1 Información General

1.1 Identificación del estudio

Título: The Efficacy of the Greenhabit method (mHealth) for Lifestyle Modification in Diabetes
Código o número de identificación del protocolo
Versión y fecha: V03 19/03/21

1.2 Identificación de promotor

Nombre y dirección del promotor.

Chantal Linders, Greenhabit BV, Groningen

1.3 Identificación de investigadores principales de los centros participantes

Nombre y cargo de todos los investigadores responsables de la realización del proyecto y la dirección y números de teléfono de los centros del estudio.

Dr. Ramon Estruch, Servicio de Medicina Interna, Hospital Clínic, IDIBAPS, Universidad de Barcelona, ext. 2233

Dr. Rosa Casas, Lab. Medicina Interna, CELLEX 4B, 4 planta (IDIBAPS), Hospital Clínic, Universidad de Barcelona, ext. 2907

2 Justificación

BACKGROUND

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose leading overtime to microvascular and macrovascular complications [1,2]. The main types of diabetes include type 1 diabetes (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM)., but monogenic diabetes syndromes (neonatal diabetes, maturity-onset diabetes of the young), diabetes due to diseases of the exocrine pancreas (cystic fibrosis, pancreatitis), and drug- or chemical-induced diabetes are less common types of diabetes [2].

According to the World Health Organization (WHO) [3], there are about 60 millions of diabetics in Europe, whom 10.3% are men and 9.6% are women aged ≥ 25 y, and its prevalence is increasing among all ages. Overweight and obesity, sedentary habits and unhealthy diets are behavioral risk factors directly associated with higher risk of appear [3,4]. The WHO has recently reported that 3.4 million people annually death because of high blood glucose levels in worldwide. Furthermore, it is expecting that this number will be doubled between 2005 and 2030 [3]. The International Diabetes Federation estimated that health expenditure for diabetes and related complications was US$ 105.5 billion in Europe in 2010 and is expected to reach US$ 124.6 billion in 2030 [3].

For T2DM patients, management is initially focused on lifestyle changes that include daily physical activity, weight management, healthy diets and use of oral hypoglycemic medications sometimes. The management of these risk factors leads to improve the health and prevent the appearance of possible complications associated with these diseases [5–8].

Nowadays, advances in digital health technology, especially mobile smartphone technology ("apps"), have been rapidly developed to improve the self-management skills of individuals in the management of diabetes and other chronic diseases [9–11]. Currently, there are more than 100,000 health-related applications are available in the Apple App Store (iOS operating system; Apple Inc.) and Google Play Store (Android operating system; Google) [12,13]. In 2017, there were more than 318,000 mobile health applications available to consumers worldwide [14].

Mobile phone apps are widely used in the T2DM management and account for 16% of the total number of disease-specific apps available to consumers [14]. In fact, more than 120 apps are available in iTunes and Google Play for diabetes management [15].

Nevertheless, apps for diabetes management have shown great promise toward improving mental and physical health. Nowadays, there is strong evidence for the efficacy of mobile phone apps for lifestyle modification in T2DM [12]. There is enough research, that using mobile app may have beneficial effects in the prevention and treatment diabetes, as it improves self-efficacy and self-care, increases knowledge of disease and enhances physician-patient communication. These challenges are achieved through delivering information, education, self-management, therapeutic advice, and drug guidance, which is provided by the app itself [16]. T2DM patients find in app an advisory service in which patient store its personal data such as glucose concentrations, glycated hemoglobin (HbA1c), blood pressure (BP), body weight, among others. In this way, prestored validated algorithms facility that participants can take treatment decisions more easily [17]. Theoretically, the use of these features could help patients adhere to diet, exercise, and medication management plans, which could lead to improved diabetes-related outcomes.

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3 Objetivo y Finalidad del Estudio

HYPOTHESIS

App-enabled, self-managed and prescribed preventive interventions effectively reduce T2DM and cardiovascular risk factors (including BP measurements, lipid profile, glucose metabolism parameters (glucose concentrations, HbA1c, HOMA index), body weight and adiposity parameters, as well as, anxiety, depression. In addition, it improves the effects on health-related quality of life (HRQoL) and increases adherence to preventative treatments as compared to a control group.

