Randomized Controlled Trial of Calcium Supplementation in Healthy, Nonosteoporotic, Older Men

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Background: There is no consistent evidence, to our knowledge, that calcium supplementation affects bone mineral density (BMD) in men, despite male osteoporosis being a common clinical problem.

Methods: To determine the effects of calcium supplementation (600 mg/d, 1200 mg/d, or placebo) on BMD in men, we conducted a double-blind, randomized controlled trial for a 2-year period at an academic clinical research center. A total of 323 healthy men at least 40 years old (mean age, 57 years) were recruited by newspaper advertisement. Complete follow-up was achieved in 96% of subjects.

Results: The BMD increased at all sites in the group receiving calcium, 1200 mg/d, by 1% to 1.5% more than those receiving placebo. The results for the group receiving calcium, 600 mg/d, were not different from the placebo group at any BMD site. There was no interaction between the BMD treatment effect and either age or dietary calcium intake. There were dosage-related, sustained decreases in serum parathyroid hormone ($P < .001$), total alkaline phosphatase activity ($P = .01$), and procollagen type 1 N-terminal propeptide ($P < .001$) amounting to 25%, 8%, and 20%, respectively, in the group receiving calcium, 1200 mg/d, at 2 years. Tooth loss, constipation, and cramps were unaffected by calcium supplementation, falls tended to be less frequent in the group receiving calcium, 1200 mg/d, but vascular events tended to be more common in the groups receiving calcium vs the group receiving placebo.

Conclusion: Calcium, 1200 mg/d, has effects on BMD in men comparable with those found in postmenopausal women but a dosage of 600 mg/d is ineffective for treating BMD.

Trial Registration: actr.org.au Identifier: 012605000274673

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Calcium supplementation is widely regarded as a fundamental component of the prevention and treatment of postmenopausal osteoporosis. Although the evidence for prevention of bone loss by calcium supplements has been almost entirely generated in studies of postmenopausal women, it has been assumed that calcium plays a similarly important role in the prevention of other forms of osteoporosis, including male osteoporosis. For example, the recent report of the US Surgeon General recommended increases in calcium intakes across the entire population, including men. With increasing male longevity, the problem of fractures in older men is growing, and with it, the need to have evidence-based interventions for osteoporosis prevention.

Few studies have assessed the effect of calcium supplementation on bone mineral density (BMD) in older men, and there is virtually no trial data assessing its effects on male fracture rates. The largest study to assess calcium supplementation in men alone was that by Orwoll et al, who randomized 86 healthy men to calcium, 1 g, plus cholecalciferol, 1000 U, daily and followed BMD measurements in the spine and forearm over a period of 3 years. There was no evidence of any therapeutic benefit at any of the skeletal sites assessed. In contrast, Dawson-Hughes et al showed beneficial effects on BMD in the subset of men included in their study of calcium plus cholecalciferol in healthy older adults. However, a recent trial using a high-calcium dairy product to provide an additional 1 g of calcium and 800 IU of cholecalciferol daily over 2 years produced equivocal results, with no clinically significant benefits on BMD at the spine or total hip. It is critically important to determine whether the widespread use of calcium supplements in older men is a worthwhile investment because 30% of older men experience a fragility fracture and men account for one-quarter of all hip fractures. Furthermore, this intervention may not be entirely without risk because there is evidence of increased rates of renal stone formation and possibly of myocardial infarction in women taking calcium supple-
ments. Consequently, there is a need for an adequately powered study to test whether calcium supplementation in older men has clinically significant effects on bone loss. The present study addresses this need.

**METHODS**

This was a randomized controlled trial comparing 2 dosages of calcium citrate with placebo in healthy men over a 2-year period. The study was designed to assess the effects of calcium supplementation on both bone and cardiovascular end points. The primary end point for the bone analyses, the focus of this article, was lumbar spine BMD.

