Effect of nigella sativa oil sup plementation on kidney function tests, glycemic parameters, oxidative stress, inflammation, quality of life and depression status in diabetic hemodialysis patients; study protocol for a double-blind, randomized controlled trial

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Study protocol

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Abstract

Background and objectives: The kidney is probably the most crucial target of microvascular damage in diabetes, which can ultimately eventuate end-stage renal disease (ESRD). Hemodialysis is the most usual way of renal replacement therapy in ESRD. Patients receiving hemodialysis are susceptible to many complications like hyperglycemia, inflammation, depression, anxiety, and poor quality of life. So, they constrained to consume many drugs. Medicinal herbs are used in different cultures as a reliable source of natural remedies. This study aims to determine the efficacy of Nigella sativa (NS) oil supplementation on blood glucose, kidney function tests, inflammation, oxidative stress, quality of life, and depression in hemodialysis patients.

Methods and analysis: This double-blind, randomized controlled trial will enroll 46 patients with diabetes mellitus who give hemodialysis thrice a week. Patients who have an inflammatory or infectious disease, and who receiving nonsteroidal anti-inflammatory drugs, will be excluded. Patients will be randomized to the treatment and control group, which will be recommended using two soft gel of NS and paraffin oil, respectively. Laboratory tests will be assessed at baseline and end of the study, including fasting blood sugar, glycated albumin, insulin, creatinine, blood urea nitrogen, urea, uric acid, superoxide dismutase, malondialdehyde, total antioxidant capacity, high sensitive C reactive protein, and 24-hour urine volume. Also, the kidney disease and quality of life and hospital anxiety and depression scale questionnaires will be evaluated.

Ethics and dissemination: According to our knowledge no sever adverse effect have been reported. The protocol was found to be in accordance to the ethical principles and national norm standard for conducting medical research in Iran (IR.TBZMED.REC.1399.109). Both positive and negative findings will be reported.

Trial registration: Iranian registry of clinical trials: IRCT20200411047027N1. Registered on 31 may 2020, https://fa.irct.ir/user/trial/48113/view

Introduction

Diabetes and chronic kidney disease (CKD) are pervasive diseases of the present century, which have an increasing prevalence. Diabetes is known as the leading cause of renal failure, which ultimately results in end stage of renal disease (ESRD) and the onset of dialysis or kidney transplantation(1).

By the reduction of infectious diseases and prolonging the population life, CKD has been the most critical chronic non-communicable disease for life-threatening human beings. It is expected that half of the American people will end up a lifetime with CKD(2). The prevalence of CKD in different countries depends on many factors, such as gender, age, and economic status. However, it is estimated that 14% of the world's population is involved in this disease, and accordingly, its prevalence is rising(3). The number of renal replacement therapy (RRT) in the form of dialysis or kidney transplantation is progressively rising. It is estimated that in 2010, 2.5 million people worldwide were the recipient of RRT. At the same time, at

least 2.2 million people have not been able to accept dialysis due to unavailability and therefore have died. Furthermore, the prevalence of RRT in many countries, particularly in the Asian continent, is growing, and by 2030 the number of dialysis patients reaches at least 5.4 million(4). About 50% of patients who are dependent on dialysis are diagnosed with diabetes(5), and they are prescribed insulin. Hyperglycemia by glycosylated some tissues such as glomerulus and Mesangial cells, is a decisive factor in the progression and development of renal failure.

The common indicators applied to evaluate glycemic status are fasting blood sugar (FBS), glycated hemoglobin (HbA1c), and 2-hour post prandial glucose. A relatively new index that is recommended for measuring blood sugar is glycosylated albumin (GA). Approximately 20% of patients with diabetes who reach ESRD, have less HbA1c than the pre-dialysis stage. This phenomenon is called burnt-out diabetes. Recent research has shown that in patients with diabetes mellitus undergoing hemodialysis, HbA1c indicates a pseudo-sugar, while replacement of GA, can reduce the prevalence of this phenomenon to 5% (6). So, GA is a more accurate index of blood sugar in these patients. Furthermore, GA is a predictor of survival rate and hospitalization of patients with diabetes mellitus undergoing hemodialysis. As a result, it is recommended to use this factor as an HbA1c or as a valid alternative factor along with other indicators(7, 8).

Nigella sativa (NS), is an excellent plant from Ranunculaceae and indigenous to South West Asia. This plant is used in Iranian traditional medicine to treat various disorders such as respiratory, gastrointestinal, hepatic, and renal disorders, and many of its therapeutic effects have been proven in previous researches(9). Pharmacological studies have shown anti-diabetic, antioxidant, and anti-inflammatory properties of NS, which is because of different chemical compounds of this plant. Among these compounds can be pointed to thymoquinone and nigellidin(10).

In previous studies, the positive effect of NS on the reduction of FBS and HbA1c in patients with diabetes mellitus has been well established(11-13) There are many biochemical and clinical parameters for the evaluation of renal function. The most common are glomerular filtration rate (GFR), serum creatinine, blood urea nitrogen, uric acid, and urinary analysis. The kidney disease: improving global outcomes organization has introduced the GFR index as a valid criterion for diagnosis and classification of renal failure. The rate of blood flow through the kidneys in the unit of time, is called GFR. The amount of GFR is associated with age, sex, and body surface. Accurate measurement of GFR is complicated, as the filtration process simultaneously takes over millions of glomeruli. So to measure it, we have to use the estimation formulas(14). It has had more than 20 formulas for its estimation, which the most used of them is the Cockcroft-Gault Equation(15).

Uric acid is the final product of purine metabolism during DAN and RNA synthesis. Also, the metabolism of food purine is another source of the blood uric acid. This indicator is used as a criterion for kidney function. According to cohort studies with a high population, high serum uric acid is a predictor of all death reasons, especially heart disease in dialysis patients(16). In addition, other criteria for the renal function is urine volume. Low urine volume in hemodialysis patients leads to the accumulation of toxic

substances in the body. Also, another complication is the cause of edema. Therefore, increasing urine volume is one of the therapeutic goals in hemodialysis patients.

According to the study done on patients with diabetes mellitus with renal failure, consumption of NS oil for three weeks could cause a significant increase in urine volume in dialysis patients(1).

Approximately 50% of hemodialysis patients have depression and, about 25% of them suffering from severe depression(17, 18). Several studies have shown that suicide is more prevalent among dialysis patients with depression, and their life expectancy is one third to one sixth of normal range. Depression in ESRD patients is associated with more complications and higher mortality. Also, adherence to diet and restriction of recommended fluids was lower in ESRD patients with depression(17). Depression also reduces the quality of life(17). Considering the impairment of renal filtration, the benefits and risks of antidepressant drugs in ESRD patients are controversial. A scientific documentary on the positive effect of antidepressant drugs (fluoxetine, sertraline, citalopram) was not found in comparison with placebo on quality of life in ESRD patients(17). As a result, the control and treatment of depression are one of the priorities in hemodialysis patients.

The hospital scale of anxiety and depression (HADS) is a self-administered questionnaire that is used to assess the level of anxiety and depression in patients with physical and mental health problems. Translation of HADS questionnaire, in Persian and its standardization, was conducted by Montazeri et al. in 2003(19)

Quality of life is an important criterion that shows the effectiveness of health care, health level, and a good sense of living. In addition, It predicts the occurrence of mortality and duration of hospitalization in hospitals(20). ESRD; the last stage of CKD is a chronic limiting condition that has many adverse effects on different dimensions of patients' lives(21). RRT exposes patients to a wide range of physical, psychological, economic, and social problems and affect their quality of lives(20). As there is no definite treatment for ESRD patients, many studies have been investigated to evaluate and improve the quality of life of patients undergoing hemodialysis and have introduced this index as a therapeutic target in these patients(20). Also, regular monitoring of this index as a clinical criterion, have expressed the progression of treatment of patients treated with RRT(20). The kidney disease quality of life questionnaire (KD-QOL) is a complete version of the short form 36 health survey questionnaire (SF-36) for renal patients, as well as a self-administered questionnaire. The reliability and validity of this questionnaire in Iran was carried out by Mir Saeed Yekaninejad, M., et al in 2012 (21).

