**Title:** Chronic effects of stroke on hip bone density and tibial morphology: a prospective study

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**Mini Abstract**

The study aimed to quantify the long-term effects of stroke on tibial bone morphology and hip bone density. Only the trabecular bone mineral density and estimated bone strength in the hemiparetic tibial distal epiphysis showed a significant decline among individuals who had sustained a stroke between 12 and 24 months.

**Abstract**

**Purpose:** To quantify the chronic effects of stroke on bone density and morphology in lower limb long bones during a 1-year follow-up period and identify the related factors.

**Methods:** Twenty-eight chronic stroke patients (>1 year post-stroke) and 27 age-matched healthy individuals underwent bilateral scanning of the hip and tibia using dual-energy x-ray absorptiometry and peripheral quantitative computed tomography respectively. Each subject was re-assessed one year after the initial assessment made at 12 to 166 months after the acute stroke event.

**Results:** Twenty stroke cases and 23 controls completed the follow-up assessments. At the end of the follow-up, the tibial distal epiphysis on the paretic side suffered significant decline in total bone mineral content (-1.28±0.47 mg/mm, $p$=0.013), trabecular volumetric bone mineral density (BMD) (-1.84%±0.60 mg/cm$^3$, $p$=0.007) and estimated bone strength (-2.74±0.65 g$^2$/cm$^4$, $p$<0.001). More severe decline in trabecular volumetric BMD was significantly correlated (ρ) associated with poorer paretic knee extensor muscle strength (ρ=0.447, $p$=0.048) and lower limb motor recovery (ρ=0.489, $p$=0.029) measured at initial assessment. Such bone loss remained significant among those who had sustained the stroke for 12-24 months ($p$<0.01), but not those whose stroke onset time was beyond 24 months. The changes of bone outcomes in the tibial diaphysis and proximal femur were unremarkable.

**Conclusions:** There is evidence of continuous trabecular bone loss at the tibial distal epiphysis in the paretic leg among people with chronic stroke, but it tends to plateau after two years of stroke onset. The steady state for bone outcomes may have been reached earlier in the hip and tibial diaphysis.

## INTRODUCTION

Stroke survivors have approximately 7-fold higher fracture risk than the age- and sex-matched population [1–3]. Hip fracture is the most common type of fracture, accounting for 30%-58% of all fractures following stroke [1, 2, 4]. Over 80% of hip fractures occur on the hemiplegic side, perhaps because falls onto this side are more common, and bone mass and quality are more compromised [5–8]. Bone loss and fractures have negative impact on longevity and quality of life following stroke [1, 2, 9–11] and should warrant attention.

A number of studies have attempted to examine the bone properties in people after stroke but have major limitations. Firstly, previous research that examined longitudinal bone changes after stroke were confined to measurement of bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) [9, 12–15]. While these studies consistently found that reduction in bone mineral content (BMC) and BMD on the paretic side was more severe than the non-paretic side [7, 9, 13, 15], they could not provide any information on alterations of bone structural properties after stroke due to the planar nature of DXA. Secondly, previous studies that used peripheral quantitative computed tomography (pQCT) to examine lower limb bone morphology following stroke were cross-sectional, which render them unable to capture the time course of bone structural changes post-stroke [16–19]. The immobilization after stroke could induce generalized bone changes in stroke patients [11, 13, 20]. The non-paretic side may hence also suffer bone loss, resulting in potential underestimation of the structural deterioration on the paretic side when side-to-side comparisons were made [18, 19]. To date, no study has examined the

longitudinal changes in structural properties of lower limb long bones in individuals after stroke.