OBJECTIVES

To evaluate the perceived benefit and value of the Greenhabit method for people with T2DM, in terms of information provided about the lifestyle program journey, self-awareness and better management of glucose and lipid metabolism, body weight, adiposity parameters, stress relief and dealing with psychological issues, in a personalized manner.

3.1 Variables principal y secundarias

The main variable of the study are glucose metabolism parameters (glucose concentrations, HbA1c, HOMA index), lipid profile, BP, body weight and adiposity parameters. The other variables to study are quality of life, positivity, happiness, social environment, depression, anxiety, exercise, body weight, BMI, waist circumference and others.

4 Diseño del Estudio

MATERIAL AND METHODS

Study design

A randomized controlled trial of two parallel groups will be performed.

On the 1st day of the study, a clinician will perform a clinical and analytical assessment of the participants to select the candidates. Those who meet the inclusion criteria, and after a period of reflection, must sign informed consent. Volunteers will be randomly assigned to one of two intervention groups after age and gender stratification (an intervention or control group). Half of participants will follow a pharmacological treatment for T2DM (e.g. Metformin or Sulfonylureas) and/or prescription of diet or exercise, as agreed with the patient by establishing goals. The other half will be on a similar treatment regimen but will be provided the App (Greenhabit), for self-management of the prescribed preventive treatment that will be loaded in the app. They will be monitored to assess status and evolution.

Greenhabit App

The Greenhabit smartphone app has been developed an intelligent life journey to rule individual's health based on Artificial Intelligence in 12-week of learning. It is a gamified technology that awards healthy behaviors with challenges and rewards, which increase the participation.

Although this application is only available in the Google Play Store in Dutch, in the coming months will also be available in Spanish.

The App has been designed by the Greenhabit Company to help individuals to increase their frequency of healthy behaviors through goal setting, self-monitoring, and the completion of health-related tasks in five main categories: Healthy diet, Exercise, Positive thinking, Relaxing and Social environment.

The Greenhabit method is an education based on learning new sustainable habits, the brain needs at least 68 days for this. The holistic approach (physical, mental and social) provides resilience and self-awareness, encouraging healthy habits and social engagement. It

encourages people to take control of their health. The behavioral change is measured at the beginning and is repeated at later, after of 12 -weeks of the learning.

It is noteworthy, the possibility to work with a buddy and others motivates and increases community engagement and has a positive impact on health behaviors. It makes people aware about being meaningful and what they can contribute to a sustainable environment.

The App allows measuring the wellbeing of the individuals in 5 areas of Quality of Life (Healthy diet, Exercise, Positive thinking, Relaxing and Social environment) and allows acquiring large amount of data, totally anonymized, on the behavior and the motivation of people. These data (under the permission of participants) can be processes with artificial intelligence algorithms in order to construct predictive models to understand better the mechanism of behavior change. Thus, based on the behavior and needs of the players personalized content and challenges can be offered to different players.

Everything is presented in a simple visually illustrated way. The App's main registration categories are nutrition (i.e. servings a day of fruits, vegetables, nuts, seeds and water, as well as setting goals about avoiding sugared beverages, candy, junk food, or late snacks), physical activity (distance and/or time walking, running, bicycling, stair walking, strength exercises, and total step count), stress management (relaxation exercises, yoga, mindfulness, and subjective estimation of stress, energy level, and quality of sleep), and clinic (body weight, waist circumference, blood glucose [glucose and HbA1c levels], blood pressure, lipid profile, and medication). Users must manually enter their own readings and activities. After 12-educational weeks, the player should miss the support of the game and must maintain their acquired healthy habits.

The Greenhabit App has been designed specifically for people with diabetes, but it has not been tested in a clinical population with T2DM yet. This is a sustainable ECO system that could help the European population to rule their health and to prevent develop of chronic diseases and T2DM.

Greenhabit method

We attach the Greenhabit method as Appendix 1. Data recollected by this App:

Details for signing up for the greenhabit game:

- E-mail address
- Activation code
- IP Address

Details for playing the game:

- First and last name: participants must use an "Alias"

- Address and postcode, for sending a greenhabit package: participants must give our Laboratory address to receive a greenhabit box with a book, a bottle and some rewards they will win in the game.

This data are collected with this frequency:

Age	Once
weight, to determine BMI, waist circumference	Weekly
Data about lifestyle and preferences regarding the 5 elements: nutrition, exercise, relaxation, positivity and your social environment.	Every 4 weeks
Glucose HbA1c	Every 4 weeks Outside the game under responsibility of the medical team
The above mentioned data is shown in the measurement house (insights) in which the development of weight, energy, happiness, positivity, social and work-life balance is visible only for the player in the game.	

Data treatment

The patients do not deposit medical data in the App yet; this is because we have to get an CE certificate to guaranty the safety of medical data processing. So for now we suggest that Hospital Clinic will manage the health data separate to avoid this issue. The Patient gives consent on our Privacy Policy and the use of data (not medical). The player also will need to sign a separate data and research agreement with UB/greenhabit for the purpose of this research project.

Greenhabit has signed a data processing agreement with our partner Grendel Games who has access to the data.

Grendel Games has signed a Data processing agreement with hosting partner Linode LLC as they are essentially the sub-processor. The data is stored in European data centers of Linode LLC with the head office in Philadelphia USA.

Grendel Games regularly installs security updates on this server to keep it secure. The dashboard itself is based on the "Laravel" framework, which provides authorization and authentication mechanisms that conform to industry standards.

The information is not anonymized, but is of course sent encrypted (over an https connection). We cannot completely anonymize the information because progress, photos, etc. are linked to an account: the dashboard must therefore know to which account these data belong. We do not process medical data.

All data of the patients will be destroyed after finishing the RCT research project.

Within 2 weeks, it is expected to submit to the legal authorities (Netherlands and EU compliant) the technical file and the declaration of conformity (CE marking). We will receive a digital KEY to be able to upload the documents in the next days.

We will also submit the App to the Spanish Agency for Medicines and Health Products (AEMPS) for to be evaluated. We attach the document.

5 Selección de los participantes

Recruitment of participants to study

All who met the inclusion criteria were consecutively invited to participate when attending routine appointments. Eligible participants will be patients treated in the Outpatient Clinics of Internal Medicine and Endocrine Departments at the Hospital Clínic de Barcelona who meet the inclusion criteria and do not meet the exclusion criteria. An Inclusion / Exclusion questionnaire will be administered by a clinical from the research team. Only if she/he meets the inclusion and no exclusion criteria she/he will be invited to participate in the intervention study and will be asked to sign consent.

Intervention

A total of 120 participants divided into 2 treatment groups (60 individuals per group) will be assigned randomly. The randomization will be carried out by assigning them consecutively by means of sealed envelopes, which have been prepared following a table of random numbers generated by computer. Half men and half adult women who meet the inclusion criteria and none of the exclusion criteria will be included:

Interventional group: 60 participants will receive instructions and written material with information on seasonal Mediterranean foods, shopping lists, weekly meal plans, and cooking recipes for a typical week. Participants will have also accessed a smartphone application to access a lifestyle program (Greenhabit) through which they will receive personalized recommendations and education about healthy lifestyles for 3 months.

Control group: 60 participants will receive instructions and written material with information on seasonal Mediterranean (slow Carb) foods, shopping lists, weekly meal plans, and cooking recipes for a typical week. The follow-up will be for 3 months.

Participants, who have signed the informed consent and are randomized to the intervention group, will be the researcher who provides personalized access.

5.1 Criterios de inclusión de los sujetos

Inclusion and exclusion criteria

The inclusion criteria will be as follows:

1. Patients with recent diagnosis of diabetes* (< 2 years treatment) since those with more than 5 years are more reluctant to change habits.

2. Being able to write and speak the Spanish language.

3. Own a smartphone.

4. To be able to use the Greenhabit App; age 18-75 years.

5. Have not undergone or planned bariatric surgery during the trial period.

*HbA1c > 6.5 percent or fasting plasma glucose (FPG) > 126 mg/dL twice, or a 2-hour plasma glucose value after a 75-gram oral glucose tolerance test > 200 mg/dL.

5.2 Criterios de exclusión de los sujetos

The exclusion criteria will be as follows:

1. Subjects diagnosed with type 1 diabetes (insulin dependent), gestational diabetes, maturity-onset diabetes of the young and maternal inherited diabetes and deafness.

