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Sodium ($^{23}\text{Na}$) MRI detects elevated muscular sodium concentration in Duchenne muscular dystrophy

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ABSTRACT

Objective: In boys with Duchenne muscular dystrophy (DMD), $^1\text{H}$ MRI suggested muscular edema before fatty degeneration. Using specific $^{23}\text{Na}$ MRI sequences, we tested the hypothesis that the edema is caused by an osmotic effect due to increased myoplasmic Na$^+$ content rather than inflammation that would lead to extracellular edema.

Methods: Eleven patients with DMD (mean age, 10 ± 5 years) and 1.6 healthy volunteers of similar age were examined on a 3-T system with $^1\text{H}$ MRI and $^{23}\text{Na}$ density-adapted 3-dimensional radial MRI sequences. The muscle edema was quantified on short-tau inversion recovery images using background noise as reference. Fatty degeneration was quantified on T1-weighted images using subcutaneous fat as reference. Na$^+$ was quantified by a muscular tissue sodium concentration (TSC) sequence. A novel inversion recovery (IR) sequence allowed us to determine mainly the myoplasmic Na$^+$ by suppression of the extracellular $^{23}\text{Na}$ signal from vasogenic edema. A reference tube containing 51.3 mmol/L Na$^+$ with agarose gel was used for standardization.

Results: The normalized muscular signal intensity of $^{23}\text{Na}$ as assessed by the IR sequence was significantly higher for patients with DMD than for volunteers. TSC was markedly increased at 38.4 ± 6.8 mmol/L in patients with DMD compared with 25.4 ± 2.1 mmol/L in volunteers. The muscular edema-like changes were much more prominent in patients with DMD than in volunteers. In addition, the muscular fat content was significantly higher in patients with DMD than in volunteers.

Conclusions: The elevated myoplasmic Na$^+$ concentration in DMD is osmotically relevant and causes a mainly intracellular muscle edema that contributes to the pathogenesis of DMD. Neurology® 2011;77:2017–2024

GLOSSARY

DMD = Duchenne muscular dystrophy; HypoPP = hypokalemic periodic paralysis; IR = inversion recovery; MRC = Medical Research Council; ROI = region of interest; SI = signal intensity; SNR = signal/noise ratio; STIR = short-tau inversion recovery; TA = acquisition time; TE = echo time; TR = repetition time; TSC = tissue sodium concentration.

Duchenne muscular dystrophy (DMD) manifests as progressive muscle degeneration with intramuscular fatty degeneration as the principal finding. Edema-like muscular changes, which may be inflammatory-mediated and mainly extracellular or osmotically driven and mainly intracellular, have been reported in some patients with DMD.

A recent study reported on increased myocellular Na$^+$. The absence of dystrophin modifies the expression level, distribution, and gating properties of the skeletal muscle isoform of the voltage-gated Na$^+$ channel, Na$_{\text{v}}$ 1.4, leading to an abnormally high Na$^+$ concentration under the sarcolemma in myotubes of mdx mice, which is strongly correlated with increased cell death in mdx fibers. Both cell death and Na$^+$ overload can be reversed by the specific Na$^+$ channel blocker tetrodotoxin.

These studies suggest that Na$^+$ homeostasis may play a role in the pathogenesis of the progressing muscle degeneration in DMD. This pilot study evaluates in DMD whether edema-
like muscular changes are regularly present and whether muscular Na\(^+\) content is elevated and therefore potentially explains an intramyocellular edema. An exchange of Na\(^+\) for Ca\(^+\) may account for the subsequent cascade resulting in cell death.\(^4\)

Because the muscular 3-T 23Na MRI signal is up to 50,000 times smaller than the signal received from standard proton (1H) MRI because of the short T2 relaxation time of 23Na causing a low signal/noise ratio (SNR), we used new density-adapted 3-dimensional radial acquisition techniques at 3 T with utmost SNR gain\(^2\) and weighting toward the intracellular 23Na signal\(^8\) to assess quantitatively in vivo whether the Na\(^+\) concentration is increased in patients with DMD compared with that in healthy volunteers.

**METHODS**  
*Standard protocol approvals, registrations, and patient consents.* The study was approved by the local review board and conducted according to the Declaration of Helsinki in the present form. Written informed consent was obtained from all participants.