Another unstudied area pertains to the bone changes in the chronic stage of stroke recovery. While it is known that fracture risk remains elevated long after stroke [2], whether bone loss continues in the longer term is not well established. Prospective studies suggested that during the first year post-stroke, femoral neck areal bone mineral density (aBMD) decreased by ~12% on the paretic side and ~6% on the non-paretic side [7, 13]. To date, the changes in lower limb long bones in patients after the first year post-stroke has only been investigated by de Brito et al. [12]. After the follow-up period (mean=16 months), only a small proportion (15.1%) of their chronic stroke cases (time since stroke = 33.4±17.9 months) sustained a significant change in femoral neck aBMD. In addition, time since stroke onset was not significantly associated with change in femoral neck aBMD, indicating that the steady-state level may have been reached at first year post-stroke. However, bone geometric changes were not assessed in their study. In another study, Sato et al. [21] compared the level of bone resorption and formation markers between people within one year of stroke onset and those within 1-2 years of stroke onset. It was found that serum concentration of pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP) (a bone resorption marker) was higher in the former group than latter group whereas the level of bone Gla protein (a bone formation marker) was similar in both groups. Their results indicated that bone resorption, which was exaggerated in the early phase of stroke, had slowed down in the chronic phase. Taken together, it is likely that attenuation of bone structural changes may also occur as the patients enter the chronic stage of stroke recovery (after 1 year post-stroke).

To address the above knowledge gaps, a prospective study was undertaken to quantify the chronic effects of stroke on density and morphology of the lower limb long bones using both DXA and pQCT during a 1-year follow-up period. As previous cross-sectional studies have identified a strong relationship between muscle function and tibial and hip bone outcomes in patients with stroke [16, 17, 19, 22], it would be interesting to determine whether a similar relationship exists in a longitudinal study. Thus, the secondary objective was to assess the association between muscle function and bone changes in individuals with chronic stroke.

## METHODS

### Subjects

The stroke cases were recruited from a local stroke self-help group in Hong Kong, China. Inclusion criteria were, i) a diagnosis of stroke, ii) ≥ 1 year after onset of stroke, iii) aged 18 or more, iv) medically stable, v) of Chinese origin, and vi) able to respond to simple verbal commands with an Abbreviated Mental Test score of 7 or higher. Exclusion criteria were other neuromuscular diseases, recent fractures in the lower extremity, metal implants in the lower extremity, taking prescribed medications for treatment of osteoporosis prior to or after stroke. Controls were identified from an existing database consisting of individuals who had joined previous research in the University, and should fulfill all criteria described above, except that they did not have any history of stroke.

### Demographic data

The relevant demographic data (e.g., medical history, medications, etc.) were obtained by interviewing the subjects. The walking capacity was evaluated with the Six Minute Walk Test [23]. The physical activity level was assessed using the Physical Activity Scale for the Elderly [24].

**Bone imaging**

The same experienced technician conducted bone imaging to the subjects initially and at 1-year follow-up using both pQCT and DXA.

*pQCT: Bone Size, Geometry and Mechanical Properties:*

pQCT (XCT 3000, Stratec Medizintechnik GmbH; Pforzheim, Germany) was used to generate three-dimensional cross-sectional scans of the tibia. After obtaining a scout view, an anatomical reference line was placed at the cortical end plate of the distal medial edge of the tibia. A voxel size of 500 microns and scan speed of 25mm/sec were used to obtain 2.3 mm thick scans at (i) tibial distal epiphysis (4% of the total tibia length proximal to the reference line), a region containing both cortical and trabecular bone and (ii) tibial diaphysis (66% of the total tibia length proximal to the reference line), a cortical region.

For image analysis of the distal tibial epiphysis, CALCB Contour Mode 2 and Peel Mode 2 were used. A density threshold of 169 mg/cm$^3$ was used to detect the outer contour of the bone and trabecular bone was separated from cortical and subcortical bone using a density threshold of 400 mg/cm$^3$ [25]. For tibial diaphysis, cortical bone analysis was performed using CORTBD (Mode 1), with a threshold of 710 mg/cm$^3$ [25]. These thresholds were chosen after taking reference from previous pQCT studies

in patients with stroke [26, 27]. All image analyses were performed using customized software (Stratec software, Version 6.0). Regarding the precision of the pQCT scanner, the least significant change (LSC) values for the outcome variables are displayed in Table 1. Any change that exceeds the LSC represents a real change that was beyond the variations stemming from repeated measurements.

*DXA measurements: Hip areal bone mineral density*

Dual-energy X-ray Absorptiometry (DXA) (Hologic Inc, Bedford, MA, USA) was used to assess the total hip aBMD ($g/cm^2$) on both sides. The LSC value for hip BMD is also shown in Table 1.

