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ORIGINAL ARTICLE

A conceptual and disease model framework for osteoporotic kyphosis

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Abstract

Summary This paper presents a multi-method research project to develop a conceptual framework for measuring outcomes in studies of osteoporotic kyphosis. The research involved literature research and qualitative interviews among clinicians who treat patients with kyphosis and among patients with the condition.

Introduction Kyphosis due to at least one vertebral compression fracture is prevalent among osteoporotic patients, resulting in well-documented symptoms and impact on functioning and well-being. A three-part study led to development of a conceptual measurement framework for comprehensive assessment of symptoms, impact, and treatment benefit for kyphosis.

Methods A literature-based disease model (DM) was developed and tested with physicians ($n=10$) and patients ($n=10$), and FDA guidelines were used to develop a final disease model and a conceptual framework.

Results The DM included signs, symptoms, causes/triggers, exacerbations, and functional status associated with kyphosis. The DM was largely confirmed, but physicians and patients added several concepts related to impact on functioning, and some concepts were not confirmed and removed from the DM.

Conclusions This study confirms the need for more comprehensive assessment of health outcomes in kyphosis, as most current studies omit key concepts.

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Keywords Conceptual framework · Disease model · Health-related quality of life · Kyphosis · Qualitative · VCF

Introduction

Approaches for developing relevant content of patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) assessments to evaluate new medical products have been well described [1–3] and involve input from multiple stakeholder groups. Steps in this process include conducting qualitative interviews among clinicians and patients, development of a disease model and conceptual framework, documenting item development, and compiling the information to support the measurement strategy for submission to regulatory agencies. The disease model presents a summary of key aspects of the condition under study, providing an organizing structure from which to derive the conceptual framework [4]. The conceptual framework is a clear diagram or description of the relationships among concepts [5], domains, and items in the PRO or ClinRO instrument. The consequences of using an inadequate conceptual framework for measurement using a PRO or ClinRO include challenges for scoring, analysis, and interpretation, ultimately affecting evaluation of the endpoint for supporting a label claim [6]. Despite their importance, in practice, conceptual frameworks are often absent, as are examples of the development of such frameworks.

Vertebral compression fractures (VCFs) are prevalent, with 1.7 million VCFs occurring each year in the USA and European Union. Approximately 85 % of all VCFs occur in patients with osteoporosis (OVCFs). The symptoms of OVCF are sudden back pain and symptoms related to nerve compression. After acute symptoms subside, many patients with VCFs will have developed irreversible spinal deformity (kyphosis) associated with several significant health consequences including increased mortality, decreased quality of life, impaired physical functioning, increased future fracture risk, reduced lung functioning, impaired balance, and increased incidence of falls [7–16].

The conventional treatment strategies for OVCF are non-surgical management approaches focusing primarily on pain relief, including bed rest, physiotherapy, bracing, and analgesics. Analgesic treatment typically escalates from NSAIDs to narcotics, including opioids. Bed rest fails to address the development of vertebral deformity and its subsequent disability, and immobility from bed rest can contribute to loss of muscle mass, pain, impaired balance and strength, and increased risk of falls and subsequent fractures [14, 15]. Interventional vertebral augmentation treatments, such as balloon kyphoplasty (BKP) and vertebroplasty (PVP), are designed to correct vertebral fractures. BKP and PVP are two minimally invasive interventions for percutaneous injection of bone cement. In PVP, the cement is injected directly into the fractured vertebrae. In BKP, an inflatable bone tamp is used to reduce the fracture, restoring vertebral anatomy, and a controlled cement injection follows. While both are minimally invasive surgical approaches, they target different treatment outcomes: PVP aims to achieve spinal stabilization and pain relief, whereas BKP additionally aims to correct and prevent spinal deformity.

This article documents the process of developing a measurement disease model and conceptual framework for use in evaluating the effectiveness of efforts to prevent or treat OVCF-related spinal deformity (kyphosis). The study employed literature review and qualitative research among patients and clinicians to develop a disease model and a conceptual framework that defines the appropriate outcome measurement strategy for future clinical studies. The concept elicitation and content validation techniques used in this study conform to the currently accepted standards for developing patient-reported outcome (PRO) or clinician-reported outcome (ClinRO) measures for use as endpoints in clinical trials [2–4].

