostitutes in northern Thailand has also suggested that abnormalities of the vaginal flora and clinical bacterial vaginosis may be associated with an increased risk of HIV-1 infection.[8] We did a population-based study of women in rural Uganda to see whether abnormal vaginal flora and bacterial vaginosis were associated with HIV-1.

Methods

We are doing a continuing randomised community-based trial of control of sexually transmitted diseases (STDs) for AIDS prevention in Rakai District, southwestern Uganda. The objectives of that study are to find out whether intensive community-based STD control can reduce STD incidence and prevalence, and whether reductions in STDs can lead to decreased HIV-1 transmission. During the initial survey round of that trial (November, 1994, and June, 1995) and before STD treatment, all consenting women aged 15–59 years in the communities were enrolled into the present study. The procedures for obtaining written informed consent were approved by institutional review boards in Uganda, and at Columbia University, Johns Hopkins University, and the National Institutes of Health, USA. All data were collected in the women's homes, and 7098 (93% of women present at the time of the survey) agreed to be interviewed to provide sociodemographic, behavioural, and health information. This study included representative samples of whole communities and achieved high participation rates, and the enrolled women reflected the whole population.

Of the 7098 women enrolled, 6423 (90·5%) provided a venous blood sample for HIV-1 and syphilis serology. HIV was diagnosed by positive results from two EIAs (Recombigen EIA, Cambridge Biosciences, Cambridge, MA, and Organon EIA, Organon Teknika, Durham, NC, USA). If EIA results conflicted, we used western blot to confirm the diagnosis (Cambridge Biosciences, MA, USA). Active or recently treated syphilis was diagnosed with the non-treponemal toludine-red unheated serum test (TRUST, New Horizons, Columbia, MD, USA) and positive results were confirmed by a qualitative *Treponema pallidum* haemagglutination

Vaginal flora morphology (score)	Number of women	HIV-1 prevalence	Risk ratio (95% CI)
Normal (0–3)	820	14·2%	1·0
Intermediate (4–6)	1497	19·5%	1·38 (1·13–1·68)
Moderate bacterial vaginosis (7–8)	2101	20·5%	1·45 (1·20–1·75)
Severe bacterial vaginosis (9–10)	300	26·7%*	1·89 (1·46–2·43)
Any abnormal vaginal flora (4–10)	3782	20·6%	1·49† (1·32–1·68)

*p<0·0001. †Risk ratio of prevalent HIV-1 infection in women with abnormal flora (scores 4–10) relative to women with normal flora (scores 0–3).

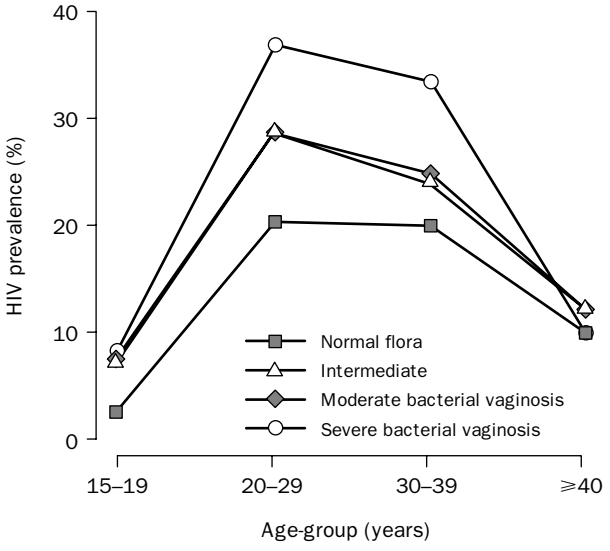
Table 1: **Association of vaginal flora morphology and prevalence of HIV-1**

test (TPHA, Sera-Tek, Miles Inc Diagnostics, Elkhart, IL, USA). Serological tests were done at the Uganda Virus Research Institute, Entebbe, and samples were sent for quality control to Johns Hopkins University, USA.

