

# Health-related quality of life (HRQoL): an update in multiple endocrine neoplasia type 1

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## ABSTRACT

**Purpose:** Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant cancer syndrome characterized by the development of multiple neuroendocrine tumors. The condition requires lifelong surveillance and multiple medical and surgical therapies throughout the patient's life.

For all these reasons, a diagnosis of MEN1 can be a psychological shock for the patient, as well as his/her relatives. Over the past two decades, clinicians have started to consider the emotional, psychological, relational and social aspects of MEN1 patients' lives, as these may be important considerations in the clinical and therapeutic management of these patients.

**Methods:** This paper reviews and critically analyzes perceptions of MEN1-related quality of life (QoL) in patients diagnosed with the syndrome and in relatives, highlighting the unique features of MEN1 syndrome compared with a single tumor diagnosis.

**Results:** Interestingly, studies in MEN1 patients have shown that a relatively high percentage of them, despite having a complex multi-tumor syndrome, were moderately optimistic (50%), self-reporting a normal QoL. This positive response correlated with the fact that these patients were cared for at dedicated referral centers, where personalized care and constant follow-up provide them with reassurance that they are receiving high quality of management of their disorder.

**Conclusions:** The possibility of having access to a clinical referral center for this complex rare disease, together with the support of a dedicated patient association, emerged as the ideal model for the management of post-diagnosis shock, and appeared to contribute to the preservation of good health-related quality of life in MEN1 patients.

## KEYWORDS

Multiple endocrine neoplasia type 1, neuroendocrine tumors, quality of life (QoL), health-related quality of life (HRQoL).

## Health-related quality of life and its importance in clinical practice

Health-related quality of life (HRQoL) is a multidimensional concept that includes physical and mental health, psychological state, emotional and relational perceptions, social support and socioeconomic status. It goes beyond direct measurements of population health, life expectancy and causes of death, and focuses on the impact that health status has on the quality of life of a group or of single individuals. Health includes not only the absence of disease, but also a state of well-being and the ability to react in the face of changing circumstances. The World Health Organization (WHO) defines quality of life (QoL) as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”<sup>[1]</sup>. Accordingly, an individual's HRQoL also takes into account the positive aspects of his/her life, such as positive emotions and life satisfaction.

Mental health is an important component of global health, and one of the principal parameters determining HRQoL, which the WHO defines as “a state of complete physical, mental and

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social well-being, and not simply the absence of disease”. Mild to moderate mental disorders affect approximately 20% of the working-age population, and are mainly highly treatable problems, such as anxiety and depression<sup>[2]</sup>. Mental disorders negatively impact not only an individual's well-being, but also their networks, their work productivity and on society as a whole. People with severe mental illness die up to 20 years younger, have much higher unemployment rates, and are poorer than the general population<sup>[2]</sup>. Education contributes to a higher general QoL because of its positive effects in terms of improving habits and encouraging a healthy lifestyle mindset, better social interactions, active citizenship, greater earnings and productivity; more educated people typically have lower unemployment

rates, better health, more social connections, and greater engagement in civic and political life.

For decades, medicine tackled only the clinical manifestations and physical symptoms of diseases; helping people to live longer in good physical health was the main objective of health policy. Since the 1980s, however, the concept of HRQoL has been evolving and progressively entering clinical practice: the patient's QoL is now considered a key aspect when setting up patient care. In recent decades, there has been a growing recognition of the value of including the patient's self-perceived health status in the anamnesis, collecting data on this aspect, integrating the personal experience of illness into clinical and therapeutic management of disease, and evaluating the impact of mental distress and disease-derived anxiety and depression on the efficacy of therapy and the correct adherence to medical treatments. Self-perceived health status is a subjective measure of general health which has important consequences for individual QoL. Indeed, people who consider themselves to be in poor health may be more likely to be depressed, have reduced social function, and lead less productive and satisfying lives. Furthermore, self-perceived health status is an important determinant of the perceived need (and demand) for health care and other health services.

