**Study Protocol**

**TITLE OF THE STUDY**

**Improving blood sugar control through patients’ choice of evidence-based spices and foods with hypoglycaemic effect – A series of randomized controlled trials.**

**ABSTRACT**

**Introduction:**

Type 2 diabetes patients often do not reach desired control of glycaemia despite guidance on changing lifestyle and diet as well as the use of conventional anti-diabetic medication. In recent years, an array of comparative clinical studies has demonstrated the anti-diabetic effect of 10 common spices and food products. However, these studies have gone largely unnoticed. Therefore, we propose an approach that could be appealing and appropriate for diabetic patients with poorly controlled diabetes: they would be encouraged to eat what they like within a list of food products with hypoglycaemic effects.

**Method:** This project will be conducted as a series of randomized controlled trials with 2 groups: 1. training patients about hypoglycaemic spices and foods alongside their usual anti-diabetic treatment *versus* usual anti-diabetic treatment alone. To better appreciate of the impact of such an approach in various cultures, a series of similar studies will be conducted in a range of countries, including at least Ethiopia, Iraq Serbia, Thailand, the UK, etc…. The primary outcome will be glycaemia change, measured with FPG and - if available- HbA1c over 3 months.

**Expected results:** Confirmation of the hypothesis thatproposing a choice of spices and foods with hypoglycaemic effect to diabetic patients is feasible and can help better control diabetes.

**Keywords**: diabetic, glycaemia, natural products, food, nutrition, HbA1c, Fasting Blood Glucose

**BACKGROUND**

The present introduction is from one of our articles entitled “Effectiveness of medicinal plants for glycaemic control in type 2 Diabetes: An overview of meta-analyses of clinical trials” (Willcox et al., 2021).

**DEFINITION OF DIABETES**

Diabetes is defined by NICE as a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia) (1). There are two types of diabetes:

1. a. Type 1 Diabetes – is defined as the pancreas’s inability to produce insulin, which is caused by an autoimmune response that results in the destruction of insulin-producing beta cells in the pancreas.
2. b. Type 2 Diabetes – characterised by insulin resistance whereby the pancreas is unable to produce enough insulin to regulate blood glucose levels, or pancreas beta cells become unresponsive to insulin.

**HEALTH AND ECONOMIC IMPACT OF DIABETES**

Globally, it is estimated that 415 million people are affected by diabetes (2). In the UK, 4.7 million people are living with diabetes, which is expected to rise to 5.5 million by 2030 (3). Over 90% of patients with diagnosed diabetes have Type 2, and three out of five cases can be prevented (2). Interestingly, this is also reflected in the financial and economic costs of diabetes. The NHS estimates that each year approximately £10 billion are spent on the direct costs of diabetes and a further £13.9 billion on indirect costs (4).

The growing burden of diabetes can mainly be attributed to its complications. Patients often struggle to manage their glucose levels effectively, and consequently remain in hyperglycaemic states. This can be extremely harmful to the patient and lead to several microvascular complications such as retinopathy, neuropathy, and nephropathy, whilst significantly increasing the risk of macrovascular complications e.g., ischaemic heart, peripheral vascular and cerebrovascular disease (5, 6). Studies have shown that adults with diabetes have a two-to-three-fold increased risk of heart attacks and strokes (7). Diabetes is also the leading cause of blindness in adults of working age (14%), chronic kidney disease and has a significant impact on patients’ quality of life (8, 9).

**DIABETES OVERVIEW**

Because diabetes is a progressive disease, it can be quite difficult to identify and diagnose as symptoms develop slowly. The hallmark symptoms of T2DM include polydipsia, polyuria, and polyphagia (2).

Many factors that can increase the risk of diabetes. Obesity is a major contributing factor to the development of diabetes, and recent research has suggested that obese people are up to 80 times more likely to develop type 2 diabetes than those with a BMI less than 22 (healthy weight) (10, 11). Narayan et al., supported this finding and reported that lifetime diabetes risk at 18 years of age increased from 7.6% to 70.3% between underweight and very obese men and from 12.2% to 74.4% for women (12). This highlights the strength of association between increased BMI and increased prevalence of diabetes.

Researchers have also identified a clear association between physical inactivity and diabetes (13, 14). A strong association has also been shown between inactivity and diabetes-related comorbidities e.g., cardiomyopathy, accentuating the major impact lifestyle factors have on the progression of diabetes (14).

Hypertension has been shown to have a strong relationship with the prognosis of diabetes (15). Hypertension is defined as 140/90 mmHg, and reports show that over 50% of people with diabetes are affected by hypertension (16). Raised systolic blood pressure of 20mmHg increases the risk of diabetes by 58%, and a higher diastolic BP of 10mmHg was associated with a 52% higher risk of diabetes (15, 17). However, lifestyle intervention such as reduced salt intake, increased intake of fruit and vegetables, increased exercise and smoking cessation has been shown to promote aspects of metabolic and vascular health that can help control blood pressure. Subsequently, this reduces the risk of complications and leads to the prevention or delay of a diagnosis of T2DM (18).

Factors such as family history have been shown to increase the risk of developing T2DM. Scott et al., conducted a study on 13,869 individuals that illustrated a family history correlated with a high incidence of T2DM (19). Research has shown that if both parents have the condition, the risk of developing T2DM is 75% and 90% if an identical twin has the disease (20). There is also a higher prevalence of diabetes amongst people of South

Asian descent (6 times more common) and African/African-Caribbean origin (three times more common) (21, 22).

