Research Protocol

The tongue features associated with chronic kidney disease (CKD)

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The tongue features associated with chronic kidney disease- study protocol for a randomized crossover trial

I. Study Objectives

The objectives of this protocol are to apply the noninvasive ATDS to evaluate tongue manifestations in patients with CKD, and to provide valuable information for clinical doctors, which can be used to facilitate the early detection and diagnosis of CKD, to analyze the current status of patients, and to dynamically schedule treatment plans. This protocol is a cross-sectional, case-controlled observational study investigating the usefulness of the ATDS in clinical practice by examining its efficacy as a diagnostic tool for CKD.

II. Background and Rationale

Chronic kidney disease (CKD) is an important global public health problem. According to related literatures, the prevalence of CKD is about 11% .(1) CKD is a progressive disease. If it progresses to end-stage renal disease (ESRD), renal replacement therapy: dialysis and renal transplantation, is required to maintain life(2). The growing prevalence and progression of chronic kidney disease (CKD) raises concerns about our capacity to manage its economic burden to patients, caregivers, and society. The societal direct and indirect costs of CKD and end-stage renal disease are substantial and increase throughout disease progression. There is significant variability in the evidence about direct and indirect costs attributable to CKD and end-stage renal disease, with the most complete evidence concentrated on direct health care costs of patients with advanced to end-stage CKD.(2)

CKD, also called chronic kidney failure, is described as a sustained reduction in glomerular filtration rate or evidence of structural or functional kidney abnormalities.(3) Chronic kidney disease (CKD) refers to all five stages of kidney damage, from very mild damage in stage 1 to complete kidney failure in stage 5. CKD symptoms include pain, itch(pruritus), peripheral numbness, sleep disturbances, depression, fatigue, nausea and vomiting. Factors that contribute to these symptoms include anaemia, uraemic toxins, reduced renal capacity, chronic disease-related inflammation, and psychological stress associated with long-term illness.(4)

If it progresses to end-stage renal disease (ESRD), renal replacement therapy, including hemodialysis, peritoneal dialysis and kidney transplantation, is required to maintain life. Therefore, it is essential to find effective and conservative treatment methods to delay the progression of CKD.

Diagnosis in traditional Chinese medicine (TCM) is based on four procedures, observation, smelling or listening, inquiry, and palpation. Tongue diagnosis, serving as a vital non-invasive tool to provide useful clinical information, plays a pivotal role in TCM.The tongue is considered to reflect the physiological and pathological condition of the body, as well as the degree and progression of disease, through the meridians that connect the tongue to theinternal organs.By observing tongue features, TCM practitioners can probe qi-blood, yin-yang disorders which are important in treatment selection and prognosis.[18,19] Clinically, practitioners observe tongue characteristics, such as tongue color and shape, fur color and thickness, and the amount of saliva, to help deduce the primary pattern of a patient. However, tongue diagnosis is often biased by subjective judgment, which originates from personal experience, knowledge, diagnostic skills, thinking patterns, and color perception/interpretation. The inconsistency of subjective diagnosis can be improved by using the development of validated instruments. The automatic tongue diagnosis system (ATDS) has shown high consistency and can provide objective and reliable information and analysis of tongue features, facilitating doctors in making effective observations and diagnoses of specific diseases. [10] [18] Previous studies have been conducted on exploring the association between tongue characteristics and specific diseases, including rheumatoid arthritis,[11] breastcancer,[12,13] type 2 diabetes,[14] metabolic syndrome,[15] eczema,[16] dysmenorrhea,[17] and functional dyspepsia,[22] gastroesophageal reflux disease(). However, to the best of our knowledge, no study has yet been performed on the comprehensive scrutiny of tongue features in patients with CKD using ATDS.