However, although self-assessment of personal health status has the advantage of covering aspects that are difficult to detect clinically, such as incipient disease, disease severity, physiological and psychological reserves and social function, it is a subjective assessment that can be strongly influenced by the patient's social and cultural background. Therefore, caution is needed when making between-country comparisons of perceived general health.

Recently, QoL assessment has also started to be taken into consideration in the clinical management of rare and/or oncological diseases — situations in which the diagnosis represents a trauma for patients and their families, mainly due to the uncertainty of the disease outcome. Depression, anxiety and fear appear to be normal responses to a diagnosis of such importance, and often manifest with clinical symptoms such as pain, nausea, appetite changes, insomnia and/or fatigue<sup>[3]</sup>.

Self-assessed HRQoL is usually evaluated using QoL scales (QoLSs) that measure aspects like psychological state, satisfaction, control, involvement, commitment, social connections and work-life balance, as perceived by the individual. HRQoL self-assessment mainly involves the administration to patients of one or more specific questionnaires.

One of the most widely used HRQoL questionnaires is the 36-item Short-Form Health Survey (SF-36), a generic multi-dimensional health survey consisting of 36 questions divided into 8 different QoLSs: three of these concern the evaluation of “physical health” (PF = physical functioning, RP = role limitations due to physical health problems and BP = bodily pain), two investigate “general health” (GH = general health perceptions, VT = vitality, energy or fatigue), and three measure “psychological and emotional health” (SF = social functioning, RE = role limitations due to emotional problems, MH = general mental health, covering psychological distress and well-being)<sup>[4]</sup>. The Life Orientation Test (LOT) is a standard psychological tool for measuring optimism. The first version of this test had

twelve questions, each measuring optimism and pessimism objectively. An improved version of the LOT, known as LOT-Revised (LOT-R) and including only six questions, was subsequently developed and is now the most used. LOT questions can easily be applied to all individuals irrespective of their age or social and cultural background, and they allow investigation of simple aspects of life, such as statements of personal feelings about the self, others and life, both in general and when feeling stressed or happy<sup>[5]</sup>.

The Impact of Event Scale (IES) is a 15-item questionnaire that was initially developed for the assessment of aspects of post-traumatic stress disorder, but is now commonly used to evaluate the impact of a number of traumatic experiences. A 22-question revised version (IES-R) has been developed specifically for assessing emotional response to and distress caused by a traumatic event, including the diagnosis of a severe and potentially lethal disease<sup>[6]</sup>.

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report rating scale, specifically designed to measure levels of anxiety (7 items) and depression (7 items). Scale scores range from 0 (no distress) to 21 (maximum distress)<sup>[7]</sup>.

The Patient-Reported Outcomes Measurement Information System (PROMIS) is an online platform, supported by the National Institutes of Health, aimed at developing new ways to measure patient-reported symptoms, such as pain and fatigue, and aspects of HRQoL. Using PROMIS, it is possible to evaluate and monitor over 300 measures of three main health domains (physical health, mental health and social health) in adults and children, and it can be used both in the general population and in individuals living with chronic conditions<sup>[8]</sup>.

The Cancer Worry Scale (CWS) is an 8-item scale used to measure worry about the risk of developing cancer, the level of fear in cancer patients, and the impact of worry and fear on daily functioning among individuals at risk of hereditary cancer<sup>[9]</sup>.

Finally, the Griffin guide defines four prudential values, which, evaluated according to individual characteristic combinations, constitute essential aspects of a person's overall QoL. These four values are: the ability to enjoy a certain sense of autonomy, not merely being a victim to circumstances beyond one's control; the enjoyment of pleasure, life should not only contain pain and suffering; the enjoyment of a certain level of deep personal relationships; and the enjoyment of having accomplished something in life, leaving an imprint. These values correspond well to components identified in QoL surveys<sup>[10]</sup>.

