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REVIEW

Psychosocial and behavioural factors in heart transplant candidates – an overview

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Summary

Mortality among heart transplant (HTX) candidates remains high. This review of the literature shows that psychosocial characteristics like depression, social isolation and coping strategies contribute to morbidity and mortality in heart failure (HF) patients, and may also be relevant to the prognosis of HTX candidates. Based on the research to date, physical activity favourably affects subjective and objective parameters not only in HF patients, but also in HTX candidates. Depression is prevalent among HTX candidates, especially in ischaemic patients, and seems to be related to earlier transplantation. Findings on the effects of depression on pretransplant mortality are conflicting. Not much is known concerning social isolation, coping, nutrition, or weight loss in this patient group. Identification of modifiable psychosocial and behavioural variables related to clinical status in this patient group is clearly needed and will aid the development of behavioural interventions to supplement medical therapies.

Background

Heart transplantation (HTX) provides an option to prolong the life of patients with stage D (end-stage) heart failure (HF) [1]. HTX is indicated if medical treatment is already optimized and all other surgical options provide no further benefit [1], such that the estimated 1-year survival is below 20% [2]. In addition to specific medical criteria [3], the following psychosocial conditions have to be met: patients have to be psychologically stable without evidence of recent substance abuse [3,4]. The German guidelines for organ transplantation also emphasize the necessity of patient compliance [5], which is often judged by the patient's ability to adhere to drug therapy and lifestyle recommendations, such as smoking cessation [4,6].

Partly due to the persisting scarcity of donor organs (only 537 of the 713 patients on the Eurotransplant waiting list in 2004 received a donor heart) *average* waiting times for *all* patients have increased over the past years. For example, in 2000, the percentage of patients waiting 12–23 months was 16.1%; in 2004, it was 23.6%. The percentage of patients waiting longer than 24 months nearly doubled (from 3.5% to 6.3%) [7].

Adult HTX candidates suffer from fatigue, lack of energy due to their HF [8–11], perceive their condition as stressful [10,12,13], and report high levels of depression [14,15]. These preoperatively assessed unfavourable psychosocial factors also appear to be related to outcomes *after* HTX [16–24].

Dew *et al.* [25] provide a conceptual framework linking psychological, behavioural and social factors to patients' post-transplant experience. In this view, the transplant is seen at the core, surrounded by the physical, psychological, behavioural and social domains, which are all affected by the transplant experience. It is conceivable that these domains also play a role in the pretransplant experience. Studies of cardiac patients have already shown that the factors implicated by Dew *et al.* (e.g. depression, social isolation, poor health behaviours) can influence a variety of health outcomes, including hospitalizations, cardiac events and mortality [for overviews see 26,27–29].

Unfortunately, very little is known about the role of psychosocial and behavioural characteristics in the

Table 1. Psychosocial and behavioural characteristics related to adverse outcomes in both heart failure patients and heart transplant candidates.

Components	Specific characteristics
Psychological	Clinical depression
	Depressive symptoms
	General distress
	Negative emotions (anxiety, hostility, anger)
	Coping strategies (particularly avoidant coping)
Social	Being unmarried
	Lack of perceived emotional support
	Lack of perceived instrumental support
	Perceived social isolation
Behavioural	Lack of physical activity, exercise
	Insufficient salt restriction
	Insufficient fluid restriction

survival of HTX candidates *before* transplantation, although several of these characteristics (e.g. mood disorders, coping style, availability of support, compliance with dietary and fluid restrictions, substance abuse) are usually evaluated in potential HTX candidates [25].

First, we briefly consider medical prognostic factors in HTX candidates on the Eurotransplant waiting list. Secondly, we review studies of psychosocial and behavioural factors that (i) are relevant to the pretransplant experience (Table 1); and (ii) have been linked to outcomes such as hospitalization and mortality in both adult patients with HF and HTX candidates, and waiting list events like transplantation, combined endpoint transplantation/death or delisting due to clinical improvement.

Prognosis on the waiting list

To estimate a HF patient's mortality risk, different risk scoring systems have been developed that integrate various medical risk markers [30–33]. Specifically developed for HTX candidates was the 'German Transplant Society Score' (GTSS) [34]. The GTSS was derived in the 1997 cohort of all patients registered for HTX in Germany and was validated in the total 1998 cohort. Based on the patients' clinical profile, each patient is assigned an urgency value and a left ventricular HF score (using cardiac index and left ventricular ejection fractions, LVEF)*. Stratification of patients by the GTSS into patients with low, medium and high mortality risk yielded acceptable concordance between observed outcomes and predictions [34].

Using the GTSS, Smits *et al.* [35] predicted waiting list mortality for all *elective* transplant candidates for five Eurotransplant countries from 1998 to 2001. During this time period, about 16% of all 2825 elective HTX candidates died in the first year on the Eurotransplant waiting list [35]. Controlling for all other variables in the model, death was predicted by type of end-stage disease [lower risk for patients with dilated cardiomyopathy (DCMP) compared to patients with coronary artery disease (CAD) or other diseases], and disease severity estimated by the GTSS calculated at the time of listing. Within 1 year of listing, 37.4% in the high-risk group died, 23.7% in the medium-risk group and 14.3% of the low-risk patients [35].

Interestingly, despite having advanced HF, some patients waiting for a new heart are taken off the waiting list due to improvements in their health status [1,36–38]. This was the case for 9% of all adult patients listed in Germany in 1997 [39]. These patients are usually reported as drop-outs and are not the focus of investigation. One exception is a small retrospective study that compared patients delisted due to improvement in LVEF and/or New York Heart Association (NYHA) class with patients delisted due to deterioration in their health status. At the time of listing, these groups did not differ regarding NYHA class, LVEF, or medication. However, improved patients were younger, had waited longer, and were more often female than deteriorated patients [40]. Unfortunately, this sample was very small and no psychosocial or behavioural variables were reported.

Psychosocial and behavioural factors in HF patients and HTX candidates

Psychosocial factors

Depression

The term depression refers to (i) the clinical diagnosis of a mental disorder based on criteria published in the International Statistical Classification of Diseases [41]; and/or (ii) elevated values on questionnaire items assessing depressive symptoms, such as sad feelings, negative thoughts and decreased energy.

Depression, regardless of assessment method, is very common among patients with heart disease. Prevalence rates for clinically diagnosed major depression vary between 14% and 25% both for patients with myocardial infarction and those with confirmed HF [42–44]. In ambulatory patients with advanced HF referred for transplantation, 29% had a diagnosis of clinical depression [45].

*Neither a right ventricular heart failure score (based on mean pulmonary arterial pressure, pulmonary vascular resistance, central venous pressure), a systemic score (based on sodium, heart rate, creatinine, bilirubine, peak VO_2 and mean arterial pressure) nor additional factors like AB0 blood group, age, or body surface area added significant amounts to the prediction of mortality [34].

The percentage of patients with elevated depression scores based on questionnaire assessment is even higher, ranging from 35% to 77% [44,46–49]. This applies to both HF patients and those listed for HTX [24,50], especially to those with ischaemic heart disease [24]. Furthermore, HTX candidates' depression scores increase significantly during the first 4 months of waiting time [51]. Preliminary findings from the multi-site study 'Waiting for a New Heart' revealed that 38% of the patients' depression scores in the Hospital Anxiety and Depression Scale (HADS) [52,53] exceeded the established cut-off for clinical depression [54,55]. In addition, average depression scores were higher in patients with ischaemic HF than in patients with DCMP [56], replicating previous findings [24].

Heart failure symptoms together with restricted daily activities are more prevalent among depressed HF patients than that among nondepressed HF patients [46,50,57–60]. Additionally, depression in HF patients is associated with a further decline in self-reported daily activities over 6–12 months [48,61]. In some studies, depression is also associated with objective functional limitations in VO_2max (peak oxygen consumption) [62,63], 6-min walk distance [45,63,64], and judgements of functional capacities by partners [65]. Relationships of depression to LVEF are inconsistent [45,55,59,63,64,66,67]. Clearly, the relationship of depression to different markers of disease severity warrants more thorough investigation.

Nevertheless, elevated depression in HF and HTX candidates is of relevance for several reasons:

(**1**) Recent prospective studies suggest that depression is an independent predictor of mortality in HF patients regardless of HF aetiology. Depression was associated with twofold mortality rates after 1 year [44], after 2 years [58,62], and after 5 years in patients with underlying DCMP [42]. In the study by Jünger *et al.* [62] the influence of depression on mortality increased up to an eightfold risk after 30 months independently of NYHA class, LVEF, VO_2max, medication, and aetiology. After an average of 3 years, 41 depressed outpatients who were evaluated for HTX candidacy were at higher risk for transplantation or for the combined endpoint transplantation/death (but not for mortality alone) than 101 nondepressed HTX candidates [45]. These findings were observed independent of age, NYHA class and other established markers of disease severity [45]. Interestingly, in this study, 59% of the depressed patients had DCMP, whereas only 22% had an ischaemic aetiology. Nevertheless, the finding of higher probability for HTX in depressed patients causes some concern. For example, Zipfel *et al.* [24] note that heightened depression scores *before* HTX were associated with higher mortality among ischaemic HF patients *after* HTX, but not while waiting. This relationship did not hold for DCMP patients. Whereas depression did not increase the mortality risk during the waiting period in the Zipfel *et al.* study [24], another study found evidence that signs of general psychological distress did [68]. The authors categorized transplant candidates into groups of patients with 'low stress' and 'high stress' according to their questionnaire scores. Group membership independently from NYHA-class predicted 1- and 5-year mortality on the waiting list, with patients with high stress showing greater probability of dying than those reporting relatively low stress.

(**2**) Depressed patients have difficulties with compliance for medications [69,70] and regular exercise [71]. This is of particular importance in the transplantation population, as nonadherence with immunosuppressive drugs and clinic appointments after HTX can lead to rejection and death [18,72,73]. However, a recent study found no association of medication nonadherence with depression. But this sample was heterogeneous in relation to organs patients were listed for [74].

(**3**) Depression in ambulatory HF patients is positively associated with hospitalizations and clinic visits [42,44,45,57].

(**4**) Depressed HF patients incur higher healthcare costs than nondepressed HF patients [75]. Differences in the use of psychological therapy did not account for the higher costs observed among depressed patients [57,75].

Other negative emotions

Anxiety, hostility or anger are less well studied in HF patients in general and in HTX candidates in particular. Interestingly, a single study examining patients *after* transplantation, reported that angry and hostile feelings were associated with an eightfold risk of developing transplant vasculopathy [18].

Regarding anxiety measured by standardized questionnaires, studies including HF patients with NYHA classes ranging from I to IV [67,76] and patients evaluated for transplantation [77] did not find elevated anxiety scores compared to patients without known heart disease [76] or healthy persons [67,77]. However, Majani *et al.* [77] excluded all NYHA class IV and female patients, thereby reducing the sample of potentially anxiety-prone subjects. Comparing all patients on the HTX waiting list to a healthy norm population, revealed, higher levels of anxiety among wait-listed HTX patients [24]. Early results from the 'Waiting for a New Heart' study corroborate this finding [54], with 16% of the 55 newly listed patients scoring above the anxiety cut-off in the HADS compared to 5.8% of the norm population [78].

The role of anxiety in the prognosis of HF is not well investigated. Unlike depression, anxiety did not predict

1-year-mortality in HF patients [67]. Also elevated anxiety scores in HTX candidates had no impact on mortality before and after HTX [24].