2. Subjects with any serious chronic disease, alcoholism or other drug addiction, or gastrointestinal diseases that prevent an adequate diet will be excluded.

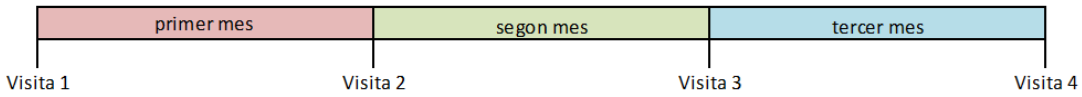
3. Those who take vitamins or nutritional supplements during the month prior to the study will also be excluded.

4. Being pregnant.

6 Tratamiento y calendario del estudio

DURATION OF TREATMENT AND STUDY TIME

The study period will be one year, including all the time between the drafting and adaptation of the protocol until the closing of the study with delivery of the final report. The treatment time will be three months.



Visit 1 and 4: Before beginning and End of Intervention

All the participants will have a face-to-face interview with the dietitian at baseline and after 3-months (end of study) in which they received instructions and written material with information on seasonal Mediterranean foods, shopping lists, weekly meal plans, and cooking recipes for a typical week. In these individual sessions, each participant will be provided with descriptions of seasonal foods, shopping lists, weekly meal plans and cooking recipes. In addition, individual interviews will include a 137-item validated food frequency questionnaire (FFQ) and personal individual recommendations for changes to be introduced in the participant's diet in order to achieve a personalized goal plus a 47-item questionnaire about education, lifestyle, history of illnesses and medication use. In both groups (intervention and control group), participants will be encouraged to increase the intake of vegetables (>=2 servings/d), fresh fruit (>=3 servings/d), legumes, nuts, fish or seafood (>=3 servings/wk), and to use olive oil for cooking and dressings. Energy restriction will not specifically be advised in any group, and physical activity will be promoted in both groups.

Finally, at baseline, 4, 8 and 12 weeks, trained personnel performed anthropometric measurements. Height and weight of volunteers will be measured using a wall-mounted stadiometer and calibrated scales, respectively. Waist circumference will be measured midway

between the lowest rib and the iliac crest using an anthropometric tape. BP will be measured in triplicate with a validated semiautomatic oscillometer (Omron, Hoofddorp, The Netherlands). The clinical history will be also collected. In addition, participants will be cited at 8 a.m to blood extraction. They should be come in fasting. Fasting blood and spot urine will be obtained for basic hematologic and biochemical analysis for all participants (HbA1c, glucose and lipid profile). Also, samples of fasting blood and spot urine are collected at baseline, at 6 weeks and 3 months were stored for futures studies. This will perform by a nurse who will be blinded to which group each participant belongs.

Only, participants allocated to intervention group will receive the Greenhabit smartphone App.

Different aspects of quality life (HRQoL) will be evaluated using previous validated tests at baseline, 6 weeks and 3 months (end of study):

ENERGY

Healthy diet: a 14-item dietary screening questionnaire will be used to assess adherence to the Mediterranean (Slow Carb) diet. This is a brief questionnaire assessing adherence to the Mediterranean diet, which was used in the PREDIMED trial for assessment and immediate feedback [19].

Physical activity: The International Physical Activity Questionnaire (IPAQ), the Spanish version, to measure physical activity programs [20]. This questionnaire has been used in various international studies and its validity and reliability have been evaluated, suggesting its use in different countries and languages. This instrument provides information on energy expenditure estimated in 24 hours, in the different areas of daily life; has the advantage of being applicable to large samples of different socioeconomic levels given its simplicity in both administration as in obtaining the scores.

SF-36: The Short Form-36 Health Survey (SF-36) is one of the most widely used and evaluated generic health-related quality of life (HRQL) questionnaires. It is a generic scale, applicable to both patients and the general population, which provides a profile of the state of health. It has been useful for evaluating health-related quality of life in the general population and in specific subgroups, comparing the burden of a wide range of diseases, detecting the health benefits produced by a wide range of different treatments, and assessing health status individual patients. The questionnaire covers 8 scales: Physical function, Physical role, Body pain, General health, Vitality, Social function, Emotional role, and Mental health. The Spanish version is a suitable instrument for use in medical research, as well as in clinical practice [21].

