Endocrine late sequelae in long-term survivors of childhood non-Hodgkin lymphoma

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Received 12 July 2011; revised 30 August 2011; accepted 23 September 2011

Background: Aim of this study was to investigate the long-term endocrine effects of treatment of childhood non-Hodgkin lymphoma (NHL).

Patients and methods: A single-center cohort of 84 survivors (22 females) was included in this retrospective study. Median age was 21 years (9–40 years) and time after cessation of therapy 12 years (4–30 years). Height, weight, percentage fat, lean body mass (LBM), bone mineral content (BMC), bone mineral density of total body (BMD_{TB}) and bone mineral density of lumbar spine (BMD_{LS}) were measured. Thyroid-stimulating hormone (TSH), free thyroxin (FT4),

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insulin-like growth factor-1 (IGF-1), inhibin B and anti-müllerian hormone (AMH) levels were measured. Results were compared with Dutch controls.

Results: Height was lower in survivors [mean standard deviation score (SDS) $-0.36$, $P = 0.002$], but further analysis showed that shorter stature was already present at diagnosis (mean SDS $-0.28$, $P = 0.023$). Body mass index, percentage fat, BMC, BMD$_{TB}$ and BMD$_{LS}$ were not different from controls. LBM was lower in survivors (mean SDS $-0.47$, $P = 0.008$). TSH, fT4 and IGF-1 were normal in all survivors. Three of 20 adult females had low AMH levels and 23 of 42 adult males had low inhibin B levels.

Conclusions: Twelve years after cessation of treatment, NHL survivors did not develop adiposity, osteoporosis or thyroid disease. Male survivors may be at risk for infertility.

Key words: anthropometry, bone mineral density, endocrine sequelae, fertility, late effects, non-Hodgkin lymphoma

introduction

Six percent of children with a malignancy suffer from non-Hodgkin lymphomas (NHLs) [1]. Currently, the 5-year survival for childhood NHL is ~80%. Because of this high survival rate and since treatment is administered in a growing and developing individual, long-term side-effects are an important issue. Treatment of NHL consists of intensive chemotherapy, in rare cases combined with radiotherapy. Treatment schedules involve high doses of corticosteroids, which may cause reduced bone mineral density, osteoporosis and obesity [2]. Both normal and decreased bone mineral density (BMD) have been reported in long-term survivors of other malignancies treated with chemotherapy including corticosteroids [3–9]. In addition, altered body composition, especially obesity, was observed during and after treatment of acute lymphoblastic leukemia (ALL) [10–19]. Other endocrine or metabolic sequelae that have been described in NHL and ALL survivors are growth hormone deficiency, hypothyroidism, insulin resistance and dyslipidemia [18–20]. Moreover, infertility or impaired reproductive outcome has been described in survivors of childhood cancer [21–25].

So far, studies on endocrine long-term effects in survivors of childhood NHL are scarce and often limited by small sample sizes or by the fact that data of NHL survivors have been combined with that of survivors of other malignancies [20, 26–31]. Therefore, we investigated endocrine late sequelae after childhood NHL in a single-center cohort.

patients and methods

patients

We identified all survivors who were alive and ≥24 years after cessation of therapy on 1 January 2009 and were treated for childhood non-B-NHL, B-cell type lymphoma (B-NHL) or large-cell anaplastic lymphoma (LCAL) at the Erasmus Medical Centre-Sophia Children’s Hospital from 1975 to 2003. Survivors that visited the Late Effects Registration (LATER) outpatient clinic were eligible for analysis. The local ethical committee approved the study and consent according to the Helsinki Declaration was obtained [32]. Outpatient clinic visits and performance of dual-energy X-ray absorptiometry (DXA) scans took place from July 2003 to November 2008. As they received similar treatment regimens, the LCAL survivors will be analyzed together with the B-NHL group. Baseline characteristics and treatment details of survivors are summarized in Table 1.