**RECRUITMENT**

Newspaper advertisements were placed soliciting “men aged at least 40 years, in good general health” for a study of the effects of calcium supplementation on BMD, cholesterol level, and blood pressure. Exclusion criteria were any major active disease, including coronary heart disease, hypertension, diabetes mellitus, untreated hypothyroidism or hyperthyroidism, liver disease, malignant lesion, or metabolic bone disease; an estimated 5-year cardiovascular risk of more than 15%, serum creatinine level higher than 0.002 mg/dL, serum 25-hydroxyvitamin D level lower than 10 ng/mL; lipid-lowering therapy or use of testosterone, anabolic steroids, glucocorticoids, or bisphosphonates in the previous year; and lumbar spine or total hip BMD Z score lower than –2. Study questionnaires were sent to 909 men who answered the advertisements, and 570 of these were returned. Prospective subjects were excluded for the following reasons: medications (62 subjects), low BMD (15 subjects), abnormal findings from blood tests (20 subjects), or questionnaires that were returned after recruiting had closed (3 subjects). Thirty-one men failed to have blood tests, and 50 men (13% of those eligible) declined to enter the study. (To convert serum creatinine to micromoles per liter, multiply by 88.4. To convert serum 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.)

Subjects’ baseline characteristics are shown in Table 1. No men were taking cholecalciferol supplements, but multivitamins were taken by 35 men (P = .33 for between-group comparison). The first subject was randomized in April 2004, and the last subject completed the study in July 2007.

**PROTOCOL**

Qualifying subjects entered a 1-month run-in phase during which all took placebo. Those achieving a higher than 70% rate of compliance proceeded to randomization. Treatments were allocated randomly using computer-generated random numbers (Microsoft Excel 2003; Microsoft, Redmond, Washington) within blocks of random sizes in multiples of 3. Randomization was performed prior to the commencement of the study by the study statistician (G.D.G.) and conveyed to a staff member who dispensed the study medication into numbered containers. This individual had no direct contact with other study staff or with trial participants. Subjects were allocated a study number according to the sequence of their enrollment. Trial regimens were as follows: placebo before breakfast and elemental calcium, 600 mg, in the evening (600 mg/d group); calcium, 600 mg twice daily (1200 mg/d group); or placebo twice daily (placebo group). Medications were supplied by Mission Pharmacal, San Antonio, Texas. Compliance was assessed by...
Secondary end points were specified as changes in hip and total body BMD. Assuming a standard deviation for change in spine BMD in men of 3.1%, this study is adequately powered (80%) at the 5% significance level with 3 groups of 100 participants to detect differences of 1.2% between any of the groups. Smaller changes are unlikely to be clinically significant.

Data were analyzed on an intention-to-treat basis (ie, all randomized subjects) using a mixed-models approach to repeated measures (using SAS statistical software, version 9.1; SAS Institute, Cary, North Carolina). Missing, at-random data were dealt with by multiple imputation using a maximum likelihood method. Statistically significant main and interaction effects were explored using the method of Tukey, and a 5% significance level was maintained throughout. Orthogonal contrasts were constructed to test first- and second-order trends. The mid-P approach was used to calculate P values and 95% confidence intervals (CIs) for rates. This approach preserves accuracy while providing exact confidence intervals. Data are presented as mean (SE) unless stated otherwise.

**RESULTS**

**SUBJECT DISPOSITION AND ADHERENCE**

The disposition of the 323 men who entered the study is shown in Figure 1. Complete follow-up was achieved in 96% of subjects, and the proportions of randomized subjects still receiving the trial medication at study end were as follows: placebo group, 93%; 600 mg/d group, 91%; and 1200 mg/d group, 86% (P = .19 for between-group comparisons). There was a nonsignificant trend for more men in the 1200 mg/d group to cite gastrointestinal symptoms as the reason for discontinuing trial medication (placebo group, 2; 600 mg/d group, 3; and 1200 mg/d group, 6; P = .18). Among those still receiving trial medication, the mean tablet compliance rates were as follows: placebo, 85%; 600 mg/d group, 86%; and 1200 mg/d group, 83% (P = .67). At their final visit, subjects were asked if they could identify their treatment allocation; 68% said they did not know, and 20% correctly identified their treatment allocation, consistent with the proportion expected by chance.