6643 (93·6%) of the enrolled women provided two self-administered vaginal swabs; one swab was used for *Trichomonas vaginalis* culture[9] (InPouch TV culture system, BioMed Diagnostics, Santa Clara, CA, USA), and the second swab was rolled on a slide for gram-stain diagnosis of bacterial vaginosis. Predominant normal, large, gram-positive *lactobacillus* morphotypes indicated normal flora and small gram-negative or variable rods (*Gardnerella* or *Bacteroides* morphotypes) or curved gram-negative or variable rods (*Mobiluncus*) indicated abnormal flora or bacterial vaginosis. We graded severity of abnormalities in vaginal flora and bacterial vaginosis with a standardised, quantitative, morphological classification developed by the Vaginal Infection and Prematurity Study Group.[1,10,11] Normal flora was scored 0–3; intermediate or transitionally abnormal flora 4–6; moderate bacterial vaginosis 7–8; and severe bacterial vaginosis 9–10.[10,11] These classifications have been validated against conventional clinical diagnoses (based on vaginal pH >4·5, amine odour after addition of potassium hydroxide, clue cells, and milky discharge), shown to have high sensitivity and specificity, and to have good interobserver agreement.[9,10]

Slides were read by experienced laboratory technicians in Uganda and samples were sent to the University of Pittsburgh for quality control (SLH). The correlation coefficient between scores assigned in Uganda and Pittsburgh was r=0·75. Because of limitations of logistics, time, and costs, we read a representative random sample of 4718 (71·0%) of the 6643 gram-stained slides.

Women were also asked to provide a first-void urine sample for diagnosis of current *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections by DNA amplification with urinary ligase chain reaction (Abbott LCx Probe System, Abbott Laboratories, Abbott Park, IL, USA). These ligase chain reaction assays have been shown to have high sensitivity and specificity.[12,13] 6743 (95%) women provided urine samples, but detection of gonorrhoea and chlamydia was done only for 1541 women because of resource constraints. Because these cervical infections occur mainly at younger ages, women younger than 29 years were oversampled.



Age-specific prevalence of HIV infection associated with vaginal flora morphology scores
Normal=0–3; intermediate=4–6; moderate bacterial vaginosis=7–8; severe bacterial vaginosis=9–10.

We estimated the risk ratio of HIV-1 frequency among women with abnormal vaginal morphology relative to the frequency of HIV-1 among women with normal, lactobacillus-predominant flora (scores 0–3). Emphasis was placed on any abnormalities of vaginal flora (scores 4–10) as well as moderate or severe bacterial vaginosis (scores 7–8 and 9–10). We used 95% CIs of the risk ratio and χ^2 analysis to test significance. To adjust for potential confounding by age and sexual activity, we investigated associations between HIV-1 and vaginal flora morphology among women aged 15–19 years, and by 10-year age-groups of 20–29 years, 30–39 years, 40–49 years, and 50–59 years, by reported numbers of sexual partners in the previous year (none, one, or more than two), and by the presence or absence of symptoms suggestive of HIV-1-associated illness (WHO clinical staging for HIV-1 disease stages 3–4,[14] including weight loss, prolonged diarrhoea, fever or cough, Kaposi's sarcoma, oral thrush, or herpes zoster). We also investigated the association between bacterial vaginosis and the rate of HIV-1 infection among women with and without evidence of concomitant genital-tract infections with *N gonorrhoeae, C trachomatis,* or trichomonas, or serological evidence of syphilis. Finally, we used multiple logistic regression[15] to estimate the odds ratio of risk of HIV-1 infection associated with abnormal vaginal flora after adjustment for age, sexual activity, trichomoniasis, syphilis, and community of residence.

Results

We enrolled 7098 women, of whom 6643 (93·6%) provided a vaginal swab for gram-stain diagnosis of vaginal flora. We analysed a random sample of 4718 interviewed women aged 15–59 years for whom laboratory results were available on HIV-1 status, syphilis serology, vaginal microflora, and trichomonas infection. In addition, we did urinary ligase chain reaction testing for chlamydia and gonorrhoea infections in 1541 of these women. We found a high rate of STDs and genital-tract infections in the total population. The rate of HIV-1 infection was 19·5%, and 10·2% of women had active or recent syphilis. The proportion of women with moderate bacterial vaginosis was 44·5% and with severe bacterial vaginosis was 6·4% (total bacterial vaginosis 50·9%). *T vaginalis* was detected in 22·4% of women. Among women aged 15–29 years with urinary ligase chain reaction results, the rate of gonorrhoea was 2·4% and *C trachomatis* 3·6%.