anthropometry

Height was measured using a Harpenden stadiometer and compared with Dutch normative values [33]. Height of survivors of other ethnicities was compared with normative values for these ethnicities [34, 35]. No data on target height were available. Weight was measured on a standard clinical balance. Body mass index (BMI) was calculated as weight (kg)/(height (m))$^2$. BMI of survivors <20 years was compared with Dutch normative values for this age group [31]. BMI of survivors of other ethnicities was compared with normative values for these ethnicities [34, 35]. BMI of survivors aged ≥20 years was compared with Dutch normative values of the MORGEN (Monitoring Project on Risk Factors and Health in the Netherlands) study, a large epidemiologic study conducted in The Netherlands from 1993 to 1997, in which 10 219 males and 12 139 females aged 20–59 years were registered [36]. Reference values of subjects aged 20–40 years in the MORGEN study, i.e. 9126 subjects (5103 females), were used because all our survivors were <40 years.

body composition and bone mineral density

Bone mineral density of total body (BMD$_{TB}$) and bone mineral density of lumbar spine (BMD$_{LS}$) were measured using DXA scan (Lunar Prodigy, Madison, WI). To correct for bone size, we calculated bone mineral apparent density of the lumbar spine (BMD$_{ADLS}$), as described by Kroger et al [37]. A DXA scan of the total body also assesses body composition, i.e. lean body mass (LBM) in grams, percentage fat and bone mineral content (BMC) in grams.

The results of survivors that were <20 years were compared with those for a control group consisting of 444 healthy children and young adults (256 females) measured on the Lunar DPX-L device [38]. Because outcomes of Lunar Prodigy and Lunar DPX-L can differ, a formula, derived from simultaneous measurements on Prodigy and DPX-L in healthy individuals, was used to enable comparison of outcomes. The results for the survivors that are aged ≥20 years were compared with those for a control group consisting of healthy young adults [58 males and 83 females; median age 23 years (range 18–37 years)], who were measured on the Lunar Prodigy device [3].

laboratory measurements

All blood samples were taken during regular consultation at the LATER outpatient clinic. Blood samples were processed within 2 h after withdrawal, and serum was stored at $-20^\circ$C until assay. Free thyroxin (fT4) levels were measured by chemoluminescence assays (Vitros ECI immunodiagnostic system; Ortho Diagnostics, Rochester, NY). Normal values, determined in our laboratory, were 11–25 pmol/L (interassay variability coefficient (VC) % 4.7%–5.4%) for fT4. The normal values for thyroid-stimulating hormone (TSH) are 0.4–4.3 mU/L (interassay VC% 2.5%–4.1%). Insulin-like growth factor-1 (IGF-1) and TSH levels were assessed according to the Immulite 2000 (Diagnostic Products Corp., Los Angeles, CA). Age-adjusted normal values for IGF-1 were used.
to calculate standard deviation scores (SDSs), according to Elmlinger et al. [39]. Anti-müllerian hormone (AMH) levels <1.0 µg/l are considered abnormal. AMH was measured using an in-house double-antibody enzyme-linked immunosorbent assay; intra- and interassay coefficients of variance (CVs) were <10% and <5%, respectively [40, 41]. The reference values of follicle-stimulating hormone (FSH) and inhibin B for male adults in our institute are 2.0–7.0 U/l and 150–400 ng/l, respectively. Within-assay and between-assay CVs for FSH were 5% and <10%, and for inhibin B 9% and 15%, respectively [42]. The cut-off value of 150 ng/l for inhibin B is taken as it has been shown that this provided the highest sensitivity and specificity in identifying low semen quality [43].