## Multiple endocrine neoplasia type 1 (MEN1)-related quality of life

Multiple endocrine neoplasia (MEN1) is a rare congenital endocrine cancer syndrome characterized by the development of multiple neuroendocrine tumors in a single patient, principally at the level of the parathyroid glands, anterior pituitary and gastro-entero-pancreatic tract. Other endocrine and non-endocrine tissues can also be affected, albeit less frequently, giving rise to over 20 different possible combinations of tumors and lesions<sup>[11]</sup>.

Affected patients develop multiple multiglandular tumors over the course of their life, which manifest asynchronously,

making it necessary for them to undergo, over time, multiple invasive surgical interventions and/or multiple and chronic drug treatments, as well as continuous follow-up monitoring for possible relapses. In short, MEN1 patients, regardless of whether their diagnosis is clinical or genetic, need a life-long specific diagnostic surveillance program with routine biochemical and radiological screenings. Tumoral glands overproduce hormones and can be responsible for the related endocrine syndromes which contribute to reducing these patients' QoL, increasing their morbidity, and, together with malignant progression of some MEN1 tumors, shortening their life expectancy with respect to the general population. Moreover, given the genetic nature of the disease — it is caused by germinal heterozygote inactivating mutations of the MEN1 tumor suppressor gene — tumors present a high rate of post-operative recurrence, necessitating further interventions and thus increasing the risk of surgically-induced severe damage of the operated organ and adjacent structures. Affected patients have a 50% chance of transmitting the genetic defect, and thus the disease (the penetrance for mutation carriers is up to 100% after the age of 50), to their offspring<sup>[12]</sup>.

All these aspects contribute to negatively impacting an individual's psychological state following a diagnosis of MEN1.

Over the years, different research groups have investigated HRQoL in MEN1 patients. To do so, they applied questionnaires commonly used in other chronic or tumor diseases, given that, unfortunately, there are currently no dedicated questionnaires for MEN1 or other inherited multiple tumor syndromes.

Here we review, and critically discuss, the interesting preliminary results obtained by these studies, and the importance of assessing HRQoL in MEN1 patients in order to better manage their disease and tailor diagnostic, therapeutic and follow-up approaches in this setting.

Berglund *et al.*<sup>[13]</sup>, in 2003, were the first to analyze HRQoL in this population, by administering four questionnaires — the LOT, the IES (i.e., the original unrevised versions), the HADS and the SF-36 — to 29 of 36 recruited Swedish MEN1 patients. HRQoL was assessed twice: during the recruitment visit at the hospital, and again six months later, when the patients repeated all four questionnaires at home. In all 29 patients, the diagnosis of MEN1 caused psychosocial distress, and the scores changed only marginally between the hospital visit and those measured six months later at home. A higher degree of depression was found in patients classified as having more severe disease and requiring extensive treatments; according to the authors, this group of patients needs psychosocial support after hospital discharge. According to the SF-36 scores, these MEN1 patients had a more negative personal perception of their own general health and social outcomes with respect to the general population. MEN1 patients were pessimistic about their uncertain future, manifesting fear about what might happen to them, their children and their other relatives in 70% of cases. This pessimism may also be related to uncertainty about the progression of the disease and how this could negatively influence their daily activities and ability to maintain their current work situation. In this study, both the LOT and the IES showed some limitations which reduced the strength of the analysis: in fact, the unrevised version of LOT fails to cover aspects related to

patient's future expectations, while the original IES does not include the hyperactivation subscale.

