Inger Karin Lægreid

Quality of life in older dialysis patients

Influencing factors and research challenges

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
Faculty of Medicine
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Norsk sammendrag av avhandling :

«Livskvalitet hos eldre i dialyse».

Blant dialyse-pasientane er det dei eldste aldersgruppene som aukar mest. Få av desse blir nyretransplantert, det betyr livslang dialysebehandling. God livskvalitet i dialyse er derfor svært viktig.
Avhandlinga ville primært undersøke kva betydning start-tidspunkt i dialyse har og seie for livskvalitet hos dei eldste dialyse-pasientane (≥ 75 år), samt undersøke kva betyding ernæring status, fysisk funksjon og komorbiditet (andre sjukdomar enn nyresvikt) har for livskvaliteten til desse pasientane.

Resultata frå studiane i avhandlinga viser at dei eldste pasientane i dialyse har dårligare livskvalitet samanlikna med yngre dialysepasientar og med den generelle befolkninga på same alder og kjønn. Dette gjeld spesielt fysiske dimensjoner. Vi fann sterk samanheng mellom fysisk funksjon og livskvalitet. Vi viste og at mange av pasientane hadde ernæringssvikt og andelen som hadde ernæringsproblem var avhengig av klassifiserings-system. Vi fann ingen samanheng mellom start-tidspunkt i dialyse og livskvalitet, dette er i samsvar med resultat frå andre nylig publiserte studier. Dei seinare år har det vore ein tendens internasjonalt til å starte tidlegare i dialyse hos eldre, våre funn gir ingen haldepunkt for gevinst i form av betre livskvalitet ved å starte tidleg. Vi fann ingen statistisk samanheng mellom komorbiditet og livskvalitet.

Prosjektet var frå starten planlagt som ein norsk multisenterstudie, der ein ved loddtrekning (randomisering) skulle samanlikna livskvalitet hos dei som starta tidleg i dialyse med dei som starta seint. P.g.a. for få pasientar inkludert vart denne studien avslutta.. Etter avslutning av denne studien gjennomførte vi ein spørje-undersøkelse til alle nyrelegar i Norge for å få svar på kvifor det er så vanskelig å rekruttere nyresviktpasientar til randomiserte studier. Svara vi fekk tyder på at nyrelegar ønsker å bestemme sjølv når dialyse-behandlinga skal starte, dei var og opptatt av arbeidspress for dialyse-sjukepleiarar og kapasitet på dialyse-avdelinga.

For å finne svar på dei opprinnelege forskningspørsmåla vart det gjennomført ein tverrsnitts-studie, med utgangspunkt i Norsk Nefrologi-register der alle som starter i dialysebehandling i Norge blir registrert. Spørje-skjema med spørsmål om pasientane sin livskvalitet og ernæring vart sendt til alle som var >75 år og i dialyse pr. 1.1.2009. Det vart sendt ut 320 skjema og det kom svar frå 250. I tillegg blei det gjort ein sub studie på ernæring og livskvalitet på same pasientgruppe i Nord- og Sør-Trøndelag, der ein målte væskestatus og kropps-samansetning ved hjelp av bio-impedance, samt målte muskelstyrke og overarms-omkrets. Denne pasient-gruppa svarte og på same spørreskjema som i den nasjonale studien.

Studien viser at det er viktig å få større fokus på ernæring hos dei eldste pasientane i dialyse. Det vil være viktig å bli einig om kva metodar ein skal bruke for å identifisere dei som har risiko for å utvikle ernærings problem, slik at tiltak som kost-veiledning og ernærings tilskot kan vurderast.
Det kan vere eit stort potensial for å betre livskvalitet hos gamle dialysepasientar ved å stimulere til auka fysisk aktivitet, ved t.d fysisk trening i regi av dialyse-avdelinga.

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Summary in English

In the last decades, older patients represent the fastest growing subgroup of the dialysis patients. For most of these patients, dialysis treatment will be lifelong. Quality of life (QoL) is therefor an important outcome.

The decision to start dialysis treatment is partly based on the patient renal function assessed by glomerulofiltration rate (GFR) ("normal" values > 90 ml/min). It has been a tradition to start dialysis treatment when GFR fell below 10 ml/min (late start). There has been a tendency internationally to start earlier in diaysis treatment (on a higher GFR), especially in the elderly. The documentation for the benefit of this has been scarce. There is also poor knowledge about what factors influence quality of life in the elderly dialysis patients.

This doctoral thesis was originally planned to explore the impact of the start point of dialysis treatment on QoL in the older dialysis patients (≥75 years of age), and also to explore the impact of nutritional status, physical function and comorbidity on QoL in these patients.

The project was planned as a Norwegian multi-center study, with randomization to early and late start in dialysis, and the hypothesis was that early start would give better QoL. Due to few patients included, the study was closed. After the closure of the study, we did a survey among Norwegian nephrologists where they were asked why it was so difficult to recruit chronic kidney disease patients to randomized studies. The answers implied that the nephrologists wanted to decide for themselves when to start dialysis treatment, and they thought that the patients wanted to postpone dialysis treatment. The nephrologists were also concern about workload for the staff and capacity on the dialysis ward.

To find the answers on the original research question we did a cross-sectional study, with data from the Norwegian Renal Registry (NRR), where all patients who initiate dialysis treatment are registered. Questionnaire with questions about the patients QoL and nutritional status was mailed to all patients ≥ 75 years of age and in dialysis treatment 01.01.2009. It was mailed 320 questionnaires and we received answers from 250. These data were supplemented with medical data from NRR, collected from start at dialysis and Annual report 2008. It was also done a minor, more detailed study on nutritional status and QoL in elderly (≥75 years) in North - and South Trøndelag. In this study hydration status and body composition was measured by bioimpedance spectroscopy and it was also done a clinical examination and

measured muscle strength and arm skinfold (triceps skinfold). The same questionnaire regarding QoL and nutritional status used in national study was admitted.

The results from these studies showed that the elderly patients in dialysis reported poorer QoL, poorer than what others have found in younger dialysis patients and poorer than in the general population at the same age and gender, especially physical domains.
We found a strong association between physical function and QoL. We also showed that many older patients had nutritional problems, and the frequency of nutritional problems depended on which classification system that was used. We found no association between starting point in dialysis and QoL, this is in accordance with recently published studies. Our findings did not show any benefit in QoL of starting early in dialysis for the older CKD patients. We found no association between comorbidity and QoL.

The thesis implies the importance of greater focus on nutritional status in the older patients. It is important to agree upon which assessments to use for identification of patients at nutritional risk, and consider dietary advice and nutritional supplements. Bio-impedance gave information of important changes in body composition that was not revealed by other assessment methods, it was easy to use and can be a useful tool in assessment of nutritional status and hydration status in the elderly in dialysis.

It can be a potential to improve QoL in older dialysis patients by stimulating more physical activity and offer physical exercise training in the dialysis ward. It is also important with further studies to explore the benefit of physical training in this age group.

Contents

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Trondheim October 2012

Inger Karin Lægreid

List of papers

1. Lægreid IK, Aasarød K, Jordhøy M.
   Recruitment in End-Stage Renal Disease (ESRD) why is it so difficult?
   Scand J Urol Nephrol. 2011 Sep; 45(4): 285-9. Epub 2011 Apr 15.

2. Lægreid IK, Aasarød K, By A, Leivestad T, Jordhøy M
   The impact of nutritional status, physical function, co-morbidity and early vs. late start in dialysis on quality of life in older dialysis patients.
   Submitted to Hemodialysis International August 2012

3. Lægreid, IK, Aasarød K, By A, Jordhøy, M
   Nutritional problems, Overhydration and the association of Quality of Life in elderly dialysis patients.
   International Urology and Nephrology, Epub September 2012

Abbreviations and definitions

BMI	body mass index
BIS	bioimpedance spectroscopy
CKD	chronic kidney disease
EORTC	European Organization for Research and Treatment of Cancer
ESRD	End Stage Renal Disease
HGS	hand grip strength
HD	Hemodialysis
HRQoL	Health related quality of life
KDQoL	Kidney Disease Quality of life
MDRD	Modification of Diet in Renal Disease
NRR	Norwegian Renal Registry
PD	Peritoneal dialysis
PEW	Protein-energy wasting
QoL	Quality of life
MOS SF36	The Medical Outcome Study 36-item Short Form
SGA	Subjective global assessment
TSF	Triceps skinfold
WHO	World Health Organization
eGFR	estimated glomerular filtration rate
Kt/V	fractional urea removal rate, dialysis adequacy

Early start in dialysis eGFR> 10 ml/min

Late start in dialysis eGFR < 10 ml/min

Preface

In the last decades, older patients represent the fastest growing subgroup of the dialysis population. For most of these patients, dialysis treatment will be lifelong. Quality of life (QoL) is therefore an important outcome. The knowledge about which factors that may influence QoL of older dialysis patients is, however, scarce. There is, also, a clear tendency to start dialysis treatment earlier, and without documented benefits for the patients QoL.

We wanted to investigate which impact early vs. late start in dialysis would have for the QoL patients' ≥ 75 years of age starting in dialysis, and to investigate the predictive value of nutritional status, physical function and comorbidity. The project was originally planned as a Norwegian multicentre randomised study, where patients ≥75 years of age planned for dialysis treatment should be randomised to early start (estimated glomerular filtration rate, eGFR> 10 ml/min) or late start (eGFR< 10 ml/min). Nutritional status, physical function and comorbidity were to be assessed at baseline. QoL was defined as the primary outcome measure.

A great effort was made to give thorough and widespread information about the study, both in writing and through meetings with nephrologists and dialysis-nurses throughout the country. Despite this and an overall positive feedback, the rate of inclusion was too low and the study was closed. We assumed that difficulties in complying with the randomization procedure were the main reasons for the poor recruitment. Thus, we changed the study design to an observational study; where the patients should be included when they starting dialysis therapy. New information procedures were carried out. However, after a year this study also had to be closed due to few patients included.

Based on this experience, we decided to explore why it was so difficult to enrol older dialysis patients onto clinical studies. To answer this, a survey including a questionnaire to all nephrologists in Norway was carried out (Paper 1). To answer our original research questions, we decided for a cross-sectional study; linked to The Norwegian Renal Registry (NRR) where all patients starting in dialysis treatment are registered. Questionnaires including quality of life, nutritional status and physical functioning assessment were mailed to all patients ≥ 75 years of age, and the patients who answered

were included in the study and gave access to medical data from the NRR. A compliance of 73 % was achieved (Paper 2). For a more detailed investigation of the relation between nutritional status and quality of life in older dialysis patients, we also did a minor study including thorough assessments of body composition and nutritional parameters of patients ≥ 75 years from our university hospital's catchment area (Paper 3).

Overall, due to major recruitment difficulties, a strong randomised design had to be abandoned and replaced by a weaker one. Despite this, we find that our final results significantly contribute to the understanding of the relationship between QoL, starting point in dialysis, nutritional status and physical function in older dialysis patients, and points to remediable factors that by adequate assessment methods and interventions may improve the treatment and poor QoL of these patients. Our results also contribute to an understanding of the general difficulties in conducting clinical trials among dialyses patients as well as demonstrate the patients' ability and willingness to participate. They may therefore be of substantial help for future research targeting older dialysis patients, for whom increased research efforts are clearly needed.

Background

Chronic kidney disease

The total prevalence of chronic kidney disease (CKD) in Norway is 10.2% and 11.7% in US (1999 -2000) (1). Each year, a small proportion progress to end stage renal disease (ESRD), 2.5 times more in US than Norway, possibly due to a higher prevalence of type 2 diabetes mellitus. The prevalence for CKD in the elderly (> 70 years) is higher and reported to be 47 % in US (2), 35% in Europe (1) and 28% in China (3).

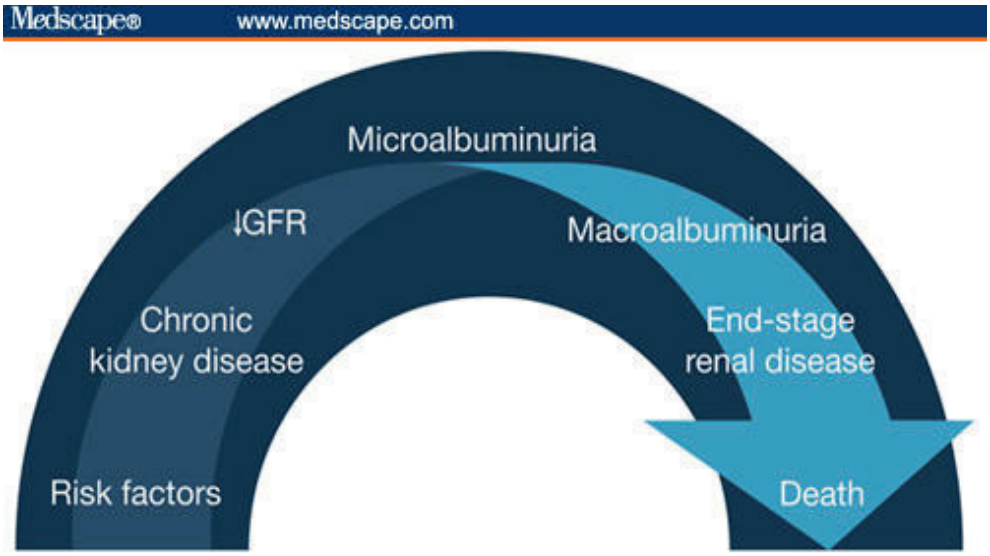


Figure 1 Development of End-Stage Renal Disease (ESRD)

In 2002, a classification system for different degrees of renal dysfunction from the earliest kidney damage to end stage renal disease was developed by the Kidney Disease Outcomes Quality Initiative (KDOQI), depending on markers of kidney damage (albuminuria) and level of kidney function i.e. glomerular filtration rate (GFR). It has, however, become apparent that when applying this system, the prevalence of CKD is particularly high in the older individuals. Thus, there is still debate whether the KDOQI classification system is suitable,

especially for older person as they maybe misclassified due to a low eGFR as a result of a "normal" reduction of kidney function with age (4).

Table 1. Definition of CKD Stages 1–5 according to the KDOQI 2002 classification system

	GFR (mL/min/1.73 m^2)				
	≥90	60–89	30–59	15–29	<15
Normo albuminuria	No CKD	No CKD	Stage 3	Stage 4	Stage 5
Micro albuminuria/macroalbuminuria	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5

Findings should be present for more than 3 months.

The main causes of CKD are renal vascular disease, diabetes mellitus, cystic kidney disease and glomerulonephritis (Annual report, NRR 2010). Risk factors for developing ESRD are age, gender, hypertension, hypercholesterolemia, smoking and diabetes mellitus (5).

Renal replacement therapy

CKD progressing to ESRD can be treated with renal replacement therapy; dialysis or renal transplantation. Dialysis can be done in institutions with hemodialysis (HD) or at home with peritoneal dialysis (PD). PD can be done manually as continuous ambulatory PD (CAPD) or with a machine; automated PD (APD). The kidney function (glomerular filtration rate, GFR) can be assessed with several methods; serum-creatinine, estimating GFR with equations (Cochroft Gault and the Modification of Diet in Renal Disease, MDRD are based on serum-creatinine and age, sex, ethnic origin and body size), creatine clearance and urea clearance, based on blood tests and 24 hour urine collection, Cystatin C, iohexol clearance and inulin clearance, which is gold standard. The updated European Best Practice Guidelines (EBPG) recommends to initiate dialysis treatment when GFR < 15ml/min and with the following; uremic symptoms, and/or inability to control hydration status and/or blood pressure, and/or a

progressive deterioration of nutritional status, and for most patients the need to start will be in the range 9 – 6 ml/min/1.73 m^2 (6).

In 2009, the overall incidence rate for renal replacement therapy (RRT) for end stage renal disease (ESRD) in Europe (ERA-EDTA registry 2009) was 125 per million populations (p.m.p) per year. The overall mean age was 62.9 years, ranging from 47.6 years (Russia) to 69.5 years (Belgia, Dutch speaking) (7). The overall prevalence (ERA-EDTA registry 2009) was 730 p.m.p.

During 2010 a total of 505 new patients entered renal replacement therapy (RRT) in Norway, i.e. an incidence rate of 103.3 per mill. inhabitants. A majority were males (67.1 %). Median age at start was 66.0 years, mean 62.4 years, ranging from 5.7 to 93.1 years. By the end of 2010, 4193 patients in Norway received renal replacement therapy, i.e. prevalence of 857, 8 per million inhabitants. Median age by the end of the year was 60.3 years, mean 58.2 years and range 1.2 - 93.2 years. (NRR; Annual report 2010)

In US the incidence rate for ESRD for the oldest (> 75 years of age) has increased by 12 % since 2000, and the adjusted rate of prevalent ESRD for those 75 years and older has grown 37% since 2000 (5). In Norway there has been the same trend, in 1994 there were 10% of patients > 75 years of age starting in RRT, in 2010 there were 27% starting RRT in the age group 75 years+.