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of NHL survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHL survivors</strong></td>
</tr>
<tr>
<td>N (male/female)</td>
</tr>
<tr>
<td>Age at follow-up (years)*</td>
</tr>
<tr>
<td>Age at diagnosis (years)*</td>
</tr>
<tr>
<td>Duration of treatment (months)*</td>
</tr>
<tr>
<td>Follow-up time (years)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specification of chemotherapy</th>
<th>n (%)</th>
<th>TCD (mg/m²)</th>
<th>n (%)</th>
<th>TCD (mg/m²)</th>
<th>n (%)</th>
<th>TCD (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>79 (94)</td>
<td>15 000 (1500–30 000)</td>
<td>31 (97)</td>
<td>6900 (1500–20 000)</td>
<td>48 (92)</td>
<td>15 000 (1500–30 000)</td>
</tr>
<tr>
<td>Vincristine</td>
<td>78 (93)</td>
<td>11 (2–141)</td>
<td>32 (100)</td>
<td>18 (7–141)</td>
<td>46 (88)</td>
<td>9 (2–25)</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>76 (90)</td>
<td>1800 (1000–42 500)</td>
<td>28 (88)</td>
<td>3000 (1200–9800)</td>
<td>45 (87)</td>
<td>1800 (1000–42 500)</td>
</tr>
<tr>
<td>Corticosteroidsb</td>
<td>71 (85)</td>
<td>3413 (710–28 670)</td>
<td>30 (94)</td>
<td>4407 (1840–26 490)</td>
<td>39 (75)</td>
<td>1418 (700–28 670)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>65 (77)</td>
<td>180 (60–480)</td>
<td>29 (91)</td>
<td>280 (160–480)</td>
<td>36 (69)</td>
<td>180 (60–480)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>69 (82)</td>
<td>5500 (360–16 200)</td>
<td>18 (56)</td>
<td>3000 (2000–6000)</td>
<td>51 (98)</td>
<td>5800 (360–16 200)</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>9 (11)</td>
<td>12 000 (4000–16 000)</td>
<td>1 (3)</td>
<td>4000 (NA)</td>
<td>8 (15)</td>
<td>120 000 (6000–16 000)</td>
</tr>
<tr>
<td>Busulfan</td>
<td>1 (1)</td>
<td>480 (NA)</td>
<td>0</td>
<td>NA</td>
<td>1 (2)</td>
<td>480 (NA)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>1 (1)</td>
<td>140 (NA)</td>
<td>0</td>
<td>NA</td>
<td>1 (2)</td>
<td>140 (NA)</td>
</tr>
</tbody>
</table>

*Median (range).

bTCD prednisone plus TCD dexamethasone (dexamethasone was converted to prednisone using factor 6.67).

NHL, non-Hodgkin lymphoma; LCAL, large-cell anaplastic lymphoma; TCD, total cumulative doses; NA, not applicable.

anthropometry

Height and weight measurements were available in all survivors (N = 84). BMI was within the normal range in survivors and height was lower compared with controls (Table 2). Males and females were not different with respect to BMI (mean SDS −0.01 versus 0.21, P = 0.434) or height (mean SDS −0.43 versus −0.16, P = 0.279); however, male survivors reached a lower height compared with controls (mean SDS −0.43, P = 0.002). Non-B-NHL survivors and B-NHL/LCAL survivors were not different with respect to BMI (mean SDS −0.08 versus 0.13, P = 0.409) and height (mean SDS −0.41 versus mean SDS −0.32, P = 0.705). BMI and height of six patients treated with radiotherapy (including two patients who were treated with bone marrow transplantation) were not different from those of Dutch normative values. In linear regression analysis with height (SDS) as dependent variable, age at follow-up, sex and type of NHL were not significant (Table 3). We additionally carried out a longitudinal analysis to investigate height at different time points, namely at diagnosis; 6 months after diagnosis and 1, 3, 5 and 10 years after diagnosis. Interestingly, height was already significantly lower in NHL survivors as compared with healthy controls at diagnosis (mean SDS −0.28, P = 0.023) and continued to be low at all investigated time points (P < 0.001).
18 February 2018

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versus 0.23, survivors did not differ in percentage fat (mean SDS 0.00 males (mean SDS compared with healthy controls, LBM was significantly lower (mean SDS 2 versus 0.15, P = 0.14, P = 0.08, B-NHL/LCAL survivors were not different with respect to BMDTB (mean SDS 0.14) 0.002). Radiotherapy N=5

Table 2. Anthropometry, body composition and bone mineral density in NHL survivors