**BONE MINERAL DENSITY**

In the lumbar spine, there was no difference in BMD between the 600 mg/d group and the placebo group over the 2 years of the study (Figure 2). In contrast, the 1200 mg/d group showed an increase in BMD of more than 1% in the first 6 months, and they maintained this difference through the end of the study. Post hoc testing confirmed that the differences identified by analysis of variance were indeed between the 1200 mg/d group and the other 2 groups. In the total hip BMD, the placebo and 600 mg/d groups were again indistinguishable, whereas the 1200 mg/d group showed an increase in BMD (Figure 2). In contrast to the lumbar spine BMD, this increase was progressive, increasing 0.9% more than the placebo group in the first 12 months and then by a further 0.5% in the second half of the study. When the changes in total hip BMD from months 12 to 24 were analyzed using a mixed-models approach to repeated measures, there was a significant time-treatment interaction in year 2 of the study (P = .03).

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**TABLE OF SUBJECTS**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Received calcium, 600 mg/d</th>
<th>Received calcium, 1200 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>323</td>
<td>108</td>
<td>108</td>
</tr>
<tr>
<td>323 were eligible, consented to participate, and were randomized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>107 received placebo group; all received intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>108 received calcium, 600 mg/d; all received intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>108 received calcium, 1200 mg/d; all received intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 died</td>
<td>1 died</td>
<td>1 died</td>
</tr>
<tr>
<td>2 did not complete follow-up</td>
<td>1 did not complete follow-up</td>
<td>5 did not complete follow-up</td>
</tr>
<tr>
<td>104 completed follow-up</td>
<td>106 completed follow-up</td>
<td>99 completed follow-up</td>
</tr>
<tr>
<td>99 were still taking study tablets</td>
<td>98 were still taking study tablets</td>
<td>93 were still taking study tablets</td>
</tr>
</tbody>
</table>

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**Figure 1.** Flowchart for subject disposition.

Tablet counts. All visits took place at a clinical research facility in a tertiary medical center. Participants and study staff were blinded to treatment allocation throughout the study.

**MEASUREMENTS**

Subjects’ BMD was measured at 6-month intervals in the lumbar spine, both proximal femora, and total body using a Prodigy dual-energy x-ray absorptiometer (DEXA) (GE-Lunar, Madison, Wisconsin). Mean total hip results are used. Vertebral morphology was performed at baseline and 2 years using the Prodigy scanner. Subjects were asked at each 6-month visit about fractures. If any were reported, the relevant radiograph or medical report was obtained. Subjects kept a falls diary. Grip strength was measured in triplicate in the dominant hand. Height was measured using a Harpenden stadiometer (Holtain, Crymmych, Wales). Dietary calcium intake was assessed using a food frequency questionnaire, and serum total alkaline phosphatase activity. These assays

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**Figure 1.** Flowchart for subject disposition.
To determine whether the effect of calcium on total hip BMD was influenced by dietary calcium intake, successive 100 mg/d cut points from 400 to 1000 mg/d were considered. The cohorts with intakes above and below these points had similar responses to the intervention. Dietary calcium was distributed with a median of 790 mg/d and an interquartile range of 560 to 1080 mg/d. If dietary calcium (stratified by median), baseline serum 25-hydroxyvitamin D level (stratified above or below 32.05 ng/mL), age (stratified by median), or exercise (stratified by median) were included as covariates in an analysis of covariance model, there was no change in the time-treatment effect ($P < .001$ for all comparisons). The $P$ values for the interactions of these variables with the time-treatment effect were as follows: $P = .52$ for calcium, $P = .54$ for 25-hydroxyvitamin D, $P = .62$ for age, and $P = .92$ for exercise. A total of 129 men had a baseline 25-hydroxyvitamin D level of less than 32.05 ng/mL.