III. Procedures

A. Research and Design

Subject Selection/Sample

Inclusion criteria & Exclusion criteria:

All individuals were recruited were informed of the study purpose, procedures, potential risks and benefits, and then the consent form were signed. Subjects will be eligible if they satisfy the following criteria: age over 20 years old; with CKD stage 3-5 including dialysis patients , or who without symptoms and visit clinic for health examination; volunteered to join this research and signed the institutional review board agreement. Both men and women will be enrolled. Subjects with any of the following conditions will be excluded: cancer; acute infection; unable to protrude the tongue stably; risk of temporomandibular joint dislocation

Study setting

The trials will be conducted at the Changhua Christian Hospital. This study will adhere to the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) [15] to allow for greater completeness, transparency and accuracy of reporting. This protocol is a cross-sectional, case-controlled observational study investigating the usefulness of the ATDS in clinical practice by examining its efficacy as a diagnostic tool for CKD stage 3-5 patients. After giving their consent, participants will undergo tongue image capturing using the ATDS. The ATDS examination will be performed under constant environmental conditions and by the same educated operator. The tongue images of both groups: experimental and control groups, were collected by the validated Automatic Tongue Diagnosis System (ATDS) with the corresponding tongue features automatically extracted. We analyzed the data of the subjects and the tongue features from the ATDS.

Eligibility criteria

Information including demography, body mass index (BMI, kg/m2), estimated glomerular filtration rate (eGFR) and CKD Staging were gathered for each subject. The duration of CKD history, comorbidity and complication in experimental group were also collected. Tongue images were collected for each subject to further derive the relevant tongue features of every participant. All personal details and photographs of subjects recruited were encrypted to ensure confidentiality.

Ethics

This research protocol adheres to the principles of the Declaration of Helsinki and has been approved by the institutional review boards of the Changhua Christian Hospital (No. : 190404). Informed consent will be obtained from each participant before any treatment is given. All subjects will have the right to withdraw from the study at any time.

B. Measurement/Instrumentation

Information including demography, body mass index (BMI, kg/m2), estimated glomerular filtration rate (eGFR) and CKD Staging were gathered for each subject. The duration of CKD history, comorbidity and complication in experimental group were also collected. Tongue images were collected for each subject to further derive the relevant tongue features of every participant. All personal details and photographs of subjects recruited were encrypted to ensure confidentiality.

Primary outcome measures. Nine primary tongue features will be extracted from the ATDS as follows: tongue shape: small and thin, moderate, large, and fat; tongue color:

slightly white, slightly red, red, dark red, and dark purple; tooth mark: includes number, average covering area, maximum covering area, minimum covering area, and organs corresponding to the covering area; tongue fissure: amount, average covering area, shortest length, and longest length; fur color: white, yellow, and dye; fur thickness: none, thin, thick; fur amount, average covering area, maximum covering area, minimum covering area, and organs corresponding to the covering area; saliva: includes total area and the amount of saliva (none, little, normal, excessive); ecchymosis: amount, average covering area, maximum covering area, minimum covering area, and organs corresponding to the covering area; red dots: number, average covering area, maximum covering area, minimum covering area, and organs corresponding to the covering area. Feature identification will be further subdivided into 5 segments (spleen–stomach, liver-gall-left, liver-gall-right, kidney, and heart–lung area) according to the theory of traditional Chinese medicine.

Statistical Considerations:

A. Sample Size:

We calculated the sample size will be about 500 with power=0.9,alpha=0.05, effect size convention r=0.3, and an anticipateddrop-out rate of 10%, using G∗Power 3.0.1.0 software which isdownload from http://www.gpower.hhu.de.. Every effort will be made to reduce attrition; consent documents will emphasize the importance of complete data and encourage patients to return for the follow-up visit.

B. Randomization:

Patients will be randomized to one of the two treatment options with equal allocation. In an attempt to balance severity across treatment cohorts the randomization scheme will be stratified by baseline severity of RLS symptoms as measured by the International Restless Legs Severity Scale (severe vs. very severe). The randomization scheme will be generated by the study statistician with varying block sizes and uploaded to a web-based randomization program. After the patients eligibility has been confirmed and consent documents signed the research coordinator will randomize the patient to one of the two treatment options via the web-based randomization program. The PI will not randomize patients or have access to their treatment assignments.

C. Analysis plan:

All statistical analyses will be performed using the SPSS statistical package program, version 17.0 (SPSS Inc., Chicago, IL). Chisquare tests will be applied for categorical data and Analysis of variance tests will be applied for continuous data. Logistic regression will be used to estimate the odds ratio and the probability of a binary response, based on one or more independent variables. P-values <.05 will be considered statistically

significance.For study-related patient data (case report forms) a unique identifier will be used. Study-related documents will be kept in a locked cabinet in a locked office. A separate list (paper-only) will be made containing the unique identifier and the name of each participant. This list will be kept separate from the study related documents. Study databases will be stored on a password protected computer network in a locked office and kept for 5 years.

IV. Bibliography

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