*Patients and volunteers.* Eleven patients (10 boys and 1 woman having a X-chromosomal translocation; for a detailed genetic report, see appendix e-1 on the Neurology® Web site at www.neurology.org) with genetically proven DMD (mean age 10 ± 5 years) were included prospectively in this study (table 1). The control group included 16 healthy volunteers without any evidence of muscular or cardiovascular disorders (mean age 16 ± 9 years). All volunteers had full muscle strength at physical examination and presented regular findings on 1H MRI. Of all study participants, only 5 of the 11 patients with DMD were treated with glucocorticoids (table 1).

*Patient examination protocol.* 1H and 23Na MRI were performed on both calves in all subjects and also on both lower forearms and hands in one boy with DMD (patient 10 in table 1) with complete fatty degeneration of lower leg muscles on a 3-T clinical magnetic resonance system (MAGNETOM Trio; Siemens, Erlangen, Germany). Specific hardware for broadband spectroscopy and a CE-certified double-resonant birdcage coil (32.59 MHz/123.2 MHz; Rapid Biomed Inc., Würzburg, Germany) were used for the 23Na and 1H measurements. All subjects tolerated the whole MRI examination well except for one 10-year-old boy with DMD (patient 8) who ended the examination before the first sequence because of claustrophobia despite the fact that both parents were present.

*Muscle strength grading.* Muscle strength was quantified immediately after the MRI examination using the nonlinear grading system defined by the British Medical Research Council (MRC)\(^7\) and included strength testing of foot dorsiflexion and plantarflexion and hip and knee flexion and extension.

**MRI protocol.** The imaging protocol comprised axial T1-weighted turbo spin-echo (repetition time [TR]/echo time [TE] = 700/10 msec; matrix of 275 × 448; section thickness of 3 mm) and axial short-tau inversion recovery (STIR) (TR/TE = 6920/65 msec; matrix of 176 × 320; section thickness of 4 mm) 1H MRI sequences to detect edema-like and lipomatous muscular changes. Then, 2 23Na pulse sequences based on a density-adapted 3-dimensional radial sequence\(^5\) were performed with an ultrashort TE of less than 0.5 msec to minimize T2* weighting, because the 23Na T2* signal decays biexponentially with a fast component of 0.5 to 3 msec.\(^8\) The first sequence was a spin-density image contrast (TE/TR = 0.3/100 msec; α = 90°; voxel...
size of $5 \times 5 \times 5 \text{ mm}^3$; acquisition time [TA] = 8 minutes 20 seconds) to quantify the muscular tissue sodium concentration (TSC), and the second sequence was an inversion recovery (IR) sequence\(^6\) to suppress the $^{23}\text{Na}$ signal emitted by free Na\(^{+}\) ions (e.g., CSF or vasogenic edema, as well as the $^{23}\text{Na}$ signal received from the extracellular space) to achieve a weighting toward intracellular $^{23}\text{Na}$ (TE/TR = 0.3/124 msec; inversion time = 34 msec; voxel size of $6 \times 6 \times 6 \text{ mm}^3$; TA = 10 minutes 20 seconds).\(^{6}\)

**Analysis of $^{23}\text{Na}$ and $^1\text{H}$ MRI data.** A radiologist with 11 years of experience in musculoskeletal MRI analyzed the $^{23}\text{Na}$ radial MRI scans by positioning regions of interest (ROIs) on different muscles of the subject’s lower leg. For exact positioning, the $^1\text{H}$ MRI scans were used as reference. When distinct lipomatous degeneration of certain muscles was observed on $^1\text{H}$ MRI, the ROIs were positioned in an area of more intact muscle (e.g., tibialis posterior instead of soleus muscle in patient 10). Supplementary ROIs were placed on 2 reference phantoms, one filled with 51.3 mmol/L Na\(^{+}\) in saline solution to imitate Na\(^{+}\) with unrestricted mobility (e.g., within extracellular fluid) and one filled with 51.3 mmol/L Na\(^{+}\) in 5% agarose gel to imitate Na\(^{+}\) with restricted mobility (e.g., within the cytoplasm). With the selected inversion time of the IR $^{23}\text{Na}$ sequence, complete signal suppression of a reference tube filled with 51.3 mmol/L Na\(^{+}\) in saline solution was obtained, whereas the signal of the 51.3 mmol/L Na\(^{+}\) in agarose gel reference tube was not eliminated and used for normalization. For normalization, the ROI values positioned on the soleus muscles on the $^{23}\text{Na}$ MR images were divided by the ROI values positioned on the 51.3 mmol/L Na\(^{+}\) in the agarose gel reference tube. Given the known Na\(^{+}\) concentration of the reference tube, the average muscular TSC was calculated by linear extrapolation. Hereby, interindividual and intraindividual comparisons were permitted and the observed signal intensity (SI) was considered to mirror muscular Na\(^{+}\) concentration.