HAPINESS

H.A.D.S: The Hospital Anxiety and Depression Scale (H.A.D.S) is a validated rapid self-assessment screening tool. Although not used for diagnostic purposes, is very convenient for self-assessment of anxiety and depression in patients with somatic or mental problems, which is very much used today [22]. The scale sensitivity and specificity are comparable to other self-assessment screening tools. This test has been widely used in people with T2DM [23].

POSITIVITY

LOT-R: 'Life Orientation Test' (LOT) assesses the psychometric properties of an optimism test and that has been adapted to Spanish using the multidimensional graded response model

(MMRG). The substantive results suggest that the properties of the Spanish adaptation are similar to those of the original test. The methodological results show that the model has some advantages with respect to traditional analyses [24]. This 10-item scale evaluates an individual's expectations about life consequences; it has three positive and three negative items. This test has also been widely used in people with T2DM [25].

SOCIAL

DASI: The Duke-UNK functional social support questionnaire is a functional social support questionnaire whose objective was to measure "perceived functional social support". The quality of social support has been shown to be a better predictor of health and well-being than the number of friends or the frequency of visits, the so-called structural measures. Explore the qualitative or functional aspects of social support. It is a self-administered 8-11 item questionnaire [26,27].

WORK-LIFE BALANCE

Also, based on SF-36 [21].

These validated tests will be asked during volunteers' health journey (intervention group) or will be self-administered in the case of the control group.

Intervention monitoring protocol

Weekly phone calls

There will be an intervention follow-up protocol. All participants will receive a phone call every 15 days recalling the follow-up of the study and assessment of the occurrence of possible side effects.

7 Estadística

7.1 Tamaño de la muestra

The total number of participants to be included is 120. According to our experience, this involves conducting about 180 interviews. Power calculations based on an estimated intervention-induced intergroup difference of 0.8 in HbA1c% with a standard deviation of 2.75 showed that 104 subjects are necessary to recognize as statistically significant a difference greater than or equal to 0.05 units (alpha (α) risk = 0.05 and a beta (β) risk of 0.2 in a bilateral contrast). A follow-up loss rate of 10% is estimated.

> 0.5 percent reduction in HbA1c is considered clinically significant, as diabetes-related complications are directly proportional to HbA1c [18].

7.2 Análisis estadístico

The results will be included in a permanent and interactive database of data, which will be analyzed with the statistical package SPSS 20.0 for Windows. The main variable of the study from which the sample size was calculated is HbA1c% in people diagnosed with T2DM [28]. The other variables to study are quality of life, positivity, happiness, social environment,

depression, anxiety, exercise, body weight, BMI, waist circumference and others.

All analyses will be according to the intention-to-treat approach. For the descriptive analysis the mean and standard deviation of the variables will be used. Like most analyzes two or more measurements will be performed and for statistical analyzes the average of all determinations made will be used. Differences will be expressed as mean (95% confidence intervals).

Comparisons within the ratio-scale variables from baseline to three months within and between the groups will be calculated using the dependent and independent-samples Student's t-test, respectively, and an analysis of variance (ANOVA, repeated measures), adjusting for energy intake, sex, and age. For the variables on an ordinal or interval scale, the Mann–Whitney U-test will be used for the independent comparisons, and Friedman's ANOVA and Wilcoxon's sign rank test will be used for the dependent comparisons. A chi-squared test will use for the nominal variables. We controlled potential confounding by age, sex, and baseline body weight, entering these variables also into the multivariable model. Within- and between-group differences are expressed as means and 95% CIs. All statistical tests were 2-tailed, and the significance level was 0.05.

8 Ética y aspectos legales

El estudio se realizará en cumplimiento de la Declaración de Helsinki (Fortaleza, Brasil, octubre 2013).

El estudio será realizado de acuerdo con el protocolo y con los requisitos legales pertinentes, a la Ley 14/2007 de 3 de julio, de Investigación biomédica, si se trata de un proyecto de investigación que nada tiene que ver con medicamentos.

Se solicitará el consentimiento informado a los pacientes antes de su inclusión en el estudio.