Table 1 shows the associations between HIV-1 frequency and vaginal gram-stain scores. Rate of HIV-1 infection was lowest among the women with normal flora (14·2%) and was substantially higher (26·7%) among women with severe bacterial vaginosis (p<0·0001). The risk ratio of HIV-1 infection associated with any abnormal flora was 1·49 (95% CI 1·32–1·68), and for all bacterial vaginosis was 1·51 (1·25–1·81).

The figure shows the age-specific rate of HIV-1 infection by morphological score. The age-specific pattern of HIV-1 infection is similar to that seen in other African populations, with a rapid increase in frequency among younger women (aged 15–29 years) and a decline among older women.[16–18] Compared with women with normal flora, the rate of HIV-1 infection was higher among those with intermediate vaginal flora abnormalities or moderate or severe bacterial vaginosis in the age-groups between 15 and 39 years, but this association was not seen in the 40–59 year age-groups. By contrast to the peak in HIV-1

Vaginal flora morphology (score)	Number of sexual partners in previous year					
	None (n=1081)		One partner (n=3462)		Two or more partners (n=177)	
	n	HIV-1 infected	n	HIV-1 infected	n	HIV-1 i infected
Normal (0–3)	218	14·2%	579	14·0%	23	17·4%
Intermediate (4–6)	382	18·1%	1067	19·6%	48	29·2%
Moderate bacterial vaginosis (7–8)	432	22·9%	1578	29·1%	91	31·9%
Severe bacterial vaginosis (9–10)	47	25·5%*	238	25·2%*	15	53·3%*
Any abnormal vaginal flora						
Risk ratio† (95% CI)	1·49 (1·16–1·90)		1·46 (1·26–1·68)		2·04 (1·16–3·59)	

*p<0·05. †Risk ratio of HIV-1 prevalence among women with abnormal flora (scores 4–10) relative to women with normal vaginal flora (scores 0–3).

Table 2: **HIV-1 prevalence associated with vaginal flora morphology and numbers of sexual partners in previous year**

Vaginal flora abnormality	Presence of concurrent STD infection							
	Gonorrhoea (n=28)		*C trachomatis* (n=40)		Trichomoniasis (n=1081)		Syphilis (n=483)	
	n	HIV	n	HIV	n	HIV	n	HIV
Normal (0–3)	2	0%	5	0%	92	8·7%	59	22·0%
Intermediate (4–6)	4	25·0%	12	25·0%	340	17·9%	153	25·5%
Moderate bacterial vaginosis (7–8)	18	44·4%	20	10·0%	567	23·3%	232	27·6%
Severe bacterial vaginosis (9–10)	4	50·0%	3	0%	32	39·0%*	39	48·7%†
Any abnormal vaginal flora								
Risk ratio‡ (95% CI)	..		..		2·62 (1·34–5·12)		1·31 (0·79–2·16)	

*p<0·001. †p<0·05. ‡Risk ratio of HIV prevalence in women with abnormal flora (scores 4–10) relative to women with normal vaginal flora (scores 0–3); risk ratio cannot be calculated for gonorrhoea or *C trachomatis* because of absence of HIV infections in the reference group with normal vaginal flora.

Table 3: **HIV prevalence associated with bacterial vaginosis in women with concurrent STDs**

rate among young women, the frequency of abnormal vaginal flora tended to increase with age. For example, 43·9% of 15–19-year-olds, 51·6% of 20–29-year-olds, 53·1% of 30–39-year-olds, and 54·9% of women aged 40–59 years had bacterial vaginosis.