In 2007, Strømsvik *et al.*<sup>[14]</sup> performed a HRQoL study in 29 Swedish MEN1 patients, monitoring their future expectations, their daily living with the syndrome, how disease-related physical, psychological and social limitations impacted their daily activities, and how these limitations influenced their QoL. The investigation was conducted through target interviews conducted at the clinic on the day of the patients' arrival by two psychologists, in accordance with the 1986 Griffin guide. The qualitative interview focused on QoL, ability to influence and control one's own life, interpersonal relationships, and the ability to achieve personal goals. In general, the interviewed patients reported that, after being diagnosed with MEN1, they tried to adapt to their new medical situation by changing their lifestyle and focusing on healthy choices, such as good dietary habits and physical activity. Interpersonal relationships with family and friends were highlighted as one of the most important aspects of their lives. Patients declared that, by learning to live with their personal risk of developing the condition, they had changed their priorities, and this "positive" attitude helped them to better manage their condition. With regard to their working lives, the patients reported that they still had a sense of control, and only minor fears concerning professional limitations related to the disease. Putting together all these data, the study showed that most patients described themselves as "healthy", despite the severity of the disease, the multiple and invasive surgeries, the long-term drug treatments, and the presence of, often disabling, physical and psychological symptoms. Moreover, they declared themselves satisfied to be in a clinical surveillance program directed by a multidisciplinary group of specialists, since this allows immediate initiation of therapy at the time of tumor development, with a greater chance of being cured permanently and maintaining a generally good QoL.

Several years later, in 2018, Peipert *et al.*<sup>[15]</sup> selected a group of 153 adults (>18 years) with a clinical diagnosis of MEN1, all resident in the US. The authors analyzed their HRQoL against other that of patients with other chronic diseases. The participants were requested to complete an original two-part online survey that had been specifically developed by the research team in collaboration with an online support group for people with MEN1 (AMENSupport). The first part of the questionnaire comprised questions about socio-demographics, diagnosis and treatment. For the second part of the survey, the 29-item PROMIS (PROMIS-29) was used. PROMIS-29 includes 4 items for each of 7 domains (anxiety, depression, physical function, fatigue, pain interference, satisfaction with social function, and sleep disturbance) plus a single 11-point rating scale measuring pain intensity. The PROMIS-29 scores of the MEN1 patients were compared with the PROMIS scores reported in the literature for other diseases, such as back pain, cancer, chronic obstructive pulmonary disease, congestive heart failure, major depressive disorder, neuroendocrine tumors, primary hyperparathyroidism, and rheumatoid arthritis. The results showed that MEN1 patients had a worse perception of their HRQoL with higher levels of anxiety, depression and fatigue. Unfortunately, the PROMIS online platform presents a recruiting limitation, in that it tends to exclude people less

familiar with social media or less able to move within the web. In addition, inserted clinical and genetic data are likely to be inaccurate as they were self-entered by patients, thus, risking to include patients who in reality were not affected by MEN1.

The same year, Van Leeuwaarde *et al.*<sup>[16]</sup> administered an 8-item questionnaire, adapted from the CWS, to a total of 285 patients, of whom 227 (80%) were eligible as MEN1 patients. The patients with MEN1 recorded a higher mean fear of disease onset (FDO) score than the patients diagnosed with other types of cancer. The results of the survey associated the subgroup of MEN1 patients presenting a high FDO with lower scores on the SF-36 scale, for all the subscales except PF, and thus indicated a lower self-perceived general HRQoL in this subgroup. The high percentage of MEN1 patients with a high FDO highlights the need for more attention to and support for aspects of disease-related fear and worry. The study also showed that an increase in the number of MEN1 clinical manifestations was directly related to higher FDO scores. Although most MEN1 patients record high FDO scores for themselves, they are more fearful of disease onset in their relatives (as reflected in even higher FDO scores). This psychological distress is associated with a lower related quality of life. CWS is an effective tool for detecting high levels of FDO in patients with cancer, but it does not allow assessment of changes in FDO and QoL over time.

