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Health-related quality of life (HRQoL) in achondroplasia: findings from LISA (Life Impact Study on Achondroplasia), a multinational and observational study in Latin America

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Introduction

- Achondroplasia is the most common form of short limb dwarfism[1]
- Birth prevalence in South America is 3.2 per 100,000[2-4]
- Limitations of the existing data on health-related quality of life (HRQoL) in Latin America:
  - Small studies, with limited number of patients
  - Lack of information regarding the link of the clinical manifestations of disease to:
    - Impact on HRQoL over a lifetime of living with the disease
    - Medical or social burden of disease

Objectives

- Describe the disease's impact in individuals with achondroplasia by evaluating the health-related quality of life (HRQoL), clinical and socioeconomic burden, and healthcare resource use
- Describe the associations between the recorded clinical characteristics of the disease and
  - Patient- and parent-reported outcome measures of HRQoL
    - Functional impact of the disease
    - Psychosocial impact: psychological and socialization
    - Comorbidities, medical and surgical complications
    - Use of health services
    - Socio-economic impact
  - Clinical measures of pain
    - Describe the associations between recorded clinical measures of pain and HRQoL
    - Investigate the determinants of HRQoL measures with height within 1 year

Methods and Study Design

- Study design:
  - **Multinational** and **observational** study with a **cross-sectional** component assessing HRQoL
    - Individuals was asked to complete a booklet of standardized questionnaires at study enrollment, referring to the self-perceived impact of the disease in their Quality of Life (QoL)
    - 1 Enrollment period: Jan/2018 to Jul/2021
  - Analysis of **retrospective** data:
    - Descriptive statistics of domain and total scores were compared to reference populations
- Eligibility:
  - Inclusion Criteria:
    - Individuals with achondroplasia in Latin America (Brazil, Argentina and Colombia) aged ≥ 3 years;
  - Other Criteria:
    - Enrollment limited by age groups (in years) as follows: 3-5 (n=20), 6-10 (n=30), 11-15 (n=30), 16-20 (n=20), 21-30 (n=20), 31-40 (n=20), 41 and over (n=35)
    - To minimize confounding bias, number of participants with limb lengthening surgery was capped at 20%

Child/Adolescent and adult questionnaires applied in the study with the outcome domains assessed

Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
Pediatric						
PedsQL*	✓	✓	✓		✓	
QoLISSY*	✓	✓	✓		✓	
WeeFIM		✓				✓
APPT				✓		
Adult						
EQ-5D- 5L*	✓	✓	✓	✓		✓
NHP	✓	✓	✓	✓	✓	
BPI-SF				✓		
WPAI						✓

QoLISSY, Quality of Life in Short Stature Youth; PedsQL, Pediatric Quality of Life Inventory Questionnaire; APPT, Adolescent Pediatric Pain Tool; WeeFIM, Pediatric Functional Independence Measure; WPAI, Work Productivity and Activity Impairment; BPI-SF, Brief Pain Inventory – Short Form; NHP, Nottingham Health Profile. *Values for reference population available (average stature or other short stature conditions).

Results

Demographics

Characteristics at Time of Enrollment	Overall EAS[1]n=172
Participants per country, n (%)	
Brazil	94 (54.6)
Argentina	37 (21.5)
Colombia	41 (23.8)
Gender, n (%)	
Male	81 (47.1)
Female	91 (52.9)
Age (years)	
Median (25th, 75th Percentile)	16.0 (8.0, 31.5)
Age subgroups (years)[2], n (%)	
3-5	20 (11.6)
6-10	35 (20.3)
11-15	29 (16.9)
16-20	16 (9.3)
21-30	25 (14.5)
31-40	23 (13.4)
≥41	24 (14.0)
Limb lengthening prior to enrollment[3], n (%)	
Yes	12 (7.0)
Time since limb lengthening (years)[4]	
Median (25th, 75th Percentile)	6.4 (2.6, 10.2)

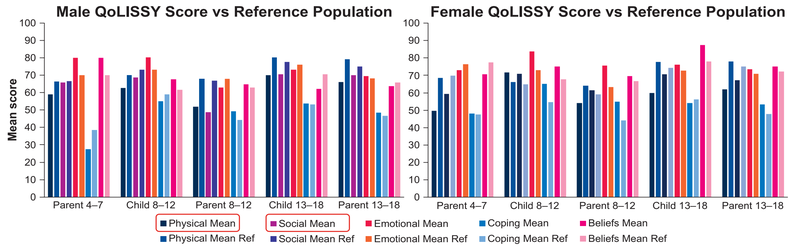
Enrolled Analysis Set (EAS): included all consented subjects with a documented diagnosis of achondroplasia and medical records available for the 3 years prior to the date of enrollment. [2]When date of birth is missing or only the year is provided, CRF collected age is used. [3]Assessment closest to enrollment date. [4]Time (years) since limb lengthening surgery = (date of enrollment – earliest date of limb lengthening surgery)/365.25.

Children and adolescent patients and their parents reported reduced QoL and lower scores in physical and psychosocial domains when compared to general population

Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
PedsQL*[1]	Reduced[4]	Reduced[4]	Reduced[4]		Reduced[4]	
QoLISSY*[2,3]	Reduced[4]	Reduced[4]	Reduced[5]			
WeeFIM		No population norms – higher dependence in lower ages (5-7 years)				No population norms – higher dependence in lower ages (5-7 years)
APPT				Mild pain, multiple sites		

*Present patient- and parent-reported outcomes: [1]Reference population: average stature individuals; [2]Reference population: other short stature conditions; [3]Most affected domains were physical, social, effect (parents) and total (child only); [4]Reduced compared with population norms; [5]Expect in Female Child population from 8-12.

HRQoL are reduced and the disease causes a psychosocial burden in the pediatric population



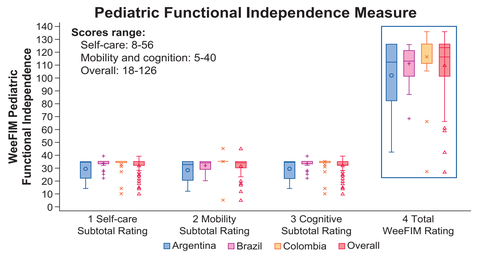
QoLISSY Mean total scores:

- 71.5 (SD: 17.5) for patients
  - Ref mean: 83.8 (SD: 12.7)
- 63.9 (SD: 18.9) for parent proxies
  - Ref mean: 82.7 (12.7)

- Most affected domains were physical, social, effect (parents) and total (child only)

Reference population: average stature children. Range: 0 (Poor quality of life) to 100 (Perfect quality of life).

WeeFIM: Functional, independence and autonomy is negatively impacted by achondroplasia

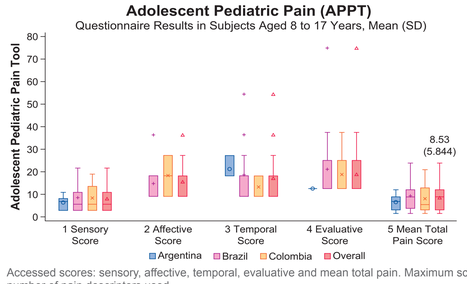


Age (n)	Overall WeeFIM score, Mean (SD)
Children and Adolescents	
5-7 (22)	95.9 (15.34)
8-12 (31)	117.2 (9.19)
13-17 (27)	124.1 (3.51)
Limb Lengthening Surgery	
5-7 (0)	–
8-12 (3)	119.0 (12.12)
13-17 (4)	126.0 (0.00)

Low scores indicate "total assistance" while high scores indicate "complete independence"

- WeeFIM measures the functional skills and performance in daily activities in children with physical or general developmental limitations or restrictions[5]
- This questionnaire assess the need for assistance and the severity of disability

Adolescent/pediatric achondroplasia population reported mild pain in several sites



- n=57 adolescent subjects (98.3%)
- 53.4% of adolescents reported at least 1 pain site
- 10.3% reported pain in 3 sites

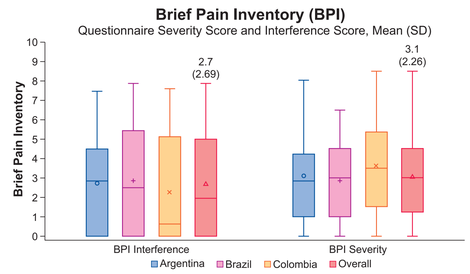
Accessed scores: sensory, affective, temporal, evaluative and mean total pain. Maximum score for all domains: 100. Higher scores indicate a larger number of pain descriptors used

Adult participants rated themselves lower than general population norms (where available)

Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
Adult Questionnaire						
EQ-5D- 5L[1]	Reduced[2]	Reduced[2] 20.3% Moderate to severe problems with mobility	26.6% Moderate or severe anxiety/ depression	Reduced[2] 25.3% Moderate to severe pain or discomfort		17.8% Moderate to severe problems or unable to do usual activities
NHP[3]	No population norms Moderate impact	No population norms Moderate impact	No population norms Moderate impact	No population norms Moderate impact	No population norms Moderate impact	
BPI-SF				Mild pain, multiple sites		
WPAI						No population norms 13.8% reduction in work, 23.1% reduction in activities

[1]Reference population: average stature individuals; [2]Reduced compared with population norms; [3]Most negatively impacted domains were energy, pain and physical mobility.

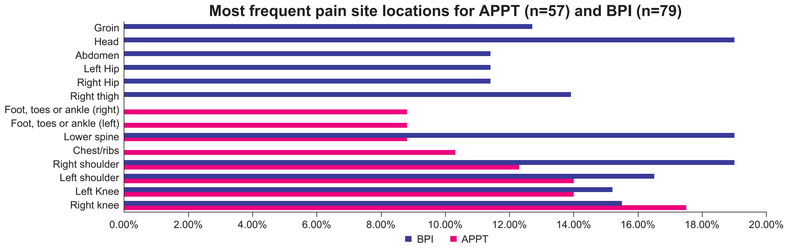
Most of the adult participants reported mild pain



- 73.4% of subjects reported experiencing pain not described as everyday minor aches and pain

Accessed scores: pain and interference. Pain: scores range from 0 (no pain) to 10 (pain as bad as one can imagine). Interference: scores range from 0 (no interference) to 10 (completely interferes). Interference scores describes the impact of pain in mood, walking ability, normal work and housework, relations with other people, sleep and enjoyment of life.

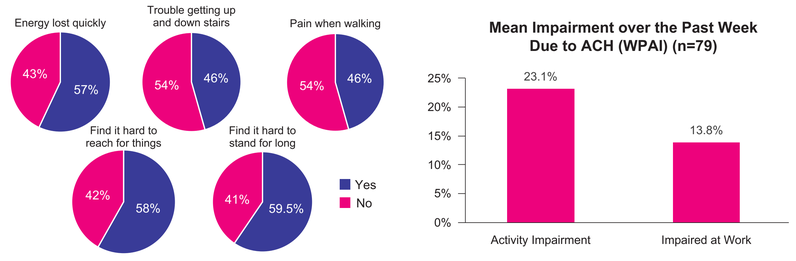
Overall achondroplasia population reported mild pain in multiple sites



- 79 (73.4%) adult subjects reported "having pain other than everyday kinds of pain today" and mild pain regardless of age
- 57 (98.3%) of adolescent subjects completed the APPT, reporting a mean (SD) number of pain sites of 1.9

BPI mean severity score was on a scale of 0 (no pain) to 10 (pain as bad as subject can imagine). Mean interference score reports interference with general activity, mood, walking ability, normal work, social relations, sleep, and enjoyment of life on a scale of 0 (does not interfere) to 10 (completely interferes). APPT: adolescent paediatric pain tool; BPI: brief pain inventory

Activities of daily living and functionality of the overall achondroplasia population are restricted



- Adults and children reported reduced physical function or mobility in the EQ-5D, Peds-QL, QoLISSY, NHP and WeeFIM
- Psychosocial function was also affected, as reported in the PEDS-QL, EQ-5D, QOLISSY and NHP

WPAI productivity refers to the mean percent impact on productivity while working due to achondroplasia over the last week; WPAI activity refers to the mean percent impact of achondroplasia on ability to do regular daily activities, other than work at a job, over the past week. ACH: achondroplasia; EQ-5D: EuroQol 5-dimension QoL questionnaire; NHP: Nottingham health profile; QOLISSY: quality of life of short-stature youth; WeeFIM: paediatric functional independence measure; WPAI: work productivity and activity impairment

Limitations of LISA

- Observational and retrospective design
  - Retrospective data review revealed gaps in medical records (with exception to the Argentinean pediatric site)
    - This study may underreport the medical burden and real-life experience of achondroplasia patients in Latin America
- The COVID-19 pandemic caused delayed and unbalanced enrollment across countries and age groups, challenges in gathering complete medical records, and disruptions in planned monitoring activities
- Due to the small number of sites involved in the study, generalization of results to a larger population should be made with caution

Conclusions

- LISA study provides the largest set of data to date from Latin America on the lifetime impact of achondroplasia
  - The study addresses the gaps in knowledge about clinical and socioeconomic burden of illness, HRQoL, psychosocial impact, and healthcare resource use for individuals with achondroplasia in Latin America
  - Despite the diversity of patients and sites across the 3 countries that participated of LISA, assessments of QoL, WeeFIM and pain questionnaires were similar
- LISA data demonstrates that subjects experience significant burden of illness across multiple domains, which impact the HRQoL
- Despite not shown in this presentation, LISA also demonstrates substantial healthcare resource use along with medical and surgical interventions in patients with achondroplasia
- The HRQoL of individuals with achondroplasia corroborates with European subjects in the LIAISE study[6]

References

1. Horton WA, Hall JG, Hecht JT. *Lancet.* 2007;370(9582):162-172; **2.** Foreman PK, van Kessel F, van Hoorn R, et al. *Am J Med Genet A.* 2020 Oct;182(10):2297-2316; **3.** Barbosa-Buck CO, Orioli IM, da Graça Dutra M, et al. *Am J Med Genet A.* 2012 May;158A(5):1038-45; **4.** Cavalcanti DP, Fano V, Mellado C, et al. *Am J Med Genet C Semin Med Genet.* 2020 Dec;184(4):986-995. **5.** Ireland PJ, McGill J, Zankl A, et al. *Dev Med Child Neurol.* 2011 Oct;53(10):944-50. **6.** Maghnie M, Semler O, Guillen-Navarro E, et al. Health-related quality of life (HRQoL) in achondroplasia: Findings from a multinational, observational study (LIAISE). *MGM.* 2021 Apr; 132(1):S127-S128. doi:10.1016/S1096-7192(21)00280-8

Presented at the 2023 ACMG Annual Clinical Genetics Meeting, March 14–18 2023, Salt Lake City, UT