The Comprehensive Dialysis Study (CDS)

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The Comprehensive Dialysis Study (CDS) is a special data collection study designed by the United States Renal System (USRDS), with baseline data collection initiated in 2005. The CDS addresses nutrition and rehabilitation/quality of life issues in incident dialysis patients. Consistent with Healthy People 2010 objectives, CDS data provide information relevant for reducing complications, disability, death, and economic costs of chronic kidney disease.

BACKGROUND INFORMATION: Nutrition

Protein energy malnutrition (PEM) is present in a large fraction of patients with end-stage renal disease (ESRD), ranging from ~20% to more than 80% of patients depending on the methods of assessment. The etiology of malnutrition in this population is often multifactorial, and reflects the interplay of complex biological and non-biological factors. The underlying causes of malnutrition can be grossly divided into those promoting reductions in dietary intake, and those associated with nutrient loss or hypercatabolism. Included among the latter are changes in plasma protein composition (e.g., hypoalbumineamia) and changes in body function and morphometry (e.g., muscle protein loss) that are ambiguous in cause and may reflect the effects of inflammation as well low dietary intake. Intake may be diminished due to prescribed dietary restrictions (e.g., low sodium, potassium, phosphorus, and occasionally low protein diets), depression and other psychosocial factors, or anorexia, due to uremia or the effects of comorbid conditions. Peritoneal dialysis may promote early satiety due to abdominal distention, and, depending on the timing, patients on hemodialysis often fail to ingest three meals a day, particularly on dialysis days (a midday dialysis session with no lunch = 3 missed meals of 21/week, or ~14% of usual intake). In the case of hemodialysis, there is loss of amino acids via the dialysate; with peritoneal dialysis, dialysance of amino acids and protein is of even greater significance. However, malnutrition in ESRD is obviously more complex, or all of PEM could be ameliorated by forced oral, enteral or parenteral feeding.

Confounding and exacerbating the effects of low intake is the systemic inflammatory response. The development of sepsis syndrome in the critically ill is the most extreme manifestation of the inflammatory response. Albeit more subtle, the effects of inflammation can be profound and clinically devastating in other, more chronic conditions, including ESRD, congestive heart failure, collagen vascular disease, and malignancy. Hypoalbuminemia is a potent risk factor for mortality and morbidity, in ESRD and in other populations, including the elderly and individuals undergoing a variety of types of non-cardiac surgery. Lowrie and Lew demonstrated in more than 12,000 patients dialyzed during 1988 an increase in the odds of death as the serum albumin concentration dropped below 4.0 g/dL, with levels less than 2.5 g/dL associated with a >10-fold increase in risk. Other investigators have confirmed these observations in smaller cohorts of hemodialysis patients. Fewer studies have been conducted among patients on peritoneal dialysis, although larger studies do show a significant inverse relation between serum albumin and death risk in this population.

While reduced dietary intake can lead to hypoalbuminemia, these effects are generally mild. In a prospective 24-week study in which healthy volunteers were subjected to semi-starvation, serum albumin decreased only moderately (4.3 to 3.9 g/dL) in spite of a 23% reduction in body weight and muscle mass. In a study of >400 hemodialysis patients, we demonstrated that inflammation,

as estimated by C-reactive protein concentrations, and dietary protein intake, as estimated from changes in urea nitrogen between dialysis sessions, appeared to exert competing effects on two proxies of nutritional status – serum albumin and serum creatinine.

Despite the widespread notion that ESRD is a wasting illness, there are few published reports evaluating changes in body weight or composition over an individual's "vintage" or duration of dialysis. A few small studies have shown an increase in body weight over time among peritoneal dialysis patients, presumably related to the several hundred carbohydrate calories infused during peritoneal exchanges. We demonstrated a significant decline in phase angle by bioelectrical impedance (a proxy for body composition) in a 54-patient cohort of UCSF hemodialysis patients followed over one year, although there were no significant changes in lean body mass by dual energy X-ray absorptiometry or any biochemical proxies of nutritional status. A large geographically and ethnically diverse cohort study is required to better understand the process of wasting in ESRD. We can explore the relations among nutritional status, physical activity and function, quality of life, employment and survival in this study.

BACKGROUND INFORMATION: Rehabilitation/Quality of Life

Functioning and well-being are concepts that refer to an individual's ability to perform various daily activities and functions and to subjective internal states, such as symptoms or feelings, that are not directly observable to others. Functioning and well-being are patient outcomes that are important in defining the value of delivered care. Major, interrelated problem areas in the functioning and well-being of ESRD patients are:

- Compromised physical functioning in relation to age- and sex-matched peers, whether assessed by performance measures or by patient report
- High frequency of depression
- Low rates of gainful employment among working-age patients

Improved understanding of these problems is needed. Increased capacity for physical activity among ESRD patients, along with their improved mental health and emotional well-being, should contribute to outcomes that are important to payers and to society, especially decreased healthcare costs stemming from decreased patient morbidity; patients' increased ability to live independently; and patients' increased ability to engage in productive activities, including employment.

