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## Psychosocial and medical determinants of long-term patient outcomes

Prihodová, Lucia

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# Chapter 1

INTRODUCTION

From the time of diagnosis, patients with a chronic condition have to deal with many consequences of their illness; they have to adapt to a new lifestyle and to changes in their health-related quality of life (HRQoL). This is particularly difficult in patients for whom the most effective treatment is associated with significant side effects, such as immunosuppressive treatment in patients after kidney transplantation (KT), or for whom treatment is not always available, such as prophylactic treatment in patients with haemophilia. The main focus of this thesis is to explore the associations between HRQoL, medication-related factors and patient outcomes in these two chronic disease groups – patients after KT and patients with bleeding disorders. Additionally, we explore specific issues in each group: psychosocial factors determining HRQoL, adherence to immunosuppressive treatment and social participation in patients after KT, and access to treatment and medical services in patients with haemophilia throughout Europe.

This first chapter summarises the existing knowledge on both conditions and describes the specific medication-related issues that affect these patients and thereby their HRQoL and long-term outcomes as well. At the end of the chapter the aims of this study, research questions and structure of this thesis are provided.

## **1.1 KIDNEY TRANSPLANTATION**

According to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), the overall incidence of Renal Replacement Therapies (RRT) in 2010 in Europe reached 123 per million population (n=91,798).<sup>1</sup> In Slovakia, approximately 800–900 patients are newly diagnosed with the last stage of end-stage renal disease each year.<sup>1</sup> According to the ERA-EDTA registry, patients are diagnosed with a last stage of end-stage renal disease (kidney failure) in later life – the average age when diagnosed was 63.3 (±13.3) years and affected about men and women equally (54.6% vs 45.4%, respectively) in 2011.<sup>1</sup> Out of these, the vast majority of patients are treated with dialysis, while less than 20% of patients undergo kidney transplantation. In Slovakia in the year 2010, 156 KTs were performed; in 2011 this number decreased to 117, and in 2012 it increased slightly to 128.<sup>2-4</sup>

KT is established as the treatment of choice among the RRT due to its proven superior effect on survival, morbidity and costs in comparison with other RRTs.<sup>5,6</sup> In addition, KT is proven to have a superior positive effect on HRQoL in comparison with other RRTs.<sup>5,7-9</sup> When compared with patients on dialysis, patients after KT also report greater independence, higher engagement in social and recreational activities and better ability to work.<sup>10</sup> Transplantation restores independence when compared with the dependence on the elimination method necessary for dialysis; however, it requires a strict adherence to a lifelong medical regimen of immunosuppressive treatment in order to maintain a well-functioning graft.<sup>11,12</sup>

## 1.2 HAEMOPHILIA

Haemophilia is a rare congenital bleeding disorder that is complex to diagnose and to manage. There are two types of haemophilia: haemophilia A, which is caused by a deficiency of coagulation factor VIII (FVIII), and haemophilia B, caused by a deficiency of coagulation factor IX (FIX). Haemophilia A is more common than haemophilia B, representing 80–85% of the total haemophilia population. Both types affect predominantly males, and 40–60% of the population have the severe form of the disease.<sup>13</sup> The incidence of haemophilia is estimated at 1 in 10,000 births, with a prevalence of 400,000 in the world; however, it has been shown that prevalence varies among countries from  $12.8 \pm 6.0$  (per 100,000 males) in high income countries to  $6.6 \pm 4.8$  (per 100,000 males) for the rest of the world.<sup>14,15</sup> The primary aim of care is to prevent and treat bleeding with the deficient clotting factor in order to prevent any further joint and muscle damage<sup>13</sup>, and therefore treatment should be started at 1–2 years of age and continue lifelong.<sup>16</sup> Factor replacement can be either isolated from human blood serum, generated from recombinant origin, or a combination of the two; however, wherever they are available and affordable, recombinant concentrates are preferable to human plasma-derived products, because of their added margin of viral safety.<sup>16</sup> Five to seven percent of patients treated with clotting factor concentrates develop an immune response to treatment inhibitors.<sup>17</sup> When compared with the general population, haemophilia patients perceived their physical health more negatively. Their mental health, on the other hand, was least influenced by disease severity and differed least between haemophilia and reference populations.<sup>18, 19</sup>

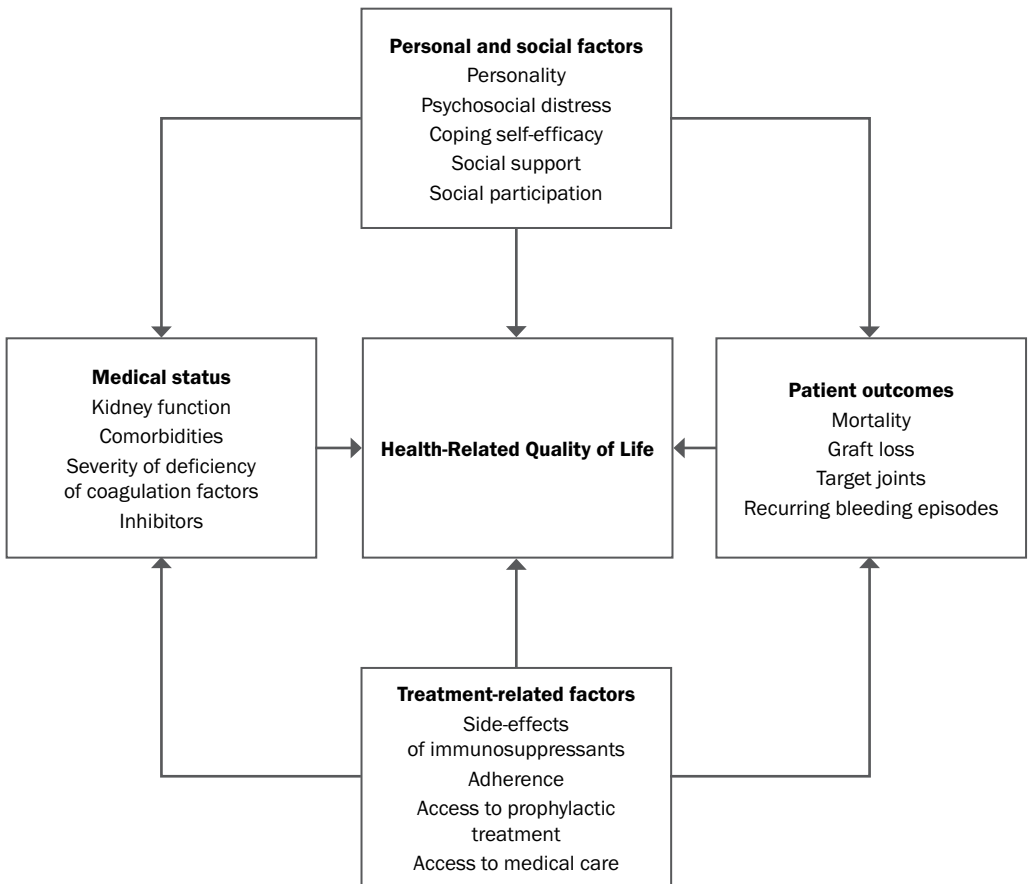
In haemophilia patients, most research on social participation focuses predominantly on the ability to work<sup>20, 21</sup> as well as on participation in physical activity and sports<sup>22, 23</sup>, with both indicating a significantly lower percentage of patients with haemophilia working than in the general population.

## 1.3 HEALTH-RELATED QUALITY OF LIFE

In its constitution, the WHO has defined health as not only the absence of disease and infirmity, but also the presence of physical, mental and social well-being.<sup>24</sup> Over the last decade, however, there has been a shift towards viewing health as a separate concept from well-being, although health is still instrumental for well-being. According to Chatterji et al. (2002) health comprises states or conditions of the human body and mind and is an attribute of an individual person, though aggregate measures of health may be used to describe populations or aggregates of individuals.<sup>25</sup> A health state is thus a multidimensional attribute of an individual that reflects his or her levels regarding the various components or domains of health.<sup>25</sup> Therefore, a health state differs from a pathology, risk factors or aetiology and from health service encounters or interventions. This was reflected through general acceptance of an approach to describing the HRQoL of individuals

in terms of multiple domains and in developing self-report instruments that seek information on each of these domains.<sup>25</sup> HRQoL is generally understood to be a part of the overall concept of quality of life related to a person's health. It consists of the physical, psychological and social domains of health and can be measured in objective dimensions (a patient's degree of health) and subjective dimensions (perceptions and currently experienced quality of life).<sup>26</sup> Therefore, in recent research, HRQoL has not only been considered as an indicator of treatment effectiveness, but also as a very important predictor of treatment outcomes, including survival, in patients with chronic diseases.<sup>27-30</sup> For the purpose of exploring the factors associated with HRQoL and their impact on patient outcomes in this thesis, the revised Wilson and Cleary model was adapted (Figure 1.1).<sup>31</sup>