<table>
<thead>
<tr>
<th>Mean SDS (95% CI)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>All survivorsb</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.05 (−0.20 to 0.29)</td>
</tr>
<tr>
<td>Height</td>
<td>−0.36 (−0.58 to −0.14)</td>
</tr>
<tr>
<td>Survivors with a DXA scan availablec</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.03 (−0.25 to 0.31)</td>
</tr>
<tr>
<td>Height</td>
<td>−0.34 (−0.62 to −0.05)</td>
</tr>
<tr>
<td>% fat</td>
<td>0.19 (−0.05 to 0.43)</td>
</tr>
<tr>
<td>LBM</td>
<td>−0.47 (−0.81 to −0.13)</td>
</tr>
<tr>
<td>BMC</td>
<td>−0.12 (−0.49 to 0.25)</td>
</tr>
<tr>
<td>BMDTB</td>
<td>−0.17 (−0.52 to 0.19)</td>
</tr>
<tr>
<td>BMDLS</td>
<td>−0.08 (−0.41 to 0.24)</td>
</tr>
<tr>
<td>BMADLS</td>
<td>−0.04 (−0.32 to 0.41)</td>
</tr>
</tbody>
</table>

aCompared with healthy controls.
bAll NHL survivors (N = 84).
cNHL survivors with a DXA scan available (N = 56).

BM, body mass index; BMC, bone mineral content; BMDTB, bone mineral density of the total body; BMDLS, bone mineral density of the lumbar spine; BMADLS, bone mineral apparent density of the lumbar spine; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; LBM, lean body mass; NHL, non-Hodgkin lymphoma; SDS, standard deviation score.

body composition

DXA scans were carried out in 56 survivors (16 females). Sex, age at follow-up, age at diagnosis and type of NHL were not significantly different between survivors with and without a DXA scan available. Percentage fat and BMC were normal in survivors (Table 2). LBM in survivors was significantly lower (mean SDS −0.47, P = 0.008) compared with controls. LBM is measured in grams and is therefore highly correlated with height (R = 0.76, P < 0.001). Linear regression analysis with height (SDS) as dependent variable carried out in the subgroup of survivors with a DXA scan available confirmed this relationship (Table 3). Males and females were not different with respect to percentage fat (mean SDS 0.13 versus 0.36, P = 0.405), LBM (−0.49 versus −0.41, P = 0.839) and BMC (mean SDS −0.15 versus −0.04, P = 0.794). However, compared with healthy controls, LBM was significantly lower in males (mean SDS −0.49, P = 0.008). Non-B-NHL and B-NHL survivors did not differ in percentage fat (mean SDS 0.00 versus 0.23, P = 0.448), LBM (mean SDS −0.67 versus −0.35, P = 0.433) and BMC (mean SDS −0.57 versus 0.18, P = 0.098), but compared with normal controls, non-B-NHL survivors had a lower LBM (P = 0.017), whereas B-NHL/LCAL survivors did not (P = 0.161).

bone mineral density

BMDTB, BMDLS and BMADLS in NHL survivors were not different from healthy controls (Table 2). Males and females were not different with respect to BMDTB (mean SDS −0.06 versus −0.44, P = 0.350), BMDLS (mean SDS −0.05 versus −0.18, P = 0.362) or BMADLS (mean SDS 0.07 versus −0.03, P = 0.801). Non-B-NHL and B-NHL/LCAL survivors were not different with respect to BMDTB (mean SDS −0.42 versus 0.04, P = 0.201), BMDLS (mean SDS −0.18 versus −0.00, P = 0.589) or BMADLS (mean SDS −0.09 versus 0.15, P = 0.504).