Since CD4 counts for the HIV-1-infected women were not available, we used the presence of symptoms suggestive of AIDS (WHO staging 3–4)[12] to measure the rate and severity of bacterial vaginosis among immunocompromised women. 55·0% of 131 HIV-1-infected women with symptoms suggestive of AIDS had bacterial vaginosis compared with 55·7% of 787 symptom-free women. 6·9% and 9·0%, respectively, of patients with symptoms and symptom-free women had severe bacterial vaginosis.

Sexual behaviour is the main risk factor for HIV-1 infection in this population;[16] therefore, we investigated whether the reported number of sexual partners during the previous year might confound the association between abnormal vaginal flora and HIV-1 infection (table 2). As we expected, the rate of HIV-1 infection was higher among women reporting several sexual partners than among those with one or no sexual partners, and this association was consistent for women with normal and abnormal vaginal flora. Frequency of bacterial vaginosis also increased with higher numbers of sexual partners; we found bacterial vaginosis in 481 (44·4%) of 1079 women reporting no partners in the previous year, 1816 (52·5%) of 3462 women reporting one partner, and 106 (59·9%) of 177 women reporting two or more partners (p<0·001). However, a higher proportion of women with vaginal flora abnormalities than women with normal flora were infected with HIV-1, irrespective of the number of reported sexual partners. The association of HIV-1 infection with increasing morphological score was significant in each stratum of sexual activity. We obtained limited information on vaginal hygiene; women were asked whether they inserted substances (liquids, herbs, powders, or leaves) into the vagina before or after intercourse. Only 4·7% of respondents reported use of such substances, and the rate of bacterial vaginosis among these women was 48·8%, compared with 52·4% among women who did not report such practices. The rate of HIV-1 infection was similar among women reporting use or non-use of these substances (17·7% and 20·6%, respectively).

We assessed HIV-1 infection associated with vaginal flora among women with concurrent STDs (table 3). The limited numbers of women with current gonorrhoea or chlamydial infections constrained analysis. We found HIV-1 infection associated with more severe vaginal flora abnormalities in 28 women with gonorrhoea, which suggests a linear trend although this was not significant (p>0·05). However, we found no such trend among 40 women with *C trachomatis* infection. Among 1081 women with positive cultures for *T vaginalis*, the risk ratio of HIV-1 infection associated with abnormal vaginal flora was 2·62 (95% CI 1·34–5·12). In 483 women with positive syphilis serology, the risk ratio of HIV-1 infection associated with abnormal flora was raised but not significant (1·31 [0·79–2·16]). However, the trend of increasing HIV-1 infection with higher morphological score among women with concurrent syphilis was significant (p=0·03).

We did multiple logistic regression with adjustment for age, number of sexual partners, trichomoniasis, and syphilis, and sample cluster to investigate the association of HIV-1 infection with vaginal floral morphology. We did not include variables for gonorrhoea or *C trachomatis* because of the small numbers of women with positive results for ligase chain reaction and the restricted age-range of women with ligase chain reaction assay results. The adjusted odds ratio for HIV-1 infection associated with any abnormal flora was 1·52 (1·22–1·90), and with all bacterial vaginosis was 1·56 (1·24–1·97). For moderate bacterial vaginosis the adjusted odds ratio was 1·50 (1·18–1·89), and 2·08 (1·48–2·94) for severe bacterial vaginosis. Trichomoniasis was not associated with frequent HIV-1 infection (relative risk 1·03 [0·87–1·24]), whereas syphilis was associated with HIV-1 infection (1·65 [1·31–2·08]).

Discussion

We found a significantly increased proportion of women of HIV-1 infection associated with depletion of vaginal lactobacilli (measured by gram-stain morphological score), particularly among women with severe bacterial vaginosis, characterised by the absence of lactobacilli (table 1). We found an association between abnormal vaginal flora and HIV-1 infection among younger women but not among older women (figure), but this cannot be explained by the age-specific rate of bacterial vaginosis. Also, the association between HIV-1 and abnormal vaginal flora was not confounded by sexual activity (table 2) or concurrent STD infection.