**Figure 1.1** Factors associated with HRQoL and their impact on patient outcomes



## 1.4 PERSONAL AND SOCIAL FACTORS

Personal and social resources are very important when facing adversities, although they are very difficult to comprehensively address since they are represented by many different constructs in current research. In this study we have considered the following personal factors: personality, distress and coping self-efficacy, and the following social factors: social support and social participation. The association between certain personality traits such as neuroticism or extroversion and HRQoL has been previously confirmed, especially when it comes to mental HRQoL in both the general population as well as in people affected by chronic conditions.<sup>32-35</sup> It is, however, argued whether this association is direct or mediated by other factors, such as psychological distress<sup>36</sup> or self-efficacy.<sup>35</sup>

Psychological distress has been confirmed as one of the factors affiliated with poor HRQoL in both the general population and chronic disease patients.<sup>37,38</sup> Furthermore, higher psychological distress in chronic disease patients was found to be associated with the severity of the disease and its symptoms,<sup>39-41</sup> with worse future health outcomes<sup>42,43</sup> and was also confirmed as an independent risk factor for disability.<sup>44</sup> In order to deal with the challenges presented by a chronic disease and with its associated psychological distress, patients are required to implement coping – cognitive and behavioural efforts performed in order to manage stressful situations.<sup>45,46</sup>

The use of effective coping strategies in the face of these challenges has a positive effect on HRQoL<sup>47-50</sup> and on psychological distress.<sup>51</sup> The coping mechanisms seem to vary depending on the type of chronic disease.<sup>52</sup> Some researchers view social support as a type of coping strategy or resource, or as a way of coping by the social system.<sup>53</sup> Social support does indeed provide benefits similar to effective coping through its positive influence on self-management adherence and thereby health outcomes in certain chronic disease groups.<sup>52,54</sup> Certain aspects of social support have, however, a negative effect – increased concerns from the social support network may lead to restrictions in social participation.<sup>54</sup> Social participation has become, along with HRQoL, an indicator of treatment effectiveness.<sup>55</sup> The ability to play important social, cultural and economic roles in the family and community has been confirmed to have a positive association with HRQoL and an inverse association with mortality.<sup>56</sup>

## 1.5 TREATMENT RELATED FACTORS

For patients after KT and patients with haemophilia, medication poses a challenge. In patients after KT the side-effects of immunosuppressive treatment play an important role, and consequently strict adherence to the prescribed protocol is necessary to prevent graft rejection. In patients with haemophilia being able to avail themselves of prophylactic treatment and appropriate haemophilia care is important in order to prevent bleeds and long-term joint damage.

### 1.5.1 IMMUNOSUPPRESSIVE TREATMENT IN KT PATIENTS: ADHERENCE AND SIDE-EFFECTS

Lifelong immunosuppression is an inevitable part of life after kidney transplantation, as it plays an essential role in the process of preventing graft rejection and improving long-term survival. Its side-effects, however, can compromise the HRQoL of KT recipients.<sup>5, 57-61</sup> Some of the most common side-effects include gastrointestinal problems, post-transplant diabetes mellitus, hypercholesterolemia, hypertension, hirsutism, gingivitis, gum hyperplasia and mood swings.<sup>57-60</sup> Even though it has been previously argued for side-effects assessments to become an essential component in the evaluation of HRQoL, the systematic assessment of symptoms and of side-effects related to immunosuppressive drugs is rarely integrated into HRQoL research.<sup>62, 63</sup> Previous studies did, however, confirm an association between a higher perception of adverse effects and poor adherence.<sup>11, 64, 65</sup>

Adherence to the immunosuppressive regimen is essential in the prevention of rejection and loss of a transplanted graft, resulting in impairment of physical or mental functions, unnecessary pain or early death, a higher number of hospitalizations and consequently higher costs of treatment.<sup>11, 12, 66-69</sup> Yet, the rates of adherence range, depending on the assessment method, from 50–90%, and poor adherence to immunosuppressive treatment is still the leading preventable cause of graft loss.<sup>11, 70</sup>

