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Quality of life in haemophilia

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Summary. There is a growing interest in patient-reported outcomes as measures for evaluating the benefits of new and existing treatments. Health-related quality of life (HRQoL) is one of these patient-reported outcomes and represents the individual experience and perception of illness/health together with the psychosocial response to disease-related and treatment-related symptoms. Generic and disease-specific HRQoL questionnaires enable us to assess and quantify the multi-dimensional perception of well-being, namely the physical components and the psychological (emotional, mental, social and behavioural) components of patient's well-being and functioning. These instruments should be standardized and validated and they should prove to be reliable, valid, specific and sensitive in a similar manner to instruments created for objective parameters. HRQoL assessment can help us to evaluate the benefits of new treatments from the perspective of patient's values and expectations. It can also help to evaluate the quality of care provided, in order to be able to improve it at a local and national level. Moreover, HRQoL assessment can be routinely assessed to monitor improvement and progress or deterioration and decline from the global point of view of each single patient, integrating the otherwise limited angle of objective signs and instrumental or lab parameters.

Keywords: haemophilia, patient outcome measure, quality of life, well-being

> It is characteristic of the military mentality that nonhuman factors (atom bombs, strategic bases, weapons of all sorts, the possession of raw materials, etc) are held essential, while the human being, his desires, and thoughts – in short, the psychological factors – are considered as unimportant and secondary...The individual is degraded...to 'human materiell'
>
> Albert Einstein, 1955[1]

Introduction

Why we should assess quality of life

Incredible progress has been made in medical sciences. We are not only able to categorize signs and symptoms into well-defined syndromes (to provide a name to a disease is always extremely reassuring to the clinicians), but we are now able to recognize the organ involved, and, more precisely, the suffering tissue, the implicated cells of that tissue, the concerned cellular organelles, the affected DNA genes, the molecular defect of that gene. With Andreas Vesalius or van Wescle, who wrote in 1543 *De humani corporis fabrica* (*On the Workings of the Human Body*) [2], the human body was no longer considered as a unit, but it was dissected into its single parts, bones, muscles and organs. Starting in 1953, with the precise description of the deoxyribonucleic acid [3] containing the genetic instructions for the development and functioning of all known living organisms including human beings, the congenitally diseased person has been regarded more and more as the carrier of a genetic imperfection. Thanks to the progress of medicine, new ways to treat these diseases have become available over time: starting with surgery in the Neolithic Age, we have become able to remove the damage in the involved organ (and today, we can transplant the organ if it cannot be repaired); subsequently, more and more effective medicines have contributed to the reparation of the suffering tissue or substitute the missing

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protein; in this day and age, we can ultimately attempt to transplant or to repair genes when they are affected, or to regenerate tissues and organs with stem cell therapy.

As a result of this exciting progress, what we have probably lost is the patient, an individual with his integrity, personality, feelings, problems, wishes and hopes. 'Individual' derives from Latin *individuus*, indivisible, from *in-* + *dividuus*, divided; an individual can be dissected in pieces only when he has lost his life. A human being is different from any other living beings for his humaneness, which cannot be placed in any organ or tissue; nevertheless, it should not be sacrificed in name of Science.

For this reason, overall well-being, as subjectively perceived by the individual affected by a disease, must not be ignored or considered secondary to other organ-, tissue-, cell-, lab test-specific but limited parameters, precise but partial surrogates of health. Medicine is a science applied to individuals, like anatomy and physiology, but completely different from these.

When the management of haemophilia was a struggle against a premature death and a pain-endured crippled life, physicians' efforts were concentrated on prolonging the patient's lifespan and in fighting pain and disability and its causes. This battle has not yet been won, but enormous progress has been accomplished and more and more physicians and patients are now struggling to improve the quality of the life of people with haemophilia.

Consequently, the study of methods to evaluate and quantify quality of life (QoL), in order to be able to monitor the outcomes of new therapies, should not be regarded as a superfluous, intellectual exercise that has recently become fashionable, but it should be considered an essential part of medical management. The subjectivity of patients, their perception and personal judgement should be at least taken into the same account as objective signs and instrumental parameters. The same concepts of 'health' and 'disease' are paradigms not mutually shared by people and their doctors. In other words, patients' assessment of their own well-being should have the same degree of importance as MRI scores or factor VIII levels.

What is quality of life?

The essence of QoL, a synonym of well-being, was already being discussed in Aristotle's time. In his *Nicomachean Ethics* [4], he announced the concept of *eudaimonia* or *eudemonia* (εὐδαιμονία), a Greek term consisting of the word 'eu' ('good' or 'well-being') and 'daimōn' ('spirit'), a contented state of being happy and healthy and prosperous: *eudemonia* should be our ultimate aspiration. Governments have tried to find objective indicators of Qol: the best known composite quality of life scale is the United Nations Development Programme's Human Development Index [http://www.undp.org]. This index is a single value that puts together health, longevity, knowledge (literacy and school enrolment) and standards of living (GDP per capita) [5]. Alternatives to this purely economic approach include attempting to measure the non-economic aspects of the QoL [6], well-being as a hierarchy of needs [7], and even the 'Gross National Happiness' [8]. This interesting approach 'links the economy with social and environmental variables to create a more comprehensive and accurate measurement tool'. In 1994, the World Health Organization has also provided a general definition of QoL [9], summarized as 'the individual's perception of his position in life in the context of culture and value system in which he lives, and in relation to his goals, expectations and concerns'.

In all of these definitions, from Aristotle to WHO, we can recognize two main subsets: QoL directly related to health (health-related quality of life, HRQoL) and QoL not related to health (non-health-related quality of life, NHRQoL); the latter consists of internal and external components, such as individual's motivation, personality, coping strategies, social networking, financial status and also geographical and societal environments [10]. Both types of QoL have a great influence on the overall concept of quality of life and they reciprocally influence each other. Therefore, it is logical that even though in individuals in good health NHRQoL factors have a major influence, in individuals with chronic illnesses HRQoL factors have a much greater importance.

As a consequence of this reasoning, HRQoL can be defined as the 'qualitative dimension of functioning' [11] or the individual experience of illness with the psychosocial response to disease-related and treatment-related symptoms [12].

Discussion

Can HRQoL be assessed?

If HRQoL is based on the subjective perception of well-being, the major issue is whether or not it can be measured objectively. It looks a contradiction in terms. Subjectivity is very suspicious in the eyes of supporters of Medicine as an exact, hard science. Psychology itself is considered by these hard-boiled

scientists to be undefined for its essence, methodology and importance. For these physicians, 'subjective' is a synonym of 'abstract' and consequently not measurable, not different from pain. By contrast, like pain, it can be assessed and quantified by means of standardized and validated instruments, which should be reliable, valid, specific and sensitive similar to instruments created for objective parameters, able to provide reproducible data, responsive to age and time influence. These instruments should take into account the multidimensional character of HRQoL, both the physical components and the psychological (emotional, mental, social and behavioural) components of the patient's perception of well-being and functioning as perceived by the patients and/or observers [13].

As a natural corollary, HRQoL instruments should include physical and mental domains and should possibly be based on patient report [14], by means of self-administered questionnaires or interviews that cover the different aspects of health. In fact, the WHO clearly stated in 1946, in its constitution, that health should be considered 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' [15].

Other methods to quantify HRQoL consist of asking patients to give an overall value to the perceived well-being or to ask observers (so called proxies, normally family members or care-givers) to rate HRQoL or to answer HRQoL questionnaires, the latter being essential to assess very small children or mentally disabled people.

An important issue concerning HRQoL assessment instruments is represented by the age of respondents: it is commonsense that well-being concepts greatly differ among small children, adolescents, young adults and elderly people. For this reason, instruments should be specifically designed for the age of patients to be investigated [16].

Another critical issue is the scope of the evaluation: if we want to have a general estimation of HRQoL, not specific to a particular disease and we want to compare our patients' status with that of patients with different diseases we must use a so-called 'generic instrument' [17]. If we aim to evaluate more precisely the health and well-being of patients with a specific disease, we should use a targeted or disease-specific questionnaire [18]. It is evident that we cannot use the same disease-specific instrument in two different diseases (i.e. a haemophilia-specific HRQoL questionnaire for patients with asthma and vice versa). More and more frequently are patients assessed with both generic and disease-specific instruments in order to get the best from each type of instrument.

In addition, since we are going to ask patients (or their proxies) for information about their perception of well-being and functioning, the questions must be immediately comprehensible, unambiguous, covering a single aspect of that specific domain we are investigating, in plain language appropriate to the age and the culture of the patient being interviewed. Therefore, these instruments must be psychometrically, linguistically and cross-culturally validated [19,20].

What HRQoL instruments are available?

Over the last 30 years, a number of generic instruments to assess HRQoL in children (http://www.euroqol.org) [21–26] and in adults [27–33] have been developed. They have differences and similarities and require a deep knowledge of them for the choice, use and interpretation. Tables 1 and 2 show the most commonly used generic instruments for adults and children. Systematic reviews on the use and results of generic HRQoL instruments have been published [34–36].

In the last five years, disease-specific instruments for children and adults with haemophilia have been developed, as shown in Tables 3 and 4 [37–46], which have been recently reviewed [47]. All of the questionnaires for children are self-completed, but the American Quality of Life for Young Patients questionnaire, which is completed by proxies and, designed for smaller children, aged 2–6 years. It is

Table 1. The most common generic HRQoL questionnaires for children.

Acronym	Name	Reference	Country
KINDL	Lebensqualitätsfragebogens für Kinder	Bullinger *et al.* [21]	Germany
CHQ	Child Health Questionnaire	Landgraf *et al.* [22]	USA
TACQOL	TNO AZL Child Quality Of Life	Theunissen, *et al.* [23]	Netherlands
Peds-QL	Pediatric Quality of life Inventory	Varni *et al.* [24]	USA
KIDSCREEN	Health Related Quality of Life Questionnaire for Children and Young People and their Parents	Ravens-Sieberer *et al.* [25]	Europe
EQ-5D Child	EuroQoL 5 dimensions (child-friendly version)	http://www.euroqol.org (2002)	UK
DCGM-37	DISABKIDS Chronic Generic Measure	Bullinger *et al.* [26]	International

Table 2. The most common generic HRQoL questionnaires for adults.

Acronym	Name	Reference	Country
QWB	Quality of Well-being Index	Kaplan *et al.* [27]	USA
SIP	Sickness Impact Profile	Bergner *et al.* [28]	USA
NHP	Nottingham Health Profile	Hunt *et al.* [29]	UK
EQ-5D	EuroQoL 5 Dimensions	The EuroQol Group, [30]	UK/Europe
SF-36	Medical Outcome Study 36-item short-form health survey	Ware and Sherbourne [31]	USA
SF-12	Medical Outcome Study 36-item short-form health survey	Ware *et al.* [32]	USA
WHOQoL	World Health Organization Quality of Life Questionnaire	Power *et al.* [33]	International

Table 3. Disease-specific HRQoL questionnaires for children with haemophilia.

Acronym	Name	Reference	Country
Hem Dux	Quality of life questionnaire for children with hemophilia	Robben *et al.* [37]	Netherlands
QUAL-HEMO	Haemophilia age-group specific quality of life questionnaire	Trudeau *et al.* [38]	France
HAEMO-QOL	Haemophilia Quality of Life Questionnaire (3 age versions)	v. Mackensen *et al.* [39]	Europe
CHO-KLAT	Canadian Haemophilia Outcomes-Kids' Life Assessment Tool	Young *et al.* [40]	Canada
na	Quality of Life for Young Patients	Manco Johnson *et al.* [41]	USA
HAEMO-QOL Index	Haemophilia Quality of Life Questionnaire Index (1 age version)	Pollak *et al.* [42]	Europe

Table 4. Disease-specific HRQoL questionnaires for adults with haemophilia.

Acronym	Name	Reference	Country
Medtap	n.a.	Flood *et al.* [43]	USA
QUAL-HEMO	Quality of life questionnaire in hemophilia	Trudeau *et al.* [38]	France
Hemofilia-QoL	Disease-specific quality-of-life questionnaire to adults living with haemophilia	Arranz *et al.* [44]	Spain
Hemolatin-QoL	Disease-specific quality-of-life questionnaire to adults living with haemophilia	Remor *et al.* [45]	South America
Haem-A-QoL	Haemophilia QoL questionnaire for adults	v. Mackensen *et al.* [46]	Italy

interesting to note that there are different versions of HaemoQoL according to children's age (4–7 years, 8–12 years and 13–16 years) in order to better capture all the aspects of their well-being in the different developmental phases. In addition, it has an index version (HaemoQoL Index) that allows for comparison among the different age groups. There are three versions of the French Qual-Hemo questionnaire: for children, for adolescents and for adults.