Areas of signal intensity equivalent to the signal received from subcutaneous fat on T1-weighted $^1\text{H}$ MRI scans were interpreted as fatty infiltration caused by chronic myopathy. One reader with 11 years of experience in musculoskeletal MRI scored the lipomatous degeneration with a 4-point semiquantitative visual scale according to Olsen et al.\(^{17}\) This scale rates intramuscular fat using the intensity of subcutaneous fat as reference and has been shown to correlate well with values found by automated computer analysis.\(^{10}\) Calf muscles included were the tibialis anterior compartment, the soleus, the medial and lateral gastrocnemius, the peroneal, and the deep posterior compartment muscles and were graded as follows: grade 1: homogeneous, hypointense signal, contrasting sharply with subcutaneous and intermuscular fat (normal muscle); grade 2: slightly hyperintense, patchy intramuscular signal changes (grade 3: markedly hyperintense, patchy, but widespread intramuscular signal changes; and grade 4: homogenous hyperintense signal in whole muscle, similar to the signal intensity of adjacent subcutaneous or paramuscular fat.

Areas of localized hyperintensity on STIR MRI scans were defined as muscular edema-like changes according to Marden et al.\(^{2}\) The presence of this criterion was evaluated with a four-point semiquantitative visual scale as follows: grade 1: homogeneous, hypointense signal, contrasting sharply with subcutaneous and intermuscular fat (normal muscle, no edema); grade 2: slightly hyperintense, patchy intramuscular signal changes on STIR (<50% of muscle cross-sectional area); grade 3: markedly hyperintense, patchy, but widespread intramuscular signal changes on STIR (>50% of muscle cross-sectional area); and grade 4: homogenous hyperintense signal in whole muscle on STIR (100% of muscle cross-sectional area).

Besides the qualitative image analysis, the lipomatous degeneration of the soleus muscle was quantified on T1-weighted images by the ratio of SI of muscle and subcutaneous fat tissue as reference using a ROI analysis (ROI\(_{\text{muscle}}\)/ROI\(_{\text{subcutaneous fat}}\)) according to Jurkat-Rott et al.\(^{11}\) of the same sections used for $^{23}\text{Na}$ MRI analysis. Attention was paid by the reader to avoid ROI placement in regions of the calves affected by signal inhomogeneities. Moreover, we also semiquantitatively assessed edema-like changes of the soleus muscle on STIR images according to Jurkat-Rott et al.\(^{11}\) using a ROI analysis with background noise as reference (ROI\(_{\text{muscle}}\)/ROI\(_{\text{background noise}}\)). The mean of the respective ratios was used for statistical analysis.

**Statistical analysis.** Data entry procedures and statistical analysis were performed using SPSS for Windows (version 11.5.1, 2002; SPSS Inc. Chicago, IL). Data were analyzed using a 2-tailed unpaired Student’s t test, and the effects of glucocorticoid administration were assessed using a 1-sided Student’s t test except for fatty infiltration. In all statistical tests, an effect was considered to be statistically significant if $p < 0.05$; $p$ values were not adjusted for multiple testing and interpretation of $p$ values was exploratory, given the pilot study character. Because there is an age-related progression of DMD and glucocorticoid medication is beneficial in DMD, we also performed subgroup analyses (one group aged younger than 10 years and one group aged 10 years and older, as well as one group without any glucocorticoid medication and one group receiving glucocorticoid medication).

Results are expressed as means ± SD for quantitative data and as the median and range for the MRC scale results.