**DIAGNOSIS OF TYPE 2 DIABETES**

Initial diagnosis of type 2 diabetes is characterised by persistent hyperglycaemia (1).

**FASTING PLASMA GLUCOSE (FPG)**

Fasting plasma glucose is a diagnostic test used to measure plasma glucose levels after fasting for at least 8 hours. FPG is typically used to determine if there are any issues with insulin functioning and as an additional test for diagnosis of diabetes (23). The test is typically conducted in the morning, and diagnosis is defined as (23):

|  |  |
| --- | --- |
| FPG | Diagnosis |
| ≥ 7.0 mmol/L (≥ 126 mg/dL) | Type 2 Diabetes |
| >5.6 – 6.9 mmol/L (> 100-125 mg/dL) | Impaired glucose regulation (Prediabetes) |
| 3.9 – 5.6 mmol/L (> 70-100 mg/dL) | Normal |

It is important to note that FPG only provides information on glucose levels at the point that the measurement was made. Naturally, plasma glucose fluctuates throughout the day and can be affected by a variety of factors (24):

1. a. Stress has been shown to increase endogenous glucose production
2. b. Exercise can decrease glucose levels
   * + 1. c. Patients may not truly abstain from food, and so the measurement is not taken in the fasting stage

As a result, FPG has a much higher biological variability as a diagnostic test in comparison to HbA1c and so there is greater scope for false results (24). When using FPG for diagnosis, FPG must be taken on two separate occasions. If the results produced are similar, a diagnosis is made (23, 25).

Nonetheless, FPG is extremely useful as a diagnostic test as it is inexpensive and globally available (24). Studies have shown that FPG and HbA1c are well correlated, and FPG can be used as a reasonable alternative to HbA1c (24, 26). Low-income areas can benefit from

using FPG, particularly where there is no access to a lab or assays to conduct HbA1c tests (26). Also, FPG does not require a healthcare professional to conduct the test and kits are

available for patients to perform the tests themselves. This is highly beneficial for areas with limited healthcare access.

**HbA1c**

HbA1c is an abbreviation referring to glycated haemoglobin. Glycated haemoglobin is created in a 2-step process that begins with the condensation of glucose with the N–terminal amino group of haemoglobin (27, 28). Glucose and haemoglobin combine non-enzymatically within the haemoglobin molecule (28). After a prolonged period of hyperglycaemia, the bonds between haemoglobin and glucose stabilise and form a covalent bond that is permanently attached to the haemoglobin molecule (29). Subsequently, the proportion of glycated haemoglobin increases with persistent hyperglycaemia. As the life span of erythrocytes is 120 days, glycated haemoglobin provides a measure of glycaemic control over the previous 2 – 3 months (29).

Due to the nature of how HbA1c is formed, it is not affected by the day-to-day variability of glucose levels (24). HbA1c is now used as a reliable and effective marker for diagnosis, prognosis, and monitoring treatment of diabetes (30, 31). HbA1c can also be used as a predictor of diabetic complications (30). UKPDS reported that a 1% reduction in HbA1c was associated with a 21% reduced risk of deaths related to diabetes, 14% reduced risk of myocardial infarction and 37% reduced risk of microvascular complications (6). This displays the strong correlation between diabetic complications and reduced HbA1c and the importance of ensuring patients can manage their blood glucose levels effectively.

To measure HbA1c, blood is taken from the arm or finger of the patient. This is conducted by a healthcare professional approximately every 3 – 6 months in diabetic patients with unstable blood glucose and annually in patients with stable glucose levels.

Diagnosis of diabetes using HbA1c is defined as:

|  |  |
| --- | --- |
| HbA1c (%) | Diagnosis |
| ≥ 6.5 | Type 2 Diabetes |
| 6.0 –6.4 | Impaired glucose regulation (Prediabetes) |
| ≤ 6.0 | Normal |

**TREATMENT OF TYPE 2 DIABETES**

According to NICE guidelines, initial treatment of diabetes involves lifestyle modifications, including changes to the diet and increased of physical activity (32).

First-line treatment for T2DM consists of making substantial lifestyle modifications. Individualised dietary advice is recommended alongside a personalised management plan that aims to reduce and maintain HbA1c to below 6.5% (33).

Pharmacotherapy is initiated if patients fail to maintain HbA1c levels below this threshold. First-line pharmacological intervention recommends standard release metformin for T2DM. The dose of metformin is gradually increased over several weeks, dependent on the patient’s tolerance, polypharmacy, personal preferences, comorbidities, and to minimise the risk of gastrointestinal side effects (32). NICE has set a general target that patients managed by lifestyle and diet combined with metformin monotherapy should aim to achieve an HbA1c of 6.5% (32). If patients are unable to maintain HbA1c of under 7.0%, drug treatment with Metformin is initiated (32). If this is not sufficiently effective, treatment is enhanced with the addition of a sulfonylurea (e.g., Glibenclamide), DPP-4 inhibitor (e.g., Sitagliptin) or thiazolidinedione (e.g., Pioglitazone) (32). If dual and triple therapy prove ineffective, insulin-based therapy is initiated, and insulin injections are used to maintain stable blood glucose levels.

**NON-ADHERENCE AND COMPLIANCE**

Non-adherence has been a growing concern and global financial burden for several years. A study conducted by Polonsky et al., showed that at least 45% of patients with T2DM fail to achieve adequate glycaemic control (34). This finding is supported by a recent retrospective study that found amongst metformin users, less than 50% of patients were adherent and a third of patients initiating metformin discontinued within 12 months (35). