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Qualitative Research to Explore the Patient Experience of X-Linked Hypophosphatemia and Evaluate the Suitability of the BPI-SF and WOMAC® as Clinical Trial End Points

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ABSTRACT

Background: X-linked hypophosphatemia (XLH) is a rare genetic disorder characterized by renal phosphate wasting and defective bone mineralization. Symptoms include bone pain, joint pain, stiffness, and fatigue. Published evidence regarding the patient experience of XLH is sparse and no XLH-specific outcome measures have been validated. **Objectives:** To understand the symptoms, impacts, and patient experience of XLH and to evaluate the face and content validity of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) and the Brief Pain Inventory Short Form (BPI-SF) for use as end points in XLH clinical trials. **Methods:** Face-to-face, qualitative, semistructured interviews were conducted with 18 adults with XLH in the United States using concept elicitation and cognitive debriefing techniques. Open-ended questioning elicited spontaneous concepts focusing on XLH-associated symptoms and functional limitations. Cognitive debriefing of the WOMAC® and BPI-SF assessed the relevance and patient understanding of item wording, recall period, and response options. **Results:** Various distinct symptom concepts were elicited including pain symptoms, dental symptoms, sensory symptoms, tiredness/fatigue symptoms, and musculoskeletal symptoms. Participants reported experiencing significant bone and joint pain, stiffness, mobility limitations, and an impact on their ability to work. Cognitive interviewing found both instruments to be relevant and well understood by most patients. **Conclusions:** The interviews generated rich, qualitative insights into the patient experience of XLH. Cognitive debriefing of the BPI-SF and WOMAC® supported their value as XLH clinical trial end points. Future research will assess the psychometric properties of these instruments for use in the XLH population.

Keywords: conceptual model, interview study, qualitative, X-linked hypophosphatemia.

Introduction

X-linked hypophosphatemia (XLH) is a rare genetic disorder characterized by renal phosphate wasting and defective bone mineralization, caused by inactivating mutations in the PHEX gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome). In the absence of functional PHEX, release of fibroblast growth factor 23 by osteocytes is greatly increased, leading to a decrease in re-absorption of calcium and phosphate [1–3]. Chronic low serum phosphorus levels lead to defective bone mineralization and consequently to rickets in children and osteomalacia (softening of the bones) in adults, the two major pathological consequences of hypophosphatemia [3,4]. Adults with XLH typically experience significant symptoms including bone pain, joint pain, stiffness, and fatigue, and may also have nontraumatic fractures, osteoarthritis, gait abnormalities, and dental abscesses, while bowing of the legs and short stature remain from childhood [3].

XLH is serious, chronically debilitating, and represents an unmet medical need. To date there are no approved treatments for XLH, although phase III studies evaluating a molecule that looks to treat the mechanistic cause of XLH are currently underway. At present, physicians typically treat the symptoms of adult patients with oral phosphate and active vitamin D metabolites [3]. Nevertheless, there are concerns about long-term complications with this treatment regime, particularly hyperparathyroidism and subsequent calcium salt deposits in the renal parenchyma (nephrocalcinosis) [5], which may become more problematic with increased dosage and duration of therapy [6]. As a result, some adult patients are treated only if they experience pseudofractures or active bone pain and osteomalacia [7].

Conflicts of interest: N. Bonner and R. Arbuckle are employees of Adelphi Values, a health outcomes agency. H. Spencer was an employee of Adelphi Values when the work was carried out.

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Published evidence regarding the impact of XLH on health-related quality of life (HRQOL) is sparse and, to date, no qualitative research documenting the in-depth patient experience of XLH has been conducted. Pain/discomfort and mobility issues emerged as the most problematic domains for patients with XLH in a study examining HRQOL in a number of rare musculoskeletal diseases [8]. In addition, the quality of life of patients with XLH has also been found to not only be impaired but also significantly worse than that of patients with a similar condition (axial spondyloarthritis) [9]. These findings are unsurprising given that pain, stiffness, and limited mobility are some of the most pertinent symptoms of XLH. Although these research studies establish a solid foundation for the exploration of HRQOL in patients with XLH, a gap remains where patient experience and patient perspective are yet to be captured. Qualitative studies that consider HRQOL impacts can help researchers better understand the patient experience and overall burden of a disease. Furthermore, qualitative studies can be used to inform conceptual model development [10]. Conceptual models provide a starting point for assessing the suitability of clinical trial end points that measure symptoms (such as pain and stiffness, which are key XLH symptoms) that cannot be fully quantified using clinical tests. This is particularly important in a condition like XLH that is characterized by internal experiences of the patient such as pain and stiffness, where patient-reported data form an important part of treatment efficacy evaluations.