**Muscle function**

*Knee muscle strength*

Peak isometric knee extensor muscle strength of both legs was measured using a hand-held dynamometer (Nicholas MMT, Lafayette Instruments, Lafayette, IN, USA). Subjects were asked to sit upright in a chair with hip and knee in 90 degrees flexion. They were then instructed to perform an isometric knee extension with maximal effort and sustain for 5 seconds and the maximal force (N) was registered by the dynamometer. Three trials were conducted to obtain the mean peak muscle strength score.

*Motor recovery*

The Impairment Inventory of the Chedoke McMaster Stroke Assessment (CMSA) was used to evaluate the severity of impairment in the paretic leg and foot among the patients with stroke [28]. Each body part was rated on a seven-point ordinal scale (1-

7), with a higher score indicating better motor recovery (e.g., 1 = no motor return, 3 = synergistic movement patterns and marked spasticity, 7 = normal movement patterns). The leg and foot scores were summed to yield the CMSA leg motor recovery score. The CMSA has been shown to have high intra-rater reliability (ICC=0.98) and inter-rater reliability (ICC=0.97-0.99) [28].

*Spasticity*

In the stroke group, the Modified Ashworth Scale (MAS) was administered to assess spasticity in the paretic leg [29]. With the participant in a supine position, the ankle joint was moved into dorsiflexion and plantarflexion alternately by the researcher and the amount of resistance to passive movements was noted. The score range was between 0 and 4, with a higher MAS score denoting more severe spasticity.

**Statistical Analysis**

Comparisons of baseline characteristics between the stroke cases and controls for binary variables were conducted using Pearson Chi-square test. Fisher's exact test was used if the assumptions for the Chi-square test were not fulfilled. For continuous variables, Shapiro-Wilk test was used to check normal distribution, and then two-sample t-test for the mean was used, if the data were normally distributed; otherwise non-parametric Mann-Whitney was used. The latter two tests were also used to compare baseline bone characteristics between sides (paretic versus non-paretic) in the stroke group, and also between the corresponding sides across groups.

For the follow-up data, we computed the percentage change for a variable $X$ as $100\{(X_{\text{follow-up}}-X_{\text{baseline}})/[(X_{\text{follow-up}}+X_{\text{baseline}})/2]\}$. If the distribution for the percentage

change was normally distributed, one-sample t-test was used to test for the difference in mean change from zero; otherwise non-parametric Wilcoxon test was used for difference from zero in median change. Again, we used two-sample tests above to test for the difference in percentage change between sides in the stroke group and between corresponding sides across groups. For between-group comparisons, the bone changes in the paretic and non-paretic sides of stroke cases were compared with the non-dominant and dominant side of controls respectively.

To further explore the influence of post-stroke duration and bone changes, the above analyses were repeated after dividing the cases into two subgroups: those between 12 and 24 months after stroke onset (Group A), and those beyond 24 months after stroke onset (Group B). To assess the relationship between 1-year percent change in bone variables and muscle function variables, Spearman's rho was used. All analyses were conducted using commercial software STATA (version 11, StataCorp LP, College Station, Texas, USA). A p-value ($p$) less than 0.05 was considered significant. However, for comparisons of bone outcomes, a more stringent criterion ($p<0.05$ after false discovery rate adjustment) was used due to the potential inflation of type I errors associated with multiple comparisons.

**RESULTS**

Twenty-eight stroke cases and 27 controls fulfilled the inclusion criteria and completed a baseline assessment. Of these, 8 cases and 4 controls were lost to follow-up leaving 20 cases (12 men) and 23 controls (14 men) with evaluable data at 12 months. The reasons for withdrawal included: fractured upper limb as a result of a fall

(n=2), cardiovascular implants installed during follow-up period (n=1), unstable blood pressure (n=1), refusing to continue (n=5) and loss of contact (n=3).

**Baseline differences between cases and controls**

In the stroke group, the average onset after stroke was 49 months (range: 12-166) when the baseline assessment was conducted. The stroke group had higher proportion of subjects with high cholesterol level ($p$=0.003). They also had significantly less physical activity ($p$=0.002), lower knee extensor strength on the paretic side ($p$=0.006), more co-morbidities ($p$<0.001) and were prescribed more therapies than controls ($p$<0.002). There were no significant between-group differences in age, sex distribution, or body mass index ($p$>0.5) (Table 2).