Methods

Research methods for this qualitative study included literature review, clinician and patient interviews, and development of a disease model and conceptual framework. Qualitative research often follows an iterative process beginning with general exploratory questions. Researchers collect and analyze patterns in data, then resume data collection to confirm or challenge the initial lines of thinking [17]. The cycle is repeated until further data collection provides no new evidence, a state referred to as theoretical saturation [18] or informational redundancy [19]. This approach was used in each phase of the qualitative research reported here.

Literature review and preliminary disease model

The goal of the literature search was to inform the development of a disease model of osteoporotic kyphosis, including signs and symptoms, causes and triggers, exacerbating factors, and impact on functioning and well-being. MEDLINE and PubMed databases were searched with the following keywords: [Osteoporosis AND Kyphosis OR spinal deformity OR vertebral fractures OR vertebral (body) height loss].The set of articles retrieved was then submitted to several further searches using the following keywords: [activities of daily living OR independence OR physical health OR quality of life OR disability]; [mental health OR anxiety OR depression OR fear OR well-being OR self-esteem OR psychosocial]; [dependence OR burden OR caregiver OR indirect cost]; [patient-reported outcome OR clinician-reported outcome]. These searches produced 235 publications. In addition, relevant publications were identified from the reference lists of these publications, and several more were offered by clinicians.

Abstracts from each manuscript were reviewed, and those judged as pertinent to the study objectives were retrieved. Articles were removed from consideration for the following reasons: (1) not in English; (2) case study data only; (3) not presenting results for functioning and well-being; and (4) redundant. After this process, 61 publications were examined for the development of the disease model.

The literature review served as the basis to develop a draft disease model. The format of the disease model in Fig. 1 was loosely based on the model described by Wilson and Cleary [20] and the reference case presented in the ISPOR PRO Good Research Practices Task Force Report on establishing and reporting evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation [2, 3]. The disease model is organized into several sections, each in a separate box in the figure. Box 1 includes signs and symptoms. A sign is an objective indication of a clinical state that can be detected and measured by a clinician or other observer but may go unnoticed by the patient. Signs are often significant for diagnosis or severity staging of medical conditions. Symptoms are experienced by patients as a change from normal functioning or emotional state and are self-reported. Box 2 includes the causes of and triggers for kyphosis due to VCFs. Box 3 includes characteristics or circumstances that could exacerbate kyphosis. This includes both aspects of the patient's spinal condition (e.g., prior fractures) as well as patient attributes (e.g., age or gender). Box 4 represents the impact of kyphosis on the patient's functioning and well-being. The

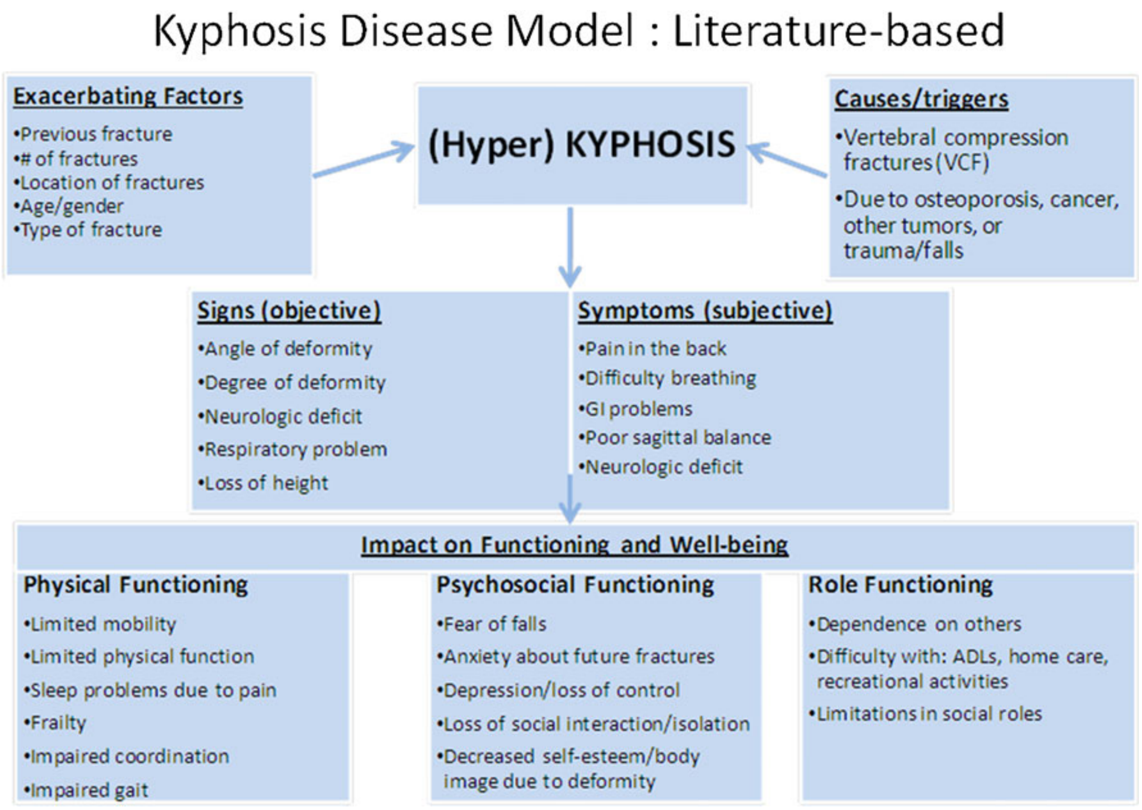

Fig. 1 Literature-based disease model

literature supported three domains of functioning and well-being: physical functioning, psychosocial functioning, and role functioning.

Clinician interviews

The objective of the clinician interviews was to test the validity of the disease model and the important concepts to be included in a measurement strategy. Ten qualitative phone interviews using an interview guide were completed with English-speaking clinicians located in the USA, UK, France, and Germany who currently treat patients with osteoporotic kyphosis. The sample included both primary care physicians (PCPs) (e.g., gerontology, internal medicine) and specialist physicians (e.g., radiology, orthopedic surgery) to attempt representation of the specialties involved in the full pathway of care for OVCF patients.

A recruitment list was provided by the study sponsor and complemented a posteriori by researchers to fulfill representativeness. Potential respondents were contacted by e-mail or fax and invited to participate in the study. The interviews centered on the symptoms, clinical and functional consequences of kyphosis, and clinician's observations of treatment benefits.

For analysis, the disease model was the basis for the initial coding schema, and each transcript was reviewed for content that substantiated or opposed concepts. Three researchers participated in coding using Excel. Each transcript was independently coded by at least two researchers. After coding, results were shared with other coders, and variations were discussed and resolved. If new concepts emerged from at least two clinician interviews, those concepts were added as new codes in the schema. Similarly, concepts were removed if at least two clinicians recommended removal.

Patient interviews

The objective of patient in-depth interviews was to explore the impact of VCF and osteoporotic kyphosis from the patient perspective. Study materials were reviewed and approved by New England Institutional Review Board. Participants were recruited using a proprietary database maintained by a market research company as well as local advertisement in the Los Angeles, California area. Informed consent was obtained from patients prior to the start of each interview using written format for face-to-face interviews or a modified script for phone interviews.

A sample size of 10–12 patients was targeted, with ten interviews completed (eight face-to-face, two phone interviews). Initial inclusion criteria included (1) adults over 50 years old who self-reported a spinal fracture related to osteoporosis at least 90 days prior to interview; (2) a majority of subjects were expected to be female (7–8); (3) half of subjects must have had kyphoplasty or vertebroplasty for a VCF within the last 2 years; and (4) half of subjects must have used non-surgical treatment for VCF. Exclusion criteria included (1) self-reported diagnosis of rheumatoid arthritis, lupus, severe osteoarthritis, cancer, asthma, or emphysema; (2) non-English speaking; and (3) inability to travel to interview site. All inclusion and exclusion criteria were reported by the patient at screening, then confirmed with the patient at the time of the interview. All diagnoses were confirmed by the patient at the beginning of the interview with the question: "Have you been told by a doctor that you have a spinal or vertebral fracture because of your osteoporosis?" After the eight face-to-face interviews were completed, modifications were made to include patients with more severe kyphosis. Interviewing patients with more severe kyphosis required conducting the last two interviews by phone instead of in person. Inclusion criteria were modified to include patients over age 65, with kyphosis due to osteoporosis and at least some difficulty in daily activities due to spine condition.

The analytic approach mirrored that of the clinician interviews, described in detail above. A discussion guide was followed, but themes were allowed to emerge, and all interviews were audio-taped and transcribed.

Conceptual framework

Following published recommendations,[1] a conceptual framework was developed by the lead author, then independently reviewed by the three co-authors, all using the content from the disease model that was confirmed as relevant by clinicians and patients as well as new concepts that emerged spontaneously during the interview process.

Results

As described in Methods, 61 publications were reviewed for development of the disease model. The initial disease model based on these publications is shown in Fig. 1. Below, we describe results from the clinician interviews and patient interviews, and synthesize the findings into the evolving disease model and finally the conceptual framework. We present the adapted disease model at the first and final stages, and provide a summary of results with supporting illustrative quotes.

Clinician interviews

Six specialists and four PCPs were interviewed. Five clinicians were located in the USA, one in the UK, two in France, and two in Germany. Most concepts from the literature-based model were confirmed by a majority of the clinicians. An outcome was considered confirmed, or verified, if the theme emerged from at least two clinicians. All confirmed concepts remained in the modified disease model. One example of a confirmed concept is "limited mobility," which impacts physical functioning. Clinician 1 stated

> *…it's getting out of bed, rising from a seated position. Typical types of things: twisting, turning motions.*

Proposed changes to the model from this phase of research are summarized below, organized by section of the model (signs, symptoms, causes/triggers, exacerbating factors, and impact on functioning and well-being).

Signs

Clinician interview data supported differentiating the deformity associated with kyphosis in terms of changes to the vertebrae from changes to the shape of the spine overall, for both angle and degree of deformity. Also, clinicians felt "neurologic deficit" should be removed.

Symptoms

Clinicians recommended adding "neck pain/mobility" and removing "neurologic deficit."

Causes/triggers

Clinicians recommended removing specific causes of kyphosis, such as "due to osteoporosis, cancer, other tumors, or trauma/falls," focusing on VCF as the lone cause/trigger.

Exacerbating factors

Clinicians referred to "grade" rather than "type" of fracture as an exacerbating factor. In addition, clinicians recommended adding immobility and narcotic use as exacerbating factors. Three clinicians mentioned the use of narcotic pain medication as a distinct risk factor in kyphosis, stating that the side effects of narcotics could exacerbate the symptoms of kyphosis and possibly lead to additional fractures due to unsteadiness and falling.

One unexpected recommendation was to remove gender as an exacerbating factor. While the literature supported that females are more often affected by osteoporotic kyphosis than are men, clinicians did not believe gender to be an exacerbating factor. Clinician 4 said

> *For a given patient, I think there is no direct impact of the gender.*

Impact on functioning and well-being

Related to physical functioning, clinicians recommended deleting "physical function" as a descriptor of functional limitations. They further recommended adding "difficulty eating" and deleting "impaired coordination" and "sleep problems," about which clinician 3 said

> *I don't see, honestly, so many problems with sleep.*

Likewise, clinician 2 said

> *…sleep disturbance and impaired coordination are not relevant in clinical practice.*

However, despite agreement among clinicians that "sleep problems" were not an issue, the patient interviews produced evidence that this was, in fact, an important concept that was related to kyphosis. This is discussed further in the *Patient interviews* section, below.

Recommendations related to psychosocial functioning included changing "depression/loss of control" to just "depression."

Clinicians indicated that role functioning comprises several areas, specifically mentioning impact of patient's ability to perform daily household activities and activities of daily living, family and social roles, and in some cases, professional roles. Take, for example, this quote from clinician 6 related to professional roles, an emerging concept:

> *…because of the pain, they become more and more isolated in all areas, meaning if they are still in their professional lives, they are usually not able to continue in the way as they would before.*

In sum, clinician interviews were valuable in modifying the literature-based disease model. Most concepts were confirmed, some were removed, and several new concepts emerged.