Total body scans showed a pattern similar to that in the lumbar spine, with no change in BMD over the study period in either the placebo group or 600 mg/d group, but an increase of 1.2% in the 1200 mg/d group during the first 6 months, followed by a more gradual increase to 1.5% above baseline at the end of the study (Figure 3). The trunk region of the total body scans showed an increase in BMD at 6 months in the 1200 mg/d group, whereas in the cortical bone of the legs, there was a more gradual separation of the 1200 mg/d group from the others, similar to that seen in the femur scans (data not shown).

During the study, 2 men in the 1200 mg/d group and 1 in the placebo group were given bisphosphonates. Exclusion of their data, or of those data from 33 men taking less than 60% of their trial medication, made no material difference to the results.

**BIOCHEMICAL ANALYSIS**

Because calcium is thought to influence BMD by decreasing circulating parathyroid hormone levels and thus decreasing bone turnover, these parameters were assessed in fasting morning blood samples. Parathyroid hormone levels showed a dosage-related decrease that was sustained to the end of the study (Figure 4). Bone turnover, assessed both by total serum alkaline phosphatase activity and by serum P1NP level, showed the same pattern of dosage-related, sustained change in response to calcium. These differences between the placebo and 1200 mg/d groups at 2 years represent proportions of baseline values of 25% for parathyroid hormone, 20% for P1NP, and 8% for alkaline phosphatase. Fasting urine calcium excretion showed a small upward trend in the 600 mg/d group but an increase of 57% in the 1200 mg/d group at 2 years, exceeding the laboratory reference range in 0%, 3%, and 4.5% of the placebo, 600 mg/d, and 1200 mg/d groups, respectively.

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**Figure 2.** Effects of calcium supplementation on bone mineral density (BMD) over 2 years. A, Changes in lumbar spine; B, mean total hip BMD. Data are given as mean±SEM (error bars).

**Figure 3.** Effects of calcium supplementation on changes in total body bone mineral density (BMD) over a 2-year period. Data are given as mean±SEM (error bars).
A total of 22 clinical fractures (6 in the 1200 mg/d group, 5 in the 600 mg/d group, and 11 in placebo group) occurred in 17 subjects (4 in the 1200 mg/d group, 5 in the 600 mg/d group, and 8 in placebo group; \( P = .43 \)) during the study (Table 2). Fracture sites included small bones of the feet, ribs, pelvis, skull, clavicle, humerus, ankle, and tibia. Except for toe fractures, all occurred after substantial trauma. There were no fractures found on vertebral morphometric analysis. Height loss, a reflection of vertebral fractures, showed no between-group differences during the study (\( P = .84 \) for treatment-time interaction).

**OTHER EVENTS**

Adverse events were reported in 75% of the placebo group, 69% of the 600 mg/d group, and 70% of the 1200 mg/d group (\( P = .16 \)). A number of adverse events possibly influenced by calcium intake were prespecified in the protocol. These included sudden death, myocardial infarction, angina, chest pain, constipation, colonic neoplasms, renal calculi, stroke, transient ischemic attack, and a composite vascular end point. The distribution of these events is shown in Table 2. There were no significant differences between groups (see Table 2 for \( P \) values).

The total numbers of falls reported during the study were as follows: placebo group, 126; 600 mg/d group, 141; and 1200 mg/d group, 94; giving fall rates of 59 (95% CI, 49-71), 65 (95% CI, 55-77), and 45 (95% CI, 36-55) per 100 subject-years, respectively. There was no difference in the fall rates between the 600 mg/d and placebo group (\( P = .44 \)), but the rate for the 1200 mg/d group is significantly less than that of the 600 mg/d group (\( P = .005 \)) and the placebo group (\( P = .045 \)). Several men had very high fall rates.