**RESULTS $^{23}\text{Na}$ MRI.** In patients with DMD, the normalized muscular $^{23}\text{Na}$ SI as assessed by the IR sequence and the TSC were increased at 0.77 ± 0.13 [TSC 38.4 ± 6.8 mmol/L, n = 10] compared with 0.50 ± 0.05 [TSC 25.4 ± 2.1 mmol/L, n = 16] in volunteers ($p < 0.001$). The TSC Na\(^{+}\) content in the subcutaneous fat tissue of all individuals was low at 12.0 ± 1.0 mmol/L in patients with DMD and 12.0 ± 1.3 mmol/L in volunteers. With the $^{23}\text{Na}$ IR sequence, the $^{23}\text{Na}$ signal emitted from vasogenic edema and vessels was sufficiently suppressed (figure 1). Because there is an age-related progression of DMD, we analyzed the $^{23}\text{Na}$ MRI findings of 2 subpopulations (one group aged younger than 10 years (n = 5; mean age 6.8 ± 1.5) and 1 group aged 10 years and older (n = 5; mean age, 13.6 ± 5.0). In the older patients with DMD, the normalized muscular $^{23}\text{Na}$ SI in the IR and TSC were 0.82 ± 0.16 [TSC 39.7 ± 6.5 mmol/L] compared with 0.73 ± 0.08 ($p = 0.28$) [TSC, 37.1 ± 7.5 mmol/L ($p = 0.57$)] in the younger group.

$^1\text{H}$ MRI. Muscular edema-like changes were present in all patients with DMD, and the mean SI ratio on STIR images was increased at 14.83 ± 3.57 compared with 6.92 ± 0.65 in volunteers ($p < 0.001$) (figures 1, B, F, and J, and 2, B, F, and H). In addition, in patients with DMD muscular fat content
Edema-like changes and increased muscular sodium are present in Duchenne muscular dystrophy (DMD).

MRI of both calves of a 10-year-old boy with DMD (patient 6 in table 1; A–D), a 16-year-old healthy volunteer (E–H), and a 22-year-old woman with DMD (patient 11; I–L): (A, E, I) T1-weighted; (B, F, J) short-tau inversion recovery; (C, G, K) $^{23}$Na inversion recovery (IR); and (D, H, L) $^{23}$Na tissue sodium concentration (TSC) images. There is fatty degeneration of the triceps surae muscles in the boy (A) and muscular edema of both soleus muscles (arrows in B) compared with normal findings in the volunteer (E–H). $^{23}$Na IR (C) and TSC $^{23}$Na MRI (D) reveal elevated signal in both soleus muscles compared with those of the volunteer (G, H). The arrowheads point to the tibial bones (C, D). Note that the signal of vessels is bright on TSC $^{23}$Na MRI (arrows in H) and that the signal of the reference tube containing free 0.3% NaCl solution (arrow in C) is suppressed in the $^{23}$Na IR sequence, whereas the contralateral reference tube filled with Na$^+$ in agarose gel is well visible.

In the woman with DMD (asterisk on right soleus muscle in I–L), fatty infiltration mainly affects the peroneus muscles (arrow in I and J) in contrast with all boys studied (mainly triceps surae muscle).
was increased with an SI ratio on T1-weighted images of 0.49 ± 0.09 compared with 0.39 ± 0.01 in volunteers (p < 0.001). In healthy volunteers, there were no differences in signal intensity on STIR, T1-weighted images, and 23Na MRI scans with increasing age.

Qualitatively, the pattern of lipomatous degeneration and edema-like changes was symmetric, except...
in the 22-year-old woman with DMD (figure 1, I and J). Her right soleus muscle exhibited more intense edema. These pronounced changes resulted in shortened calf muscles on the right side (figure e-1). In patients with DMD, the triceps surae and peroneal muscles showed mostly patchy intramuscular fatty changes, whereas the tibialis anterior and the deep posterior compartment were spared (table e-1). The median score for fatty changes of all lower leg muscles of the volunteers was 1.

In all patients with DMD, the triceps surae muscles revealed the highest degree of edema-like changes, whereas the tibialis anterior and peroneal compartments were less affected (table e-2). The median score for edema-like changes of all lower leg muscles of the volunteers was 1.