Recently, our research group<sup>[17]</sup> conducted a comprehensive survey in 76 MEN1 Italian patients, evaluating the individual's perception of disease and HRQoL in terms of both physical status and psychological, emotional, social and economic impacts. Our study is the first to analyze HRQoL in a large series of MEN1 patients through the simultaneous administration of five of the most commonly applied clinical questionnaires: a socio-demographic questionnaire, the LOT-R, the IES-R, the HADS and the SF-36. The socio-demographic questionnaire results indicated that, in spite of their disease, the majority of patients were able to shift their priorities, manage their situation well, and maintain normal interpersonal relationships with family and friends, which the patients considered one of the most important aspects of their own lives. The LOT-R test results showed that only about 30% of the interviewed patients were pessimistic, while the IES-R test revealed the presence of post-traumatic stress symptoms in 75% of our MEN1 patients: the most common symptom was intrusiveness, followed by avoidance and hyperarousal. The HADS test showed full-blown anxiety in approximately 8% of the cases and major depression in about 28%. Most patients were borderline cases (i.e., at risk of turning into psychopathological cases). The SF-36 questionnaire showed that most of the people in our MEN1 series have minimal difficulty in working or performing other daily activities due to emotional or physical problems, have good physical health, believing it to be similar to that of their peers. Patients reported being able to perform all kinds of activities, including the most demanding ones, without any particular physical or emotional difficulties, as their perceived pain was not strong enough to limit their performance, and their mood was positive. Mean scores of the SF-36 variables in MEN1 patients compared with the general Italian population confirmed a reduction in the QoL of MEN1 patients<sup>[18]</sup>. Despite this, most patients considered themselves “healthy despite everything” and

maintained good control of their working life. The fact of being under the care and supervision of a dedicated referral center for MEN1 syndrome, where they receive a personalized care from qualified specialists and constant follow-up, gave our patients reassurance regarding the high quality of the management of their disorder, and this strongly contributed to their “positive” attitude and perception of a relatively good general HRQoL. Twenty of the original 96 patients we approached refused to fill out the questionnaires, thus, the patient sample evaluated was not representative of the entire population of our MEN1 patients. It is possible that the people who did not participate in the study were, in most cases, psychologically “weaker” patients. Their absence in the calculation of self-reported HRQoL in this study could be one of the reasons for its apparently “positive” results. This fact could represent a bias of the study and the actual emotional state of MEN1 patients may be lower than that found herein.

## Discussion and main conclusions

To date only a few studies, described in the previous section, have investigated the impact of MEN1 diagnosis and manifestations on the various aspects of HRQoL in individuals affected by this syndrome. The psychological aspects influencing the clinical and therapeutic management of MEN1 and patients' QoL remain to be clearly elucidated before they can be routinely incorporated into clinical practice.

Published studies used different questionnaires, which makes it difficult to compare their results and prepare HRQoL-related guidelines for MEN1 syndrome. Unfortunately, specific questionnaires have not yet been developed to measure HRQoL in this syndrome. Generic HRQoL questionnaires are not developed specifically for complex tumor syndromes such as MEN1, and consequently their use could lead researchers to underestimate or overestimate some specific disease traits that affect patients' psychophysical status. The design of a MEN1-specific HRQoL questionnaire would likely help to increase the efficacy of analyses of this syndrome. The collection of data on MEN1 patients, at both national and international level, would provide a greater number of subjects to be analyzed, and therefore a more inclusive MEN1 population, reduce the underestimation of differences related to personal socio-demographic characteristics, and, thus, improve the statistical power of the analysis.

Despite the above mentioned critical issues and the difficulties in comparing data from studies performed with different HRQoL questionnaires, all the published works reported a clear result: a diagnosis of MEN1 is a shock, which caused all the patients immediate post-diagnosis shock. The high percentage of MEN1 individuals showing signs of post-traumatic stress after receiving the diagnosis of the syndrome is a strong indication that the psychological status of these patients needs to be monitored over time to prevent the development of anxiety, depression or other long-term psychological disorders.

The multiple invasive and/or complex surgical interventions and prolonged medical treatments that characterize the lives of almost all MEN1 patients are among the main reasons

for worsening of their QoL. On the other hand, the possibility to have easy access to constant, specialized and personalized care and follow-up at dedicated medical centers significantly improves the psychological state and QoL of these patients, as they feel involved in the decision-making process relating to their care, and consider the medical team to be knowledgeable about managing their syndrome. They thus feel confident that they will receive the best possible treatment.

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