Among the haemophilia-specific HRQoL instruments, there are differences and similarities: Table 5 shows the areas covered by the different questionnaires. It is important to note that the Italian Haem-A-QoL has a core instrument with shared items with the paediatric Haemo-QoL that allows for comparison between HRQoL of adults and children. This questionnaire for adult patients with haemophilia has been linguistically validated in over 20 languages. A version of this questionnaire has been developed for elderly patients and will be presented at Hemophilia 2008 World Congress.

Because of these instruments' multiplicity, diversity and the lack of gold standard, physicians are not encouraged to use them. The choice is not simple and must be on the basis of the aim of the evaluation, the age of patients, the design of the study, and the characteristics of the instruments available. Table 6 shows the study-related issues and Table 7, the instrument-related issues to take into account when choosing the particular instrument to use [48].

Conclusions

Can HRQoL assessment contribute to haemophilia care?

HRQoL assessment has become more and more popular: in fact, it offers the unique opportunity to have a validated measure of the patient's perception

Table 5. Common domains of haemophilia-specific quality of life (QoL) questionnaires for adult patients.

	Specific domains		
Areas	Medtap	Haem-A-QoL	Hemofilia-QoL
Physical	Physical functioning	Physical health	Physical health
	–	Sports and leisure	Joint damage
	–	–	Pain
Functional	Role functioning	Work and school	Daily functioning
Social	Psychosocial-related	Family planning	Relationship/social activities
	–	Partnership and sexuality	–
Emotional	Fear/worry	Feeling	Emotional functioning
	Positive effect	View	–
	–	Future	–
Mental	–	–	Mental health
Treatment and disease	Treatment worry	Treatment	Treatment satisfaction
	–	Dealing	Treatment difficulties
No. of domains	6	10	9
No. of items	46	46	36

Table 6. Study-related Issues for the choice of a questionnaire.

Issue	Type
Study design	Prospective/cross-sectional
	Observational/interventional
	National/international
	Cross-illness comparison
Study population	Children/Adults/Both
	Capable or not to answer a questionnaire
Study outcomes	Clinical (functioning)
	Psychosocial (quality of life, coping, etc.)
	Cost-related (cost-utility, cost-benefit, etc.)
	Patient preference
	Patient satisfaction
Time of administration	Baseline
	Short-term follow-up
	Long-term follow-up

Table 7. Instrument-related issues for the choice of a questionnaire.

Issue	Type
Who fills in the questionnaire	Children/adults/both
	Patient/proxy
Type of questionnaire	Generic
	Chronic generic
	Disease-specific
Psychometric characteristics	Reliability
	Validity
	Sensitivity
Feasibility of the instrument	Comprehensibility
	Acceptance
	Relevance
	Completion time
Validation of the instrument	Linguistic
	Cross-cultural
Areas and dimension investigated	Physical (autonomy, functioning, pain, sport and leisure)
	Mental (emotional, stress, etc)
	Coping strategies
	Social (integration and functioning, relationships)

of the overall effect of haemophilia care provided, an irreplaceable patient-rated outcome measure. It helps to weigh the benefits of old and new treatment strategies or new drugs, by asking the patient what benefit, what improvement of well-being, he has eventually obtained from that particular treatment. Knowing the patient's opinion of his health not only research benefits but also quality of the overall structure of haemophilia care and how it is delivered, promoting initiatives to correct and improve it.

In addition, HRQoL assessment can help in comparing the health care systems or haemophilia care resources among countries, in order to push governments, administrators, communities and any other stakeholders to match and harmonize their national health services to that of other countries.

Last, but not the least, HRQoL assessment can be applied in the routine assessment of patients with haemophilia, similar to the annual check-up of joint status or viral screening. It can help to verify whether or not the treatment provided to each single patient is the right one, able to maintain or to improve his QoL, which is his perception of well-being, his '*eudaimonia*', his happiness.

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