 INTRODUCTION

In juvenile idiopathic arthritis (JIA), pain results from a chronic inflammatory state induced by an overproduction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6 and tumour necrosis factor alpha. Historically, studies have shown that children with JIA have impaired physical fitness and muscle strength compared with healthy children and that these impairments might be at least partly associated with a chronic inflammatory state. Studies have also shown that children with JIA have impaired physical fitness and muscle strength compared with healthy children. However, the mechanisms underlying these impairments are not well understood. In this study, we assessed muscle function and functional abilities in children with JIA.
with a reduced muscle size compared with healthy children.²³ It is also possible that deficits in muscle function might be underpinned by an increase in muscular adiposity, yet this has yet to be studied in children with JIA. Muscle mass loss due to chronic inflammation may also trigger an increase in the adipose tissue between muscle bundles, that is intermuscular adipose tissue (IMAT), as observed in adults after muscle injury.² Because IMAT is used as a marker of functional and structural muscle impairment, patients with inflammatory diseases are expected to have higher IMAT. Research is required to determine whether this is the case because treatments aiming to improve muscle function may be different when the aim is to increase muscle mass vs decrease IMAT.

In specific relation to muscle strength and architecture (ie including muscle size as well as the angle and lengths of its fibres/fascicles), few data are available describing the effect of JIA. Quadriceps muscle thickness was found to be 75% and 90% of normal values in JIA children with and without local knee arthritis, respectively.³ While this makes sense, given that muscle cross-sectional area (CSA) is positively correlated to maximal strength⁷ owing to the quantity of contractile elements contained in the muscle (sarcomeres), fascicle (or fibre) angle is also an important determinant of force production and can impact muscular strength.⁸ A greater fascicle angle allows more contractile material to attach to a given area of aponeurosis as well as promote fascicle rotation during dynamic contraction, which increases force by reducing both the length change and velocity of sarcomere shortening within the muscle.⁹ Thus, a lesser fascicle angle, which is often observed in individuals with smaller muscles,¹⁰ might impact on muscle function in addition to the possible decreases in muscle size and might also underpin the reduced strength capacity of children with JIA shown in some studies.²³⁴ Accordingly, such changes might also impact performance of both monoarticular (eg leg extension) and multiarticular (eg jumping, stair walking) movements. Speculatively, a reduction in fascicle angle may also reduce fascicle rotation during muscle lengthening¹¹ and thus contribute to differences in muscle function observed during passive (eg range of motion of lower limbs) and active (eg landing technique during jumping) tasks in children with JIA compared with healthy controls.¹² However, to date, little is known about the effect of JIA on muscle force production capacity, dynamic functional performance, muscle size or architectural variables such as fascicle angle, or the relationships between these variables. It is also unclear whether the possible lack of difference in muscle strength reported in the most recent studies¹³ is observed in dynamic muscle function and muscle architectural measurements, and indeed in IMAT levels, in children who are administered modern treatment regimes (eg the biotherapy era).

Given the above, the purpose of the present study was to compare architectural parameters (muscle thickness and fascicle angle), muscle CSA, morphological parameters (IMAT), muscle force and functional capacities (vertical jump performance) between children with JIA and healthy peers matched for sex and chronological age. We hypothesised that, compared with their healthy peers, children with JIA would have lower muscle mass and higher IMAT as well as impaired muscle quality, which would be associated with decreased muscle strength and functional abilities as measured by vertical jump performance.

### Key notes

- The purpose of this study was to test the hypothesis that chronic inflammation in children with juvenile idiopathic arthritis (JIA) would impair muscle function and functional abilities.
- While muscle function was comparable between JIA and healthy children, vertical jump performance was lower in JIA children.
- Muscle function could not account for reduced jump performance in JIA children; thus, other factors such as fear of pain might impact their functional ability.

### 2 | MATERIALS AND METHODS

#### 2.1 | Participants

Fourteen children aged 8-18 years diagnosed with JIA according to the criteria of the International League of Associations for Rheumatology, and 14 healthy sex- and age-matched children took part in this cross-sectional study. To be included, volunteers had to perform ≤ 4 h/wk of recreational physical activity and be free of any medical contra-indication to physical activity.

Volunteers with diagnosed infection, those who had received oral corticosteroids within the last 3 months, or those with fever within two weeks prior to enrolment were excluded. For children with JIA, treatments were continued during the study. All treatments had been given for at least 3 months at the time of evaluation. Disease status (active or inactive) was evaluated according to American College of Rheumatology criteria.