Patient interviews

The patient interviews yielded very rich data about patients' experiences with kyphosis, the breadth and severity of symptoms, and the impact on functioning and well-being in particular. Patients evaluated the "symptoms" and "impact on functioning and well-being" portions of the literature-based disease model parallel to the clinician evaluation. Signs, causes/triggers, and exacerbating factors were not evaluated by patients because those aspects of the disease model are oriented more toward a clinical knowledge base than patient experience. Overall, patients generally confirmed the model but suggested several additions and deletions. A concept was considered confirmed if shared by at least two patients, although most concepts had much higher agreement. Some concepts discounted by clinicians were confirmed as relevant in the patient interviews (e.g., sleep problems).

Symptoms

Patients, like clinicians, did not confirm the relevance of "neurologic deficit." Otherwise, concepts from the preliminary disease model were confirmed. The quote below from patient T5S is one example of support for "difficulty breathing":

> *They think it has something to do with my breathing… Because it's got me kind of out of whack. It's pushing me in like a way like this [demonstrates a forward movement—appears to be hunching forward]… and it's harder to clear my lungs, I can't just sit up and get a great big breath.*

Impact on functioning and well-being

Related to physical functioning, patients agreed with clinicians that "physical function" and "impaired coordination" should be removed. In addition, "impaired gait" was removed, but "difficulty standing stationary" was added. Patient F1S supported adding this emerging concept by stating:

> *Well, first, standing is very hard for me. Standing in one position for a long time. I can't do it…I can't stand for a long time in one position. I have to move around or sit. So that's one that has affected me, because I love cooking.*

Whereas clinicians had felt "sleep problems" were not relevant for the disease model, patients specified that "sleep problems due to pain" *were*, in fact, a relevant concept. Patient T4N said

> *The pain, constant pain I could not fall asleep. I would eventually fall asleep from exhaustion, pass out and the only reason I knew what time it was is because I*

Table 1 Patient characteristics

Sex	Number
Male	3
Female	7
Age	Years
Mean (min/max)	61 (50/69)
$N \geq 65$ years of age	4
Living situation	Number
Living alone	5
Living with spouse or partner	4
Living with friends or family	1
Highest education	Number
Some college/assoc's degree	3
College graduate	4
Graduate degree	2
Race/ethnicity	Number
White, non-Hispanic	10
Employment status	Number
Not working, on disability	4
Employed full-time	3
Retired	1
Employed part-time	2

Table 2 Disease model development

Model 1: literature based	Model 2: clinician input	Model 3: patient input	Model 4: final model
Signs			
Angle of deformity	Recommended specifying vertebrae and spine	Not evaluated by patients	Angle of deformity: vertebrae Angle of deformity: spine
Degree of deformity	Recommended specifying vertebrae and spine		Degree of deformity: vertebrae Degree of deformity: spine
Neurologic deficit	Recommended deleting		
Gastrointestinal problems	No change		Gastrointestinal problems
Loss of height	No change		Loss of height
	Recommended adding: pelvic parameters		Pelvic parameters
Symptoms			
Pain in the back	No change	Concept confirmed	Pain in the back
Difficulty breathing	No change	Concept confirmed	Difficulty breathing
GI problems	No change	Concept confirmed	GI problems
Poor sagittal balance	No change	No mention of “sagittal”; only one mention of balance	Poor balance
Neurologic deficit	Recommended deleting	Not confirmed/not mentioned	
	Recommended adding: pain/lack of mobility in neck		Pain/lack of mobility in neck
Causes/triggers			
Vertebral compression fractures (VCF)	No change	Not evaluated by patients	Vertebral compression fractures (VCF)
Due to osteoporosis, cancer, other tumors, or trauma/falls	Recommended deleting		
Exacerbating factors			
Previous fracture	No change	Not evaluated by patients	Previous fracture
Number of fractures	No change		Number of fractures
Location of fractures	No change		Location of fractures
Age/gender	Recommended deleting gender		Age
Type of fracture	Recommended replacing type with grade		Grade of fracture
	Recommended adding: narcotic use		Narcotic use
	Recommended adding: immobility		Immobility
Impact on functioning and well-being			
Physical functioning			
Limited mobility	No change	Concept confirmed	Limited mobility
Sleep problems due to pain	Recommended deleting	Concept confirmed	Sleep problems due to pain
Frailty	No change	Concept confirmed	Frailty
Impaired coordination	Recommended deleting	Not confirmed/not mentioned	
Impaired gait	No change	Not confirmed/not mentioned	
	Recommended adding: difficulty eating		
		Concept emerged: difficulty standing stationary	Difficulty standing stationary
Psychosocial functioning			
Fear of falls	No change	Concept confirmed	Fear of falls
Anxiety about future fractures	No change	Confirmed as “anxiety” in general	Anxiety
Depression/loss of control	Recommended deleting: loss of control; retain “depression”	Confirmed as “depression”; “loss of control” not confirmed	Depression
Loss of social interaction/isolation	No change	Concept confirmed	Loss of social interaction/isolation
Decreased self-esteem/body image due to deformity	No change	Confirmed as “decreased self-esteem/body image”; “due to deformity” not confirmed	Decreased self-esteem/body image