### 1.5.2 ACCESS TO TREATMENT AND PATIENTS SERVICES IN PATIENTS WITH HAEMOPHILIA

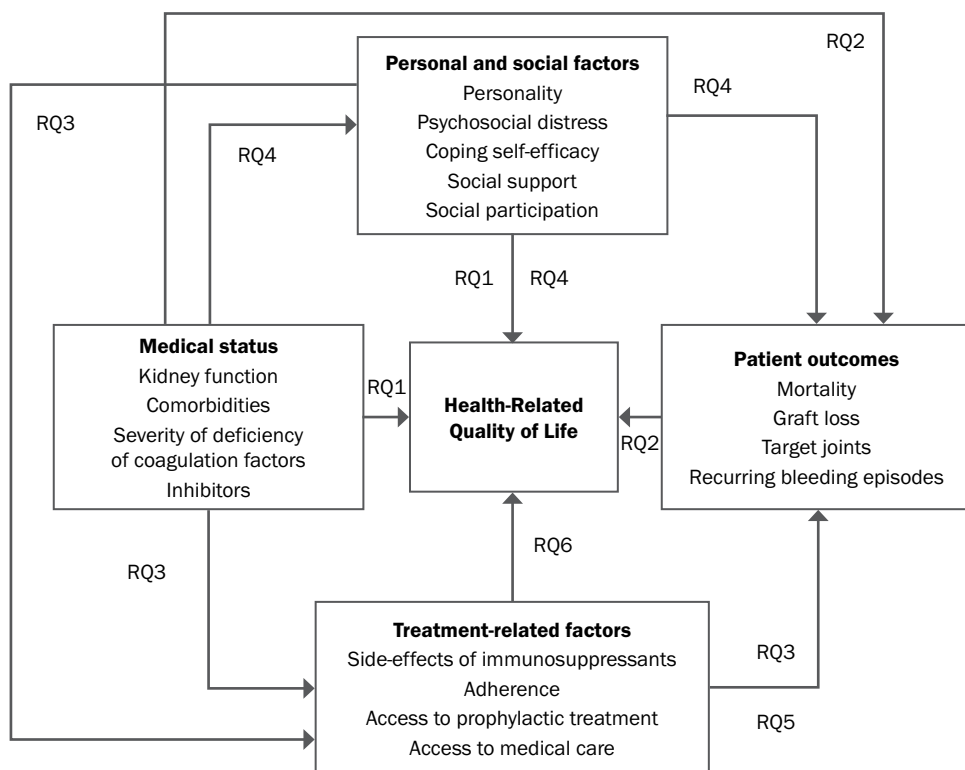
In haemophilia, prophylaxis for children with severe FVIII and FIX deficiencies is recognized as the optimum standard of care.<sup>13, 16, 71-73</sup> The World Federation of Haemophilia defines primary prophylaxis as regular continuous treatment initiated before the second clinically evident large joint bleed at the age of 3 years. A number of studies have been published demonstrating the benefits of prophylactic treatment in adults.<sup>13, 74-77</sup> In spite of the clinical benefit of continuation of prophylactic therapy into adulthood, with a cost of up to €18,000 per month,<sup>78</sup> the access to prophylaxis in a number of countries is restricted due to limited resources for health care. Where prophylaxis is not feasible or appropriate, so-called "on-demand" therapy – treatment given at the time of a clinically evident bleeding – should be given as early as possible upon the onset of a bleeding episode<sup>13, 16</sup>. This type of treatment, however, leads to impaired joint function, disability and lower HRQoL.<sup>79, 80</sup> In order to optimise access to prophylactic treatment and appropriate multi-disciplinary care, a document outlining the European principles of haemophilia care was published in 2008, subsequently endorsed by both the European Haemophilia Consortium (EHC) and the World Federation of Haemophilia (WFH), and was the subject of an official launch at the European Parliament in January 2009.<sup>81</sup> The basic requirements involve the development of an organisation of medical services for patients with haemophilia, such as national patient registries, multidisciplinary comprehensive care centres and specialist services and emergency care, as well

as guidelines for optimum factor treatment, such as use of safe and effective concentrates, home treatment and delivery and the management of inhibitors. The extent to which these requirements are met in the EU countries, however, has not yet been determined.<sup>81</sup>

## 1.6 AIMS AND RESEARCH QUESTIONS

The main focus of this thesis was to explore the HRQoL, medication-related factors and patient outcomes in patients after KT and patients with haemophilia. The second aim was to explore the psychosocial factors determining HRQoL and adherence to immunosuppressive treatment and social participation in patients after KT. Finally, we were aiming to assess the level of access to treatment and medical services in patients with bleeding disorders throughout Europe. A model of the relationships examined within this thesis is presented in Figure 1.2. Based on previous literature, several research questions have been formulated.