Elderly in dialysis

The oldest patients are the fastest increasing subgroup in the dialysis population in the developed countries, and the referral and acceptance of older patients onto dialysis is increasing (5, 8). This is due to the fact that incident rates of end stage renal disease (ESRD) in the older adults are increasing, and an improved survival of diseases associated with kidney disease such as diabetes and coronary heart diseases (9, 10). The survival of the oldest dialysis patients is documented from a report from the French Peritoneal Dialysis Registry which showed a median survival of 27 months in a population with mean age 82 years at start in dialysis (11).

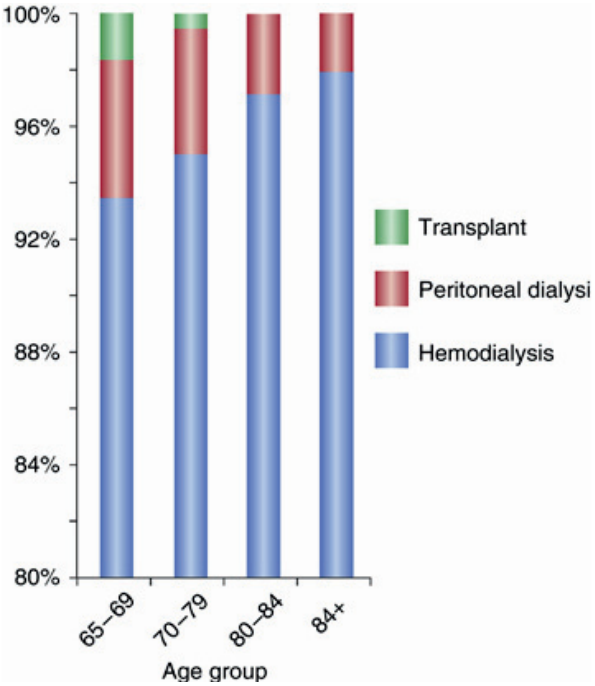


Figure 2. Initial renal replacement therapy modality in the United States in 2008, according to age group. (Tamura, 2012) (12)

As shown in Figure 2, peritoneal dialysis (PD) is less prescribed than hemodialysis (HD) with older age, and this pattern is the same in Europe as in the US (13, 14). The NECOSAD study from the Netherlands (15) reported that it was the expected inability to perform the dialysis exchanges that was a major reason for elderly not to start PD. In France, however, where assisted PD has been used for many years, and the assistance for the procedure is given by a community nurse, PD is predominantly a treatment for the elderly (16). Assisted APD has been documented as a feasible dialysis modality for frail elderly patients in a Danish study (17). There is no difference in the survival rates between PD and HD, reported from both US and Europe, except for elderly diabetic women (13, 18). And a study that have compared QoL between older patients in HD and PD, found similar scores (if not better) for PD vs. HD (19).

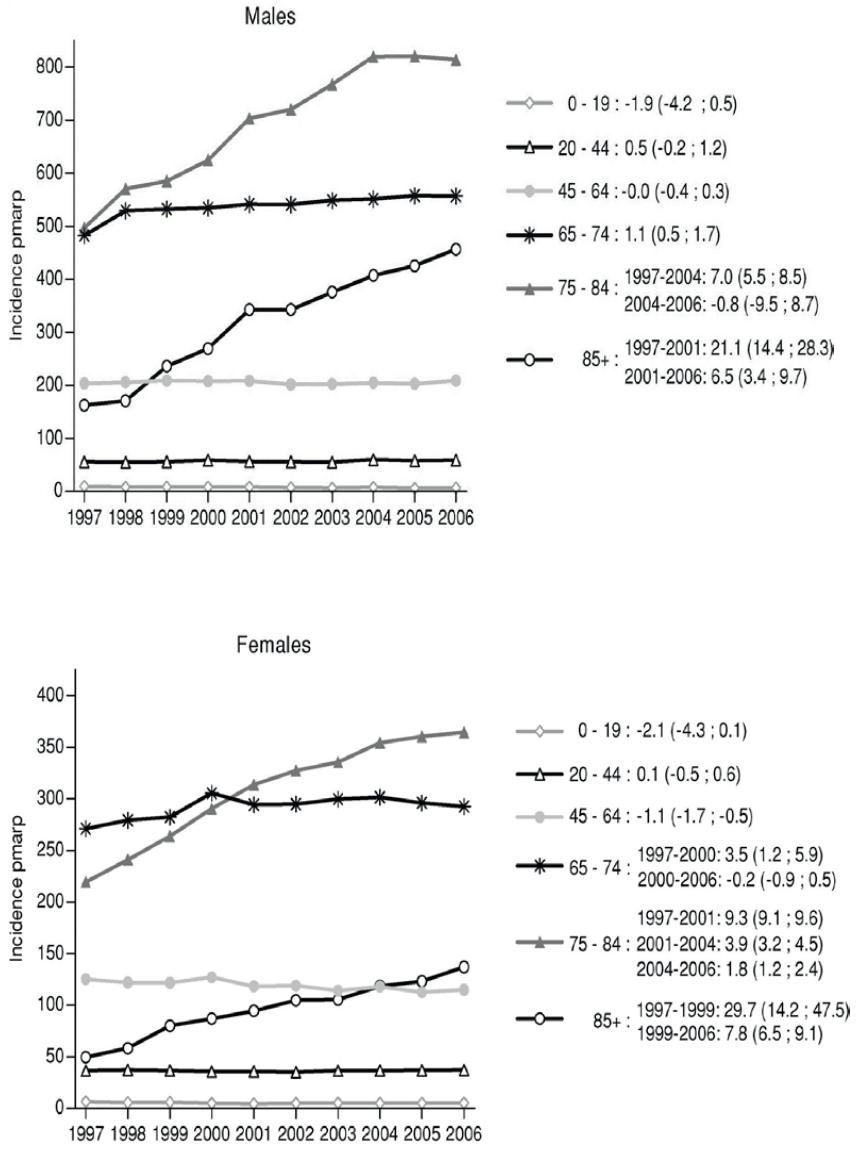


Figure 3 Incidence rates for ESRD Europe 1997 – 2006 by gender and age groups. (ERA-EDTA Registry data, 2009) (8)

Quality of life

Quality of life is defined by the WHO as a state of complete physical, mental and social well-being, and not merely the absence of disease (20). For the purpose of clinical research, the term health related quality of life (HRQoL) has been defined, referring to the patients` appraisal of their current level of functioning and satisfaction with it compared to what they perceive as ideal (21). HRQoL may be considered synonymous with subjective health assessment, and reflects the persons experience with health care interventions (22). In clinical research and practice, quality of life is limited to health related issues, and the terms «quality of life, QoL» and «health related quality of life, HRQoL" are mostly used synonymously. In this thesis we will use the term quality of life, QoL.

A large number of QoL questionnaire have been developed, most of them are multidimensional. These questionnaires can be generic; that is, suitable for general populations without reference to any disease, or condition specific, e.g. developed for cancer or kidney disease in particular, or domain specific e.g. assessing depression and anxiety (20).

SF-36

The Medical Outcome Study 36 item Short Form Health survey (MOS SF-36) is originally a generic, self-administered questionnaire, but is well documented and validated in chronic dialysis patients of all ages. The questionnaire consists of 36 items, which are summarised into 8 scales, and the 8 scales can be summarized into 2 composite scales; Physical Composite Summary (PCS) and mental Composite Summary (MCS) (23).

Quality of life in dialysis patients

The majority of the oldest patients in dialysis will not be offered a renal transplant and will be in lifelong dialysis treatment; hence, quality of life is a crucial outcome and is also recognised as a predictor for morbidity and mortality.

In general, Qol of dialysis patients seems to be substantially affected, especially the physical domains (24-29). A similar reduction in physical QoL domains have been demonstrated for other chronic illnesses like congestive heart failure (30). Others have shown a clear reduction in QoL scores in dialysis patients compared to other chronic diseases (31).

Several assessments tools have been used to assess QoL in renal disease. For chronic kidney disease the SF36 are most common, and for dialysis patients the Kidney Disease Quality of Life (KDQoL) (which includes SF36) are now most used (32). The KDQOL is generic and developed for CKD specifically. It consists of 18 scales, 8 from SF36, supplemented with 10 multi-item scales targeted at particular concerns of individuals with kidney disease and on dialysis (symptoms, effects of kidney disease on daily life, work status, cognitive function, quality of social interaction, sexual function, sleep, social support, patient satisfaction) (33).

Longitudinal studies with a follow up for 18 months have shown that QoL scores for the physical domains decline over time, more for PD than HD, whereas scores for mental domains remained stable for both modalities (24). Several other studies have also compared the QoL of PD and HD patients and found no significant difference measured up to one year after treatment start (34-36).

The older patients tend to be underrepresented in clinical studies; hence less is known about the frequency and magnitude of problems in this subgroup. It has been shown that QoL scores are poorer in older dialysis patients compared to general population at same age, and that it is the physical domain that are most affected (37-40). Comparing groups of older and younger patients in dialysis, no difference has been found for the QoL mental domains. Results regarding physical domains are more diverse; superiority of scores from the older population as well as equality has been reported (41, 42). For the oldest dialysis patients (> 75 years), however, the physical scores seem to be poorer than for younger ones (37, 43).

The most markedly QoL impairment has been revealed in patients >75 years of age who had an unplanned start in dialysis (43).

Factors that may influence QoL in dialysis

To improve treatment and prognosis, a precise identification of factors that may influence QoL is important. Several studies, have investigated medical factors related to CKD and renal replacement therapy that have been assumed to influence QoL in dialysis patients, such as referral time to nephrologist, dialysis adequacy, dialysis frequency and anemia.

Early vs. late nephrology referral

Early referral to nephrologists is documented to result in reduced mortality, better uptake of peritoneal dialysis, earlier placement of arteriovenous fistula for hemodialysis and shorter duration of hospital stay when dialysis treatment was initiated (44, 45). There are a few studies which have address referral time and quality of life as an outcome. A multicenter study showed no difference in SF36 summary scores for early vs. late referral (46). Boini et al showed a significant association between referral time and mental component summary (MCS), but not for physical component summary (PCS) (47).

Dialysis adequacy Kt/V

Kt/V (fractional urea removal rate) is a measure for dialysis adequacy, and relates K (urea clearance), t (time on dialysis) and V (volume of distribution for urea). Some studies have been done with the hypothesis that increased dialysis doses would improve QoL. The HEMO study (48) showed that a small, but statistically significant difference in bodily pain (BP) and physical component summary (PCS) in favor of high dialysis doses (Kt/V 1.45) compared to low. No statistically significant difference in QoL scores between patients who were treated high flux membrane vs. low flux was found (48). In peritoneal dialysis, the ADEMEX study (Adequacy of peritoneal dialysis in Mexico) found no evidence for long-term benefit on QoL by increasing peritoneal small solute clearance (49).

Frequency of dialysis

Longer dialysis duration either as short daily dialysis or longer nocturnal dialysis 6 nights a week have been assumed to give better outcome both on survival and QoL than conventional dialysis treatment; 4 hours trice-weekly. That nocturnal frequent hemodialysis does not improve overall QoL compared to conventional hemodialysis has recently been documented (50, 51). There is now an ongoing study organized by the Frequent Hemodialysis Network (FHN) investigating the hypothesis that frequent daily hemodialysis and/or nocturnal dialysis would give better QoL than conventional hemodialysis (52).

Anemia

Anemia is a very frequent complication of CKD and usually starts early in the course of the disease. CKD patients with anemia (Hb levels < 11g/dl) have lower QoL scores, increased cardiovascular risk and a higher risk for death (53). Many studies have demonstrated a QoL benefit by treating the anemia with erythropoietin stimulating agents (ESA) (54, 55), in general as well as for elderly in dialysis (56). There is still a debate about the optimal ESA dose regimen. So far, it has been documented that keeping the Hb in range 10.5-12.5g/dl results in better QoL scores and lower cardiovascular risk. Aiming for an even higher Hb, has not been proven to give any further QoL benefit, i.e. in studies published so far (57, 58).

Early vs. late start in dialysis

Over the last decades, there has been a trend in USA and Europe to start dialysis treatment in an earlier stage of kidney failure. Early start in dialysis treatment is usually defined as eGFR > 10 ml/min and late start < 10 ml/min. In USA in 1996, 25 % started at eGFR> 10 ml/min, whereas in 2005, this number was 54% according to United States Renal Data system (USRDS) (59). Accordingly, The European Dialysis and Transplantation Associations (EDTA) registry showed that the mean eGFR at start was 7.3ml/min in 1999, and 8.1ml/min in 2003 (60). The trend to start early is particularly strong among older patients. Data from The French Renal Epidemiology and Information Network (REIN) have shown that 19 % of younger dialysis patients below 65 years started with eGFR> 10 ml/min, 38% in the age groups between 75 and 84 years, and 48% of those aged 85 years and more (61).

However, several studies have shown that early start may be associated with higher mortality (59, 61). This could be due to the older age of these patients. It may also be explained by the difficulties in estimating GFR by equations, in patients with ESRD. Patients with small muscle mass will have low levels of serum creatinine and the result is falsely high levels of estimated GFR in patients who in fact are in poor status with high mortality risk (59, 61-63).
Only one randomised study comparing early to late start has hitherto been conducted and published. This is the Initiating Dialysis Early and Late (IDEAL) study, which concluded that there was no difference in survival or QoL between those who started early vs. late in dialysis (64). In the IDEAL study, the mean age was 60 years (SD 12.3). To our knowledge there are no studies addressing QoL in older dialysis patients with early start.

Comorbidity

Older age is highly correlated to the presence of co-morbid disorders (65). A French study showed that for patients > 75 years of age at start of dialysis, 85% had at least one comorbidity and 36% had three or more (66). In hemodialysis patients in general, comorbidity is found to be associated with mortality as well as QoL (26, 67). To which extent comorbidity affects the QoL of the older dialysis patients has not been fully confirmed (19, 68). Comorbidities like malignancy, severe behavioural disorders, low BMI, reduced mobility and congestive heart failure are strongly associated with 2-year mortality among the elderly patients in dialysis, and diabetes, cardiovascular diseases and chronic respiratory disease were also significantly related to a higher risk of death, but with lower hazard ratio (66).

There is no consensus for assessing and grading of comorbid diseases in chronic kidney disease, and in some registry studies only the number of comorbid diseases has been registered without using any particular indexes. In other studies, varying comorbidity indexes have been used; Index of coexistent disease (ICED), Charlson comorbidity index (CCI), Whrigt – Khan Index and Davies index (69, 70). Three of these are developed for dialysis patients; ICED, Whrigt-Khan and Davies. CCI is a generic index, developed from patients' hospitalized in general internal ward. There is one study comparing the use of the four indices on dialysis patients (71). The ICED had greater discriminatory ability than the CCI, Davies and Whright-Khan indices to predict 1 year mortality, but it takes about 50 minutes to complete in comparison with the three others which take 15-20 minutes to complete.

The Davies comorbidity index is based on seven domains, i.e. malignancy, ischemic heart disease, peripheral vascular disease, left ventricle dysfunction, diabetes mellitus, systemic collagen vascular disease and other significant pathology. Whether the patient has an active or present disease on any of these domains is registered. The comorbidity score for each patient is calculated as the sum of the number of domains affected, giving a theoretical range from zero to seven. Based on this score, the mortality risk is classified into low (0 comorbidities), medium (1-2 comorbidities) and high (≥ 3 co-morbidities) (72, 73)

Functional status

Decline in physical function is a feature of normal aging. Among elderly dialysis patients there is a high prevalence of functional disability. A Canadian study of 162 HD patients > 65 years (mean age 75 years) showed that 95% had at least one instrumental activity of daily living (IADL) dependency with a median of five (74). A study of patients starting dialysis at 80 years of age showed that within 6 months after start in dialysis, more than 30% of patients had functional loss requiring community support or transfer to nursing home (75). A cohort study of older hemodialysis patients (mean age 70 years) have shown that they had 1.18 fall/patient year vs. older person in community dwelling (age 74 – 78 years) had 0.32 – 0.70 fall/person year (76). Another study have showed that more than one accidental fall was associated with increased mortality (77).

Few studies have hitherto addressed the impact of physical function on quality of life in older dialysis patients (78). Physical function is, however, closely connected to most aspects of life, including autonomy and independent living, and a Cochrane review of training studies in elderly showed significant improvement in physical domains of QoL with training (79). Similar results have been reported for younger dialysis patients (80, 81).

In the Dialysis Outcomes and Practice Patterns Study (DOPPS) higher physical exercise frequency was found to be associated with significantly better scores on both mental and physical component of SF36 (82). One pilot trial has demonstrated that intra-dialytic low-intensity training was safe and also improved physical performance in older hemodialysis patients (mean age 69) (83).

Nutritional status

To maintain good nutritional status it is essential that there is a balance between bodily requirements and intake of nutrients (84). In patients with chronic kidney disease (CKD) nutritional deficits are highly prevalent and may lead to deteriorated nutritional status as renal function worsens. The nutritional problems can be both uremia-related and dialysis related (Figure 4). Uremia-related problems include reduced appetite and several hormonal alterations; higher levels of counter-regulatory hormones (Glucagon, PTH) and resistance to anabolic hormones (insulin, growth hormone, Insulin-like growth factor 1: IGF-1). As the number of functioning nephrons declines in chronic kidney disease (CKD), it leads to net retention of hydrogen ions and development of progressive metabolic acidosis, which can promote protein degradation (85, 86). Dialysis related problems is caused by increased energy consumption, many nutrients (amino acids, proteins, water soluble vitamins and glucose) are lost during dialysis session. Other dialysis-linked factors are dialysis fluids (endotoxins) and dialyzer membranes, which give a risk of exposures to inflammatory stimuli.

The reported prevalence of nutritional deficits varies substantially between studies, ranging from 20% to 50% of the patients (87-89). This inconsistency may be explained by a similar wide variation in terminology as well as diagnostic criteria. The International Society of Renal Nutrition and Metabolism (ISRNM) recommend using the term "protein-energy wasting" (PEW) to describe loss of body protein and fuel reserves (muscle and fat tissue) (88). Protein-energy wasting (PEW) are reported to be present in 20 -50% of the dialysis population. According to the ISRNM PEW is diagnosed if at least one parameter is found below recommendation in three of four categories: **1.biochemical criteria** (low se-albumin, low se-prealbumin, low se-cholesterol), **2**.**low body mass** (BMI < 24) unintentional weight loss over time, total body fat percentage < 10 %), **3**.**decrease in muscle mass** (muscle wasting) **4.low protein or energy intakes** (low dietary protein, low dietary energy intake for at least 2 months) (88).

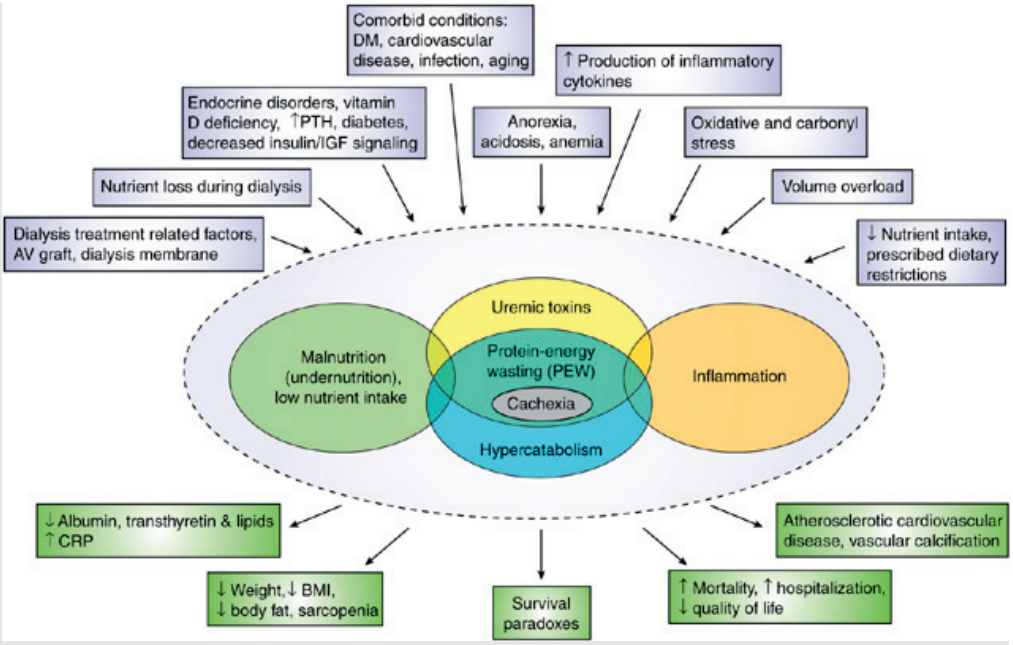


Figure 4. Schematic representation of the causes and manifestations of the protein–energy wasting syndrome in kidney disease (Fouque D,2008) (88)

Furthermore ISRNM suggests using the term cachexia for the most severe form of protein and energy mass depletion, assumed to affect about 10% of ESRD patients. There is still no generally agreed upon definition of cachexia. However, a Consensus conference in 2006 decided for the following: "Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity" (89).

In accordance with this definition, the following criteria for the diagnosis of wasting disease (cachexia) in adults were proposed (89): **weight loss** of at least 5% in 12 months or BMI < 20 kg/m², plus at least 3 of the following criteria: **1. decreased muscle strength, 2. fatigue**

(defined as physical and/or mental weariness resulting from exertion**), 3. Anorexia** (limited food intake or poor appetite), **4. low fat free mass index** (lean tissue depletion), and **5. abnormal biochemistry**; increased inflammatory markers CRP (> 5.0 mg/L), anaemia (Hb< 12 g/L) or low serum albumin (< 3.2 g/dl)(5).

According to proposed definitions (88, 89) changes in body composition, in particular loss of lean tissue (including muscle mass) is important features of both PEW and cachexia, but also a phenomenon of aging.

For patients in maintenance dialysis, poor nutritional status may affect QoL and morbidity, and is associated with decreased survival despite adequate dialysis treatment (87, 90). Malnutrition in elderly haemodialysis patients influences overall survival despite adequate dialysis treatment (87, 91). The Hemodialysis study (HEMO) showed that markers of poor nutrition were associated with decreased physical function scores (SF 36) (92, 93). Nutritional deficit at start of dialysis is strongly associated with mortality (94). Malnutrition – Inflammation Score (MIS) which is a comprehensive score of SGA, comorbidity including number of years on dialysis, BMI , se-albumin and TIBC have been found to correlate with quality of life (SF 36) and mortality (95-97).

Hydration status

Adequate control of the extracellular fluid volume is a principal goal of renal replacement therapy in patients with end-stage renal disease (ESRD). Chronic fluid overload may significantly contribute to hypertension, accelerated arteriosclerosis and the high prevalence of left ventricular hypertrophy observed in ESRD patients. Removal of excess fluid is therefore considered crucial for blood pressure control and, thus, for cardiovascular protection in dialysis therapies (98). Overhydration increases the mortality (99) and may also impair quality of life in hemodialysis patients (100). For this reason as well as to avoid hypotensive episodes during dialysis sessions (99), it is essential to determine the patients` dry weight. Dry weight may be defined as the target weight after dialysis treatment at which the patient is as close as possible to a normal hydration state without experiencing symptoms that are indicative of over- or underhydration (101). Thus, for dialysis patients, assessments of body composition are important, not only to assess nutritional status, but also to determine their hydration status.

Assessment of nutritional status.

Changes in nutritional status will eventually result in changes in body composition, plasma concentration and immune competence (102). Traditional methods to evaluate nutritional status therefor include loss (or gain) of body components relative to previous measurements and relating the values in a given patient to normal standards. Measurements of height and weight of the human body (anthropometry) is basic in all evaluation of nutritional status.

Anthropometry

Body weight is a simple measure of total body components and is compared to an "ideal" or desirable weight. Body mass index (BMI) is defined as body weight (kg)/ height $(m)^2$ and is used by the World Health Organization (WHO) to define cut-off points for normal weight, underweight, overweight and obesity in the general population (103). However, measures like weight and BMI cannot distinguish between body fat, muscle mass and water (104), although a high BMI can be an indicator of body fat, and a low BMI can be an indicator of low lean body mass.

Changes in body weight can be intentional or unintentional, unintentional weight loss can be a sign of underlying disease, but in dialysis patients it can be confounded by changes in hydration status.

Skin fold measures

Skinfold thickness has been showed to be the most simple, long-established and inexpensive method for assessing body fat in patients on long-term hemodialysis therapy (105, 106).

Triceps skinfold (TSF) has been found to be independent predictor of all-cause mortality in haemodialysis patients (107).

Muscle strength

Hand grip strength (HGS) is a valid method for assessing muscle-strength, a marker of muscle mass, and has shown strong correlation with lean body mass (108-110). A systematic review has concluded that HGS is a useful tool for continuous and systematic assessment of muscle mass related to nutritional status in patients on dialysis (111, 112). HGS may be used as a reliable nutritional marker in hemodialysis, measured before or after HD sessions (113).

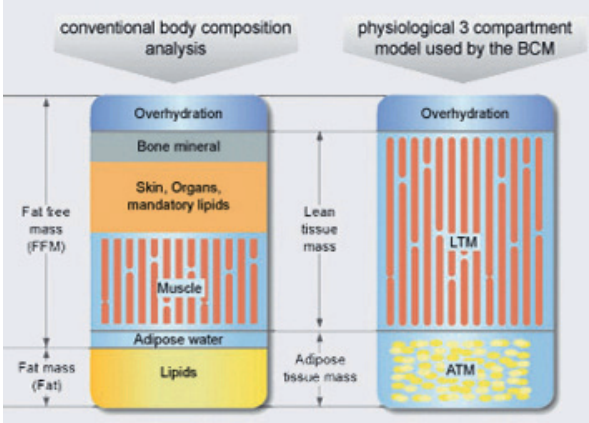
Body composition

Several devices are developed to assess body composition. Dual-energy x-ray absorptiometry (DEXA) is considered the gold-standard method, but this is an expensive method and not available for all dialysis units. Imaging techniques like magnetic resonance imaging (MRI) and computed tomography scanning (CT) are also used to measure body composition, but have so far mostly been used in research.
Portable devices like near-infrared (NIR) interactance and specially bioimpedance spectroscopy (BIS) are easy to use and are relatively inexpensive. BIS is validated against available gold standard methods with good accordance, and may be used to evaluate nutritional status as well as to determine hydration status (114).

Dry weight may be estimated by ultrasound of the inferior vena cava, radionuclide dilution techniques and echocardiography. These methods are expensive and time consuming, most often clinical surrogate parameters are used such as interdialytic weight gain, ultrafiltration rate or blood pressure. BIS can be done bedside. A recent study showed increased all-cause mortality in hyperhydrated patients compared to normohydrated (hazard ratio =3.4). The hydration status was measured with whole-body bioimpedance spectroscopy (115).

Figure 5. Model of whole bioimpedance spectroscopy

Body weight = LTM + ATM + OH



The three compartments (LTM, ATM and OH) are identified from measurements of body weight, height, **intracellular (ICW) and extracellular water (ECW)** determined by **whole body bioimpedance spectroscopy (BIS).**

(www. bcm--fresenius.com)

Subjective Global Assessment (SGA)

Several assessments tools have been developed for the assessment or screening of nutritional status; Nutritional risk screening (NRS 2002) (116), Malnutrition Universal Screening Tool (MUST) (117), Mini Nutritional Assessment (MNA) and Subjective Global Assessment (SGA) (102).

The SGA is based on the clinical judgment of four subscales representing the patient recent weight changes, dietary intake and gastrointestinal symptoms, loss of subcutaneous fat and signs of muscle wasting(102, 118). SGA has been modified from a 3 point scale to a 7 point scale, and is validated in dialysis patients in large observational studies like DOPPS and

CANUSA (93). The European Best Practice Guidelines (EBPG) on nutrition recommends 7 point SGA scale because of its greater sensitivity and specificity (119).

Nutritional parameters' as assessed by the SGA has in previous studies of younger dialysis patients showed a positive correlation with SF36 physical composite summary (PCS), but not with mental composite summary (MCS) (120, 121). The SGA has been found reliable and valid to assess protein-energy wasting (94, 112, 122, 123), and can be used to differentiate dialysis patients with severe malnutrition from those with normal nutritional status. It has been questioned if SGA is a reliable tool to measure the degree of malnutrition (93).

Norwegian Renal Registry

The Norwegian Renal Registry (Norsk Nefrologiregister) was formally constituted in 1994 as collaboration between The Norwegian Renal Association (Norsk Nyremedisinsk Forening) and Oslo University Hospital-Rikshospitalet, with the latter as the formal owner. National data on renal replacement therapy (RRT) have been collected within The Renal Association since 1980, and the transplant center has stored data on transplanted patients since the sixties. Further, Norwegian renal units had reported to the ERA-EDTA-registry since the late sixties.

The NNR consists of data from all the county-centres in Norway. These centres are responsible for reporting data from all Norwegian patients receiving renal replacement therapy (RRT) for chronic kidney failure at start of dialysis and thereafter annually. Deadline for the completion of the annual data is by the end of March.

Aims of studies

The overall aim of the present thesis was to provide knowledge about older dialysis patients' QoL in particular, to identify factors that may influence it, and thereby enable improved treatment. Furthermore, we aimed at providing a better understanding of the general recruitment problem for RCTs addressing dialysis patients, and thereby facilitate future research among these patients

The specific aims were

1. to explore possible reasons for the recruitment failure in a Norwegian multi centre RCT targeting end stage renal disease (ESRD) patients > 70 years which was designed to compare the impact on quality of life (QoL) of early or late start of dialysis (Paper 1)

2. to describe the QoL of the Norwegian dialysis population aged 75 years or more, and to explore the impact on QoL of nutritional status, physical function, comorbidity and early vs. late start in dialysis (Paper 2)

3. to assess the feasibility of using bioimpedance spectroscopy (BIS) to measure body composition and hydration status in dialysis patients aged 75 years and more, to describe the hydration and nutritional status of these patients in detail and to further explore the association between hydration status, nutritional status and quality of life (Paper 3)

Material and methods

Study design and population

Paper 1

This paper addresses the first of the specific aims, and describes a survey among Norwegian nephrologists. To explore the mechanisms behind the recruitment problems for the planned randomised controlled trial, a questionnaire was distributed to all Norwegian nephrologists by email. The participants were identified by a list from The Norwegian Nephrologists Association. This list includes all nephrologists in clinical nephrology practice, who takes the final decision about the patients' starting in dialysis treatment. The questionnaire was followed by a reminder four weeks later. The questionnaire could be returned by post or fax.

In Norway, there are 108 registered nephrologists (November 2008). At the time of the survey 73 of these were practising clinical nephrology. We mailed the questionnaire to all 108 nephrologists, and received answers from 39 (36 %), 31 (79%) were men and 24 (61.5%) were > 50 years. The answers were given anonymously.

Paper 2

This paper addresses the second of the specific aims and reports the result from a cross-sectional study.
All patients ≥ 75 years (n=320) who according to the Norwegian Renal Registry (NNR) were in dialysis by January 2009 and alive by September 2009 were asked to participate and mailed the study questionnaire (September 2009). The questionnaire included assessments of QoL and nutritional status. A reminder was sent 2 weeks later. We received answers from 233 (73%).

Medical data from the responders were collected from the NNR and included data registered at start of dialysis treatment and in the Annual Report 2008; this Annual Report includes data on biochemical parameters, blood pressure, medications, physical status, and new co-morbid diseases up to March 2009.

Paper 3

This paper addresses the third specific aim and reports the result of a observational study. Chronic dialysis (haemodialysis, HD and peritoneal dialysis, PD) patients over 75 years of age, living in South and North Trøndelag Counties and on dialysis in January 2008 were asked to participate in the study. A total of 34 patients ≥ 75 years were registered, 10 were excluded (1 due to language problems, 4 were too ill, 1 was transplanted and 4 due to practical problems), and thus in total 24 entered the study.

Assessments

Recruitment questionnaire (paper 1)

The introduction to the questionnaire that was administered to all Norwegian nephrologists comprised a short study description including the design and research questions. The questionnaire itself presented eleven statements which cited possible reasons for not including elderly ESRD patients into the RCT (See Appendix). The responding nephrologists were asked to rate the importance of each of these statement on a 6 point scale ranging from 0 (unimportant) to 5 (very important). Responses were anonymous, only gender and age (> or < 50 years) were registered.

Norwegian Renal Registry (paper 2)

The data reported to the Norwegian Renal Registry (NRR) when a patients starts in dialysis therapy are: blood tests (hemoglobin, creatinine, calcium, phosphate, PTH), height, weight, dialysis modality, access type in hemodialysis, primary kidney disease, comorbid diseases and medication (antihypertensive drugs, erythropoiesis stimulating agents ESA and statins).

The annual report includes: blood tests (haemoglobin, cholesterol, and albumin), blood pressure, weight, dialysis frequency and weekly treatment hours.

Quality of life (paper 2 and 3)

QoL was measured with a Norwegian validated translation of the Medical Outcomes Study 36 item Short Form health survey (MOS SF-36) (124). The questionnaire consists of 36 items, which are summarised into 8 scales; physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE) and mental health (MH). For each item the scores are summarised and transformed to the eight 0 – 100 scales, (0 = poorest possible health state, 100= best possible health state) according to the SF 36 normed-based scoring algorithms (125). To reduce the number of statistical comparisons, the 8 subscales can be summarized into Physical Component Summary (PCS) which consists of PF, RP, BP, GH and VT, and the Mental Component Summary (MCS) consisting of MH, RE, SF and VT (126).

Nutritional parameters

Anthropometry (paper 3)

Body weight and height were measured before dialysis. After the dialysis session the patient was weighed again to calculate dry weight body mass index (BMI = BW (kg)/ height (m) ^{2})
The mid-upper arm circumference (MAC) was measured with the millimetre tap at the midpoint of the non-fistula arm, between the olecranon and acromion.
The triceps skinfold (TSF) was measured at the same midpoint using a skinfold calliper.

Hand grip strength (HGS) assessment was done with a single spring handgrip dynamometer, while patient was sitting in an upright and relaxed position. The measurements were repeated three times and the highest score was recorded (108, 127, 128). We classified the patients as

having “decreased muscle strength” when HGS values were below 85% of the normal age and gender adjusted values (129). All measurements were done by the same person.

Subjective Global Assessment (SGA)

The Subjective Global Assessment (SGA) of nutritional status covers medical history (weight loss during the last 6 months, changes in food intake and gastrointestinal symptoms) and physical examination (assessment of subcutaneous fat loss, muscle wasting and oedemas) (102). In the cross-sectional study and observational study a Norwegian version was used (130). In paper 3 the patients' SGA scores was evaluated and classified as described by Detsky et al (102). Each patient was classified as either; A (normally nourished) meaning stable or increased weight, normal body composition and no symptoms related to poor nutrition; B (moderately malnourished) implying weight loss up to 10% of total body weight without subsequent stabilization or weight increase, reduced energy intake but normal BMI (BMI > 20 kg/m²) or; C (severely malnourished) meaning that the patient had weight loss more than 10% in 6 months, clear physical signs of impaired nutrition, oedemas and BMI < 20.

In the cross-sectional study the questionnaires were mailed to the patients hence, no physical examination was possible. The patients were therefore classified into group A, B and C as stated, based on their reports on first part of the questionnaire and their BMI, as recommended by the ESPEN guidelines in 2002 (116). The classification was independently made by two trained reviewers, a nephrologist and a nutritionist respectively. In case of disagreement, the classification was discussed to reach consensus.

The EORTC QLQ-C30

Anorexia may clinically be defined as a reduction of or loss of appetite (131). EORTC QLQ-C30 is a 30 item questionnaire, a validated measure for QoL for cancer patients (132). In the questionnaire there are two symptom scales regarding gastrointestinal symptoms: nausea-vomiting scale (2 items) and appetite loss (1 item). The items are scored on a four point categorical scale ranging from “not at all” to “very much”. Before statistical analyses, the items scale scores were linearly transformed to a 0-100 scale where the higher scores represent more symptoms (133, 134).

Cachexia

We based our cachexia classification in paper 3 on the definition by Evans et al (89) and in addition to weight loss and/or low BMI, we used the following of the defined criteria; 1; decreased muscle strength measured with hand grip strength (HGS), 3; anorectic symptoms (assessed by Appetite scale from EORTC QLQ-C30) 4; low LTI (< 10 percentile), as measured by bioimpedance spectroscopy and 5; CRP> 5 or se-albumin < 3.2 g/dl.

Bio-impedance spectroscopy (BIS) (paper 3)

We used whole body bio impedance spectroscopy (BIS) to assess body composition in terms of extracellular (ECW), intracellular (ICW) and total body water (TBW), and to estimate lean tissue mass (LTM) and fat tissue mass (FTM). The measurement was made with the patient in a supine position, with electrodes placed on the hand and the foot, using the Body Composition Monitor (BCM) from Fresenius Medical Care, Germany. The BCM measures the impedance spectroscopy at 50 frequencies. The calculation of ECW, TBW and ICW by this method is validated against corresponding reference methods, i.e. sodium bromide dilution, deuterium dilution, and the total body potassium (135) respectively. The calculated body composition (fat and fat free mass) has been validated against dual-energy X-ray absorptiometry, DEXA and air displacement plethysmography (136, 137). The cut off threshold to define overhydration was set to an excess of ECW of > 15%, which is comparable to overhydration of ~ 2.5 L, and is associated with higher mortality rates (99). LTM and FTM were normalized to body surface area to obtain lean tissue index, LTI (LTI = LTM/height^2) and fat tissue index (FTI = FTM/height^2). The values for LTI and FTI were compared to an age (18 – 80 years) and gender match reference population(138). Values below the 10th percentile were regarded as a clinically significant reduction in muscle mass or fat mass.

Comorbidity

To assess comorbidity in the cross-sectional study (paper 2) we used medical data from the NRR, which records 6 possible comorbid diseases at start of dialysis; left ventricular hypertrophy (LVH), coronary disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus type II and malignancy. We divided the patients into 3 groups; 1) no comorbid disease, 2) 1-2 comorbid diseases, and 3) ≥3 comorbid diseases.

To assess co-morbidity in the observational study (paper 3), the Davies Comorbidity index was applied. This index is based on seven domains, i.e. malignancy, ischemic heart disease, peripheral vascular disease, left ventricle dysfunction, diabetes mellitus, systemic collagen vascular disease and other significant pathology, and whether the patient has an active or still present disease on any of these domains is registered. The comorbid score for each patient is calculated as the sum of the number of domains affected, giving a theoretical range from zero to seven. Based on this score, the mortality risk is classified into low (grade 0, zero score), medium (grade1, score of 1-2 comorbidities) and high (grade 2, score of ≥ 3).(72, 73)

Statistical methods

Paper 1

Descriptive statistics were used. For each of the eleven statements that were presented for the nephrologists, we calculated mean score with range, and the frequencies for all score-possibilities. The statistical package SPSS for Windows version 15 was used.

Paper 2

Medical and demographic parameters and QoL scores were compared between groups defined according to gender, dialysis modality and early versus late start in dialysis. For the medical and demographic data, Students' t-test was used to test for statistical significance. For the

quality of life (SF-36 and EORTC) scores, which were not normally distributed, we used the Mann-Whitney U test. However, to ease the interpretation and the comparison to findings of other studies, we chose to present the SF 36 (QoL) scores in terms of group means.

The association between SF-36 scores and the following variables: early versus late start in dialysis, comorbidity, nutritional status (SGA classification) and physical capacity (SGA score and SF-36 physical functioning score) was tested by both the Kruska Wallis and the Wilcox rank sum tests. We also tested for trends in differences of SF-36 scores between groups defined according to comorbidity, SGA classification (A, B, C) and physical capacity using the Jonckheere (Kendall Tau) test.

The SPSS version 18 was used for descriptive statistic and the simple group comparisons, whereas the Stata version 12.0 was used for the tests of association and trends. Statistical significance was defined as $p < 0.05$, and clinical significance for the difference between QoL scores was defined as a difference of 10 or more

Paper 3

All statistical analysis was performed using the statistical package SPSS for Windows version 15. We used descriptive statistics, and for the same reason as in paper 2, comparisons of QoL score between groups were done with non-parametric methods; Mann-Whitney U test, $p < 0.01$ was considered significant. A difference in SF36 scores > 10 points between groups was considered as clinically significance (139). The Spearman coefficient of correlation was used to test correlation between bioimpedance measures (LTI, FTI) and hand grip strength (HGS), BMI, serum albumin and anthropometric measures

Main results and review of papers 1-3

Paper 1: Recruitment in End-Stage Renal Disease (ESRD) why is it so difficult?

A Norwegian multicentre RCT targeting end stage renal disease (ESRD) patients > 70 years was initiated to compare the impact on quality of life (QoL) of early or late start of dialysis. Due to poor inclusion the RCT was closed. The aim of the present study was to explore possible reasons for the recruitment failure. A questionnaire was distributed to all Norwegian nephrologists. The questionnaire presented eleven statements which cited possible reasons for not including elderly ESRD patients into the RCT in question. The statements included reasons related to physicians and patients' attitudes, consequences of the randomisation procedure, constraints (dialysis capacity and workload at the dialysis unit) and need for economical support to nurses and physicians.

The highest rated reasons for non-inclusion were the physician's wish to decide the timing of dialysis individually and the patient's wish to postpone the start of treatment. High mean scores were also found for reasons related to workload and capacity at the dialysis unit, whereas influence on the doctor-patient relationship and competing studies were judged not to be important.

Paper 2: The impact of nutritional status, physical function, co-morbidity and early vs. late start in dialysis on quality of life in older dialysis patients.

The aim of this cross-sectional study was to assess the quality of life (QoL) of the Norwegian dialysis patients aged 75 years or more, and to explore the impact on QoL of nutritional status, physical function, comorbidity and early vs. late start in dialysis.

Overall, 320 patients in dialysis (HD and PD) ≥75 years of age, representing all Norwegian dialysis patients within this age group at the time, were invited to participate, 233 were included. The defined outcome measure was QoL as assessed by the SF 36 questionnaire. Nutritional status was assessed by the SGA. Additionally, weight changes and body mass index (BMI) were measured. To determine the patients physical function, we used a question from SGA regarding physical capacity, and the physical function scale (PF) of the SF36. Comorbidity data was retrieved from the NRR and the patients were divided into 3 groups depending on how many comorbid disorders that was present.

The results showed that SF 36 scores were poor, and poorer than for norm population of the same age and gender. There was a tendency towards lower scores for female vs. men and PD vs. HD patients, but these differences were not statistical significant. The patients who started early in dialysis (eGFR > 10 ml/min) (n=52) had mean eGFR 12.82 ml/min, whereas those who started late (n=142) had mean eGFR 7.09 ml/min. Nutritional status according to the SGA (n=220) was found to be normal (SGA A) in 51.4% of the patients, 32.3% were moderately malnourished (SGA B) and 16.4% were serious malnourished (SGA C). No comorbid disorder was reported for 21.3%, 1-2 co-morbid diseases for 54.5% and ≥3 comorbid disorders were present in 23.4% of the patients.

Normal self-reported physical capacity was present in 18% (39 patients), whereas 35% (n=77) reported “some activities”, 35% (n=76) reported to be “mostly in chair” and 6 patients (3%) were “mostly in bed”.

There was no statistical significant association between QoL (SF 36 scores) and early vs. late start in dialysis, nutritional status assessed by SGA (A, B or C) or number of comorbid diseases. There was a clear statistical significant association between SF 36 scores and physical capacity.

Paper 3: Nutritional problems, Overhydration and the association of Quality of life in Elderly dialysis patients.

The aim of this pilot study was to test the feasibility of using bioimpedance spectroscopy (BIS) in daily clinical practice, to describe the hydration-, and nutritional status of a cohort of elderly dialysis patients, and to explore the association between these parameters and the quality of life (QoL).

All patients over 75 years of age being in chronic dialysis by January 2009 (n=34) living in North- and South Trøndelag counties were asked to participate in this pilot study, 24 patients were entered. Hydration status and body composition were assessed by bioimpedance spectroscopy (BIS), and nutritional status using the subjective global assessment (SGA), BIS, anthropometric measures and biochemical parameters. Based on these assessments the patients were classified as being cachectic or not according to newly defined criteria (Evans Consensus criteria). QoL was measured using the SF-36.

Six patients (25%) were identified as being cachectic, 37.5% had a body mass index (BMI) below 24, and whereas according to SGA 91 % were moderately and seriously malnourished. BIS showed that the lean tissue index (LTI) was low (below 10^{th} percentile) in 46 % and detected overhydration in 35%. Compared to non-cachectic and normohydrated patients, those who were identified as cachectic and overhydrated reported consistently poorer QoL. For cachectic patients, the differences were clinically significant for all SF-36 scales. BIS was easily applicable when used before dialysis.

General discussions

Research challenges and choice of methodology

A randomised controlled trial (RCT) is considered the gold standard study design to investigate the effect of treatment interventions. The random allocation minimizes selection bias or confounding and leads to the creation of treatment groups that have comparable prognosis with respect of defined outcome (140).
There are four main reasons why RCT should not be performed; 1) Experimentation may be unnecessary (classic example are introduction of hemodialysis treatment for ESRD), 2) Inappropriate (when the outcome is rare), 3) Impossible (clinicians refusal to participate, legal obstacles and/or ethical consideration) and 4) Inadequate (may have low external validity or poor generalisation due to extensive inclusion and exclusion criteria) (141).

In nephrology, few RCTs have been successfully carried out and reported (142), and several large studies more recently published, have had negative outcomes (57, 58, 143-145). Recently the IDEAL-study, a randomised study from Australia and New Zealand investigating survival and quality of life in early vs. late start in dialysis, reported no differences in survival or QoL (146). It is has been questioned whether these findings are representative for the general dialysis population. In the recruitment process, a large number of patients were excluded, i.e. 3000 patients were screened and only 828 patients were included, and there were very few patients > 75 years of age. Overall, it seems difficult to perform randomised clinical studies in nephrology, and this corresponds with our experience (Paper 1).

The RCT that we planned and initiated cannot be fitted into any of the situations where a RCT should not be performed, and the nephrologists at the various dialysis units throughout the country were initially positive to the study. Still, we did not succeed. To investigate our research questions, we first switched to an observational study, but the recruitment to this study also was too low. We therefor chose to perform a cross-sectional study (paper 2), based on self-report and registry data from The Norwegian Renal Registry, and a smaller observational study (paper 3).

The primary aim of the original trial was to investigate the impact on QoL of early start versus late of dialysis, in patients with ESRD > 70 years of age. The optimal timing for initiating chronic dialysis is widely discussed, and for the elderly in particular. Little is known about the optimal timing and whether early vs late start gives the best outcome for survival or quality of life. Secondary aims were to investigate the impact of possible prognostic factors (nutritional status, comorbidity and physical function) on the patients QoL.

A cross sectional study design can determine prevalence and is quick and easy, but do not differentiate between cause and effect or the sequences of events (147). The cross sectional study evaluates exposure and outcome at the same point in time (148). In our study (paper 2), we obtained cross-sectional data on QoL, physical function and nutritional status, which provided us the opportunity to investigate the association between quality of life and the two latter factors at one point of time. To analyze the association between QoL, the eGFR at start of dialysis and comorbidity, we took advantage of data from the NRR. Including the annual report, these data are both prospective and longitudinal. However, being cross-sectional, the QoL data was collected without regard to differences in time from the start of dialysis and the comorbidity registration to the assessment point. Differences in the length of dialysis treatment and interrcurrent events may therefore influence the association between these factors and the patients QoL. Furthermore, the patients having early and late start were not randomly allocated, hence, a possible selection bias cannot be ruled out. Overall, due to design, the data do not allow us to determine any causal effect between QoL and the investigated factors.

The use of registry data also poses another limitation. The data was not collected for the purpose of the present study, i.e. no further information was available than the one that was registered in the data base. For the analysis of comorbidity this was a particular problem, as we found these data to be limited. A considerable strength of the study, however, is that the NRR includes all Norwegian patients on dialysis, and the rate of missing data was lower than reported from similar registry studies (149).

In paper 3 we used an observational study design; i.e. a study without any experimental interventions. Such studies provide estimates and examine associations of events in their natural settings (147).

In this study we wanted to describe the patients' nutritional status in detail, explore more thoroughly the association between nutritional status and QoL and to test the feasibility of

bioimpedance spectroscopy in a small cohort of elderly dialysis patients. In this setting an observational study design was appropriate, and could provide valuable information in this group of older dialysis patients, as few studies have addressed this age group in particular.

Discussion of the main findings

Causes of recruitment failure for the RCT

Recruitment onto clinical trials is a challenge, and several barriers, both from the physicians and the patients' perspective have been reported. These included characteristics of individual patients, difficulties with the process of inviting the patients and concerns about adverse consequences for the patient and the patient-physician relationship (150).

In the present study, a questionnaire, which cited possible reasons for not including elderly ESRD patients into the RCT in question, was distributed to all Norwegian nephrologists. The response rate was low. Only 39 out of 108 nephrologists completed the questionnaire. However, the respondents were found to reflect the age and gender distribution among Norwegian nephrologists, and assuming that only practising nephrologists found it relevant to answer, a response rate of 53% (39/73) among these physicians could be estimated.

The highest rated reasons for non-inclusion were the physician's wish to decide the timing of dialysis individually and the patient's wish to postpone the start of treatment. Workload for the physician and capacity at the dialysis unit was also judged as important reasons. Fear of losing professional autonomy is a known reason why physicians may be reluctant to enrol patients onto clinical trials (151), and in consistency with our results, time constraints and lack of staff are other factors reported as likely to obstruct a successful enrolment (152). Lack of proper incentives, disagreement about the relevance of the research question and lack of

enthusiasm for the trial have also been cited as causes of recruitment problems (151-153). In this study, the results indicated that the physicians found the trial highly relevant, and opposed to what has been reported by others (150), the influence on the doctor - patient relationship was judged not to be important.

Age and performance status are two patient related factors known to influence trial enrolment, and particular problems are related to the older and frail population (154, 155). The elderly do not actively seek clinical trials (156). The frail and/or elderly also tend to be "selected out" by health professionals (157). Some cancer trials have reported that the older the patients, the less likely they were to be referred (156). This may be due to comorbid conditions as well as functional impairments that makes it difficult to invite the patient to participate, or to obtain informed consent (158). Our questionnaire did not include any statements that might have revealed whether the patients' age influenced the recruitment. However, the fact that our trial addressed older patients, might explain why patients' preferences for delayed treatment was ranked as a main reason for the recruitment problems. Other studies have shown that the patients' wishes to postpone treatment as well as to choose their own treatment pertains especially to older people (158). The possible frailty of the patients, however, did not seem to affect the nephrologists' willingness to include patients. It was not considered important that study inclusion would be too much of a burden for the patient.

Overall, our results indicate that the participating nephrologists consider their own as well as the patients' opportunity to decide treatment and timing by themselves to be of major importance. This attitude may represent a serious obstacle to the conduct of any randomized trial. As our response rate was low, it may be questioned whether the findings are representative. However, taking the relative deficiency of RCTs within the field of nephrology into account, they clearly deserve attention. Health professionals' gatekeeping, based on personal attitudes, is a well-described problem in health care research (159), and comparing the response rate for the present survey and our recruitment problems for the RCT to the high response rate in our cross sectional study (where the question about study participation was addressed directly to the patients), changes in physicians attitude may be necessary for successful enrolment in future trials within nephrology.

The results from paper 1 do not explain why the recruitment in the multi-center observational study where the patients should be included when initiating dialysis treatment, also failed. It

may, however, be due to some of the same recruitment problem as in the RCT; workload for the physician and capacity at the dialysis unit, time constraints and lack of staff. And it may also reflect a reluctant attitude to clinical trials participation in general.

Quality of life

For both the cross sectional study and the smaller observational study, the SF-36 was used to assess the patients' QoL. The Kidney Disease Quality of Life (KDQOL) that is developed for patients in dialysis in particular might have been a more appropriate choice. However, by the time our study was initiated, this questionnaire was not available in a validated Norwegian translation. Thus, we chose to use the SF-36 which is also widely used and well validated among dialysis patients (23). In the cross sectional study, all Norwegian dialysis patients aged 75 years and more were addressed, and the response rate was good, in particular when taking the age and the assumed frailty of these patients into account. In the smaller observational study, only patients living in South Trøndelag County were targeted. Ten out of 34 registered dialysis patients above 75 years of age were not included. Except that four of these patients were too ill to participate, the reasons for not being included were related to more random issues such as practical constraints. Hence, we find that any systematic error in the selection of patients for this study was minimized. All of the 24 patients who were enrolled in the study completed the SF-36.

In both studies (paper 2 and 3), we found that the QoL scores from the elderly dialysis patients were poor and that the physical items were most affected. Compared to studies in younger dialysis patients and the general population of the same gender and age, the QoL scores in our studies were poorer (160, 161).

Our QoL results are consistent with those found in other studies with older dialysis patients, with marked reduction in physical domains but smaller reduction in mental domains (39, 40, 43). In the Dialysis Outcomes and Practice Patterns Study (DOPPS) where 8000 hemodialysis were included from 12 countries (Europe, United Nations, Japan and New Zealand), the patients were divided in three age groups; < 45 years, 45 – 74 years and > 75

years and QoL were registered. There were a significant fall in physical composite summary (PCS) score for all countries with age, but the mental composite summary (MCS) remained unchanged with age (162). The same pattern was reported from a study from Hong Kong which compared symptom-burden and QoL in older ESRD on dialysis and in palliative care. They found impaired QoL and high symptom burden (fatigue, cold aversion, pruritus, lower torso weakness and sleep difficulty) in both groups, and a negative correlation between number of symptoms and QoL of all domains (163). This can suggest that a better control of symptoms in ESRD patients can improve QoL.

The QoL scores in our study were not significant different in PD and HD patients. The North Thames Dialysis Study (NTDS) showed already in 2002 that survival and QoL were similar for HD and PD patients who were > 70 years at the start of dialysis (19). In spite of this there has been a reduction in PD penetrance for older patients both in Europe (except France) and US, it may be due to the increase use of satellite HD. The recent published study from UK (Broadening Options for Long-term Dialysis in the Elderly, BOLDE) which compared QoL for patients > 65 years of age on PD and HD, showed that QoL was similar, if not better, in those on PD (164).

Based on the methodology used, the fact that all patients within a defined region (Norway and Trøndelag Counties respectively) were targeted, and the high compliance rate, we find that our QoL results are reliable. One limitation is, however, the lack of information about those patients who did not complete the SF-36. According to reports from other settings, the patients who are most severely ill are those who are most likely not to comply will self-report assessments (165, 166). Provided that this was the case in our studies, the overall population of elderly dialysis patients experiences an even more pronounced QoL deterioration than revealed by our results. In any case, our results are in accordance with the finding of others, and clearly indicate that there is a considerable room for improvement of the older dialysis patients QoL, in particular the physical domains.

Early vs. late start in dialysis

In the original RCT, the primary aim was to find out if early start in dialysis would give better QoL for elderly patients. The randomized design as well as the observational study following the patients from start of dialysis and onward, had to be abandoned, and the cross sectional study including the use of NRR data cannot provide evidence of a causal connection between QoL and kidney function at the start of dialysis. The patients were not selected to early versus late start by random, our data do not include any longitudinal assessments, and the time frame between the QoL assessment and start of dialysis varied between patients. Furthermore, the NRR did not include any QoL measures when dialysis was started; hence, no baseline scores to be used as reference for the later assessments were available.

However, as concluded in the previous section on QoL, we find that our QoL data give a reliable description of the patients' QoL at the point of assessment which varied from 8 to 236 months after start of dialysis. These data revealed that there was no QoL difference between the patients who had started late versus early in dialysis. The same conclusion was drawn from the IDEAL-study, which is the only randomised study hitherto performed (64). Another observational study also showed that there was no difference in QoL between early and later starters after 12 months, although the early starters were found to have better QoL immediately after the initiation of dialysis treatment. (25). We cannot rule out that there was a difference at initiation of dialysis treatment (25), but despite the methodological problem, our results are in accordance with those reported by others.

In our study, a low number of patients started early in dialysis (27%) compared to data from the older population (> 75 years) in US and France, where 54% and 38% respectively started with eGFR > 10 ml/min (59, 61). The older patients in our study also had lower mean eGFR at start of dialysis than reported from others. i.e. in 2010, the mean eGFR at start for patients > 75 years in US was 12.2 ml/min, while in our study population the mean eGFR was 8.6 ml/min (5).

Why Norwegian nephrologists seem not to follow the same trend as in Europe and US and to start dialysis earlier for the oldest patients is not known. Data from NRR shows a great variation in accepting older patients (> 65 years of age) in dialysis treatment in the different counties (NRR, Annual report 2004), and this might suggest a different attitude to accept the oldest patients to dialysis treatment among the nephrologists.

The modified study design (paper 2) cannot give a causal connection between starting point in dialysis and QoL, but based on our results and the findings of others it is reasonable to conclude that starting point in dialysis treatment does not have impact on long term quality of life.

Comorbidity

The presence of other diseases than CKD is likely to impose the dialysis patients with additional symptoms and functional impairments that may influence their QoL. For younger dialysis patients, an association between comorbid conditions and QoL, specially for physical composite score (PCS) has been shown (26). Among older patients comorbidities are more frequent and often multiple, hence we found it particularly relevant to investigate which impact such conditions had on the elderly dialysis patients QoL.

For the observational study (paper 3), where the patients were examined and assessed by the study principal investigator, a thorough comorbidity registration using the Davies comorbidity index could be performed. Davies comorbidity index is validated for dialysis patients (72). For the cross-sectional study (paper 2), we could only use the data that was available from the NRR. As the registration were different, it is difficult to compare the frequency of comorbid diseases between our 2 studies. Both studies revealed that comorbid disorders were frequent, and the findings are consistent with the registration being more comprehensive in the smaller observational study (paper 3). In paper 2 there were 21% with no comorbid disease, and 55% with 1-2 diseases and 24% with ≥ 3 diseases. In paper 3 (Davies comorbidity score) there were none patients with low mortality risk (no comorbid disease), 63% with medium risk (1-2 comorbid diseases) and 37% had a high risk (≥3 comorbid diseases).

The frequency of comorbid disorders in the two studies, are, however comparable to registrations from the UK and France (66, 149), and in the Broadening Options for Long-term Dialysis in the Elderly (BOLDE) study from UK (132). In the BOLDE study the frequencies of comorbid disorders were reported for HD and PD patients, no comorbid disorders were reported in 17% (HD) vs 21% (PD), 1-2 disorders in 66% vs. 49% and ≥ 3 comorbid disorders in 13% vs. 34%, respectively. The registries from UK and France listed the number

of comorbidity diseases, while in the BOLDE study a comorbidity index was used (Davies-Stokes comorbidity index).

The results regarding the impact of the registered comorbidity on the patients QoL are not quite consistent between our two studies. In the cross-sectional registry study (paper 2) we did not find any association between comorbidity and QoL. This is the same conclusion as in the BOLDE study; where Davies-Stoke comorbidity index was used, and where increasing co-morbidity was found to have a negative impact on QoL only when malnutrition was present (19). Limitations to our results are the difference in time between the QoL assessments and the comorbid registration, and the lack of information about the severity of the disease. Furthermore, many conditions that are important for elderly were not registered, e.g. cognitive function, vision and hearing disability, chronic obstructive lung disease and depression.

In paper 3 we found a clinically, but not a statistically significant association between comorbidity and QoL, for the physically items (PF, RP, VT and RE). In this study we used a validated comorbidity index, the comorbidity burden was registered at the same time as the QoL, and the lack of statistical significance might be explained by the small sample size. The revealed trend supports our initial hypothesis that comorbid disorders may affect QoL and points in the same direction as the results of studies among younger dialysis patients (167).

Overall, adding our results to the findings of others, no conclusion regarding the impact of comorbid disorders on older dialysis patients QoL can be drawn. The conflicting results between the BOLDE study and the studies among younger dialysis patients indicate that comorbid disorders may have a different impact on the well-being of younger compared to older dialysis patients. The BOLDE findings are supported by the results from our cross-sectional study, but as discussed, the latter are subject to serious limitations. We found that it is somewhat contradicting results from our smaller observational study that need attention. To identify factors that contribute to the poor QoL of older dialysis patients is necessary to enable improvements. Hitherto few studies have addressed the impact of comorbidity on QoL, and as our observational study suggests that this may be important, further studies are advocated. To be able to draw firm conclusions, larger studies are needed and it is also important that validated comprehensive indexes including the severity of the diseases are applied.

Physical function

Among older dialysis patients, a high prevalence of functional disability has been revealed (75). Physical impairments are likely to affect QoL negatively, as has been shown for younger hemodialysis patients (78, 80).

In our study, we used the question regarding functional capacity from SGA, which is a validated questionnaire for dialysis patients, to determine the patients' physical function. We also used the physical function scale (PF) from the SF 36. No performance tests could be applied due to the study design. However, strong correlations between self-reported function and performance tests as well as observer rated physical function have been documented (168, 169).

We found a clear association between the self-reported score from the SGA and QoL scores (SF36) (paper 2). We also found an association between the physical function (PF) score from the SF36 and the other SF36 domains. To investigate the latter, the patients were divided in three groups according to their scores on PF, SF36 scale. A clear trend across groups was found i.e. the group with lowest PF, also scored lowest for the other SF 36 domains (BP, GH. VT, SF, RE, MH and RP).

Our results are consistent with the findings of Johansen et al (170), which showed that dialysis patient who reported lower levels of physical activity also reported lower physical and mental composite score (SF12). In a study by Wanderley et al (168) higher physical activity levels (self-report) and better physical fitness (performance tests) were also found to be associated with higher scores of several domains measured by SF 36.

Overall, these results suggest that if improvement in physical function can be achieved, both the physical and mental QoL dimensions will improve. The question is whether physical rehabilitation of the older and frail population is possible.

For HD patients in general, a systematic review and meta-analysis have demonstrated the benefit of rehabilitation in terms of exercise training i.e. increased lean body mass and muscle strength, and reduction in heart rate variability and QoL (78). Exercise training during dialysis has also been reported to improve functional capacity, ameliorate depression and increase well-being and QoL (82, 171). The rehabilitation potential among older dialysis patients has been more poorly described. However, a few studies has established the feasibility of an

exercise program for low- functioning older HD patients (83), and one study showed moderate improvement in QoL scores after 12 weeks (172). Even for cancer patients with advanced disease, a significant improvement of physical performance was achieved after 6 weeks of exercise (173).

Based on our results and the findings of others, more attention to physical function in older patients in dialysis is warranted. There is a need of larger trials to confirm the association between the mental QoL domains and physical capacity, but there seems to be a huge potential for an overall QoL improvement among older dialysis patients through physical rehabilitation and exercise.

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Nutritional status

Nutritional problems among the older dialysis were one of the main foci in both the cross-sectional (paper 2) as well as the observational study (paper 3).

We did not use the modified 7 point SGA scale, which is recommended in the European Best Practice Guidelines on nutrition (119) because it was not available in Norwegian language.

In the cross-sectional study, nutritional status was assessed by the SGA using patients self-report only. To classify the patients into SGA A (normally nourished), B (moderately malnourished) and C (severely malnourished), we used the patients score as well as their BMI, as recommended by the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines for nutrition screening 2002 (116). The BMI we used for the SGA classification was calculated from the weight that the patients reported on the SGA without reference to the dialysis session. We found that SGA status A was present in 51.4 %, SGA B in 32.3% and 16.4 % were severely malnourished (SGA C). In the observational study, the patients SGA status was determined by the patients score as well as a physical examination, and in this study the majority of the patients (91 %) were found to be moderately or severely malnourished. The discrepancy in these results between the two studies might be related to the selection of patients and the difference in sample size. In the cross-sectional study, the

study sample was large and representative of the older population, whereas the observational study had a small sample size representing only one geographic region. Another explanation is that the clinical examination (paper 3) revealed signs of malnutrition that could not be identified by the patients score and their BMI. Furthermore, BMI as a parameter for nutrition may be connected with errors in dialysis patients. BMI reflects weight, and both weight and weight changes may be misleading due to overhydration, ultrafiltration and difficulties in estimating dry weight. Thus, an underestimation of the nutritional problems in the cross sectional study cannot be ruled out.

For the cross sectional study, we had access to NRR data, and the patients' BMI was also calculated based on these, i.e. the weight at the start of dialysis and by the time of the Annual report 2008. As these assessments were made at a different point of time than the SGA, we found that they could not be used for the SGA classification. However, the weight reported to NRR is defined as dry weight, and should therefore be reliable. At the start of dialysis and at the Annual report, 43 % and 51 % of the patients respectively had a BMI below normal range for elderly patients (BMI < 24). This mainly corresponds to the percentage with low BMI in the observational study (37.5% below 24, weight assessed after dialysis). In both studies, a considerable number of patients reported unintentional or substantial weight loss, and in the observational study 50 % reported appetite loss and 46 % had a LTI below the tenth percentile.

Overall, the two studies include a large and representative number of older dialysis patients. The response rate on the SGA was high, and except for the methodological problems related to the lack of a clinical examination in the cross sectional study, the methods that were used for assessment are validated and/or well recognised. Both studies revealed a high frequency of malnutrition, a frequency that was higher than reported from most studies on nutritional status in dialysis patients in general (94, 127). We conclude that malnutrition indicating nutritional deficits represent a particularly serious and common problem among older dialysis patients. This corresponds to reports of nutritional status in the older general population (174).

In the smaller observational study, the nutritional assessments were thorough and included bioimpedance spectroscopy (BIS). Loss of muscle mass is an important feature of severe nutritional deficits such as cachexia and protein energy wasting, and therefore important to detect. As exemplified by our results, muscular depletion is difficult to reveal by simpler measures. Six out of 11 of our patients with low LTI had BMI within normal range, whereas

four out of nine patients with BMI < 24 did not have muscle loss. We also found that very few patients had low FTI (<10th percentile) even if they had low muscular mass, and despite a high frequency of malnutrition, measures of triceps skin fold were higher than reported from younger populations (128, 175). These findings underline the importance of assessing body composition to reveal nutritional risks in the elderly dialysis patients where muscle mass tend to be replaced by fat as a part of the aging process, or by water as a result of overhydration.

Based on the assessments of weight loss > 5% or BMI < 20, decreased muscle strength, anorexia, low fat free mass (Lean tissue index, LTI < 10 percentile) and abnormal biochemistry (CRP > 5 or serum albumin < 3.2 g/dl), the patients who participated in the observational study were classified as being cachectic or not according to the definition by Evans et al. We found that a large proportion of the patients were cachectic.

As recommended by the International Society of Renal Nutrition and Metabolism (ISRNM), it would also have been relevant to identify protein energy wasting (PEW) which is regarded a pre-stage of the more serious cachexia. According to the ISRNM definition, three out of four criteria should be fulfilled for the PEW diagnosis, i.e. abnormal biochemistry, low body mass, decreases in muscle mass and low protein or energy intake (see also introduction page 22). The biochemical parameters that are included in the first criterion are se-albumin, pre-albumin and se-cholesterol. At the nephrology clinics in South Trøndelag County where the patients for the observational study were recruited, pre-albumin is not routinely assessed, and we found se-cholesterol difficult to use as a parameter for nutrition since a majority of the patients were on statin treatment. Furthermore, detailed registrations of protein/energy intake as proposed in criteria 4 are time consuming, require assistance of skilled personnel, and could not be carried out for practical reason in our study. The procedure might also be too extensive for most clinical settings (176). Thus, we found the PEW criteria difficult to apply, and hence, we find that using the proposed cachexia definition may be an alternative to ensure that the most seriously nutritionally depleted patients are identified.

In the observational study (paper 3) we used several different tools to assess nutritional risk (BIS, SGA, anthropometry and self-reported appetite), but there was no consistent overlap between the assessments. This underlines the need for a general agreement on how poor nutritional status should be identified and which definitions and assessments tools that should be used in this group of patients.

We investigated the association between QoL and nutritional status. In the cross-sectional study we did not find any association between QoL and SGA status, unintentional weight changes or BMI. This might be due to the assessments we used; our SGA classification depended only on patients self-report, without clinical investigation, and weight changes can be a difficult parameter in dialysis patients because of the ultrafiltration and the difficulties in estimating dry weight.

In the observational study we classified the patients as cachectic or not, and when we compared the SF- 36 scores for cachectic vs. non-cachectic patients, we found clinically significant differences for all subscales, but only for PF, this difference was statistically significant. Opposed to the results of the cross-sectional study, these findings are consistent with the results of sseveral studies among younger dialysis patients, which have shown a clear correlation between nutritional status and QoL (120, 121). Based on this, the methodological problems in the cross-sectional study, and the comprehensiveness of the assessments in the observational study, we tend to believe that the latter gives the most correct picture of the influence of nutritional status on older dialysis patients QoL. However, a different QoL impact of nutritional status in older compared to younger patients cannot be ruled out, hence larger studies are needed for confirmation.

The high proportion of patients with nutritional deficits in our studies, and in particular the high proportion with muscular depletion, as revealed in the observational study calls for more attention to nutritional status and the need for nutritional supplements for older dialysis patients. To avoid severe muscle wasting (sarcopenia), a higher protein intake in the elderly (> 0.8 g/kg/day) is recommended, and this could be done by the use of nutritional supplements like amino-acids mixtures. Inflammation contributes to anorexia and catabolism, but this is not a contraindication to nutritional intervention as inflamed patients do respond and improve their survival as well as non-inflamed patients (177).

To be able to appropriately intervene with the major problem of nutritional impairments among dialysis patients, it is, however, of crucial importance to identify the patients at risk. BMI, weight and se-albumin are not sufficient parameters for this. As shown in our observational study, three out of six patients classified as cachectic had a normal BMI, and an equal number had a normal se-albumin level. Furthermore, we revealed that serious muscular depletion frequently is hidden in a normal BMI. Thus, for assessment, the systematic use of

validated tools such as the SGA including both medical history and physical examinations seems necessary, and routine use of body composition measures such as BIS is also advocated.

Overhydration

BIS detected overhydration in 17 patients and serious overhydration in 8 patients (33 %), which is a higher frequency than reported from a European multi centres study (114). Another study with younger dialysis patients also showed 25% with serious overhydration (178). Our result may suggest that overhydration is also a greater problem among the oldest dialysis patients. To our knowledge no studies has addressed the problem of hydration status in the elderly dialysis population.

A study limitation is that the BIS assessments were only done before dialysis, based on the patients' preferences. This is adequate for hydration status, but may affect the estimates for measures like LTI and FTI. A smaller study demonstrated that pre- and post-treatment LTI mean may vary 1.12 kg ± 1.7, indicating that our LTI results might be overestimated (179).
The age reference range for the Body Composition Monitor (BCM; Fresenius) is from 18 to 80 years, and there are few studies addressing the elderly dialysis population > 75 years of age and the studies have small sample sizes. Thus reference values for the older population might be connected with some uncertainty

Our results indicate that overhydration may negatively affect QoL, particularly the physical domains, which is the same finding as in a study from Chang et al in younger dialysis patients (100).

Due to the cross-sectional design and the small sample size, our results should be interpreted with caution, but the low QoL scores associated with serious overhydration and the low lean tissue index could be generalized to the older dialysis population.

Conclusions

Our randomised trial failed, and as suggested by the findings in the survey among Norwegian nephrologists, there might be several explanations for the recruitment failure, including practical constraints and lack of incentives. The most important reason seems to be the wish to decide treatment on an individual basis.

Our results confirm that the QoL of older dialysis patients is poor and that there is a room for improvement. As low physical capacity seems to have a profound impact on all QoL dimensions, and increased focus on physical rehabilitation seems pertinent. In accordance with results from other trials, our findings indicate that the patient's long term QoL does not benefit from an early start of dialysis. We found no difference in QoL between HD and PD patients.

Nutritional problems were frequent among our older patients, both among those who participated in the cross sectional as well as the observational study. In the latter, where comprehensive registrations were conducted, only a small minority of the patients were within normal or optimal range on all parameters used for nutritional assessment. A high proportion had pathological body composition, most of whom had severe muscular depletion, and a quarter of the patients were classified as being cachectic. Furthermore, our study demonstrates how the reported frequency of poor nutritional status may vary with assessment method and classification. We found that BIS was easy to use, and that it can be a useful supplement in assessment of nutritional status in daily dialysis practice.

Our results does not confirm any association between nutritional status and QoL although the smaller observational study showed that cachectic patients had clinically significant poorer QoL on all scales compared to non-cachectic patients. The findings of this study also suggest that hydration status may influence QoL.

Clinical implications

- A change in attitude among Norwegian nephrologists towards RCT seems warranted.

- We did not find any association between early vs. late start in dialysis and long term quality of life. Based on our results concerning QoL and the fact that previous studies have not found any survival benefit for patients starting early in dialysis, there is at the present time no convincing data supporting earlier start in dialysis in the elderly.

- We have found in our cohort of elderly patients that 80% were in HD and only 20% in PD. We did not find any significant difference in QoL scores between HD and PD. Our finding supports the greater use of PD in older people, as most PD patients can be treated at home.

- We found that physical function and QoL showed a clear statistically association (except for role emotional, RE). It is important with more attention to physical function in older patients in dialysis. There seems to be a huge potential for QoL improvement through rehabilitation and physical exercise training.

- The majority of the study patients had nutritional deficits. We have demonstrated that the prevalence of nutritional deficit depends on assessment method. There is a need for a general agreement on how nutritional status should be assessed and reported, both in the clinics and research. Our findings call for more attention to nutritional status in elderly dialysis patients, including more thorough assessments and the use of nutritional supplements when indicated. More focus is clearly needed as well as larger studies to confirm our findings.

- The PEW classification includes a criterion based on dietary intake. This procedure might be too extensive for most clinical settings. We showed that the patients could be classified as cachectic or not by using easy applicable tools, and could thereby identify patients with a serious nutritional risk. We recommend the use of this cachexia definition.

- Bioimpedance spectroscopy can be a useful tool to estimate hydration status and body composition, and it is easy to use in daily clinical practice. We found that near half of the patients had low muscle mass (LTI < 10^{th} percentile) measured by BIS. We have also shown that overhydration probably also give reduced quality of life, accurate assessment is crucial, giving further arguments to routine use of BIS.

Areas for future research

Nutritional status

- Agree on a classification systems to be used to define nutritional status
- Further studies on quality of life and nutritional status in the older dialysis patients
- Intervention studies with special attention to the older in dialysis

Physical function

- Further studies on interventions with exercise training in older dialysis patients are advocated.

Hydration status

- There is a need for studies with bio impedance spectroscopy (BIS) to assess hydration status especially in the oldest (> 75 years) dialysis population, in order to make BIS a more reliable tool to assess hydration status in the oldest dialysis patients.

Suggestions for the NRR

In our study (paper 2) where we used medical data from NRR, we found that there were few missing data compared to other registries. However, we find that more complete data on comorbidity, like other chronic diseases common to CKD patients (ex. chronic obstructive lung disease, psychiatric diseases like depression) as well as inclusion of longitudinal quality of life assessments could considerably improve the utility of this registry.

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Papers 1-3

Paper I

Is not included due to copyright

Paper II

The impact of nutritional status, physical function, co-morbidity and early vs. late start in dialysis on quality of life in older dialysis patients.

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Abstract

Background: For the majority of the older patients in dialysis, the treatment will be lifelong. Thus, quality of life (QoL) is a crucial outcome. Our aim was to assess the QoL of older Norwegian dialysis patients and to investigate the impact of early (estimated glomerular fraction rate, eGFR ≥ 10ml/min) versus late (eGFR < 10ml/min) start in dialysis, comorbidity, nutritional status and physical capacity.

Methods: A self-report questionnaire including SF-36 (QoL) and the Subjective Global Assessment (SGA) (nutritional status) was mailed to all patients (n = 320) ≥ 75 years registered in the Norwegian Renal Registry (NRR) as being in dialysis by September 2009. Reply was received from 233 patients (73%). Medical data including comorbidities and eGFR at dialysis start (obtained for 194 patients) was retrieved from the NRR. Functional capacity was determined from the SGA.

Results: Compared to reports from younger dialysis patients, our patients scored poorer on all SF-36 subscales. Early start in dialysis was registered for 52 patients, 142 patients started late, 51.4% were well nourished (SGA A), 32.3% moderately malnourished (SGA B) and 16.4% were severely malnourished (SGA C). No significant association between any SF-36 scores and early vs. late start, nutritional status or comorbidity was found. Better physical function was significantly associated with better scores on all SF-36 scales.

Conclusions: Our results indicate that physical function is important to all QoL aspects. Increased focus on physical rehabilitation seems pertinent. Early start of dialysis treatment was not associated with better long term QoL scores.

Keywords: older, dialysis, quality of life

Introduction

For several reasons, the oldest patients are the fastest growing subgroup of the dialysis population in developed countries. The general population is aging and the survival of diseases associated with kidney failure improves[1, 2]. Hence, the incidence of end stage renal disease (ESRD) in older adults is increasing [3], and also the acceptance of older patients onto dialysis [4]. The majority of the older patients will not be offered a renal transplant and will be subjects to lifelong dialysis. In general, Qol of dialysis patients seems to be substantially affected, especially the physical domains, which also declines over time[5-8]**.** Comparing groups of older and younger in dialysis, no difference has been found for the QoL mental domains. Results regarding physical domains are more diverse; superiority of scores from the older population as well as equality has been reported[9, 10]. For the oldest dialysis patients (> 75 years), however, the physical scores seem to be poorer than for younger ones[7, 11].

Over the last decades, there has been a trend in USA and Europe to start dialysis early, in particular among the oldest patients (age > 75 years)[12, 13]. Some studies indicate that early start is connected with a higher mortality [12, 13], which may be explained by a larger proportion of older patients [14]. The only published randomised trial comparing early to late start of dialysis, the IDEAL study, found that neither survival nor quality of life improved by an early start[15]. To our knowledge no studies have addressed the impact of early start on QoL in older dialysis patients in particular.

Older age is associated with higher frequency of health related problems such as nutritional deficits, comorbidity and reduction in physical capacity. This may be attenuated in older ESRD patients [16-19 20].

In general, nutritional deficits and protein energy wasting (PEW) are frequent problems in the dialysis population[21-23], and implies an increased risk of negative health outcomes such as

mortality risk and QoL deterioration[24, 25]. Comorbid disorders are common among dialysis patients > 75 years [18], and for haemodialysis patients in general, co-morbidity is found to be associated with mortality as well as QoL [26, 27].

Decline in physical function is a feature of normal aging. Among older dialysis patients, a high prevalence of functional disability has been revealed [19]. Physical impairments are likely to affect QoL negatively, as has also been shown for younger hemodialysis patients[28, 29]. There are few studies addressing these issues in the older dialysis patients, thus, the impact on QoL is poorly documented.

The aim of the present study was to assess the QoL of the Norwegian dialysis population aged 75 years or more, and to explore the impact on QoL of nutritional status, physical function, comorbidity and early vs. late start in dialysis.

Subjects and Methods

All patients ≥ 75 years (n=320) who, according to the Norwegian Renal Registry (NRR) were in dialysis by January 2009 and alive by September 2009 were asked to participate and mailed the study questionnaire (September 2009). A reminder was sent 2 weeks later. We received answers from 233 (73%).

Medical data were collected from the NRR and included data registered at start of dialysis treatment and in the Annual Report 2008. The NRR consists of data from all the dialysis centres in Norway. These centres are responsible for reporting data from patients with chronic kidney failure at start of dialysis and thereafter annually. Deadline for the completion of the annual data is by the end of March, thus The Annual Report 2008 includes data on

biochemical parameters, blood pressure, medications, physical status, and new co-morbid diseases up to March 2009.

The questionnaire mailed to the patients in this study, included assessments of QoL and nutrition. QoL was measured with a Norwegian validated translation of the Medical Outcomes Study 36 item Short Form health survey (MOS SF-36)[30, 31]. The SF-36 is a self-administered questionnaire that is widely used and validated in chronic dialysis patients of all ages [9, 11, 32-34]. The 36 items are summarised into 8 scales, physical function (PF), role physical function (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional function (RE) and mental health (MH). For each scale the scores are transformed to scores ranging from 0 -100 (100= best possible health state) [35]. The patients' scores in this study were compared to a norm population of the same age and gender [30] and to younger dialysis patients [36].

We also used three items from The European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30), i.e. the nausea-vomiting scale (2 items) and the appetite scale (1 item). These items are scored on a four point categorical scale ranging from "not at all" to "very much" transformed into 0-100 scales where the higher scores represent more symptoms [37]. The patients score were compared to a norm population of the same age and gender [38].

Nutritional status was assessed by the Subjective Global Assessment of Nutritional status SGA [39], using a translated Norwegian version [40]. The SGA has two parts. The first includes questions on medical history (present weight, weight loss during the last 6 months, changes in food intake, gastrointestinal symptoms and physical capacity) and may be answered by the patients. The second part covering assessment of subcutaneous fat loss, muscle wasting and oedemas, should be filled in by health professionals. The patients are thereafter classified as either; SGA A= normally nourished, B= moderately malnourished and C = severely

malnourished. In this study, the questionnaires were mailed to the patients hence, no physical examination was possible. The patients were therefore classified into group A, B and C as stated, based on their reports on the first part of the questionnaire and their BMI, calculated from weight and height reported on the SGA questionnaire [41]. The classification was independently made by two trained reviewers, a nephrologist and a nutritionist respectively. In case of disagreement, the classification was discussed to reach consensus.

The patients' body mass index (BMI) was calculated according to standard formula (body weight (kg)/ height (m) ²). The patients' height was retrieved from the NRR data. Information about the patients' weight was available from the NRR at start of dialysis and the Annual Report 2008 as well as from the SGA (September 2009). BMI was calculated for the corresponding three points in time. To estimate weight changes (delta weight), we used weight at start of dialysis minus weight from the Annual Report.

To assess co-morbidity, we used medical data from the NRR, which records 6 possible co-morbid diseases at start of dialysis; left ventricular hypertrophy (LVH), coronary disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus type II and malignancy. We divided the patients into 3 groups; 1) no comorbid disease, 2) 1-2 co-morbid diseases, and 3) ≥ 3 co-morbid diseases.

To determine physical function we used the scores from the SGA item where the patients are asked to rate their functional capacity into 4 categories (normal activity, able to be up, mostly sitting in a chair or mostly in bed), as well as the physical function scale from the SF-36.

We defined early start in dialysis at eGFR ≥ 10 ml/min and late start at eGFR< 10 ml/min.

Statistical analysis

Medical and demographic parameters and QoL scores were compared between groups defined according to gender, dialysis modality and early versus late start in dialysis. For the medical and demographic data, Students't-test was used to test for statistical significance. For the quality of life (SF-36) scores, which were not normally distributed, we used the Mann-Whitney U test. To ease the interpretation and the comparison to findings of other studies, the SF- 36 (QoL) scores are, however, presented in terms of group means.

Furthermore, the association between SF-36 scores and the following variables: early versus late start in dialysis, comorbidity, nutritional status (SGA classification) and physical capacity (SGA score and SF-36 physical functioning score) was tested by both the Kruska Wallis and the Wilcox rank sum tests. We also tested for trends in differences of SF-36 scores between groups defined according to comorbidity, SGA classification (A, B, C) and physical capacity using the Jonckheere (Kendall Tau) test.

The SPSS version 18 was used for descriptive statistic and the simple group comparisons, whereas the Stata version 12.0 was used for the tests of association and trends. Statistical significance was defined as $p< 0.05$, and clinical significance for the difference between QoL scores was defined as a difference of 10 or more [42].

The study was approved by The Regional Committee for Research Ethics in Norway

Results

Demographics

A total of 233 dialysis patients were included, 67% men and 33% women (Table 1). For four of the patients dialysis modality was not registered (three men and one woman).

Insert Table I

Overall, 182 (79%) of the patients were followed by a nephrologist for more than four months prior to dialysis initiation (early referral). Early start of dialysis (eGFR≥ 10 ml/min) was registered for 52 (23%) of the patients, 142 (62%) had a late start, whereas for 39 patients, the eGFR at start of dialysis was not recorded in the NRR (Table 1). The proportions of early and late start did not differ between genders or dialysis modality.

Co-morbidities at start of dialysis according to the NRR is shown in Table 1, 48 patients (21%) had no comorbidity, 128 (55%) had 1-2 comorbid diseases and 55 (24 %) had ≥ 3 co-morbidities. Data was missing for 2 patients.

The mean age of the patients was 80.4 years, median 80.0 years; range (75 – 94 years) (Table 2). There was no age difference between genders or between groups according to dialysis modality (Table 2).

Insert Table 2,

HD patients had significally longer dialysis vintage than PD patients. Otherwise, no difference between genders, HD and PD patients or early vs. late start in dialysis was revealed. The use of both erythropoiesis stimulating agents (ESA) and statins increased from start of dialysis to the Annual Report 2008 (Table 1 and 2).

Nutritional status

Information about height was missing for 39 patients. Mean BMI at start of dialysis, by the time of the Annual report 2008 and based on the SGA data (September 2009) was 25.1 (median 24.4, range 15.4- 44.3) (Table 1), 24.3 (median 23.9, range 13.5-41.3) (Table 2) and 24.3 (median 24.0, range 15.2-43.5) respectively. Although the BMI showed only minor changes from start of dialysis to the Annual Report 2008, a majority of the patients who had

data available on both time points (n = 185) had experienced weight changes, equally with weight loss (49%) and weight gain (42%) (Table 3).

Insert Table 3

Completion of the SGA was missing for 13 patients; hence SGA status (A, B or C) could be determined for 220 patients (Table 3). For seven of these, the SGA classification was based on weight changes, nutritional symptoms and food intake since BMI could not be calculated due to missing values about height. SGA status A was present in 51.4 %, SGA B in 32.3% and 16.4 % were severely malnourished (SGA C).

There were no association between SGA status and eGFR at start of dialysis, serum cholesterol, treatment months, serum albumin and haemoglobin (Table 3).

Scores for EORTC QLQ-C30 items were available for 214 (92 %) of the patients. Nausea-vomiting scores were clinically significant higher for our patients compared to norm data[38], both for men and women, indicating more symptoms in our patients. For appetite loss scale the difference between our population and norm data was below clinical relevance.

Quality of life outcomes

The SF-36 scores for the overall study population as well as scores according to gender, dialysis modality and early versus late start in dialysis are presented in Table 4.

Insert Table 4

There were 226 patients who completed the SF-36 form. Missing data for the various SF-36 subscales was observed for 7 patients (SF) to 20 patients (RE).

Compared to a Norwegian norm reference population of same age and gender [30], we found that both females and males reported clinically significant lower scores on SF-36 scales. These differences in scores were generally high, reaching 40 point for vitality (VT) (data not shown).

Compared to scores from a younger cohort of Norwegian dialysis patients, the women in our study reported clinically significant poorer physical function (PF), role physical function (RP) and role emotional function (RE), whereas our male patients reported clinically significant poorer scores for PF only (Table 4).

Except for statistically significant higher scores for social function among women compared to men, we found no clinically or statistically significant difference in QoL scores between genders, patients starting early or late in dialysis, or between HD and PD patients (Table 4). Furthermore, comparing SF-36 scores between patients in the three comorbidity groups as defined, no clinically or statistically significant difference was found (data not shown). Overall, there were also only minor variations between the SF-36 scores of patients classified as SGA A, B and C (data not shown), and no statistically significant trend between SGA groups was observed.

Finally we compared the SF-36 scores between patients according to their own physical capacity ratings in the SGA questionnaire and found a clear statistically significant trend, i.e. the highest score for physical capacity corresponded to the highest score for SF-36, except for RE (Table 5).

Insert table 5

When the patients were divided into three groups according to the SF-36 physical function (PF) scores; i.e. patients scoring 0-33, 34-66, and 67-100 points respectively, and the scores

on the other SF-36 subscales (RP, RE, MH. GH, SF, BP and VT) were compared between these groups, statistically significant linear trend for all subscales were found with the highest scores among those patients who were in the group with the highest PF scores (Figure 1).

Insert Figure 1

Discussion

In this cross-sectional study addressing Norwegian dialysis patients ≥ 75 years of age, we found that quality of life as assessed by the SF-36 in general was poor. For all dimensions, the scores were substantially lower than scores from a norm population beyond 70 years of age [30], and most scores were also lower compared to younger Norwegian dialysis patients [36], in particular for physical domains. No significant association between the QoL scores and comorbidity, early vs. late start in dialysis and nutritional status was found. All QoL domains were, however, clearly associated to the patients' physical function.

Few studies have hitherto addressed the impact of physical function on quality of life in older dialysis patients [29]. In younger dialysis patients, however, significant improvement of physical QoL domains as a result of training has been documented [28 43]. Similar results have been reported from a Cochrane review of training studies in elderly [44]. Our results indicate that physical function is highly important, not only to the physical, but also the mental QoL domains of older dialysis patients. Thus, maintaining these patients` independence and physical performance seems crucial to their overall wellbeing. An existing potential for rehabilitation through physical exercise, even for seriously ill patients, is documented among advanced cancer patients [45] as well as in a pilot trial of older haemodialysis patients [46]. Further studies on training interventions in older dialysis patients are advocated.

No difference in quality of life between early or late start in dialysis were observed in our study, the same conclusion was drawn from the IDEAL-study[15]. Our results, however, must be interpreted with caution due to a low number of patients starting early and a lower mean eGFR at start than reported from others, i.e. in 2010, ,mean eGFR at start for patients > 75 years in US was 12.2 ml/min, while in our study population the mean eGFR at start was 8.6 ml/min [4]. Furthermore we did not have any QoL registration at start of dialysis nor any longitudinal assessments. In a previous study early starters were found to have better QoL than late starters immediately after the initiation of dialysis treatment, but the difference disappeared after 12 months[6]. We can not rule out that this would also be the case among our patients.

Opposed to studies on younger dialysis patients showing a positive correlation between nutritional status and SF36 physical composite score (PCS)[47, 48]; we found no significant association between QoL and SGA status, unintentional weight changes or BMI. These findings should be interpreted in light of the assessment methods we used. Our SGA classification depended only on patients` report without any clinical investigations. BMI reflects weight, and both weight and weight changes can be a difficult parameter in dialysis patients because of the ultrafiltration and difficulties in estimating dry weight. However, many of our older dialysis patients had a low BMI, reduced food intake and unintentional weight loss, indicating that focus on nutritional status is highly important. To identify nutritional risks, we find that adding methods other than weight and BMI are necessary.

For younger dialysis patients, an association between comorbid conditions and QoL, specially for physical composite score (PCS) has been shown [27]. This finding was not confirmed in our study population. A limitation of the co-morbidity registration in our study is the lack of information about the severity of the disease. Many conditions that are important for elderly were not registered, e.g. cognitive function, vision and hearing disability, chronic obstructive

lung disease and depression. Thus, we cannot rule out that the results would have been different with more a complete registration of co-morbid diseases. The frequency of comorbid disorders in our study, is, however comparable to registrations from the UK and France [18, 49], and in the Broadening Options for Long-term Dialysis in the Elderly (BOLDE) study from UK, increasing co-morbidity was found to have a negative impact on QoL only when malnutrition was present [50].

The study was based on self-report and register data from NRR, and we had only access to NRR data from the patients who accepted to enter the study. Thus, a limitation of the study is the lack of information regarding the non responders. However, the NRR includes all Norwegian patients starting in dialysis, there were few missing data compared to other renal registries[18, 51], and we had a high response rate (73%). Overall, we find that our findings may be representative for older dialysis patients in general. We also find that more complete data on comorbidity as well as inclusion of longitudinal quality of life assessments could considerably improve the utility of this and comparable registries.

Our results confirm that the QoL of older dialysis patients is poor and that there is a room for improvement. As low physical capacity seems to have a profound impact on all QoL dimensions, increased focus on physical rehabilitation seems pertinent. In accordance with results from other trials, our findings indicate that the patient's long term QoL does not benefit from an early start of dialysis. Nutritional problems were frequent among our older patients. By the methods used in this study, we could not confirm any association between nutritional status and QoL. Increased focus on nutritional status seems, however, still necessary.

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Table 1 Patients characteristic at start of dialysis treatment

	All (n = 233)			Male (n=156)			Female (n=77)		
	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)	n
eGFR at start, (MDRD), ml/min	8.63	(3.32)	194	8.61	(3.2)	130	8.65	(3.42)	64
Early start, ml/min	12.82	(3.09)	52	12.50	(3.38)	37	13.65	(2.45)	15
Late start, ml/min	7.09	(1.66)	142	7.09	(1.58)	93	7.11	(1.84)	49
Body mass index (BMI)kg/m²	25.1	(4.6)	196	25.3	(4.8)	127	24.5	(4.3)	64
Hemoglobin g/L	11.1	(1,5)	194	11.1	(1.5)	130	11.0	(1.4)	64
		n	(%)		n	(%)		n	(%)
Dialysis modality									
Hemodialysis (HD)		188	(82)		130	85		58	76
Peritoneal dialysis (PD)		41	(18)		23	15		18	24
Access HD									
Catheter		99	(43)		64	(41)		34	(44)
AV fistula		53	(23)		39	(25)		14	(18)
Use of									
Erythropoiesis stimulating agents (ESA)		156	(67)		103	(67)		52	(68)
Statins		132	(56)		91	(59)		39	(51)
Primary kidney disease, n (%)									
Glomerulonephritis		37	(16)		24	(15.9)		12	(15)
Pyelonephritis		15	(6)		11	(7.3)		4	(5)
Polycystic kidney disease		15	(6)		8	(5.3)		7	(9)
Renovascular disease		108	(47)		7	(48.3)		31	(40)
Diabetes		19	(8)		5	(3.3)		11	(14)
Others		40	(17)		30	(18.7)		11	(14)
Co-morbidity, n (%)									
Left ventricular hypertrophy		60	(26)		41	(27)		18	(23)
Peripheral vascular disease		51	(22)		32	(27)		18	(23)
Cerebrovascular disease		41	(18)		24	(16)		14	(18)
Malignancy		46	(20)		35	(23)		10	(13)
Coronary disease		107	(46)		80	(53)		31	(40)
Diabetes mellitus II		56	(24)		31	(21)		23	(30)

Table 2. Patients'characteristics at the Annual report 2008

		All (n=233)		Male (n= 156)		Female (n=77)		p-value[1]	Hemodialysis (HD) (n=188)		Peritoneal dialysis (PD) (n=41)		p-value[2]
	n	Mean	SD	Mean	(SD)	Mean	(SD)		Mean	(SD)	Mean	(SD)	
Age	230	80.4	(3.7)	80.6	(3.8)	80.0	(3.5)	0.31	80.4	(3.7)	80.0	(3.8)	0.50
Haemoglobin g/L	230	11.6	(1,2)	11.7	(1.2)	11.3	(1.2)	0.009*	11.5	(1.2)	11.7	(1.1)	0.28
Blood pressure, systolic	230	141	(22)	142	(22)	141	(22)	0.76	141	(22)	141	(18)	0.95
Blood pressure, diastolic	230	72	(12)	72	(12)	70	(11)	0.23	72	(13)	70	(9)	0.36
Cholesterol	226	4.3	(1.3)	4.3	(1.2)	4.4	(1.3)	0.28	4.3	(1.3)	4.2	(1.1)	0.53
Albumin g/L	229	37.8	(4.4)	38.0	(4.2)	37.3	(4.6)	0.22	37.1	(4.4)	37.4	(4.0)	0.55
BMI kg/m²	223	24.3	(3.9)	24.4	(3.3)	24.2	(4.8)	0.73	24.3	(4.0)	24.2	(3.4)	0.95
Treatment months[3]	230	36.7	(28.7)	36.3	(24.9)	37.6	(28.4)	0.74	38.9	(30.8)	27.2	(15,2)	0.019*
Dialyses per week (HD)	188	2.7	(0.5)	2.7	(0.6)	2.7	(0.5)	0,46					
Use of													
ESA; n (%)		206 (88)		134 (89)		71 (91)			169 (90)		36 (88)		
Statins; n (%)		143 (61)		98 (65)		45 (58)			112 (60)		30 (73)		

[1] Comparisons between genders (Students' t-test)
[2]Comparisons between HD and PD patients (Students' t-test)
[3] from start in dialysis to 01.09.2009

Table 3. Nutritional parametres according to SGA classification

	All (n=220)		**SGA A (n=113)**		**SGA B (n= 71)**		**SGA C (n=36)**		**P values**
	mean	**(SD)**	mean	(SD)	mean	(SD)	mean	(SD	
Se albumin g/L			38.3	(4.0)	37.2	(4.6)	37.3	(4.9)	0.59
Se cholesterol 2008			4.3	(1.2)	4,2	(1,2)	4,6	(1,6)	0.70
eGFR at start (ml/min)			8.5	(2.9)	8.8	(4.2)	8.5	(2.9)	0.84
Hemoglobin 2008 g/L			11.5	(1.2)	11.7	(1.2)	11.4	(1.3)	0.47
Treatment months			37.7	(31.2)	33.1	(24.2)	39.9	(30.5)	0.62
BMI kg/m² at start of dialysis			24.8	(3.8)	25.8	(4.9)	23.0	(2.7)	0.13
BMI kg/m² Annual report 2008			25.6	(3.7)	24.0	(3.4)	20.7	(2.9)	0.000[1]
Appetite loss (EORTC QLQ-C30) n=208	12.2[2]	(23.0)	13.2	(24.2)	11.1	(20.2)	13.5	(25.2)	
Nausea/vomiting (EORTC QLQ-C30) n=214	22.4[3]	(25.0)	19.0	(22.6)	29.4	(28.5)	24.7	(25.7)	
	n	**%**	n	%	n	%	n	%	
Unintentional weight loss	49	(26)	16	(17)	18	(35)	12	(38)	
Reduced food intake	30	(14)	13	(12)	12	(21)	5	(16)	
Weight loss up to 2008	91	(49)	37	(41)	31	(56)	17	(56)	
Weight gain up to 2008	77	(42)	44	(48)	19	(35)	11	(37)	

[1] statistical significant $p < 0.05$

[2] Scores from norm population: Appetite loss: male: 8.6, female: 15.3

[3]Scores from norm population: Nausea/vomiting scale: male: 3.3, female: 8.4

Table 4. Quality of life scores (SF 36) according to gender, dialysis modality and start in dialysis.

	All (n = 226)		Male (n = 149)		Female (n = 76)			HD (n=167)	PD (n=33)		Early start (n= 45)	Late start (n= 124)		*Norwegian dialysis pts* *Male (n= 199)*	*Female (n = 102)*
	Mean	(SD)	Mean	(SD)	Mean	(SD)	p-value[1]	Mean	Mean	p-value[2]	Mean	Mean	p-value[3]	*Mean*	*Mean*
PF	40.9	(27.4)	40.5*	(27.4)	39.9*	(26.7)	0.93	41.5	37.8	0.62	39.9	40.2	0.80	*56.7*	*49.9*
RP	17.9	(32.8)	19.3	(34.2)	17.0*	(31.8)	0.65	19.3	11.1	0.07	16.7	15.4	0.95	*24.0*	*26.5*
BP	57.3	(30.2)	55.5	(29.4)	58.0	(31.7)	0.69	56.8	61.8	0.31	56.9	55.7	0.83	*60.1*	*52.7*
GH	45.7	(23.3)	44.8	(21.4)	48.5	(25.7)	0.40	46.3	44.2	0.74	50.0	44.7	0.12	*44.0*	*41.7*
VT	39.3	(22.2)	38.5	(21.0)	39.1	(22.2)	0.77	40.1	33.3	0.33	38.2	38.7	0.83	*44.4*	*42.9*
SF	63.0	(29.2)	60.1	(28.6)	68.0	(29.2)	0.04	61.5	70.5	0.10	58.7	63.5	0.30	*66.2*	*65.6*
RE	42.7	(43.7)	47.4	(44.5)	38.6*	(42.0)	0.22	43.8	40.7	0.62	41.7	45.3	0.76	*52.6*	*57.1*
MH	73.6	(20.2)	72.2	(20.3)	73.3	(17.6)	0.39	73.9	72.3	0.62	73.2	73.3	0.82	*75.5*	*72.6*

PF = physical function, RP = role physical function, BP = bodily pain, GH = General health, VT = vitality, SF = social function, RE = role emotional function, MH = mental health;

[1]Comparison between genders (Mann Whitney U test)

[2,] between HD and PD (Mann Whitney U test)

[3] between patients starting early and late in dialysis (Mann Whitney U test)

* Clinically significant, > 10 points difference in scores between study population and data from younger Norwegian dialysis patients

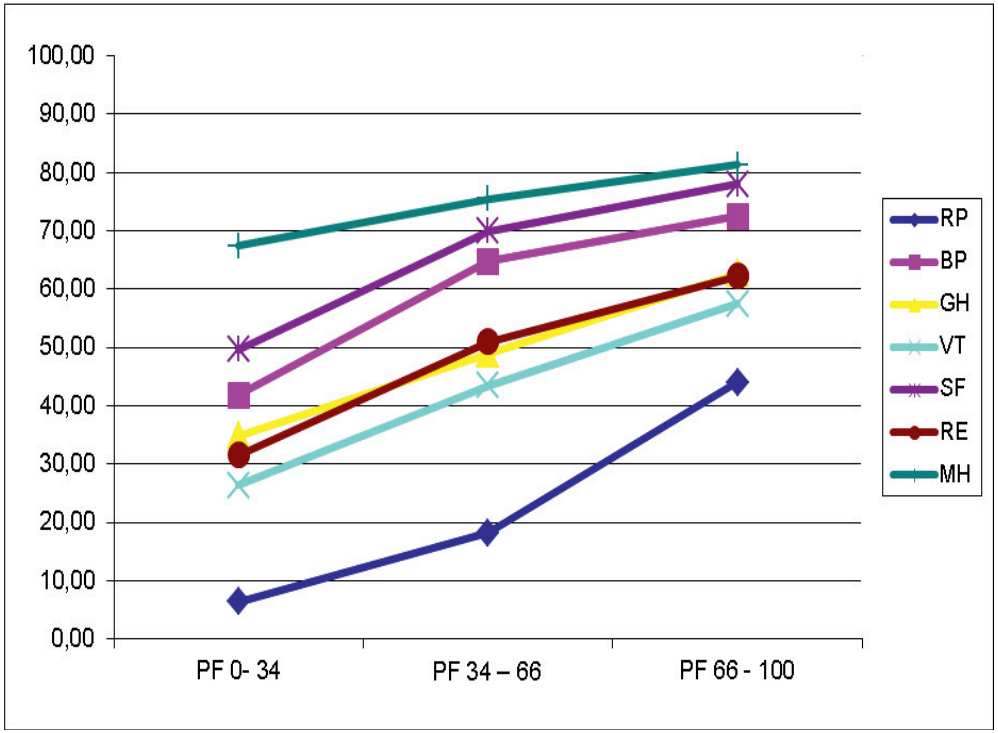
Table 5. SF- 36 scores according to physical capacity as rated in the SGA questionnaire

SF 36 scores	Normal N= 39		Some activities N= 77		Mostly in chair N= 76		Mostly in bed N= 6		P values[1]
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	
PF	47.6	(28.8)	40.0	(26.6)	37.7	(27.6)*	29.3	(32.4)*	0.042
RP	34.4	(40.1)	17.2	(32.5)	11.9	(28.1)*	0*		0.001
BP	67.0	(29.6)	57.7	30.0)	52.8	(29.0)*	27.7	(25.7)*	0.003
GH	51.5	(23.2)	45.8	(24.5)	43.2	(20.8)	29.8	(23.8)*	0.026
VT	45.5	(24.4)	39.4	(23.3)	35.8	(20.6)*	34.3	(20.7)*	0.040
SF	71.3	(32.1)	63.6	(27.8)	57.7	(28.2)*	57.1	(38.1)*	0.011
RE	57.9	(43.6)	36.9	(41.9)	41.8	(44.2)*	22.2	(40.4)*	0.095
MH	77.1	(21.7)	74.1	(20.9)	72.6	(17.8)	50.0	(20.7)*	0.029

*** > 10 points difference in SF 36 scores compared to the group with normal physical capacity**

[1] trend analysis (Jonckheere trend test)

Figure 1. SF 36 physical function divided in 3 groups and the association with the other SF36 subscales.