The study was approved by the governing ethics committee (Comité de Protection des Personnes Sud-Est VI – Clinical trial number NCT 02977416). In accordance with the Declaration of Helsinki of the World Medical Association, all experimental procedures were clearly explained to the participants, who gave their written consent before testing began.

#### 2.2 | Anthropometric and maturation assessment

Body mass was assessed to the nearest 0.1 kg with a digital weight scale. Standing height was measured using a mural stadiometer with the participants barefoot. Body mass index was then calculated as mass (kg) divided by height squared (m²). Maturity status was assessed with the Tanner’s stage by the hospital paediatrician.

#### 2.3 | Physical activity level

Physical activity level was assessed by the French version of the International Physical Activity Questionnaire, which estimates
physical activity levels. Total metabolic equivalent (MET) in minutes per week was calculated as described in previous studies.\textsuperscript{14} Moderate-to-vigorous physical activity was assessed as activity >3MET min/d. Physical activity with low intensity, such as walking, was characterised as <3MET min/d.

2.4 | Muscle architecture and quality assessment

Muscle architecture of superficial thigh muscles (rectus femoris, vastus medialis and vastus lateralis) was evaluated with ultrasound (LogicScan 128 CEXT-12, Telemed) using an 8 MHz probe (focus 34 mm, depth 60 mm). Subjects lay in a prone position on a massage table. The scanning head was coated with water-soluble transmission gel. The probe was applied perpendicularly to the skin with minimal pressure to conserve muscle architecture.

Cross-sectional area (CSA) of thigh muscles and intermuscular adipose tissue (IMAT) were assessed using peripheral quantitative computed tomography (pQCT XCT 3000, Stratec Medizintechnik GmbH). The right thigh was placed in the pQCT antenna, so that the femoral condyles were in line with the laser. An anteroposterior scout-view was run to detect the junction between tibial plate and femur, which matched the starting position of the measurement. A measure was made at 40% of the length between the greater trochanter and the mid-patella of the right leg. Each tomographic slice was analysed to obtain soft tissue composition at 40% of the length using contour mode 3 (threshold -100 mg/cm\(^3\)) to locate the skin surface and peel mode 2 (threshold 40 mg/cm\(^3\)) to locate the subcutaneous fat-muscle boundary. The algorithm proposed by Schiferl\textsuperscript{15} was used. This technique allows minimisation of movement effects that could promote imaging errors. Moreover, obtaining a clean image allows minimisation of noise, which could invalidate the results. Soft tissue variables of interest included CSA (mm\(^2\)), IMAT area (mm\(^2\)) and subcutaneous adipose tissue area (SubFat in mm\(^2\)).

2.5 | Muscle strength and functional measures

2.5.1 | Maximal voluntary isometric contraction (MVIC)

Volunteers sat on a custom-made dynamometer with a hip angle of 40° (0° = standing position). Their upper body was strapped to the back of the chair, and they were asked to grip the chair to prevent countermovements. Their right ankle was strapped to a force sensor (Model F2712, 0-1000 N force range, Meiri Company, Bonneuil-sur-Marne, France). After a standard warm-up consisting of repeated isometric knee extensor contractions at progressively higher intensities, volunteers were asked to perform MVICs at different, randomised joint angles (29°, 66°, 76°, 87° and 103° [0° = full extension]) in order to determine the force-angle relationship. These angles were chosen over a wide range of muscle lengths (ie at short [29°], optimal [66°, 76°, 87°] and long [103°] muscle lengths). The angles of 66°, 76° and 87° were used with reference to previous studies showing an optimal angle of 75.6° ± 5.3°, 77.3° ± 6.5° and 76.3° ± 8.3° in children of similar age.\textsuperscript{16} Two measurements were made at each angle to check reproducibility. A third trial was performed if the difference between the two measurements exceeded 5%. Volunteers were urged to produce maximal voluntary force during isometric contractions. After resting for 5 minutes, volunteers then performed two maximal isometric knee extensor contractions at their optimal angle (76.3° ± 8.2° for JIA and 68.6° ± 14.4° for healthy children). The two trials were separated by 2 minutes of recovery. The best trial was retained to obtain MVIC force.

2.5.2 | Vertical jump height

The volunteers were asked to perform two squat jumps (SJ) and two countermovement jumps (CMJ) following standard guidelines. For SJ, the volunteers were to flex their knees at 90° with hands on hips to prevent countermovements induced by their arms. The volunteers were to hold this position for 3 seconds and then jump. The guidelines for CMJ were similar, except that the volunteers were told not to stop between standing and flexing positions. In both exercises, the volunteers were asked to jump as high as possible.