Our results are broadly consistent with findings from a smaller investigation of 144 Thai prostitutes reported by Cohen and colleagues.[8] In that study, the investigators found an association between HIV-1 infection and a clinical diagnosis of all bacterial vaginosis or evidence of any abnormal vaginal flora. However, morphological evidence of bacterial vaginosis was not associated with HIV-1 infection.

The investigators note that the prostitutes have many sexual contacts and often douche after intercourse, which may have affected the vaginal microflora detected by gram stain.[8]

Our study can show only associations between vaginal flora and the frequency of HIV-1 infection; we do not know the duration of HIV-1 infection so we cannot ascertain whether the abnormalities in vaginal flora occurred before or after seroconversion. Although we cannot show cause and effect from cross-sectional data, we can draw indirect inferences about the plausibility of possible causal associations. Immunocompromised HIV-1-infected women are known to have increased rates of vaginal candidosis and may have increased severity of pelvic inflammatory disease.[19,20] Therefore, immunosuppression due to HIV-1 infection could plausibly increase the frequency or severity of bacterial vaginosis. If HIV-1 infection did cause or exacerbate bacterial vaginosis, we would expect to see such effects in all age-groups, especially among older women with higher rates of bacterial vaginosis and HIV-1 infection of longer duration. In addition, the frequency of bacterial vaginosis, especially severe bacterial vaginosis, was similar among HIV-1-infected women with and without symptoms, which suggests that more advanced HIV-1 disease is not associated with more frequent or severe bacterial vaginosis.

However, evidence also suggests that depletion of vaginal *L acidophilus* might increase the risk of HIV-1 acquisition. In-vitro studies by Klebanoff and Coombes[2] have shown that hydrogen-peroxidase-producing *L acidophilus* in vaginal fluid inhibit HIV-1 viral replication and that this viricidal activity is abolished in the presence of lactobacilli that do not generate peroxide. The investigators suggest that a deficiency of hydrogen-peroxidase-producing lactobacilli may enhance HIV-1 survival in the genital tract. In addition, studies of vaginal immune defence have shown that a low vaginal pH (<5) inhibits lymphocyte proliferation, whereas an alkaline environment is associated with activation of CD4 lymphocytes.[3] The investigators speculate that the increased pH seen with vaginosis may increase the risk of HIV-1 transmission by providing more activated HIV-1 target cells in the vagina. If these hypotheses are correct, the increased HIV-1 prevalence associated with abnormal vaginal flora would be most pronounced among younger women in whom HIV-1 infection is likely to be more recent and incidence is highest.[16–18] We found the high HIV-1 frequency associated with disturbed vaginal flora only among younger women (figure). Therefore, the age-specific pattern is more consistent with the hypothesis that abnormal flora, particularly severe bacterial vaginosis, increases the risk of HIV-1 acquisition. This inference is further supported by preliminary data from a prospective study of prostitutes in Mombasa, Kenya, among whom the presence of lactobacilli was associated with a decreased risk of HIV-1 acquisition.[21]

The association between HIV-1 infection and abnormal vaginal flora is unlikely to be because of confounding by sexual activity since the increased rate of HIV-1 infection associated with abnormal flora was seen consistently among women with multiple sexual partners, even though the number of sexual partners is a determinant of HIV-1 risk (table 2).[8,16] Bacterial vaginosis may predispose women to cervical infections with gonorrhoea or *C trachomatis*, or alternatively, these cervical infections may exacerbate abnormalities of vaginal flora.[6,7] In additon, ulcerative and non-ulcerative STDs may be associated with increased risk of HIV-1 infection, either because of similar risk behaviours, or because these infections may increase the risk of HIV-1 acquisition.[22] However, our data suggest that the association between bacterial vaginosis and HIV-1 infection is not due to concomitant infection with STDs such as *N gonorrhoeae, C trachomatis, T vaginalis,* or syphilis (table 3). The association between HIV-1 infection and disturbed vaginal flora may, however, be due to other unknown confounding factors.