Exercise interventions can improve ESRD patients' physical functioning. Exercise interventions typically are of relatively brief duration, however, while usual physical activity reflects the individual's lifestyle habits and preferences and therefore may be ongoing. Little is known about the contribution of usual (naturally occurring) physical activity to ESRD patients' outcomes over time.

In the presence of a chronic health condition, the risk of depression may increase as disability increases. We found that functional impairment and depressed mood increased over three years in both older dialysis patients and age-matched controls, but functional impairment and depression were significantly higher among older dialysis patients. The two groups did not differ at follow-up on reported life satisfaction, however.

The extent of dialysis patients' "true" inability to work is unknown. Assessing inability to work must take into account the patient's physical and psychological well-being as well as Social Security disability status. Patients are much more likely to continue a job held prior to starting ESRD therapy than they are to return to work after starting ESRD therapy. Thus, patients who

are employed in the year prior to starting dialysis are a critical target group and it is important to identify predictors of continued employment in these individuals.

STUDY DESIGN

Study Population

Based on historical rates of incidence, 335 dialysis facilities will be selected for inclusion in the study; 296 facilities are expected to be eligible and cooperate. For each sample facility, patients will be identified in the Renal Management Information System (REMIS). REMIS is the system used by the Centers for Medicare and Medicaid Services to determine the Medicare coverage periods for ESRD patients and serves as the primary mechanism to store and access information in the ESRD Program Management and Medical Information System Database. The REMIS system is updated on a daily basis and is the primary source of information on all ESRD patients in the Medicare system. CMS has agreed to provide the USRDS with on-line access to the REMIS system for the purposes of identifying new dialysis patients. A computer analyst at the USRDS will be given secure access to REMIS and will be able to query the system on a daily basis for incident patients. As patients are identified, their names will be forwarded to the facilities in the sample for the presentation of the informed consent forms. The selection of dialysis facilities will proceed as follows: The facility sampling frame with approximately 4000 facilities will be sorted by network (18 regions of the country), then by state within network. This sorting provides implicit stratification of facilities by geographic area of the country. Systematic random sampling (equal probability sampling) will be used to select a sample of facilities for the quality of life (QOL) component. Because of more complex logistics involved in the nutrition component of the study, fewer centers with larger numbers of patients will be selected, using systematic probability proportional to estimated size sampling.

Methods

Potential participants will be given a 1-page “Dear Patient” letter by dialysis facility personnel and told that a full packet will be mailed to them at their home address. A complete study packet with the “Dear Patient” letter and the appropriate consent form to review (QOL or QOL + nutrition) will be mailed to the potential participants. In addition, potential participants will receive an Instruction Sheet to assist them in completion of the documents. They will also receive a Participant Information Sheet to provide the telephone survey staff when best to contact them. The dialysis facility staff will complete a Participant Availability form if the potential participant is unavailable or unable to respond on his or her own (e.g., relocation, cognitive impairment, non-English or Spanish-speaking). If the consent form is signed, the patient can be enrolled, given questionnaires and if applicable, provide blood samples. If the potential subject does not return the Participant Information Sheet indicating whether he or she is interested in participating, we will contact the potential subject by telephone to provide study information and answer any questions. Additional copies of the written study information will be sent if requested.

Once enrolled, patients will be contacted by an external group of professional interviewers, who will use Computer-Assisted Telephone Interviewing to complete the Patient Questionnaire and the Brief Food Frequency Questionnaire. The laboratory of Dr. George Kaysen at UC Davis, will coordinate blood drawing and shipment. Blood will be drawn with the routine monthly laboratory values and will not require any additional needle sticks. Serum will be transported by licensed personnel to the laboratory of Dr. George Kaysen (UC Davis) for frozen storage and determination of C-reactive protein (an inflammatory marker) prealbumin (a nutritional and inflammatory marker), albumin (another nutritional and inflammatory marker) and creatinine (a

marker of kidney function and muscle mass). C-reactive protein and prealbumin are not routinely measured in hemodialysis patients.

Dialysis unit staff will not participate in the research in any way, other than in handing informed consent documents to potential participants. The Director of the Division of Compliance Oversight at the Office for Human Research Protections (Kristina Borror, PhD) has determined that the dialysis centers are not engaged.

After one year, subjects in the nutrition substudy will be asked to repeat the questionnaires. After completion of the 1-year questionnaires, participation will cease. Within three years after study completion, frozen specimens will be transported to the NIH Biorepository and the clinical data will be prepared for public use.

Eligibility Criteria

1. Must have been on dialysis for no more than 6 months.
2. Must be able to speak English or Spanish.
3. Must be able to provide written informed consent.
4. All participation will be voluntary and this will be stated on the consent forms.

Remuneration

A check for $25 after completion of the telephone survey will be mailed to the subject from the USRDS Data Coordinating Center within 4 weeks. Social security numbers are already available to the USRDS from documents completed at dialysis units.

OBJECTIVES

To determine the natural history of nutritional status in incident ESRD patients.

To determine to what degree inflammation (as defined by elevated C-reactive protein) influences the natural history of nutritional status in incident ESRD patients.