Table 2 (continued)

Model 1: literature based	Model 2: clinician input	Model 3: patient input	Model 4: final model
		Concept emerged: moodiness	Moodiness
		Concept emerged: frustration	Frustration
		Concept emerged: Diminished self-worth	Diminished self-worth
Role functioning			
Dependence on others	No change	Concept confirmed	Dependence on others
Difficulty with: ADLs, home care, recreational activities	No change	Concept confirmed	Difficulty with: ADLs, home care, recreational activities
Limitations in social roles	No change	Concept confirmed	Limitations in social roles
	Recommended adding: limitation in family roles	Concept emerged: limitation in family roles	Limitation in family roles
	Recommended adding: limitation in professional roles	Concept emerged: limitation in professional roles	Limitation in professional roles
		Concept emerged: slower pace of activities	Slower pace of activities

> *would toss and turn look up at the clock and all of a sudden I would pass out and then when I woke up, I could see that it had been approximately an hour.*

Related to psychosocial functioning, patients modified “anxiety about future fractures” to “anxiety” in general and modified “depression/loss of control” to “depression.” Patients also added “moodiness,” “frustration/anger,” and “diminished self-worth.” These were concepts not expressed by clinicians or literature. One example of diminished self-worth was expressed by patient T5S:

> *I don’t like to have to depend on somebody else. Like more worthless I guess. It’s just because I…I mean*