At the 4% site, the paretic side had significantly lower total volumetric bone mineral density (vBMD) ($p$=0.001), trabecular vBMD ($p$=0.005) and estimated bone strength ($p$=0.011) than the non-paretic side by 5.9%, 4.0% and 7.8% respectively in the stroke group (Table 2). The total cross sectional area (CSA) was significantly greater ($p$=0.014) on the paretic side than the non-paretic side. None of the variables showed a significant side-to-side difference among controls. Between-group analysis revealed no significant results (Table 3).

At the 66% site, the cortical area ($p$=0.022) was smaller and the estimated bone strength value (polar stress-strain index, p-SSI) ($p$=0.009) was lower on the paretic side when compared with the non-paretic side in the stroke group, by 5.3% and 6.1% respectively. Similar to the 4% site, none of the pQCT variables showed a significant

side-to-side difference in controls. Between-group analysis also revealed no significant results.

In the stroke group, the total hip aBMD on the paretic side was also significantly lower than the non-paretic side ($p$=0.018) (Table 3). The side-to-side comparisons for the control group, and the between-group analysis did not yield significant results.

**Bone changes during 1-year follow-up**

During the 12-month follow-up period at the 4% site, total BMC, trabecular vBMD and estimated bone strength on the paretic side showed a significant decline by 1.28%, 1.84% and 2.74% respectively, which exceeded their respective LSC values (Table 4). On the non-paretic side, only trabecular vBMD suffered a significant decline (by 1.31%) that exceeded the LSC values (Table 4). No other bone changes at this skeletal site were above the LSC values among both stroke cases and controls.

Few statistically significant changes were detected during the follow-up period in the tibial diaphysis among the stroke cases (Table 4), and only the decline in cortical BMC (by 1.31%) on the non-paretic side exceeded the LSC values. During the follow-up period, the total hip aBMD decreased significantly on the paretic side (Table 4), but it did not exceed the LSC value.

**Influence of time since stroke onset: sub-group analysis**

In the secondary analysis, the stroke group was divided into two sub-groups (Group A: onset at 12-24 months, Group B: onset >24 months) to explore the possible relationship between bone changes and time since stroke onset (Table 5). Besides the

difference in duration after stroke, Group B was found to have a significantly shorter six-minute walk test distance than Group A (Group A: 318.1 ± 31.42 m, Group B: 201.7 ± 34.5 m; $p$=0.035). Women in Group B also had a significantly longer post-menopausal years than Group A (Group A: 9.3 ± 4.3, Group B: 25.9 ±2.1; $p$=0.029). Otherwise, no significant difference in other demographic variables was found between the two groups.

At the 4% site, the decline in total vBMD ($p$=0.009), trabecular vBMD ($p$=0.001) and estimated bone strength ($p$=0.006) on the paretic side was significant only in Group A, but not Group B. Of these, the decline in trabecular vBMD and estimated bone strength was beyond the LSC values. On the non-paretic side, both Group A and B sustained a statistically significant decline in total vBMD (Group A: $p$=0.003; Group B: $p$=0.006) and trabecular vBMD (Group A: $p$=0.005; Group B: $p$=0.012) while Group B also had significant increase in total CSA ($p$=0.016). However, only the change in trabecular vBMD in group B was above the LSC value.

At the 66% site, significant changes were only observed in Group B on the non-paretic side, where cortical BMC ($p$=0.009) and cortical CSA ($p$=0.007) suffered significant decline. Among the two, only the decline in cortical BMC exceeded the LSC value.

At the hip, none of the 1-year percentage change values reached statistical significance in either Group A or Group B.

**Correlation with leg muscle function**

Correlation analysis was only performed for variables that showed a significant decline above the LSC values during the follow-up period. At the 4% site, it was found that more reduction in trabecular vBMD at the 4% site on the paretic side during the 1-year follow-up period was significantly associated with weaker knee muscle strength ($\rho$=0.447, $p$=0.048) and poorer CMSA score ($\rho$=0.489, $p$=0.029), but not spasticity ($\rho$=-0.162, $p$=0.495) measured at initial assessment. The correlations between the above factors and 1-year percentage change in total BMC and estimated bone strength on the paretic side, as well as in trabecular vBMD on the non-paretic side were not statistically significant ($p$>0.05).