Avoidant coping

Possibly not anxiety itself, but the way patients cope with health threats (severe symptoms, anticipated surgery, fear of death) and anxiety, might be of importance for patients' health status. The term 'avoidant coping' encompasses different coping strategies like denial or repression of thoughts and feelings associated with the threat. They include both behavioural and cognitive responses to expected and experienced threats [79,80]. For example, in studies using questionnaires to assess coping, fewer avoidant than active or positive coping strategies were reported by patients with advanced HF [81] and by HTX candidates [12,82]. Albeit seldom reported, avoidant coping in HF patients, HTX and lung TX candidates appears to be positively associated with fatigue, anxiety, depression [81,82], pain, and difficulties in daily activities [83]. Avoidant coping might even influence survival in HF and HTX patients. One prospective study found an effect of avoidant coping (i.e. 'behavioural disengagement') on higher 6-year mortality in 119 HF patients, controlling for NYHA class, proatrial natriuretic peptide, age, sex, and neuroticism (i.e. disposition to experience negative affect) [84]. In addition, HTX patients with a mean survival of only 4 months after transplantation had reported more denial in the pretransplant evaluation than patients who were still alive after an average of 38 months [85].

Social isolation

Lacking social integration (network size or frequency of interactions) and deficient social support (perceived availability of or satisfaction with emotional, instrumental or informational support) constitute social isolation [86]. This is regarded as an important risk factor for illness and mortality in general [87] and in CAD patients in particular [86,88].

In studies with HF patients, social isolation emerged as an independent risk factor for mortality (for an overview see [89]). Unmarried patients had higher mortality rates than married patients after 12 and 24 months in a small study with DCMP patients [90]. Also, perceived lack of social integration predicted 2-year mortality independently from depression and disease severity in 119 HF outpatients (71% NYHA class II) [91]. Interestingly, perceived lack of instrumental support (e.g. not receiving help from spouse) was unrelated to mortality in this study [91]. Perceived deficiencies in the emotional component of social support were associated with an eightfold risk of rehospitalization and death in elderly female HF patients 1 year after their first HF hospitalization, but not in their male counterparts [92].

In addition, social isolation in HF patients was linked to negative emotions [60,93,94], an increase in depressive symptoms over 1 year [95], and to remission of depression after 24 weeks [57].

The importance of perceived social support and having an adequate social support network has also been recognized for HF patients listed for HTX [36,96–98]. Interestingly, in a study of HTX candidates, patients' depression was positively associated with their spouses' behavioural disengagement [99], suggesting that lack of spousal support may be detrimental to the patient's mental health. To our knowledge, the role of social support in pretransplant health status and survival has not been investigated.

Summary-psychosocial factors

To summarize, there is some evidence confirming the role of psychosocial variables in outcomes of both HF patients and HTX candidates (Table 2). Depression is common among both patient groups. It is associated with subjective and partly with objective functional limitations, and may adversely affect adherence to treatment recommendations. Moreover, depression seems to predict mortality in HF patients in general; however, in HTX candidates, early results regarding pretransplant mortality are conflicting. Findings such as depressed patients being transplanted sooner than nondepressed patients, but dying sooner after HTX, warrant further investigation. Elevated anxiety scores seem to be especially prevalent in HTX candidates. However, the sparse results available to date do not implicate any prognostic relevance of pretransplant anxiety on pretransplant health status. In this context, it could be fruitful to further investigate how patients cope with the experience of negative emotions, and if they feel socially isolated, especially regarding emotional support, which also might be of importance for the survival of HTX candidates.

Health behaviour/lifestyle

The European Society of Cardiology emphasizes weight reduction in case of obesity, sodium and fluid restriction, quitting smoking, moderate alcohol consumption and physical activity in the treatment of chronic HF [100]. Similar lifestyle changes have been recommended for HTX candidates [4,98,101].

Physical activity

Still 60% of the European population hold the view that HF patients need rest and should avoid physical activities

Table 2. Prognostic relevance of psychosocial and behavioural characteristics in patients with HF and in HTX candidates.

Variable	Population	NYHA	Result	Reference
Depression	HF patients of varying diagnoses	II–IV	Twofold mortality risk after 1 year	[44]
		I–IV, I–III	Twofold mortality risk after 2 years	[58,62]
		I–III	Eightfold mortality risk after 30 months	[62]
	HF patients with dilated CMP	I–IV	Threefold mortality risk after 5 years	[42]
	HF outpatients evaluated for HTX	2.7 ± 0.7	Depression diagnosis linked to heightened probability to reach endpoint of HTX and HTX/death	[45]
	HTX candidates (dilated and ischaemic CMP)	II–IV	No heightened mortality risk pre-HTX in the entire sample; heightened mortality post-HTX only among ischaemic patients	[24]
	HTX candidates	I–IV	'High stress' associated with heightened mortality risk 1 and 5 years pre-HTX	[68]
Hostility	HTX patients	Not specified	Eightfold risk of developing transplant vasculopathy	[18]
Anxiety	HF patients	II–IV	No heightened 1-year mortality risk	[67]
	HTX candidates (dilated and ischaemic CMP)	II–IV	No heightened mortality risk pre- and post-HTX in either group	[24]
Avoidant coping	HF patients	I–IV	Higher 6-year mortality in patients reporting 'behavioural disengagement'	[84]
	HTX patients	Not specified	Shorter survival post-HTX associated with pre-HTX denial	[85]
Social isolation	HF (dilated CMP)	Not specified	Being unmarried associated with higher mortality after 1 and 2 years	[90]
	HF patients >65 years	Not specified	Eightfold rehospitalization and mortality risk after 1 year in female but not male patients lacking emotional support	[92]
	HF outpatients	I–IV	Heightened 2-year mortality in patients with high perceived social isolation independent from depression and disease severity	[91]
Exercise	HTX candidates	VO_2max <14 ml/kg/min	31 of 107 patients taken off waiting list after increase in VO_2max 85% survival rate without relisting after 2 years	[117]

NYHA, New York Heart Association functional class; HF, heart failure; CMP, cardiomyopathy; HTX, heart transplantation; VO_2max, peak oxygen consumption.

[102]. Yet several randomized studies demonstrate the benefits of physical activity in chronic HF regarding body mass index (BMI) reduction in obese HF patients [103,104], quality of life, increased VO_2max [105,106], muscle mass and objective muscle function [107,108], and decreased BNP/NT-proBNP levels [109] compared to controls. Even patients with low LVEFs (average 18%) showed improved exercise duration, quality of life and VO_2max after 3 months of exercise training [110]. In patients with NYHA class III, aerobic endurance training over a period of 6 months resulted in several improvements (e.g. oxygen uptake at the ventilatory threshold and at peak exercise, LVEF at rest), whereas control patients did not show any changes [111].

Additionally, the benefits of physical activity can be seen similarly in patients with ischaemic and DCMP [112], and even reductions in mortality have been reported in a meta-analysis of nine randomized controlled trials including patients with chronic HF [113,114].

Nevertheless, it is less clear whether HF patients who experience symptoms of dyspnoea even at rest (NYHA IV) could also benefit from physical activity. Some evidence suggests that training of single extremities like knee-extensor training can be successful [112,115]. Positive effects on VO_2max and oxidative capacity of trained skeletal muscles were also achieved by low intensity training [116].

Evidence that increases in physical activity may benefit HTX candidates comes from a study by Stevenson *et al.* [117]. Patients with DCMP were told to go for regular walks without breaks at least four times a week thereby gradually augmenting distance or duration. After 6 months, 31 of the 107 participating patients showed enhanced VO_2max and could be safely delisted. However, this was not a randomized controlled trial. Generally, not much is known what physical activities ambulatory HTX candidates perform and if activity level is associated with pretransplant survival. Preliminary findings from the 'Waiting for a New Heart' study indicate a wide range of physical activities among HTX candidates (ranging from climbing stairs to yoga) [118]. Furthermore, those who were more active also had greater VO_2max, a supportive social network, better quality of life, as well as a slightly better Heart Failure Survival Score (HFSS) [118]. To what extent physical activity predicts mortality and other outcomes during waiting time remains to be determined.

Diet

While clear guidelines (emphasizing a mostly plant-based diet low in fat and cholesterol) exist for CAD patients [119], no studies investigated if such a diet is beneficial for HF patients [120] and HTX candidates. There is some evidence that HF patients might benefit from nutritional supplements like ω-3-fatty acids [121] or vitamins and trace elements [122]. Considering the relative absence of dietary studies in these patient populations, current guidelines for HF patients and HTX candidates are limited to recommending sodium and fluid restriction [100,123].