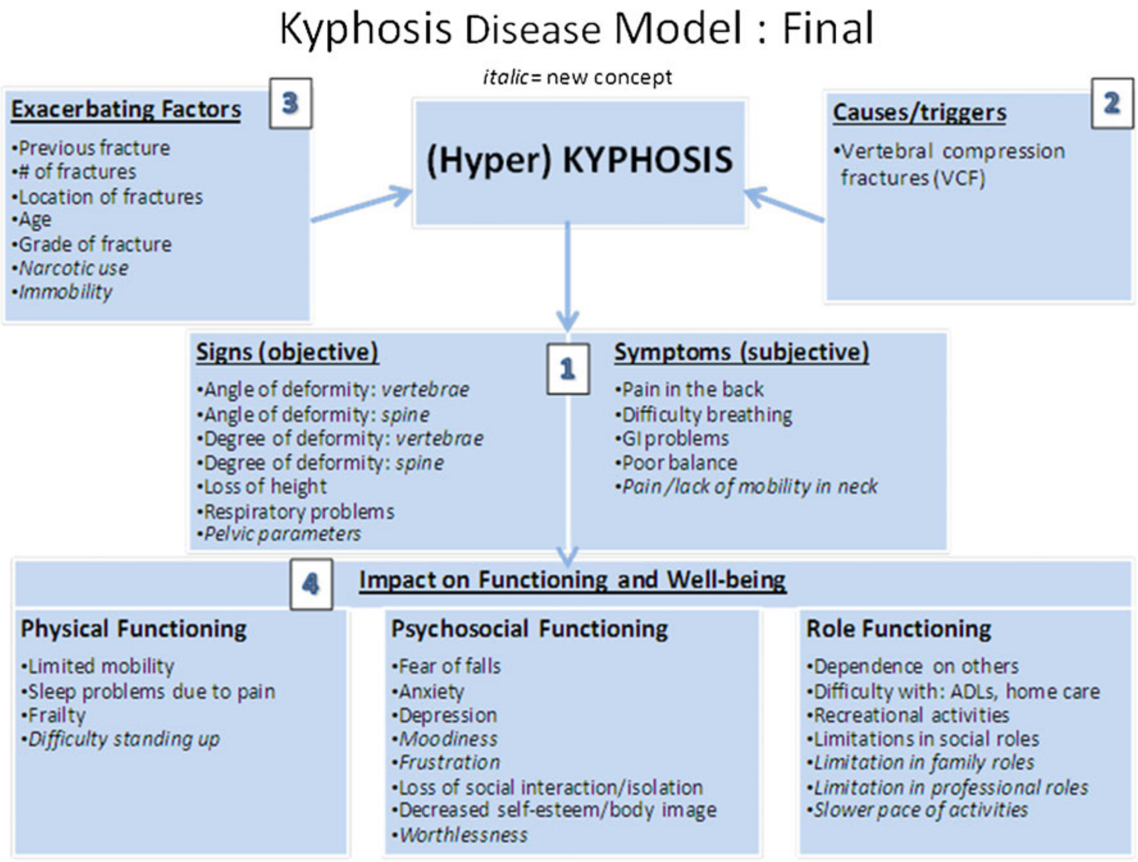

Fig. 2 Final kyphosis disease model

> *when I wanted to do something I did it. I didn't have to ask somebody or make a big production of it.*

Patients agreed with clinicians in the addition of “limitation in family roles” and “limitation in professional roles,”