Paper III

Is not included due to copyright

APPENDIX

Nefrolog: Kvinne: ☐ Mann: ☐
Alder > 50 år: ☐ < 50 år: ☐

Klinisk forskning i nefrologi.

Prospektive randomiserte studier.

Det er velkjent at det er vanskeleg og tidkrevjande å drive prospektive randomiserte kliniske studiar, i vår studie der ein skulle randomisere eldre pasienter til tidleg eller sein start i dialyse (vurdert etter eGFR) og vurdere pasientane sin livskvalitet fekk vi for få inkluderte pasienter.

Kvifor trur du det er vanskeleg å få inkludert pasientar i ein prospektiv studie som tar føre seg tidleg eller sein start i dialyse?

Vi vil be deg vurdera følgjande moglege faktorar og ta stilling til betydningen av desse ved å krysse av på ein skala frå 0-5, der 0 er "uviktig" og 5 er "svært viktig".

	0	1	2	3	4	5
1. Pasientane ønsker ikkje å delta	☐	☐	☐	☐	☐	☐
2. Pasientane ønsker å utsette beslutning om dialysestart	☐	☐	☐	☐	☐	☐
3. Deltakelse i kliniske studier er arbeidskrevande og lar seg vanskeleg gjennomføre i dagleg praksis	☐	☐	☐	☐	☐	☐
4. For å delta i ein klinisk studie er det nødvendig med økonomisk kompensasjon til lege/sjukepleiar	☐	☐	☐	☐	☐	☐
5. Randomisering er ikkje mogleg fordi legen ønsker å vurdere det beste tidspunkt for dialysestart individuelt.	☐	☐	☐	☐	☐	☐
6. Randomisering til tidleg eller sein start er ikkje mogleg fordi dialysestart krev koordinering (kapasitet på dialyseavdeling, kateterinnlegging ol)og må bestemmes individuelt.	☐	☐	☐	☐	☐	☐
7. Hypotesen for prosjektet er klinisk lite relevant	☐	☐	☐	☐	☐	☐
8. Det er vanskelig å finne pasientar pga konkurrerande studier.	☐	☐	☐	☐	☐	☐
9. Pasientane har ofte betydeleg redusert almentilstand og det vil vera for belastande å delta i kliniske studier.	☐	☐	☐	☐	☐	☐
10. Forespørsel om deltaking i kliniske studier kan ha negativ innverknad på lege – pasient forholdet.	☐	☐	☐	☐	☐	☐
11. Det er vanskelig å delta i kliniske studier pga høge krav til sikring av pasientdata.	☐	☐	☐	☐	☐	☐

SF-36 SPØRRESKJEMA OM HELSE

33911

Dato: ☐☐.☐☐.☐☐☐☐

Navn: _____ Fødselsdato: ☐☐.☐☐.☐☐☐☐

INTRODUKSJON: Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.
Hvert spørsmål skal besvares ved å sette et kryss (X) i den boksen som passer best for deg. Hvis du er usikker på hva du vil svare, vennligst svar så godt du kan.

1. Stort sett, vil du si at din helse er

   ☐ Utmerket
   ☐ Meget god
   ☐ God
   ☐ Nokså god
   ☐ Dårlig

2. Sammenlignet med for ett år siden, hvordan vil du si at din helse stort sett er nå ?

   ☐ Mye bedre nå enn for ett år siden
   ☐ Litt bedre nå enn for ett år siden
   ☐ Omtrent den samme som for ett år siden
   ☐ Litt dårligere nå enn for ett år siden
   ☐ Mye dårligere nå enn for ett år siden

3. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	☐	☐	☐
b. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	☐	☐	☐
c. Løfte eller bære en handlekurv	☐	☐	☐
d. Gå opp trappen flere etasjer	☐	☐	☐
e. Gå opp trappen en etasje	☐	☐	☐
f. Bøye deg eller sitte på huk	☐	☐	☐
g. Gå mer enn to kilometer	☐	☐	☐
h. Gå noen hundre meter	☐	☐	☐
i. Gå hundre meter	☐	☐	☐
j. Vaske eller kle på deg	☐	☐	☐

33911

4. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

		Ja	Nei
a.	Du har måttet **redusere tiden** du har brukt på arbeid eller på andre gjøremål	☐	☐
b.	Du har **utrettet mindre** enn du hadde ønsket	☐	☐
c.	Du har vært hindret i å utføre **visse typer** arbeid eller gjøremål	☐	☐
d.	Du har hatt **problemer** med å gjennomføre arbeidet eller andre gjøremål (for eksempel fordi det krevde ekstra anstrengelser)	☐	☐

5. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som for eksempel å være deprimert eller engstelig)?

		Ja	Nei
a.	Du har måttet **redusere tiden** du har brukt på arbeid eller på andre gjøremål	☐	☐
b.	Du har **utrettet mindre** enn du hadde ønsket	☐	☐
c.	Du har utført arbeidet eller andre gjøremål mindre **grundig** enn vanlig	☐	☐

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

7. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?

☐ Ingen ☐ Meget svake ☐ Svake ☐ Moderate ☐ Sterke ☐ Meget sterke

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

33911

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 uken
For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det.
Hvor ofte i løpet av de siste 4 ukene har du:

	Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Følt deg full av tiltakslyst?	☐	☐	☐	☐	☐	☐
b. Følt deg veldig nervøs?	☐	☐	☐	☐	☐	☐
c. Vært så langt nede at ingenting har kunnet muntre deg opp?	☐	☐	☐	☐	☐	☐
d. Følt deg rolig og harmonisk?	☐	☐	☐	☐	☐	☐
e. Hatt mye overskudd?	☐	☐	☐	☐	☐	☐
f. Følt deg nedfor og trist?	☐	☐	☐	☐	☐	☐
g. Følt deg sliten?	☐	☐	☐	☐	☐	☐
h. Følt deg glad?	☐	☐	☐	☐	☐	☐
i. Følt deg trett?	☐	☐	☐	☐	☐	☐

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følesesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.) ?

☐ Hele tiden ☐ Nesten hele tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

11. Hvor RIKTIG eller GAL er hver av de følgende påstander for deg ?

	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
a. Det virker som om jeg blir syk litt lettere enn andre	☐	☐	☐	☐	☐
b. Jeg er like frisk som de fleste jeg kjenner	☐	☐	☐	☐	☐
c. Jeg tror at helsen min vil forverres	☐	☐	☐	☐	☐
d. Jeg har utmerket helse	☐	☐	☐	☐	☐

Vennligst kontroller at du har besvart alle spørsmålene

Skjema utarbeidet ved Enhet for anvendt klinisk forskning / Kontor for klinisk kreftforskning
Tlf.: 73 86 72 71/73 86 84 44

SGA for ERNÆRINGSSTATUS

Denne siden kan fylles ut av pasient eller pårørende

Navn:

Fylt ut dato:

Matinntak
Sammenliknet med ditt normale,
har matinntaket ditt siste måneden vært
☐ uendret
☐ mer enn vanlig
☐ mindre enn vanlig

Hvis mindre
☐ små mengder vanlig mat
☐ for det meste supper og drikker
☐ veldig lite eller ingen ting
☐ sondeernæring eller intravenøs ernæring

Fysisk kapasitet
Den siste måneden vil jeg beskrive aktiviteten min som
☐ normal, ingen begrensninger
☐ ikke normal, men er oppe og har noen aktiviteter
☐ sitter for det meste i stol
☐ tilbringer det meste av tiden i senga
☐ fullt sengeliggende

Symptomer
De siste ukene har jeg hatt følgende problem som har hindret meg fra å spise tilstrekkelig
(flere enn ett kryss hvis aktuelt)

☐ ingen problem
☐ liten appetitt
☐ diaré
☐ forstoppelse
☐ smerter
☐ sår i munnen
☐ munntørrhet
☐ spiser alene
☐ maten smaker annerledes
☐ annet _____
☐ kvalme
☐ oppkast

Vektendringer

Høyde: ☐☐☐ cm Vekt: ☐☐☐ kg

Har du hatt ufrivillig vekttap? ☐ja ☐ nei Om ja, hvor mye ☐☐ kg

Tidligere normalvekt: ☐☐☐ kg På hvor lang tid? ☐☐ mnd

De siste 2 ukene har vekten min:

☐ vært stabil ☐ økt ☐ minsket ☐ vet ikke

Denne siden fylles ut av lege, sykepleier eller klinisk ernæingsfysiolog

Diagnose _____

Metabolsk påvirkning _____ (0-3)

0 = ingen,
1 = litt
2 = en del
3 = svært mye

(Med metabolsk påvirkning menes eventuelt feber, infeksjon, kjent økning i CRP)

Fysisk påvirkning

Deklive ødem _____ (0-3) Tap av underhudsfett _____ (0-3)

Pleuravæske _____ (0-3) Tap av muskelmasse _____ (0-3)

Ascites _____ (0-3)

(Deklive ødem; i føtter/ankler hos oppegående pasienter, over hofte/bak hos sengeliggende pasienter. Ascitesvæske kan utgjøre mange kilo og derfor maskere eventuelt vekttap.)

(Tap av underhudsfett og muskelmasse inspiseres på muskelgrupper og hudområder der det faller naturlig å undersøke i løpet av konsultasjonen. Hender og ansikt kan inspiseres uten at pasienten behøver å kle av seg. 1-3 brukes ved grader av synlig tap. 3 innebærer at pasienten er betydelig avmagret. Vurderingen er subjektiv.)

Vurdering av ernæringstilstanden (ring rundt)

A - Velernært

Pasienten har ikke hatt vekttap, har ingen ernæringsrelaterte symptomer,
normal kroppsbygning, ingen tegn til underernæring,
velges også når pasienten har hatt noe vekttap, men er i positiv energibalanse og har god symptomkontroll

B - Noe/mistenkt underernært

Velges når pasienten har hatt vekttap og ikke oppnådd stabilisering/økning i vekt,
har sikkert redusert matinntak og ernæringsrelaterte symptomer,
noe tap av fettvev og muskelmasse, men har normal KMI. KMI >20 for alder opp til 65 år, KMI > 24 for alder over 65 år

C - Alvorlig underernært

Pasienten har hatt alvorlig vekttap.
Synlig tap av fettvev og muskelmasse, kan ofte ha ødemer. KMI er vanligvis < 20, (<24 for alder over 65 år)

Vurdering av vekttap

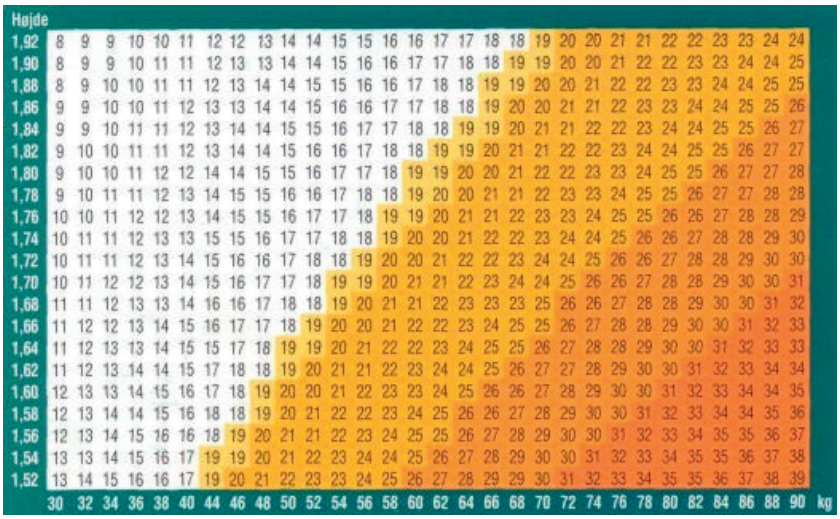
Tid	Alvorlig vekttap (%)
1 uke	> 2
1 mnd.	> 5
3 mnd	> 7.5
6 mnd.	> 10

% vekttap beregnes slik:

$$\frac{\text{vekttap i kg} \times 100\%}{\text{tidligere vekt}}$$

Vurdering av KMI

$$KMI = \frac{\text{Vekt (kg)}}{\text{høyde}^2\ (m^2)}$$



Overvekt	KMI = > 25
Normalvekt	KMI = 20-25
Undervekt	KMI = < 20

Dato: ☐☐.☐☐.☐☐☐☐ Sykehusnr.: ☐☐☐ Pasientnr.: ☐☐☐

Davies komorbiditets-indeks.

☐ Ved dialysestart
☐ 6 mnd etter dialysestart

Den registerar 7 sjukdomstilstandar vanlege for nyresvikt-pasientar.

Komorbid score er ein summasjon av desse, teoretisk maks 7.

Komorbid score graderast i 3 risiko-nivå:

1. Låg risiko - grad 0 : ingen komorbide tilstandar ☐
2. medium risiko - grad 1 : 1-2 komorbide tilstandar ☐
3. høg risiko - grad 2 : > eller lik 3 komorbide tilstandar ☐

Komorbide tilstandar:

1. Malignitet - non-cutan, aktiv tilstades / under behandling. Tidlegare malignitet som er antatt å vere helbreda skal ikkje registrerast. ☐ Ja ☐ Nei
2. Ischemisk hjertesjukdom: tidlegare hjerte-infarkt, angina pectoris, positiv coronar angio, påvisbar ischemiske forandringar på kvile-EKG. ☐ Ja ☐ Nei
3. Perifer vasculær sjukdom: inkluderar distal aorta, nyrearterier, underextremitetskar og cerebrovasculær sjukdom. Inkluderar anten symptomatisk sjukdom i desse kargebet eller signifikant stenose (> 50 %) bildemessig eller ved Doppler UL. ☐ Ja ☐ Nei
4. Venstre ventrikkel dysfunksjon: klinisk lungeødem (ekskluderer overvæsking) og / eller moderat til alvorleg venstre-ventrikkel dysfunksjon på eccocardiografi. ☐ Ja ☐ Nei
5. Diabetes mellitus - type 1 eller 2. ☐ Ja ☐ Nei
6. Systemisk collagen vasculær sjukdom - gjeld systemisk vaskulitt, reumatoid artritt eller systemisk sklerose, anten aktiv eller er under behandling. ☐ Ja ☐ Nei
7. Anna signifikant patologi - definert som ein alvorleg tilstand som påverkar overlevelse i den generelle befolkning. Til dømes: alvorleg KOLS (kronisk obstruktiv lunge-sjukdom), cirrhosis, psykose ☐ Ja ☐ Nei

Totalt Ja ☐

Desse tilstandane skal det ikkje aktiv undersøkjast for, det skal kun registrerast opplysningar som alt er tilgjengeleg i pasienten sin journal.

Livskvalitet Tilleggs spørsmål

Sykehusnr.: ☐☐☐ Pasientnr.: ☐☐☐

☐ Dialysestart ☐ 3 mnd etter dialysestart ☐ 6 mnd etter dialysestart

Dato: ☐☐.☐☐.☐☐☐☐

Spørsmål om appetitt

Vi er og interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss i den boksen som best beskriver din tilstand. Det er ingen "riktige" eller "gale" svar.

I løpet av siste måned:	Ikke i det hele tatt	Litt	En del	Svært mye
1.Har du hatt dårlig matlyst?	☐	☐	☐	☐
2.Har du vært kvalm?	☐	☐	☐	☐
3.Har du kasta opp?	☐	☐	☐	☐

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