**Muscle strength.** Patients with DMD presented with paresis in the lower legs at physical examination except for a 7-year-old boy with DMD (tables 1 and e-3). The paresis was symmetric except in the 22-year-old woman with DMD (patient 10 in table 1), most lower leg paresis in the lower legs at physical examination except in the 22-year-old woman with DMD (figure 2), whereas the muscles of the 22-year-old woman with DMD (patient 11) had only moderate fatty degeneration (figure 1).

**Effect of glucocorticoid medication.** Because glucocorticoid medication is beneficial in DMD, we analyzed 2 subpopulations (one group without any glucocorticoid medication (n = 5; mean age 10.8 ± 7.2 years) and one group receiving glucocorticoid medication (n = 5; mean age 9.6 ± 1.8 years). In patients with DMD without glucocorticoid medication, the normalized muscular \(^{23}\text{Na}\) SI in the IR and TSC was 0.82 ± 0.16 [TSC 41.4 ± 7.7 mmol/L] compared with 0.73 ± 0.1 (p = 0.14) [TSC, 35.4 ± 4.6 mmol/L; p = 0.09] in the treated group. In the untreated group, muscular edema-like changes were slightly higher with an SI ratio on STIR images of 16.30 ± 4.50 compared with 13.36 ± 1.76 in the group with glucocorticoid medication (p = 0.11). In the untreated group, muscular fat content was 0.43 ± 0.02 on T1-weighted images compared with 0.55 ± 0.09 in the treated group (p = 0.02).

**Effect of age on lipomatous and edema-like changes.** The lipomatous degeneration and the degree of edema-like muscular changes were clearly age-dependent (tables e-1 and e-2). Although on the median, patients with DMD younger than 10 years had normal muscles on T1-weighted MRI, the muscles of patients with DMD aged 10 years or older had markedly patchy, but widespread, intramuscular fatty changes of their lower leg muscles except the relatively spared deep posterior and tibialis anterior compartment (table e-1). In the oldest boy with DMD (age 14 years; patient 10 in table 1), most lower leg muscles had been replaced by fatty tissue with a low Na\(^{+}\) content (comparable to the low Na\(^{+}\) content of the subcutaneous fat tissue). In addition, because of the lack of residual muscle volume, edema-like changes could scarcely be detected on STIR images (figure 2), whereas the muscles of the 22-year-old woman with DMD (patient 11) had only moderate fatty degeneration (figure 1).

**DISCUSSION** In our pilot study, we demonstrated that all patients with DMD exhibit muscular edema-like changes, even in the early disease stage that shows no lipomatous muscle changes. Furthermore, with the aid of 3-T \(^{23}\text{Na}\) MRI, an elevated myoplasmic Na\(^{+}\) concentration was seen in patients with DMD compared with healthy volunteers, which may be osmotically relevant and cause the muscle edema. Our data support the hypothesis that similarly to patients with hypokalemic periodic paralysis (HypoPP) in whom both increased myoplasmic Na\(^{+}\) concentration and muscular edema have been observed by STIR \(^1\text{H}\) and \(^{23}\text{Na}\) MRI,\(^{11}\) the Na\(^{+}\) overload leads to muscle weakness and degeneration. However, the relative Na\(^{+}\) increase was not equivalent to the relative increase in STIR signal. This may be related to the fact that the applied STIR sequence does not allow for quantitative measurement of the muscular water content. Thus, the myoplasmic Na\(^{+}\) concentration and the STIR signal cannot correlate on a linear scale. There is a pathophysiologic similarity in DMD and HypoPP because both reveal a membrane leakage. In HypoPP there is an aberrant pore in the voltage sensor,\(^{12}\) and in DMD there is reduced mechanostability of the sarcolemma due to the lack of dystrophin, which may open stretch-activated cation channels as has been observed in myotubes from dystrophic \(mdx\) mice.\(^{13}\) Therefore, the intracellular Na\(^{+}\) accumulation, as indicated by our \(^{23}\text{Na}\) IR MRI results, may cause the edema-like changes in DMD. Thus, in DMD and HypoPP alike, the muscle edema might be mainly osmotic and intracellular. This mechanism differs from the conventional view that immune-mediated changes in vascular permeability produce a vasogenic edema in DMD.\(^2\) The importance of the immunologic inflammation in DMD may have been overrated. This interpretation would explain why immunosuppressive agents such as cyclosporin A had no additive value in DMD.\(^{14}\)