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**Table 2. Protocol-Specified Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo Group</th>
<th>Calcium Groups</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina or chest pain</td>
<td>0</td>
<td>1 0</td>
<td>.37</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
<td>1 2</td>
<td>.37</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0</td>
<td>0 1 1</td>
<td>.61</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>0</td>
<td>0 3</td>
<td>.95</td>
</tr>
<tr>
<td>Any of the above</td>
<td>0</td>
<td>2 3</td>
<td>.24</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>0 1</td>
<td>.60</td>
</tr>
<tr>
<td>Renal calculus</td>
<td>1</td>
<td>0 0</td>
<td>.36</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>2 3</td>
<td>.87</td>
</tr>
<tr>
<td>Fractures</td>
<td>8</td>
<td>5 4</td>
<td>.43</td>
</tr>
<tr>
<td>Death, nonsudden</td>
<td>1</td>
<td>0 0</td>
<td>.37</td>
</tr>
</tbody>
</table>

\( ^\text{a} \) Data are given as number of men with each adverse event. There were no colonic neoplasms or strokes. There were no significant differences between groups for any of these events.
so the results were also analyzed as the numbers of men having at least 1 fall, which were as follows: placebo group, 51; 600 mg/d group, 43; and 1200 mg/d group, 42 (P = .16).

Cramps were assessed at the 2-year visit by questionnaire.16 There were no significant differences among groups in responses: the percentages of patients with cramps in the preceding 6 months were comparable: placebo group, 47%; 600 mg/d group, 43%; and 1200 mg/d group, 51% (P = .58), as were the frequencies of cramps in those reporting this problem (P = .94). Grip strength showed no between-group differences during the study (P = .80 for a treatment-time interaction). Two men each lost 1 tooth over the duration of the study (1 each in the placebo and 600 mg/d groups).

The present data establish that 1.2 g of calcium given in a divided dose produces a substantial benefit to BMD throughout the skeleton in vitamin D–sufficient men. This benefit occurs independent of age and dietary calcium intake. The increases in BMD are more rapid in the spine than in the total hip, possibly because the higher trabecular bone content of the spine results in a more obvious remodeling transient. Separate assessment of trabecular and cortical bone using computed tomography would be necessary to be sure of this explanation. It is of interest to compare these changes with those reported in the “control” groups of recent treatment studies of male osteoporosis, in which subjects also received calcium supplementation. An increase in spine density of about 1% in the first 6 to 12 months is apparent in many of these studies,17,18 which may represent a calcium effect, although in 1 study19 the effect of calcium alone seemed even greater. These similarities in BMD changes suggest that calcium supplementation is likely to be of value in the treatment of osteoporosis in men, although undertaking a study such as the one described herein in men at high risk of fractures would not be ethically justifiable.

The present data provide much greater certainty as to the effects of calcium supplements on BMD in men than has been available previously. The trial by Orwoll et al2 studied healthy men of much the same age, but there were only 77 subjects in total. Bone mineral density was measured with quantitative computed tomography, which is less precise than the technique used in the present study. Thus, that study may have been underpowered as a result of both small study numbers and less sophisticated BMD technology. Superficially, the present results seem to be in substantial agreement with those of Dawson-Hughes et al,3 in that our high-dosage group experienced marked beneficial effects on BMD at all sites. However, the benefits in that study were produced with a nocturnal calcium supplement of 500 mg/d (as citrate-malate) together with 700 IU cholecalciferol. Thus, that study3 is comparable with our 600 mg/d group, which showed no effect of calcium supplementation on BMD. The men in the study by Dawson-Hughes et al were older (mean age, 71 years), but our study subjects extended well into that age range, and our analyses show no interaction between age and treatment effect, so this is unlikely to be the explanation. The additional use of cholecalciferol by Dawson-Hughes et al3 might be relevant to the greater effect they found. The present findings are much more conclusively positive than the recent report by Daly et al.4 That study was somewhat smaller, used a dairy product intervention, and was not blinded. Thus, it is possible that subjects in the control group changed their diet or lifestyle to compensate for the fact that they were not receiving the active intervention. Although there were positive trends in that study,4 it did not provide sufficient evidence of efficacy to justify a firm endorsement of calcium supplementation in men.