Our continuing prospective study of HIV-1 incidence will help to find out whether pre-existing abnormalities of vaginal flora, especially bacterial vaginosis, increase the risk of HIV-1 acquisition. Because depletion of vaginal lactobacilli or bacterial vaginosis are common disorders, even a modest increase in the relative risk of HIV-1 transmission could lead to substantial attributable risk. Since we cannot, at this time, find out whether the association between abnormal flora and HIV-1 is causal, we have not estimated the attributable risks for this Ugandan population. If subsequent studies suggest a causal association, treatment of abnormal flora or of bacterial vaginosis with inexpensive and effective drugs such as metronidazole,[23] might be an economic and feasible means of reducing HIV-1 transmission.

Contributors

Nelson Sewankambo is the principal investigator in Uganda and is responsible for supervision of field research. Ronald Gray is the senior epidemiologist in the USA. Maria Wawer is the principal investigator in the USA and is responsible for overall design and conduct of the study. Lynn Paxton is the expatriate technical coordinator and epidemiologist in Uganda. Denise McNairn is the chief technician in charge of the laboratories in Uganda. Fred Wabwire-Mangen is a coordinator and field epidemiologist. David Serwadda is a coinvestigator and field public-health coordinator. Chuanjun Li is the data coordinator and computer programer and analyst. Noah Kiwanuka is the physician in charge of field activities. Sharon Hillier is the microbiologist responsible for vaginal flora morphology. Charlotte Gaydos and Thomas Quinn did the ligase chain reaction tests for chlamydia and gonorrhoea. Joseph Konde-Lule is a coinvestigator and responsible for public-health activities. All authors contributed to the design, data collection and analyses, and writing of the paper.

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Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis

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Summary

Background Small increases in bone mass are commonly seen with existing treatments for osteoporosis, which reduce bone remodelling and primarily prevent bone loss. Since these drugs reduce but do not eliminate risk of fractures, an anabolic agent that would increase bone mass and potentially cure the underlying skeletal problem is needed.

Methods We did a 3-year randomised controlled trial to find out the effects of 1–34 human parathyroid hormone (hPTH [1–34], 400 U/25 μg daily subcutaneously) in postmenopausal women with osteoporosis taking hormone-replacement therapy (n=17). The controls were women taking hormone-replacement therapy only (n=17). The primary outcome was bone-mineral density of the lumbar vertebrae, with bone-mineral density at other sites and vertebral fractures as secondary endpoints.

Findings Patients taking hormone-replacement therapy and PTH (1–34) had continuous increase in vertebral bone-mineral density during the 3 years, whereas there was no significant change in the control group. The total increase in vertebral bone-mineral density was 13·0% (p<0·001); 2·7% at the hip (p=0·05); and 8·0% in total-body bone mineral (p=0·002). No loss of bone mass was found at any skeletal site. Increased bone mass was associated with a reduction in the rate of vertebral fractures, which was significant when fractures were taken as a 15% reduction in vertebral height (p=0·04). During the first 6 months of treatment, serum osteocalcin concentration, which reflects bone formation, increased by more than 55%, whereas excretion of crosslinked n-telopeptide, which reflects bone resorption, increased by only 20%, which suggests some uncoupling of bone formation and resorption. By 6 months, there were similar increases in both markers, which gradually returned towards baseline as the study progressed. Vertebral bone-mineral density increased most during the first year of PTH treatment.

Interpretation We found that PTH has a pronounced anabolic effect on the central skeleton in patients on hormone-replacement therapy. PTH also increases total-body bone mineral, with no detrimental effects at any skeletal site. The increased vertebral mass was associated with a reduced rate of vertebral fracture, despite increased bone turnover. Bone-mass changes may be consistent with a reduction in all osteoporotic fractures. If confirmed in larger studies, these data have important implications for the treatment of postmenopausal osteoporosis.
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Introduction

Therapaeutic options for osteoporosis are limited. In the USA only three agents are approved by the Food and Drug Administration—oestrogens, salmon calcitonin, and alendronate. These agents primarily reduce bone turnover, mainly by reducing the activation of new remodelling units within the skeleton.[1] Therefore, although they may lead to an early increase in bone mass,