As pretransplant obesity seems to be associated with post-transplant mortality [4,124], weight loss is recommended for obese HTX candidates. On the contrary, greater BMI and elevated cholesterol levels have recently been discussed as protective factors in chronic HF patients [125–127]. Clearly, more research is needed to elucidate the nature of this relationship and possible mechanisms.

In this context, it is noteworthy that HF patients show increased energy expenditure even at rest [128,129] in response to increased respiration and cardiac muscle work [130]. In addition, energy intake seems to be a crucial issue. In one study, HF patients ingested less calories and protein than physically inactive healthy people of the same age and weight, resulting in a negative energy balance [128]. Possibly, HF related symptoms like early satiety, gastrointestinal problems [131], loss of appetite and a dry mouth [132] account for this reduced nutritional intake.

Due to these problems related to ingestion, and possible difficulties associated with the adoption of a low sodium diet in daily life [133], lifestyle interventions seem to be of special importance. For example, patients receiving comprehensive nutrition therapy (implementing sodium and fluid restriction, establishing weight goals) had improved sodium and fluid consumption, weight, and fewer emergency visits than the control group (receiving nutrition education only) [134].

Unfortunately, not much is known about food selection, nutritional behaviour, and its role in health status and survival of HTX candidates.

Summary-health behaviour lifestyle

In sum, accumulating evidence suggests that physical activity is beneficial even in patients with advanced HF and in HTX candidates. Regular exercise improves quality of life. It positively affects muscles, catecholamines, and VO_2max and seems to reduce mortality. Yet, its role in the survival of HTX candidates has to be further elucidated. In regard to diet and nutrition, it remains unclear, what kind of diet is beneficial for the prognosis of HF. The only recommendations made are reduced salt and fluid consumption together with weight monitoring. However, unhealthy eating behaviour or symptoms associated with ingestion and digestion might be important factors in the negative energy balance often observed in this population. In view of these issues, studies are needed that more strongly concentrate on eating and drinking behaviour and its conditions.

Discussion and perspectives

This overview confirms that physical activity benefits HF patients and might have positive effects in ambulant HTX candidates. In addition, psychosocial factors like depression, social isolation and coping appear to play a role in HF and those patients with end-stage disease listed for cardiac transplantation. However, the role of these factors in pretransplant outcomes is still understudied. Moreover, it seems important to investigate interrelationships of these factors and their role in the prognosis of advanced HF. For example, depression and lacking partner support might influence each other reciprocally as implicated in the study by Burker *et al.* [99]. Furthermore, psychosocial factors like depression or lacking support might impair health behaviour and compliance, thereby indirectly influencing prognosis.

A limitation of our review is inclusion of research findings obtained from populations other than HTX candidates (due to the paucity of research conducted in this group). Although most of the reported studies statistically controlled for disease severity within study sample, HTX candidates clearly differ from HF patients in many characteristics, such as disease severity (e.g. HF stages B and C), and, most likely, in psychosocial and behavioural status. Thus, results based on HF patients may not generalize to patients waiting for a new heart.

Additionally, there is some debate, that not all listed patients but only the most severely ill benefit from HTX [39,135–138]. Therefore, Deng *et al.* argue that only patients in most urgent need should receive donor hearts while for all other patients alternative treatments should be developed [136,138–140]. To supplement pharmacological and mechanical interventions both for HF patients in general and for HTX candidates in particular educational and behavioural interventions have been suggested [136,141–143]. For the latter group, this seems especially important in the light of the persistent donor organ scarcity, long waiting-times and considerable waiting-list mortality.

Therefore, identification of modifiable behavioural and/or psychosocial variables related to survival on the waiting list remains an important issue. The recently launched prospective multi-centre study 'Waiting for a New Heart:

Do psychosocial variables and health behaviour predict outcomes in patients listed for heart transplantation' [54] aims at making contributions to this task. Studies such as this one may be useful to develop and evaluate psychosocial and behavioural interventions as adjunct to medical treatments.

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