At the 66% site, the correlation between 1-year percentage change in cortical BMC over the non-paretic side and the above factors was also not significant statistically ($p$>0.05).

## DISCUSSION

This is the first study to examine the changes in bone density and macrostructure in lower limb long bones in people after one year of stroke onset. The principal finding is that the change in bone density and strength index at the tibial distal epiphysis on the paretic side was more pronounced than that at the tibial diaphysis. The bone changes reported here were modest compared with acute and subacute stroke patients reported in previous studies.

### Differences in bone properties between stroke cases and controls

The bone outcomes measured at the three skeletal sites (tibia distal epiphysis and diaphysis, hip) were generally more compromised on the paretic than non-paretic side

at baseline. The findings are largely in line with previous cross-sectional DXA and pQCT studies comparing the bone properties in people with chronic stroke [15, 18, 19, 22]. To some degree, the side-to-side differences in bone outcomes among chronic stroke patients as reported in the current study and previous research may reflect the impact of stroke on bone health during the period between stroke onset and the time when the initial assessment was conducted. The magnitude of the side-to-side differences in bone parameters was also much lower than that in the upper limb bone sites [30–33].

**Tibial bone changes during 1-year follow-up**

The follow-up data revealed that the bone changes in the tibial distal epiphysis were more pronounced than the diaphyseal site. At the 4% site, the reduction in total BMC (-1.28%), trabecular vBMD (-1.84%) and estimated bone strength (-2.74%) on the paretic side during the follow-up period were above the LSC values. No prospective study has measured the changes in pQCT outcomes in lower limb long bones in the acute and subacute phases of stroke. Therefore, we could not determine how these values would compare with the possible changes that occur in the earlier phases of stroke recovery. However, we postulate that the changes detected at the 4% site here are more modest than earlier phases of stroke (< 1 year post-stroke). First, our sub-group analysis revealed that the changes in trabecular vBMD and estimated bone strength were significant only in those stroke patients who had sustained the stroke for 12-24 months, but not those whose stroke onset was more than 24 months, indicating a decelerating rate of bone changes at tibial epiphysis as post-stroke duration increased. Second, previous studies suggested that the changes in upper limb bone properties also showed a decelerating trend after one year of stroke onset. In the same

group of chronic stroke cases, we have previously reported that none of the pQCT outcomes at the paretic radius distal epiphysis (4% site) sustained any changes that were above the LSC values during the 1-year follow-up period [32]. In contrast, Lazoura et al. [7] showed that during the follow-up period from 3 to 12 months after stroke, the reduction in trabecular vBMD in both the paretic and non-paretic radius distal epiphyses was much more impressive, at 14.0% and 6.8%, respectively. We speculate that similar trends may also take place in the lower limb long bones. It is likely that the bone changes at the tibial distal epiphysis continue to stabilize as time progresses and reach a plateau at approximately 2 years post-stroke.

In contrast, the bone changes at the tibial diaphysis site in the paretic leg were less remarkable compared with the distal epiphyseal region. The results thus indicated that the bone changes at the tibial diaphysis had levelled off as the time of stroke onset passed the 1-year mark, earlier than what was observed at the tibial distal epiphysis. The overall results thus suggested that the distal epiphysis, a region with abundant trabecular bone, may have a more protracted course of bone changes than the diaphysis, a cortical bone site.

The findings are in contrast with the upper limb changes in the same cohort of stroke cases in a previous report [32]. In the radius, none of changes were above LSC values at the distal epiphysis whereas the diaphysis showed real decline in cortical BMC and thickness during a 1-year follow-up period. The results thus indicated that the changes in the tibia (a weightbearing bone) are distinct from those in the radius (a non-weightbearing bone) after chronic stroke.

**Changes of hip bone density during 1-year follow-up**

The decline in hip aBMD reported in this study, albeit statistically significant, did not exceed the LSC values. This is in agreement with the findings of de Brito et al. [12], who reported an overall <1% loss in paretic and non-paretic total femur and femoral neck aBMD in a group of 51 chronic stroke patients with post-stroke onset of >1 year (mean onset 33.4 months) during a mean follow-up period of 16 months. This was much less than the ~12% and ~6% loss in femoral neck BMD on the paretic and non-paretic side respectively within the first year post-stroke previously reported [7, 13]. Moreover, de Brito et al. [12] also showed that the change in hip aBMD was not significantly associated with time since stroke. Taken together, the results suggested that bone loss at the hip has largely leveled off after 1 year post-stroke.