laboratory measurements

TSH measurements were assessed in 68 survivors and fT4 measurements in 67 survivors. TSH [mean 1.45 mU/l, 95% confidence interval (CI) 1.26–1.64] and fT4 levels (mean 16.5 pmol/l, 95% CI 15.8–17.1) were within the normal range in all survivors. None of the survivors were treated with thyroid hormones. None of the 71 survivors had IGF-1 SDS lower than −2 or higher than 2, which are considered to be abnormal. However, IGF-1 SDSs tend to be low in this group of NHL survivors (mean SDS −0.35, P = 0.04, P = 0.794). However, FSH levels, of whom 16 (38%) had AMH levels <1.0 µg/l. Additionally, FSH levels were high and correlated with low inhibin B levels (R = 0.70, P < 0.001). In univariate analysis, cumulative dose of administered cytarabine was significantly higher in survivors with low inhibin B versus survivors with normal inhibin B. Age at diagnosis and cumulative dose of cyclophosphamide, which have been reported to influence fertility in survivors, were not significantly higher in survivors with low inhibin B. Because of its known relation with infertility, we also calculated the alkylating agent dose by use of tertiles, as described by Green et al. [21, 22]. This enabled us to take into account the effect not only of cyclophosphamide but also of ifosfamide, busulfan and melphalan, alkylating agents that were administered in our group of NHL survivors. In linear regression analysis, after...
growth hormone deficiency did not play an important role in survivors having IGF-1 SDS lower than normal. Height compared with healthy controls, none of the 71 survivors treated with cranial radiotherapy [25, 48], most likely caused not only by direct pituitary damage resulting from cranial irradiation but also by hypothalamic damage. However, growth hormone deficiency has also been described in survivors not treated with radiotherapy [46]. Growth hormone deficiency can contribute to reduced height, obesity and osteopenia or osteoporosis. Although our survivors had a significantly lower absolute weight of tissue not including fat and bone. Lower adult height has been observed in ALL survivors [12, 44–47], and a correlation has been observed between cranial radiotherapy and reduced height. Some studies observed a correlation between chemotherapy and height [46, 47], but this is regarded as controversial. We observed height to be lower in NHL survivors 12 years after cessation of therapy, in particular in male survivors. However, as height was already low at diagnosis, it is unlikely that this is due to administered treatment. Growth hormone deficiency is a frequently occurring phenomenon in survivors of childhood cancer, especially in survivors treated with cranial radiotherapy [25, 48], most likely caused not only by direct pituitary damage resulting from cranial irradiation but also by hypothalamic damage. However, growth hormone deficiency has also been described in survivors not treated with radiotherapy [46]. Growth hormone deficiency can contribute to reduced height, obesity and osteopenia or osteoporosis. Although our survivors had a significantly lower height compared with healthy controls, none of the 71 survivors had IGF-1 SDS lower than –2, which suggests that growth hormone deficiency did not play an important role in our NHL survivors. However, it is noticeable that IGF-1 SDSs tend to be low in our group of survivors. Although a low IGF-1 level is a reasonable indicator of growth hormone deficiency, a normal IGF-1 will not rule out growth hormone deficiency. For this, a dynamic assessment of growth hormone is necessary. Since this is a retrospective study, we were not able to assess these dynamic tests. It should, moreover, be considered that these tests are more invasive for the survivors, taking consuming and therefore expensive.

Adiposity has been frequently reported not only in leukemia but also in lymphoma survivors [11, 30, 31]. In the present study, we found normal BMI and normal percentage fat in NHL survivors. Hypothyroidism, which can contribute to obesity and is reported in survivors, especially after local radiotherapy [49–51], did not occur in this group of survivors.

In patients treated for childhood cancer, treatment can have a deleterious effect on the acquisition of peak bone mass, with height being correlated to reduced height in long-term survivors of childhood NHL. We observed a lower absolute LBM and a shorter stature in NHL survivors 12 years after cessation of therapy. The lower LBM can be explained by the shorter stature of the survivors as LBM is described by an absolute weight of tissue not including fat and bone. Lower adult height has been observed in ALL survivors [12, 44–47], and a correlation has been observed between cranial radiotherapy and reduced height. Some studies observed a correlation between chemotherapy and height [46, 47], but this is regarded as controversial. We observed height to be lower in NHL survivors 12 years after cessation of therapy, in particular in male survivors. However, as height was already low at diagnosis, it is unlikely that this is due to administered treatment.