The glucocorticoid prednisolone has positive effects in DMD, both on muscle strength and function.\(^{1,15}\) Because the treated group in our pilot study revealed a less pronounced muscle edema, this anti-edematous effect could be one of the benefits of glucocorticoids. More patients are required to prove this hypothesis. At least glucocorticoids are known to de-
crease the edema surrounding a brain tumor and to repolarize neurons in idiopathic facial paresis.\textsuperscript{16} Removal of intracellular edema and cell repolarization could actually be related. One repolarization mechanism may be the up-regulation of 2-pore potassium channels.\textsuperscript{17} If our initial data are confirmed by expanded studies, there may be a rationale for replacing glucocorticoid medication in DMD by membrane-repolarizing diuretics such as acetazolamide. This carbonic anhydrase inhibitor has been proven to activate various potassium channels and to ameliorate edema and strength in HypoPP.\textsuperscript{11} The prednisolone regimen currently used in patients with DMD has some drawbacks: the dose is close to the Cushing threshold level with adrenocortical obesity, which further stresses the muscles in patients with DMD and has the inherent risk of leading to a glucocorticoid-induced myopathy. The therapeutic potential of carbonic anhydrase inhibitors in animal models of dystrophin-deficient muscular dystrophy has been reported recently.\textsuperscript{18} One patient in our population (patient 10 in table 1) was treated experimentally with acetazolamide (250 mg/day) for 4 weeks, and he reported an increase in muscle strength of both hands. The SI ratio on STIR images of the thenar muscle dropped from 10.4 to 9.4, but \textsuperscript{23}Na MRI was not available.

The \textsuperscript{23}Na MRI protocol included 2 special \textsuperscript{23}Na pulse sequences based on a density-adapted 3-dimensional radial sequence: With a spin-density image contrast, the total \textsuperscript{Na}\textsuperscript{+} concentration that reflects a volume-weighted average of the intracellular and extracellular \textsuperscript{Na}\textsuperscript{+} concentrations was assessed. Because the extracellular \textsuperscript{Na}\textsuperscript{+} concentration in tissue at 140 mmol/L is 10-fold higher than the intracellular \textsuperscript{Na}\textsuperscript{+} concentration at 15 mmol/L,\textsuperscript{19} the analysis of intracellular \textsuperscript{23}Na is limited when the aforementioned sequence is used. Thus, the \textsuperscript{23}Na IR sequence was also performed to suppress the \textsuperscript{23}Na signal emitted by extracellular edema and vessels.

However, one of the limitations of this study is that although the IR prepared \textsuperscript{Na}\textsuperscript{+} measurement enables weighting of the measurement toward intracellular \textsuperscript{23}Na, it would still have significant contributions from the extracellular pool and it does not provide a clear separation between intracellular and extracellular \textsuperscript{23}Na. The preliminary nature of our findings, given the low number of subjects, must be acknowledged as a limitation. However, our local review board gave consent to a pilot study and upon publication of convincing results recommended a multicentric trial to also assess therapy.

Improved imaging techniques such as \textsuperscript{23}Na MRI can provide a basis for exploring disease pathogenesis and mechanisms of action of medications. Our data show that \textsuperscript{23}Na MRI detects elevated muscular \textsuperscript{Na}\textsuperscript{+} concentration in DMD, which may be a general mechanism in muscular degeneration because it is also present in the chronic form of HypoPP. The \textsuperscript{Na}\textsuperscript{+} overload could lead to the muscle edema that was present in all patients with DMD and that seemed to be osmotic rather than inflammatory. Diuretics could be an option to decelerate dystrophy in patients with DMD and replace prednisolone if the effect of this glucocorticoid is mainly antiedematous.

**AUTHOR CONTRIBUTIONS**

Dr. Weber: design and conceptualization of the study, analysis and interpretation of the data, drafting the manuscript. Dr. Nagel: analysis and interpretation of the data, revising the manuscript. Dr. Jurkat-Rott: interpretation of the data, revising the manuscript. Dr. Lehmann-Horn: design and conceptualization of the study, interpretation of the data, revising the manuscript.

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**DISCLOSURE**

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