**Correlation with muscle function**

Strong relationship between muscle strength/mass and bone strength index of the paretic tibia amongst chronic stroke patients has been reported in previous cross-sectional pQCT studies [16, 17, 19]. For the first time, we demonstrated in a longitudinal study that those who had weaker knee muscle strength and poorer leg motor recovery had more substantial decline in trabecular vBMD at the 4% tibial site on the paretic side during the 1-year follow-up period. The results thus highlight the potential importance of muscle strengthening in promoting bone health/preventing bone loss in individuals with chronic stroke. A recent systematic review revealed that research on exercise intervention on lower limb bone health is scarce, with only one randomized controlled trial [34]. In that particular chronic stroke trial, it was found that a multidimensional exercise program incorporating muscle strengthening and impact exercises successfully maintained paretic hip aBMD, increased cortical

thickness at the tibial diaphysis and trabecular BMC at the distal epiphysis relative to the control group after 5 months of training [27, 35]. In addition, a non-randomized controlled trial in chronic stroke patients reported a significant gain in cortical thickness measured at the tibial diaphysis in the paretic leg after 6 months of treadmill gait training. More research is required to further evaluate the optimal exercise protocols for preventing bone loss and detrimental structural bone changes in the chronic stage of stroke.

Interestingly, spasticity did not have a significant relationship with bone changes. The results from previous cross-sectional studies are mixed, with some studies reporting significant relationship between spasticity and BMD/bone strength indices in lower limb long bones among chronic stroke patients [17], but not others [14, 19, 22]. This is in contrast with the findings of de Brito et al. [12], which is the only prospective study that evaluates bone changes after the first year post-stroke. They found that those who had more substantial spasticity (MAS score ≥2) had greater risk of sustaining significant bone loss of the total femur (OR=9.75, 95% CI=1.52, 62.6), compared with those without significant spasticity (MAS sore <2). However, their data should be interpreted with caution, as the overall change in paretic total femur aBMD was marginal (<1%), with only a small proportion of their participants (22.6%) having sustained bone loss at that skeletal site [12]. The characteristics of the participants also differed. Over 40% of the stroke cases were taking alendronate whereas none of our subjects were taking prescribed medications for treating osteoporosis. Another potential explanation of the non-significant finding in our study may be related to the use of MAS to measures spasticity. The MAS is only a 6-point ordinal scale and may not adequately differentiate individuals with different degree of

spasticity [36]. The relatively small sample size, and hence reduced statistical power, may also contribute. Moreover, the relationship between spasticity and bone changes may not be a straightforward one. While spasticity may impair leg function and functional activities such as walking [23, 37], may thus have detrimental effect on bone, mechanical loading as a result of spasticity may have a protective effect. It is unknown whether a threshold of spasticity exists above which detrimental effects on bone occurs. The relationship between spasticity and bone changes warrants further investigations.

**Limitations**

The results reported in this study reflect the bone changes in stroke patients who had regained their ambulatory function. These individuals were also quite physically active as attended regular activities in a community self-help group. The results thus cannot be generalized to those patients who suffered from a severe stroke and failed to regain their ambulatory function. Further study on people with severe stroke is needed, as the time course and characteristics of bone changes may be very different. As we were interested in studying bone changes in chronic stroke, the effects of stroke on bone during the acute and subacute phases were not evaluated. We thus could not determine whether the bone changes observed in this study were indeed attenuated compared with earlier phases of stroke recovery in the same individuals. Finally, the sample size was not large enough for us to perform multivariate analysis to identify the determinants of bone changes.

**Conclusion**

Despite the apparent attenuation of bone loss in the chronic stage of stroke, the tibial distal epiphysis still suffered significant bone loss between 12 and 24 months post-stroke, resulting in reduced bone strength index. Such changes were significantly associated with knee muscle strength and leg motor recovery measured at baseline. Further research should explore the possibility of modifying these factors in the endeavor to prevent bone loss in this patient population.

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**COMPETING INTERESTS**

No competing interests

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