As mentioned, in previous studies, the positive effect of NS on glycemic control in patients with diabetes mellitus and also improving the renal function tests has been proven, but there is no study about hemodialysis patients. Also, GA is the newest and most accurate index for the estimation of blood sugar, as well as the mortality rate in patients with diabetes mellitus undergoing hemodialysis. Nevertheless, it has not been examined the effect of NS on this factor. Furthermore, quality of life and depression are the most critical qualitative indexes in hemodialysis patients, which in this research, we consider the effect of NS supplementation on theses indexes.

The overall aim of this design was to determine the effect of NS oil supplementation on indices of renal function, glycemic indexes, oxidative stress, inflammation, quality of life and depression in patients with diabetes mellitus undergoing hemodialysis. Moreover, its proprietary objectives include: 1) determine the effect of NS oil supplementation on serum FBS, HbA1c, GA, serum insulin, insulin resistance, and the B cell function in patients with diabetes mellitus undergoing hemodialysis. 2) Determine the effect of NS oil supplementation on serum levels of urea, creatinine, uric acid, adequacy of dialysis as well as urine volume in patients with diabetes mellitus undergoing hemodialysis. 3) Ascertain the effect of NS oil supplementation on superoxide dismutase (SOD), malondialdehyde (MDA), total antioxidant capacity (TAC), high sensitive C reactive protein (hs-CRP) in patients with diabetes mellitus undergoing hemodialysis. 4) Determine the effect of NS oil supplement on quality of life and depression in patients with diabetes mellitus undergoing hemodialysis.

Methods

Study design

The present study is a randomized clinical trial controlled with placebo and two-blinded groups that conform to standard protocol items: recommendations for interventional trials statement (SPIRIT) 2013. The study will be conducted at Imam Reza Hospital of Tabriz, Iran.

Participants

In this study, the target population is patients with diabetes mellitus undergoing hemodialysis. The inclusion criteria are: an age³ 20 years; body mass index=18.5-30 kg/m^2; having type 2 diabetes mellitus; three times per week hemodialysis; being on hemodialysis for at least 6 months; ability and willingness to cooperate in the study. The exclusion criteria are having inflammatory or infectious diseases; receiving steroidal or nonsteroidal anti-inflammatory drugs, smoking, and using NS oil regularly.

Interventions

The patients are randomly allocated to either a NS oil or control group. Patients in the NS oil group will receive two soft gel of NS oil, whereas the control group will receive two soft gel of paraffin oil (each soft gel weights 1 gram). Treatment of both groups will last for 12 weeks. The selected dose is based on Kaatabi H(11), which is one of the best effective and safe interventions of NS oil supplementation in patients with diabetes mellitus. According to the predominant studies, NS oil supplementation in the mentioned dose and the term, but even in more prolonged use, did not have certain complications. just in some rare cases, mild and temporary nausea and dyspepsia and decreased appetite have been reported(12, 13, 22)Both soft gels will be prepared by the pharmaceutical company in a completely similar way in terms of shape, color, and odor. The preparation of black seed oil will be done by the cold press method by the pharmaceutical specialist.

The supplements will be available to attendees every two weeks. All patients will be asked to their usual dietary habits, physical activities, and drug regimens and report us any possible changes. In addition, every two weeks, all patients will be evaluated by interview. Furthermore, the researcher will give participants a call number to inform him if there are any side effects or other problems.

Outcomes measures

Accordance with the inclusion criteria, after explaining the objectives and method of the study, patients will be consciously entered into the study. They will be asked to obtain Informed consent. Next to that, demographic and anthropometric indices checklist for each individual are filled, and general nutritional recommendations will be taught by a nutritionist. Dietary intake of individuals will be evaluated by the 3-day food registration questionnaire (two-week days and one weekend day). Also, before the intervention, patients will be paid to complete their standard questionnaires, including KD-QOL and HADS, to assess the quality of life, depression, and anxiety. If the patient is illiterate, the information will be received by interviewing. At baseline and the end of the 12th week, 10 mL of blood will be obtained from each patient after 12 hours of fasting. Blood serum will be stored at refrigerator temperature (-70°C). Laboratory tests including renal function tests as creatinine, urea, uric acid, urine volume, indices related to blood glucose including FBS, HbA1c, GA, serum insulin, insulin resistance and β-cell function, indices related to oxidative stress and inflammation including SOD, MDA, TAC, and hs-CRP will be measured and recorded.