The failure of the low-dosage intervention in the present study to influence BMD is surprising in view of its clear impact on parathyroid hormone and on 2 independent measures of bone turnover. Parathyroid hormone was measured approximately 12 hours after the calcium dosage was given, so it is possible that its suppression, and that of bone resorption, was not maintained throughout the subsequent 12 hours. In contrast, osteoblast activity would not be expected to show substantial diurnal variation because it usually fluctuates over periods of weeks rather than hours, in contrast to the lability of osteoclasts. If once-a-day calcium supplementation produces stable reduction in bone formation but fluctuating suppression of bone resorption, this might account for its failure to markedly influence BMD. Whatever the explanation, the clear implication from the present study is that a daily calcium dosage in the region of 1 g is necessary to achieve a BMD benefit in men, and it seems preferable to give this as at least 2 doses. The clear dissociation of bone turnover and BMD changes mandates caution in the use of markers as surrogates in evaluating calcium supplements.

This study provides an opportunity to assess the effects of calcium on some other end points, although statistical power for many of these is very limited. The downward trend in fractures is consistent with a recent meta-analysis20 showing a modest decrease in fracture rates from the use of calcium. Calcium is an important signaling ion in muscle, and there has been some suggestion that calcium supplementation interacts with vitamin D to improve muscle function.21 We recently examined this in a study of postmenopausal women22 and found that calcium tended to have a negative effect on grip strength but no effect on falls. In the present study there seems to be a beneficial effect of calcium on falls, although this is unduly influenced by a small number of men with high fall rates, and after allowing for this, there is no significant effect (P = .16). This interpretation is consistent with the absence of an effect of calcium supplementation on grip strength or on the frequency or severity of cramps in the present study. A previous study23 had suggested that calcium and cholecalciferol reduced tooth loss in postmenopausal women. The present study had insufficient events to test this possibility in men, and low event rates also limited assessment of calcium effects on renal calculi and colonic neoplasms. Vascular events were also infrequent, although the nonsignificant, adverse trend is similar to the one we have recently found in postmenopausal women.8 In contrast, the Women’s Health Initiative24 reported that calcium supplementation (with cholecalciferol) had no effect on vascular events, although nonsignificant adverse trends were also present in that study.25 This is an area of great uncertainty that will require further studies, possibly on surrogate end points.
such as coronary artery calcification, or by meta-analysis of existing databases. In contrast to the use of the same calcium preparation in women,22 in men there was no evidence of constipation being more common in calcium users.

This study has a number of limitations. It is a single-center study in a predominantly white cohort of vitamin D–sufficient men, so its generalizability to other populations is uncertain. The study used calcium citrate; available evidence suggests that the calcium salt and its formulation influence its effects on calcium metabolism,26-28 such that more soluble salts may have greater effects, although this is controversial. Therefore, smaller effects might result from the use of other preparations.

In conclusion, the present study provides clear evidence that calcium supplements have a beneficial effect on BMD in men. The study size, high subject retention, and consistency across BMD measurement sites mean that the current findings are most unlikely to be subject to bias or significant experimental error. A daily dosage of 1.2 g of elemental calcium is required to achieve this effect. These findings provide a rationale for conducting randomized studies of the effect of calcium supplementation on fracture incidence in men. Such studies should also assess the incidence of cardiovascular events so that the balance of risk and benefit can be clearly determined.

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Analysis and interpretation of data: I. R. Reid, Bacon, Bolland, Gamble, Grey, and Horne.

Drafting of the manuscript: I. R. Reid, Ames, Mason, Bolland, and Grey.

Critical revision of the manuscript for important intellectual content: I. R. Reid, H. E. Reid, Bacon, Bolland, Gamble, Grey, and Horne.

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Obtained funding: I. R. Reid.

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Study supervision: I. R. Reid, Bolland, and Grey.

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REFERENCES