9 Tratamiento de los Datos y Archivo de los Registros. Confidencialidad de los datos.

Los datos recopilados nos permitirán evaluar cómo las aplicaciones móviles pueden ayudar a modificar el estilo de vida de un individuo, haciéndolo más consciente de su enfermedad. Además, permitirá a la persona tener un mejor control de la presión arterial, los niveles de glucosa en sangre, los lípidos y el peso corporal. Además, nos permitirán saber de qué manera pueden ayudar a controlar mejor situaciones de estrés / ansiedad, tristeza y mejorar su relación con su entorno (trabajo, familia y amigos).

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustará al cumplimiento del Reglamento UE 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016 relativo a la protección de las personas físicas en cuanto al tratamiento de datos personales y la libre circulación de datos, y a la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. La base legal que justifica el tratamiento de sus datos es el consentimiento que da en este acto, conforme a lo establecido en el artículo 9 del Reglamento UE 2016/679.

Los datos recogidos para estos estudios se recogerán identificados únicamente mediante un código, por lo que no se incluirá ningún tipo de información que permita identificar a los participantes. Sólo el médico del estudio y sus colaboradores con derecho de acceso a los datos fuente (historia clínica), podrán relacionar los datos recogidos en el estudio con la historia clínica del paciente.

La identidad de los participantes no estará al alcance de ninguna otra persona a excepción de una urgencia médica o requerimiento legal.

Podrán tener acceso a la información personal identificada, las autoridades sanitarias, el Comité de Ética de Investigación y personal autorizado por el promotor del estudio, cuando sea necesario para comprobar datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de acuerdo a la legislación vigente.

Sólo se cederán a terceros y a otros países los datos codificados, que en ningún caso contendrán información que pueda identificar al participante directamente (como nombre y apellidos, iniciales, dirección, número de la seguridad social, etc.). En el supuesto de que se produjera esta cesión, sería para la misma finalidad del estudio descrito y garantizando la confidencialidad.

Si se realizara una transferencia de datos codificados fuera de la UE, ya sea en entidades relacionadas con el centro hospitalario donde participa el paciente, a prestadores de servicios o a investigadores que colaboren con nosotros, los datos de los participantes quedarán protegidos por salvaguardas como contratos u otros mecanismos establecidos por las autoridades de protección de datos.

Como promotores del proyecto nos comprometemos a realizar el tratamiento de los datos de acuerdo al Reglamento UE 2016/679 y, por tanto, a mantener un registro de las actividades de tratamiento que llevemos a cabo y a realizar una valoración de riesgos de los tratamientos que realizamos, para saber qué medidas tendremos que aplicar y cómo hacerlo.

Además de los derechos que ya contemplaba la legislación anterior (acceso, modificación, oposición y cancelación de datos, supresión en el nuevo Reglamento) ahora los participantes también pueden limitar el tratamiento de datos recogidos para el proyecto que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad). Para ejercitar estos derechos deberán dirigirse al investigador principal del estudio o al Delegado de Protección de Datos del Hospital Clínic de Barcelona a través de protecciodades@clinic.cat.Así mismo tienen derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

Los datos no se pueden eliminar aunque un paciente abandone el estudio, para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos.

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 20 años tras su finalización. Posteriormente, la información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si el paciente hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

10 Gestión de muestras biológicas

The intervention study will be carried out at the Internal Medicine Department, Hospital Clínic, within the August Pi Sunyer Institute for Biomedical Research (IDIBAPS) in Barcelona. The analytical determinations will be carried out in the Laboratory of Internal Medicine of the Clinic Foundation, School of Medicine, and University of Barcelona.

The type of sample that will be collected is blood and urine for future determinations if there is funding. The idea is to study other interesting parameters such as inflammation or oxidative stress.

Finally, once the study is finished, the samples will be destroyed. The samples will be kept stored in the CELLEX Laboratory of Internal Medicine until they are used for the purposes of this study. Upon completion, the remaining samples will be destroyed. Its management will be carried out by Ana Mª Ruiz (laboratory technician).

11 Financiación

We attach the only document that we have regarding the financing.

12 Política de Publicación

The promoter agrees to make the results of the study public, whether they are positive or negative.