The process for assessing the activity of hs-CRP, MDA, SOD, and TAC will be done by Navand assay kit (Navandsalamat, Iran) according to the company package insert instruction. The serum insulin level, HbA1c, and GA will be measured by enzyme-linked immunosorbent assay (ELISA) method. Biochemistry Solutions will also measure creatinine, urea, uric acid, and FBS.

In order to determining insulin resistance and β cell function, HOMA-IR and HOMA-B formula will be used respectively(23).

$$\text{HOMA-IR} = \frac{glucose\left(\frac{mg}{dl}\right) \times insulin}{405} \qquad \text{HOMA-B} = \frac{fasting\ insulin \times 20}{fasting\ glucose - 3.5}$$

The reliability of laboratory methods by sending the first ten samples of experiments with two different names to the laboratory expert and investigating the level of agreement between them will be determined. Also, body composition will be evaluated by the bioelectrical impedance analysis (BIA) method.

Sample size

In this study, by considering α = 0.05, and the power of 90% and using primary data on creatinine outcome, based on findings of Z. Ansari, SJKDT, 2017 study (1) based on the procedure of two independent groups G-power software or Formula

$$n = \frac{(\sigma_1^2+\sigma_2^2)\left(Z_{\frac{\alpha}{2}}+Z_\beta\right)^2}{(\mu_1-\mu_2)^2}$$

The minimum sample size required for each group is 20 subjects, which with predicting 10% loss it will be 23 patients in each group.

Stratified randomization

The patients will be allocated to either a NS oil or control group by block randomization after stratification based on the frequency of hemodialysis per week (2 or 3 times per week) and the amount of blood sugar (FBS< 120 mg/dL, FBS= 120-200 mg/dL and FBS> 200 mg/dL). This process will be carried out by a statistics specialist using of RAS (random allocation software) in block sizes of 4. A trained dietician will perform blinding, and the patients and researchers will be kept blinded to the allocation.

Table. 1 Timetable of planned activities during the study directly related to participants

	Study period				
	Enrolment	**Allocation**	**Post allocation**		**Follow-up**
Time Point	Weeks -4 to -1	Week -1 to 0	Week 0	Week 12	Week 13
Enrolment:					
Eligibility screen	*				
Informed consent	*				
Allocation		*			
Intervention:					
Two placeboes soft gel daily					
Two *nigella sativa* soft gel daily					
Assessments:					
24 h food recall		*			*
Blood collection		*			*
Urine collection		*			*
Anthropometric measurements		*			*
KDQOL questionnaire		*			*
HADS questionnaire		*			*

KDQOL: Kidney Disease Quality of Life; HADS: Hospital Anxiety; and Depression Scale

Statistical analysis

The collected data will be analyzed by the statistical package for the social sciences (SPSS) version 23 software. Descriptive statistics, including frequency, percentage, and central indices and dispersion will be done. The Wilcoxon signed-rank test will determine the normal distribution of the data. If data distribution is normal, to compare the serum markers and physical components analysis among the study groups in the pre-intervention stage, independent sample t-test, and after the intervention, analysis of covariance (ANOVA) will be used by modulating the baseline values and probable variables. Paired-samples t-test will be used to compare data in each study group. If the data distribution is normal, for comparison of the serum markers and physical components analysis before the study, Mann-Whitney

test and among the study groups, Wilcoxon signed-rank test will be used (for both before and after the intervention). In all tests, the p-value< 0.05 will be considered significant. missing data will be removed from the final analysis.

Ethics considerations

The expert nutritionist will explain the purpose of the study, benefits, or side effects of the supplements to all patients before obtaining written informed consent. The volunteers will fill an informed consent form and enrolled in the study. They can withdraw their consent at any time study.