To determine to what degree dietary intake (as estimated by food frequency questionnaire) influences the natural history of nutritional status in incident ESRD patients.

To evaluate time trends in C-reactive protein, prealbumin, albumin, and other nutritional indicators, and their relation with mortality, hospitalization, functional status, physical activity, and quality of life.

To investigate baseline physical activity (as defined by the Human Activity Profile) and change in physical functioning after one year.

To investigate predictors of change in depressed mood from baseline to one year.

To identify predictors of inability to work reported by incident dialysis patients.

To identify predictors of continued patient employment from treatment start to one year.

ANALYSIS

Data will be analyzed by the Investigators. Eventually, the data will be made into a public use file for further analysis by the broader nephrology research community.

MANAGEMENT

Participants will be recruited from selected dialysis units throughout the US. The criteria for facility selection are described above. The procedures, except for blood testing, will be conducted by telephone. Blood testing will be conducted at the dialysis unit on the same day that monthly laboratory testing is routinely done. Tubes and transporting materials will be provided to the local dialysis unit, packaged by licensed personnel, and shipped to Dr. Kaysen's laboratory in Davis, CA.

CDS Questionnaire
Pre-ESRD care questions
- (at study start)

Kidney Disease Quality of Life-36 (KDQOL-36) supplemented w/ other quality of life measures
- (at study start and one year)

Human Activity Profile
- (at study start and one year)

Block Brief 2000 Food Questionnaire
- (at study start and one year)

Laboratory testing for C-reactive protein, prealbumin, albumin and creatinine
- (study start, 3, 6, 9 months and one year)

Potential subjects may elect not to participate in the cohort study. Participation will not affect medical care in any way.

SYNOPSIS

Protein energy malnutrition, depending on its definition, affects nearly half of all persons with end-stage renal disease (ESRD). Laboratory parameters of nutritional status in ESRD, such as serum albumin, prealbumin, creatinine, and normalized protein catabolic rate (a proxy for dietary protein intake) have been consistently linked to mortality and morbidity in observational studies of persons with ESRD. Quality of life, physical function and other aspects of functional status are generally reduced in ESRD, and also associated with mortality and morbidity. Using a combination of questionnaires, medical history and laboratory studies obtained within six months of starting dialysis and one year later, we will determine the early natural history of nutritional and functional status in a large representative cohort of US patients with ESRD. A better understanding of the interrelations among general health, nutrition, physical function and quality of life should help to inform the design of interventions to prevent or correct deficiencies in these parameters.

PROTECTION OF HUMAN SUBJECTS

1. The CDS has been reviewed and approved by institutional review boards at the University of California, San Francisco; Emory University; and the University of Minnesota.
2. The informed consent form specifies that participation in the study is voluntary and that subjects may withdraw at any time without penalty. It also describes the potential risks and benefits to the subject and the importance of the knowledge to be gained.

RECRUITMENT AND CONSENT

Potential participants will be identified using national registry data. A "Dear Patient" letter will be provided to potential subjects selected according to a pre-defined dialysis facility sampling plan (coordinated by Dr. Brogan, Emory University). Patients who receive study information packets but do not return any study-related forms will be contacted by telephone. They will be given additional study information and invited to ask questions to ensure that they have the opportunity to participate if they wish to do so. Study personnel will assure that potential participants understand the risks and alternatives to participation. Spanish-speaking subjects will be interviewed by Spanish-speaking personnel.

RISKS

Participation in research can involve a loss of privacy. Therefore, methods to protect confidentiality, including de-identification (using only a study ID number), password protection, no internet transmission of information, etc. are in place.

BENEFITS

The CDS will provide a better understanding of the interrelations among nutritional status, dietary intake, inflammation, physical and functional status and quality of life in dialysis patients. This could lead to new approaches or therapies that might prevent or correct deficiencies, and enhance the lives of persons with chronic kidney disease.

INVESTIGATORS

Glenn M. Chertow, MD, MPH: Director, USRDS Nutrition Special Studies Center, board-certified nephrologist, experienced in outcomes research

Kirsten L. Johansen, MD: Co-Investigator, USRDS Nutrition Special Studies Center, board-certified nephrologist, experienced in outcomes research

George A. Kaysen, MD, PhD: Co-Director, USRDS Nutrition Special Studies Center, board-certified nephrologist, Chief, Division of Nephrology & Acting Chief, Department of Biochemistry, UC Davis

Patricia A. Painter, PhD: Co-Investigator, USRDS Rehabilitation & Quality of Life Special Studies Center, exercise physiologist, experienced in research

D. Jordi Goldstein, RD, DSc: Co-Investigator, USRDS Nutrition Special Studies Center, renal dietitian, experienced in nutritional evaluation and outcomes research

Donna Brogan, PhD: Co-Director, USRDS Rehabilitation & Quality of Life Special Studies Center, experienced population survey statistician

Nancy Kutner, PhD: Director, USRDS Rehabilitation & Quality of Life Special Studies Center, experienced in outcomes research

Allan J. Collins, MD: Director, USRDS Coordinating Center, board-certified nephrologist, experienced in outcomes research, data management

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