2.6 | Data analysis

To assess muscle architecture, two measurements were made for muscle thickness and fascicle angle in each muscle, and values were calculated with EchoWave II software (version 3.6.2., Telemed). The mean of the two values obtained for each image was calculated for each parameter. Images acquired with pQCT were processed with Stratec software (version 6.20, Stratec Medizintechnik GmbH). CSA, IMAT area and the SubFat area were calculated by the formula proposed by Schiferl.\textsuperscript{17} All data were acquired and processed by the same investigator to avoid inter-rater bias.

Maximal voluntary isometric force was defined as the maximal force applied on the force sensor. Force data were digitised and exported at a rate of 2 kHz to an external analogue-to-digital converter (PowerLab 8/35; ADInstruments) driven by the LabChart Pro software (version 7.3, ADInstruments). Maximal voluntary isometric force was then normalised to muscle CSA to obtain relative force (per unit muscle surface area).

Flight time of both jumps (SJ and CMJ) was measured by the Optojump system (Microgate). Vertical jump height was calculated by OptoJumpNext software (version 1.5.1.0; Microgate) using the following formula:

\[
h = \frac{T_i^2 g}{8}
\]

where \(h\) is height (cm), \(T_i\) is flight time (seconds) and \(g\) is gravitational acceleration.
2.7 | Statistical considerations

Sample size was estimated according to (a) the CONSORT 2010 statement, extension to randomised pilot and feasibility trials, and (b) Cohen’s recommendations defining effect size bounds as: small (ES: 0.2), medium (ES: 0.5) and large (ES: 0.8, “grossly perceptible and therefore large”). With 14 patients per group, an effect size >1 can therefore be highlighted for a two-sided type 1 error at 5% and a statistical power at 80%.

Statistical analyses were performed using Stata software version 13 (StataCorp). The tests were two-sided with the type 1 error set at 5%. The continuous data were expressed as mean ± standard deviation according to the statistical distribution. The assumption of normality was assessed with the Shapiro-Wilk test. Between-group comparisons (children with JIA vs healthy controls) for the quantitative parameters (age, maturity status, stature, body mass, muscle thickness and fascicle angle, CSA, IMAT, IMAT/CSA and SubFat area) were performed using the Student t-test or Mann-Whitney test when t-test criteria were not met. Homoscedasticity was analysed using the Fisher-Snedecor test. Finally, to express the results, Hedges’ effect sizes were estimated with 95% confidence intervals.

3 | RESULTS

Characteristics of the population studied are shown in Table 1 and Table S1.

Total weekly energy expenditure and moderate-to-vigorous physical activity were lower in children with JIA than in healthy children with a moderate effect size of −0.23, CI95% [-0.45; -0.02]. However, time spent in light intensity was similar in the two groups (Table 1).

3.1 | Architectural parameters

No significant difference in muscle thickness, fascicle angle or thigh CSA was observed between the groups (Tables 2 and 3). However, there were significant differences for values obtained with pQCT in muscle quality (Table 3 and Figure 1). IMAT was not significantly different when comparing the two groups. However, IMAT normalised to CSA was significantly lower in children with JIA than in healthy controls.

3.2 | Force production and functional outcomes

Children with JIA and healthy controls showed no significant difference in force-generating capacity of the knee extensor muscles (442.86 ± 190.49 N vs 505.93 ± 179.04 N, P = .31). Specific force was similar in the two groups (~0.06 ± 0.01 N/cm²). However, functional multiarticular ability, assessed by the vertical jump, was lower in children with JIA than in healthy children for both squat jump height (18.3 ± 5.4 cm vs 24.3 ± 7.9 cm, P = .03) and countermovement jump height (19.6 ± 6.7 cm vs 25.0 ± 8.2 cm, P = .07) (Figure 2).

4 | DISCUSSION

The aim of the present study was to examine the effect of JIA on the function and architecture of muscle and on functional abilities (vertical jump performance). The results revealed no clear differences between children with JIA and healthy peers in muscle architecture (muscle thickness, fascicle angle) or muscle CSA. However, pQCT showed a significantly lower IMAT area relative to CSA in children with JIA than in healthy controls. Assessed maximal force-generating capacity during MVIC did not differ between the two groups, despite decreased performance during vertical jump in children with JIA.