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### discussion

The present study describes endocrine late sequelae in long-term survivors of childhood NHL. We observed a lower absolute LBM and a shorter stature in NHL survivors 12 years after cessation of therapy. The lower LBM can be explained by the shorter stature of the survivors as LBM is described by an absolute weight of tissue not including fat and bone. Lower adult height has been observed in ALL survivors [12, 44–47], and a correlation has been observed between cranial radiotherapy and reduced height. Some studies observed a correlation between chemotherapy and height [46, 47], but this is regarded as controversial. We observed height to be lower in NHL survivors 12 years after cessation of therapy, in particular in male survivors. However, as height was already low at diagnosis, it is unlikely that this is due to administered treatment.

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In patients treated for childhood cancer, treatment can have a deleterious effect on the acquisition of peak bone mass, subsequently increasing the risk of fractures at an older age. Reduced BMD has been described in adolescent and adult NHL survivors after stem-cell transplantation [52] and in childhood NHL survivors after chemotherapy combined with cranial radiotherapy [9, 29]. In our study, which is the largest cohort of long-term childhood NHL survivors, BMD_{TB} and BMD_{LS} were within the normal range. BMD_{LS} was still normal after correction for bone size (BMADLS). This was in concordance with the findings in long-term survivors of childhood ALL [9]. When interpreting these results, one should consider the retrospective nature of this study and the small sample sizes of the subgroups. However, as the majority of our NHL survivors were treated with chemotherapy only, these results seem comprehensible.

Infertility has been frequently reported in childhood cancer survivors [21–23]. Additionally, low AMH or inhibin B levels, which are fertility markers, have been reported [24, 25]. Notorious for causing infertility are abdominal radiotherapy and alkylating chemotherapeutic agents, like cyclophosphamide [21, 22]. Moreover, cytarabine has been described to contribute to gonadal damage in survivors of adult acute myeloid leukemia [53]. However, this was not confirmed in female childhood cancer survivors [21] and in male childhood cancer survivors, even a reversed effect was described [22]. In the present study, 3 of 20 adult female survivors had abnormal AMH levels. Two of three received both cyclophosphamide and cytarabine; however, none of them received cranial or...
abdominal radiotherapy. Interestingly, inhibin B levels were low in 55% of adult male survivors. High FSH levels in these survivors confirm that this is not a problem of pituitary or hypothalamus but of local origin. After correction for age at diagnosis and total cumulative dose of alkylating agents, cytarabine had a significant negative effect on inhibin B levels in adult males. Although groups are small and results should therefore be interpreted with caution, this effect seems substantial and has not been reported previously. Our results contradict those of Green et al. [22], which may be due to differences in reported outcomes (siring a pregnancy versus fertility markers). Inhibin B is a relatively new fertility marker but has been shown to be the most reliable serum marker for spermatogenesis [43, 54–57]. Prospective studies are needed to confirm these data, preferably with larger cohorts and including both inhibin B measurements and sperm analysis.

In conclusion, long-term childhood NHL survivors, especially males, have a shorter stature that seems to be determined by height at diagnosis and not by treatment-related side-effects. Otherwise, this study shows that long-term childhood NHL survivors do not seem to be at risk for endocrine late sequelae like osteoporosis, obesity and hypothyroidy. However, especially males might be at risk for gonadal damage, which may be related to the cumulative dose of cytarabine. To evaluate gonadal damage both in male and female NHL survivors, prospective studies of larger cohorts are required.

**Acknowledgements**

The authors would like to thank Wim C. J. Hop from the Department of Biostatistics for his valuable suggestions and comments and Manita M. P. G. M. van Baalen from the Department of Pediatric Oncology for helping recruiting data. Authorship—MMvdH-E was the principal investigator and takes primary responsibility for the paper. MvW participated in the statistical analysis. SJCMMN, RP and MH coordinated the research. MvW, SJCMMN and MMvdH-E wrote the paper. SJCMMN, MtW, AB, RP and MMvdH-E were involved in drafting and revising the article.

**Funding**

KiKa (Kinderen Kankervrij: 2009-030); Kinderoncologisch Centrum Rotterdam.

**Disclosure**

The authors declare no conflict of interest.

**References**