According to previous studies, this supplement's use is safe in the dose, as mentioned earlier, and has no side effects. In case of any acute clinical symptoms due to supplementation, the subjects will be excluded, and the researcher will pay the costs of any possible complication. Any adverse events and other unintended effects of trial interventions will be collected and mentioned in the article.

The personal information of enrolled participants will be collected, shared, and confidentiality maintained before, during, and after the study by encoding systems. The results of the experiments will be available for participants at the end. The participants will be assured that the project will not be charged for treatment interventions. If NS supplementation is effective, the control group will also take this supplement.

The benefits of participating in this study for control group, are free:

- Nutritional counseling and monthly monitoring
- Glycemic tests at the beginning and end of the study
- Kidney function tests at the beginning and end of the study
- Inflammation and oxidative stress status tests at the beginning and end of the study
- Body composition and anthropometric tests at the beginning and end of the study

All results will be delivered to the participants at the end of the study.

Discussion

Diabetes and chronic kidney disease are the most common diseases of the present century that have an increasing prevalence. Diabetes is known as the main leading cause of diabetic kidney disease(DKD), which ultimately leads to ESRD and the onset of dialysis or kidney transplantation(1) . The prevalence of RRT is increasing in many countries, and the number of dialysis patients is estimated to reach at least 5.4 million by 2030(4) Since there is no definitive and conventional treatment for ESRD patients, the aim of treatment in these patients is to prevent the progression of existing complications and improve their quality of life(24).

Nigella sativa is a healing plant that has had positive effects on renal and blood glucose indices in previous experimental and human studies(1, 13). Also, positive evidence has been reported about improving memory and quality of life and reducing depression, all of which are the common problems involved in hemodialysis patients. Despite this, no trial has been done on hemodialysis patients.

Considering the relatively low cost and very low complications of this intervention, if significant results are obtained in this study, it can be used as an adjective therapy in these patients. We designed this study to investigate the effect of Nigella sativa oil supplementation on the mentioned indices in hemodialysis patients.

Trial Status

First-stage sampling of patients is almost finished. the protocol has been submitted before the last patient. The first participant's enrollment to the trial was on 1 June 2020, and it is estimated primary sampling be completed by 20 August 2020.

Trial registration: Iranian registry of clinical trials: IRCT20200411047027N1. Registered on 31 may 2020, https://fa.irct.ir/user/trial/48113/view

Abbreviations

ANOVA: Analysis of variance; BMI: Body mass index; CKD: Chronic kidney disease; CVD: Cardiovascular disease; ESRD: End-stage of renal disease; GA: Glycosylated albumin; HADS: Hospital Anxiety and Depression Scale; HbA1c: Glycosylated hemoglobin; HOMA-B: Homeostatic model assessment of beta-cell function; HOMA-IR: Homeostatic model assessment of insulin resistance; hs-CRP: High Sensitivity C Reactive Protein ; I.R: Insulin resistance; KD-QOL: Kidney disease quality of life; N.S: Nigella sativa; RRT: Renal replacement therapy; S.G: Specific gravity; SOD: Superoxide Dismutase; MDA: Malondialdehyde; T2DM: Type 2 diabetes mellitus; TAS: Total antioxidant capacity

Declarations

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Contributions

AR, AT-E, VM, BN, and OMT-R contributed to study conception and design. AR and BN conducted the intervention and gathered data. AR, OMT-R, analyzed, and interpreted data. AR, AT-E contributed to the manuscript writing. All authors read and approved the final version of the manuscript.

Consent for publication

We have mentioned in our consent form to report their data without their names. All participants will read conditions written in this form, and optionally, they can accept participating in the current trial.

Availability of data and materials

The datasets generated during this study will be available via the corresponding author on a reasonable request.

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Competing interests

The Tabriz University of Medical Sciences funds this project. The funding body did not have any role in the design, collection, and analysis, writing of the manuscript, or submit the manuscript for publication. The authors declare that they have no competing interests

Ethics approval and consent to participate

This protocol is approved by the Ethics Committee of the Tabriz University of Medical Sciences (IR.TBZMED.REC.1399.109). This study is registered at the Iranian Registry of Clinical Trials (IRCT20200411047027N1). All participants will sign a written consent form. The consent form will be available to the editor if requested.