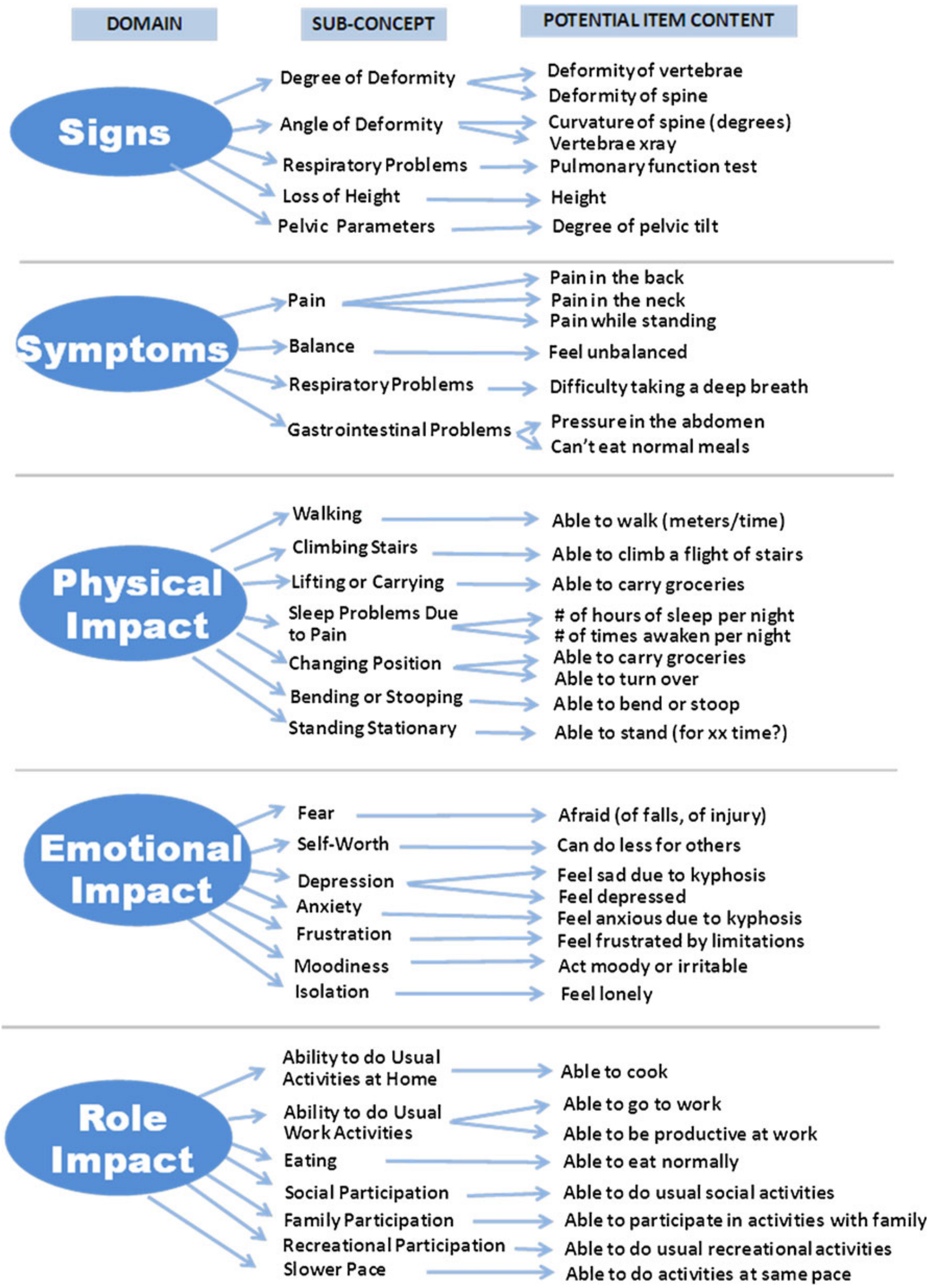

Fig. 3 Conceptual framework

and also added “slower pace of doing activities”. Patient F2S simply said

> *I do everything slower.*

In sum, patient interviews added depth and clarity to the literature-based disease model. In particular, several concepts were added to “impact on functioning and well-being” (Tables 1 and 2).

Final disease model

Figure 2 shows the final disease model that emerged from the clinician and patient interviews, which incorporates the recommended changes to the preliminary literature-based model.

Conceptual framework

Figure 3 shows the conceptual framework to support PRO measurement in kyphosis based on the findings of this study. The conceptual framework mirrors the organization of the disease model. The conceptual framework is designed to capture the concepts from the final disease model that are measurable and to translate those concepts into actual measurements. Thus, there are some differences between the disease model and conceptual framework. For example, the final disease model has “limited mobility” in physical functioning, but in the conceptual framework, this is translated to several measureable concepts such as walking, climbing stairs, and carrying groceries. Similarly, “frailty” is not specifically mentioned in the conceptual framework but can be measured with several existing items in the framework.

Conclusions

Overall, the three sources of data yielded largely consistent information but with some important exceptions. While the clinician interviews yielded considerable confirmation of the disease model, the patient interviews offered more nuanced information about the impact of kyphosis on their well-being and role functioning, broadening the perspective offered by many clinicians.

Observations from clinician respondents indicated that different patterns of signs, symptoms, and functional impact were associated with severity of disease and patient circumstances.

These concepts have been represented in a conceptual framework, designed to guide the selection of measures for future studies of kyphosis and the specification of endpoints for clinical trials.

The study confirms the need for a comprehensive assessment of health outcomes related to kyphosis. Synthesizing patient and clinician perspectives with published literature demonstrates that current approaches to evaluating kyphosis outcomes omit key concepts, specifically loss of functional independence, which is likely a major cost driver.

Limitations of this study are mainly related to sampling of patients and physicians for the interviews. While physicians from both the US and European countries were included, the sample was too small to significantly represent clinical experience from different countries. Similarly, the patient sample included US patients only, of varying levels of kyphosis severity, but self-selection may have omitted those with the greatest impairment. An additional limitation is the reliance on self-report diagnosis for the patient interviews. However, patients’ in-depth explanations during the interviews of their experiences provide additional confirmation of the diagnosis.

Based on the findings of this Kyphosis Conceptual Framework, additional research needs include critically reviewing properties of existing PRO and ClinRO assessments within the framework and establishing that scores generated from these assessments are valid, reliable, and able to detect change. It is important that the PRO or ClinRO be developed and tested in the same patient population as the intended use for the label claim [1]. Critical analysis of existing instruments may lead to recommendations for additional validation studies, modification of the existing tools, or identification of the need for the development of a new PRO or ClinRO to appropriately measure the symptoms and impact of kyphosis, and provide scores that will support the conceptual framework and, ultimately, the label claim.

Conflicts of interest Carolin Miltenburger and Luisa Alvares are employed by Medtronic Spinal & Biologics, which funded this research. Martha Bayliss and Michelle White are employed by QualityMetric, which has served as a consultant to Medtronic.

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