The measurement of pain is a contentious issue that has been extensively investigated over the years. Pain perception is highly individual and subjective in nature, but it can be assessed only through patient report. Several tools have been developed that not only quantify pain but also measure its functional or qualitative aspect [11]. The Brief Pain Inventory Short Form (BPI-SF) [12] is one of the most widely used measurement tools for assessing pain; it allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function.

Stiffness is another concept that relies on patient report for measurement in clinical trials. Measurement in conditions similar to XLH typically focuses on duration and perceived severity [13–15], but currently no standard method for measuring stiffness exists. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) is a 24-item patient-reported instrument developed to assess pain, stiffness, and physical functioning in patients with hip and/or knee osteoarthritis [16]. Despite being developed for use in knee and/or hip osteoarthritis, the WOMAC® has also been used in a number of conditions including lower back pain, rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia [17].

Through qualitative patient research, the present study sought to increase understanding of the patient experience of XLH and establish the main symptom and impact concepts of importance to patients with XLH. Through cognitive debriefing, the study also explored whether the BPI-SF and WOMAC® are relevant and appropriate instruments for measuring pain and stiffness as end points in clinical trials with adult patients with XLH, in accordance with the criteria outlined in the Food and Drug Administration Patient-Reported Outcomes Guidance [18].

Methods

Overview of Study Methods

This was a qualitative, noninterventional, interview study involving 18 US patients with XLH. The interviews aimed to generate qualitative insight into the symptoms and impacts of XLH to evaluate the relevance and suitability of the WOMAC® and BPI-SF as assessments of pain and stiffness. An evaluation of the relevance and understanding of the two instruments was also performed. Given these dual objectives, combined concept elicitation and cognitive debriefing interviews were used to generate evidence to support evaluation of the face and content validity of the WOMAC® and BPI-SF for use with patients with XLH.

Qualitative Patient Data Collection

Recruitment

Patients were informed about the study through a support group of patients with XLH (The XLH Network Inc.). Interviews were then conducted at an organized patient event with willing and eligible patients. Eligible patients were required to meet the following criteria: men or women 1) aged 18 to 65 years, 2) willing and able to provide written informed consent, 3) having a clinical diagnosis of XLH, 4) fluent in English, 5) able to read and respond to a questionnaire administered in English, and 6) willing and able to complete a 75-minute interview. Because of the rarity of XLH, the only exclusion criterion was that patients should not be currently/previously enrolled in any other clinical trial (for XLH or any other condition) at the time of the interview. This criterion was reflective of the criteria used in the clinical study, and avoided the inclusion of patients who may have experienced treatment benefit during the trial.

Patients were given an information letter summarizing the aims and objectives of the study and their involvement before giving their consent. Written informed consent was obtained from all patients before the conduct of any study activities.

Ethical approval

The study was approved and overseen by the Copernicus Group Independent Review Board (approval code: ADE2-15-166).

Interview process

Qualitative, face-to-face interviews of up to 75 minutes were conducted with adult patients with XLH at a centralized location (an annual patient day organized by The XLH Network Inc.). The first half of the interview was exploratory and focused on eliciting information related to the patient experience of XLH, specifically the symptoms and functional limitations caused by the disease. The aim of this part of the interview was to encourage patients to spontaneously mention concepts of importance to them (e.g., "Tell me about what it is like to have XLH"). Patients were then asked more focused questions designed to probe them on issues they may not have spontaneously discussed (e.g., "As a result of your XLH, have you ever experienced stiffness?").

After this, the WOMAC® and BPI-SF were cognitively debriefed [19]. Patients were asked to respond to questions using a "think aloud" methodology; this allows access to patients' genuine thoughts as they completed the assessments and thus identification of any differences among patients in the way they understood and responded to the items on each instrument [20]. Patients were also asked detailed questions about their understanding of item wording, recall periods, and response options.

Qualitative analysis

All interviews were digitally recorded and transcribed verbatim. Qualitative analysis was conducted on all transcripts by sorting quotes into concepts via thematic analysis methods using the Atlas.ti software (Atlas.ti Scientific Software Development GmbH, Berlin, Germany) [3,21]. The first two transcripts were analyzed by three researchers and compared for consistency. After this, two researchers coded the remaining transcripts and met at regular intervals to discuss the coding structure, and the process was overseen by the lead researcher. Conceptual saturation (the point