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Figures

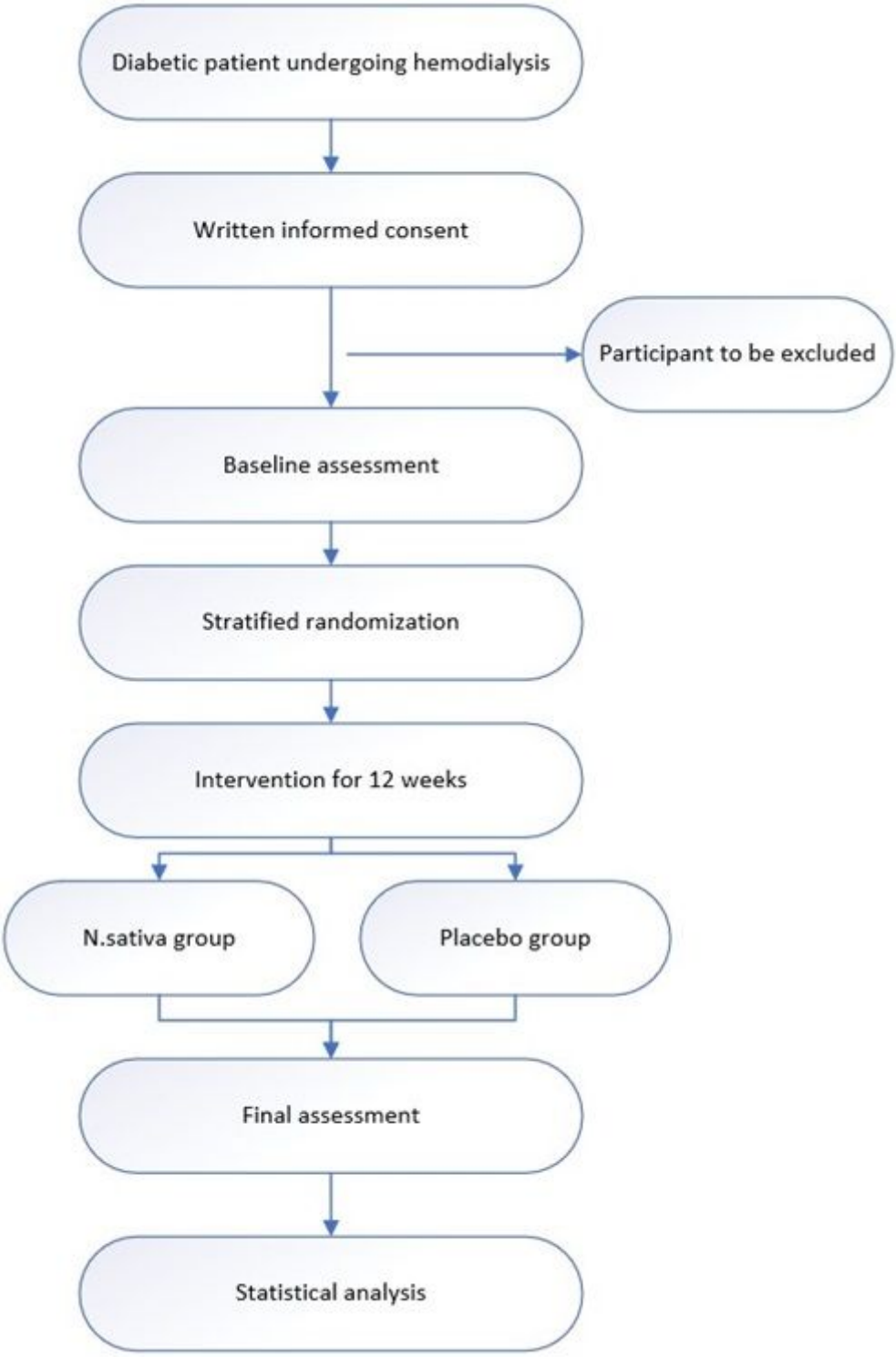

Figure 1

the overview of the study

Supplementary Files

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- SPIRIT2013checklist.pdf
- Consentform.pdf