**Figure 1.2** Model of the relationships of the key constructs examined in this thesis





**RQ1** – Are psychosocial factors, such as personality traits, psychological distress and coping efficacy, associated with HRQoL in patients after KT when controlled for relevant socioeconomic and medical factors? (Chapter 3, 4)

**RQ2** – Is HRQoL at 3 months after KT a significant predictor of future patient and graft survival? (Chapter 4)

**RQ3** – Which factors are associated with adherence in patients after KT in their first year after KT? Is the level of adherence in the first year after KT a significant predictor of future graft loss and patient mortality? (Chapter 5)

**RQ4** – Is the level of social participation in patients after KT associated with their HRQoL as well as with socioeconomic and medical factors? Is social participation a significant predictor of future graft loss and patient mortality? (Chapter 6)

**RQ5** – What is the level of access to patient care and services outlined in the European principles of haemophilia care in Europe? (Chapters 7, 8)

**RQ6** – Do differences in medical outcomes and quality of life exist in adult haemophilia patients depending on their level of access to prophylactic treatment throughout childhood? (Chapters 9, 10)

## **1.7 THE STRUCTURE OF THE THESIS**

This thesis is divided into two parts and consists of 11 chapters: General introduction (Chapters 1 and 2), Part I–Quality of life and patient outcomes in KT recipients (Chapters 3–6), Part II – Quality of life and access to treatment in patients with bleeding disorders (Chapters 7–10) and a Discussion of the study findings (Chapter 11).

**Chapter 1** “*Introduction*” provides information about quality of life, factors associated with treatment and quality of life in patients after KT and in patients with a bleeding disorder. Furthermore, a model and 6 research questions regarding quality of life, treatment factors and patient outcomes are formulated.

**Chapter 2** “*Data sources*” provides information about the samples, data sources, measures and statistical analyses used in chapters 3–10.

**Chapter 3** “*Impact of personality and psychological distress on health-related quality of life in kidney transplant recipients*” focuses on the associations between personality traits, level of psychological distress and HRQoL in patients after KT.

**Chapter 4** “*Health-related quality of life 3 months after kidney transplantation as a predictor of survival over 10 years: a longitudinal study*” explores the ability to predict long-term patient and graft survival based on their HRQoL early after KT. This chapter also explores how HRQoL at this time reflects the coping efficacy and side-effects of immunosuppressive treatment of the patients.

**Chapter 5** “*Adherence in patients in the first year after kidney transplantation and its impact on graft loss and mortality: a cross-sectional and prospective study*” explores whether the levels of adherence in the first year after KT predict future graft loss and mortality. The role of social support and side-effects of immunosuppressive treatment is also explored.

**Chapter 6** “*Social participation after kidney transplantation as a predictor of graft loss and mortality over 11 years: a longitudinal study*” explores whether social participation after KT has an impact on graft loss and mortality. The role of HRQoL and side-effects of immunosuppressive treatment is also considered.

**Chapter 7** “*Haemophilia care in Europe: a survey of 19 countries*” comprises information about the organisation of haemophilia care and treatment available at a national level in 19 European countries, with a specific focus on consensus guidelines designed to standardise the care of haemophilia throughout the continent of Europe.

**Chapter 8** “*Haemophilia care in Europe: a survey of 35 countries*” comprises information about the organisation of haemophilia care and treatment available at a national level in 35 European countries, with a main objective of identifying the differences in the availability of treatment and care.

**Chapter 9** “*A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18–35 year old men with severe haemophilia in six countries*” presents information about the organisation of haemophilia care and treatment available at a national level of six countries. The differences in quality of life, level of treatment and implications for the national health care are also explored.

**Chapter 10** “*A survey of the outcome of prophylaxis, on-demand or combined treatment in 20–35 year old men with severe haemophilia in four European countries*” presents information about the organisation of haemophilia care and treatment available at a national level of four countries. The differences in quality of life and level of treatment are also explored.

**Chapter 11** “*General discussion, implications and conclusions*” presents the condensed outcomes of this study, discusses them in the framework of the existing knowledge, argues their strengths and weakness, goes into their implications for practice and offers new possibilities for further research.

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