4.1 | Structure and quality of muscle in children with JIA

In the present study, we found a significantly lower ratio of IMAT area to CSA in the thighs of children with JIA. This unexpected result...
could be explained by a chronic inflammatory state that might be implicated in the inhibition of insulin signalling by multiple mechanisms, leading to insulin resistance. In a comparison of different individual athletes from different sports, a higher intramyocellular lipid level in oxidative fibre was explained by the opposing effects of oxidation in muscle cells and triglyceride uptake from the circulation. During detraining, the trained muscle also kept a higher myocellular lipid storage than untrained muscle. In a previous study, we showed that children with JIA have a lower lipid oxidation rate during submaximal exercise than healthy peers. Consequently, the lower IMAT content in children with JIA than in healthy children could be explained by a lower level of physical activity and a weakened oxidative metabolism.

In addition, in the present study, no impairment in the muscle thickness, CSA or fascicle angle was observed between children with and without JIA. This finding is consistent with some recent studies but inconsistent with reports prior to the biotherapy era showing reduced muscle thickness and CSA in JIA. The absence of differences between the groups for muscle structure and size could result from the efficacy of medical treatments, which potentially have positive effects on JIA by moderating inflammation and limiting loss of muscle mass. Owing to the availability, and better use, of efficacious therapies—especially methotrexate and biologicals—most children with JIA now achieve clinical remission. In the present study, JIA patients were under different medical treatments, sometimes combined: five with TNF blockade, nine under methotrexate and four under non-steroidal

### TABLE 2

| JIA (n = 14) | Healthy children (n = 14) | P   | Hedge’s g | [95% CI] |
|-------------|--------------------------|-----|-----------|----------|
| Muscle thickness (mm) | | | | |
| Vastus lateralis | 18.34 ± 4.10 | 20.42 ± 5.80 | .28 | 0.40 | [-0.33; 1.12] |
| Vastus medialis | 26.38 ± 5.24 | 24.95 ± 6.51 | .53 | -0.23 | [-0.95; 0.49] |
| Rectus femoris | 19.35 ± 4.55 | 19.53 ± 4.15 | .92 | 0.04 | [-0.68; 0.76] |
| Fascicle angle (°) | | | | |
| Vastus lateralis | 17.90 ± 3.07 | 18.68 ± 3.03 | .51 | 0.25 | [-0.48; 0.97] |
| Vastus medialis | 14.95 ± 5.19 | 16.73 ± 4.53 | .34 | 0.35 | [-0.38; 1.08] |
| Rectus femoris | 14.08 ± 2.96 | 15.49 ± 4.00 | .30 | 0.39 | [-0.34; 1.11] |

Note: Values are mean ± standard deviation.
Abbreviations: JIA, juvenile idiopathic arthritis.

### TABLE 3

| JIA (n = 14) | Control (n = 14) | P   | Hedge’s g | [95% CI] |
|-------------|----------------|-----|-----------|----------|
| CSA (mm²)   | 7174.70 ± 2793.11 | 8408.85 ± 3050.73 | .15 | 0.41 | [-0.34; 1.15] |
| IMAT (mm²)  | 1616.13 ± 712.85 | 2166.51 ± 1058.16 | .07 | 0.59 | [-0.17; 1.33] |
| IMAT/ CSA   | 0.22 ± 0.02 | 0.25 ± 0.03 | .01 | 1.00 | [0.21; 1.77] |
| SubFat area | 3258.52 ± 1324.34 | 3498.17 ± 1349.53 | .70 | 0.17 | [-0.56; 0.91] |

Note: Values are mean ± standard deviation.
Abbreviations: CSA, cross-sectional area; IMAT, intermuscular adipose tissue; SubFat area, subcutaneous adipose tissue.
anti-inflammatory drugs that are known to have adverse effects on muscle mass by inhibition of satellite cell expansion and macrophage numbers. However, their use may help decrease inflammatory levels, allowing muscle mass to be maintained; the relationship between inflammation and muscle mass needs to be clarified in future studies. Either way, muscle involvement is a putative long-term determinant of health in persons with inflammatory diseases.

4.2 Muscle function in children with JIA

The lack of between-group difference in maximal strength is consistent with the lack of difference observed in muscle size and structure. However, previous studies reported decreased maximal knee extensor strength in children with active JIA. The results of the present study suggest that children with JIA are as forceful as healthy children during brief maximal voluntary contractions of the knee extensors under isometric conditions, and neural contributions to force production may not be different between the two groups. This is consistent with previous studies showing no significant impairment in nerve conduction velocities in JIA patients aged 9-19 years, but this remains to be confirmed using non-invasive techniques such as electromyography and twitch interpolation.

However, vertical jump height assessment shows that JIA can affect performance in multiarticular dynamic movements. In other words, JIA seems to induce functional impairments in an ecological situation. These differences cannot be explained by reduced knee extensor force in children with JIA, but they may be related to jumping biomechanics. According to kinetic analysis of the lower limb joints (hip, knee and ankle) in children with JIA there is a decrease in knee and ankle torque during take-off compared with healthy controls, which may result from muscular weakness. Although there is no consensus on the landing technique, studies suggest that JIA patients could increase the range of motion on the involved side at the knee and hip and thereby adapt an increased sagittal plane motion strategy to reduce ground reaction forces and control joint loading. In other words, JIA patients may use a ‘soft’ flexion style landing rather than a stiff bounce landing. Fear of pain might account for this soft strategy during the landing to limit knee pain at impact, the knees commonly being the most sensitive area in children with JIA. Scientific evidence also points to lower nociceptive thresholds and less efficient endogenous pain control systems in JIA patients.

As 12 of the 14 subjects with JIA had knee pain in the present study, this explanation seems plausible. This hypothesis is also supported by the observation that children with JIA spontaneously avoid activities with impact such as volley ball or basketball. However, this soft-landing strategy does not necessarily indicate a “safer” or less injurious style of landing. Whether it translates into a higher or lower injury risk remains to be determined in JIA patients.

4.3 Interest in physical activity

One of the main questions arising from these findings is whether it is the inflammation induced by JIA, or the physical inactivity evoked, that is responsible for the decreased vertical jump performance. Musculoskeletal pain induced by movements may be amplified by more intense physical activity. This effect is one of the most often-evoked obstacles to physical activity in children with JIA. Thus, medical staff, family and children have historically tended to eschew physical activity, fearing worsened symptoms, pain and fatigue. Recent reviews and meta-analysis have observed that children with JIA have lower physical activity levels and higher sedentary level.

In the present study, the results of the physical activity questionnaire revealed that children with JIA were less active than healthy children. This outcome may be explained by disease status, which is responsible for the variable levels of pain and is often described as the main obstacle to PA practice. Fitness deconditioning and pain in JIA, associated with activity of disease and treatment, may also increase exercise perception in children, causing them to rate physical activity as more difficult than healthy children. In agreement with our previous study, only 28.5% of the presently assessed children with JIA met the physical activity recommendations for public health. These results suggest that children with JIA tend to be less active than their healthy peers, in particular in moderate-to-vigorous physical activity.

4.4 Limitations of the study

Several features of this study may be limiting. Firstly, during force measurements, the upper body was strapped to the back of the chair and the volunteers were asked to grip the chair to prevent countermovements. This position may have biased the measurement of knee extensor MVIC force, as the trunk and upper limbs may have helped increase the resultant force. However, both groups performed MVIC in the same conditions. In addition, all the participants were well-familiarised with the equipment and exercise procedures. A second feature is that muscle force-generating capacity was evaluated in isometric conditions and only on the knee extensors. Isometric conditions are appropriate for...
evaluating maximal force, but additional measurements of muscle force could be made in dynamic conditions at different angular velocities over a larger number of muscle groups (eg hip extensors, knee flexors and plantar flexors) to better interpret the effect of JIA on multiarticular-type functional capacities (eg vertical jump performance). Thirdly, in the present study, the sample size in each group was low (14 subjects). However, this limitation should not affect the conclusions of the study, because effect sizes and statistical power were found to be moderate-to-high. Finally, the group including JIA children displayed different subtypes of JIA, but the treatment and disease status did not allow investigation of the effects of JIA by subgroup. Larger studies are therefore required to determine more precisely the effect of different subtypes of JIA on muscle properties and functional abilities.

5 | CONCLUSION

To conclude, we observed no significant impairment of quadriceps muscle architecture or function in children with JIA compared with healthy children. However, our results show a lower IMAT area in JIA children’s thigh muscles regardless of disease status or treatment, suggesting the possibility of metabolic disorder induced by JIA. Moreover, vertical jump performance was decreased in children with JIA. Hence muscle characteristics in JIA could not specifically account for reduced functional capacities (here vertical jump performance). This could be due to different strategies to avoid pain during multiarticular dynamic activities.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ORCID

Pascale Duché https://orcid.org/0000-0001-7206-6429

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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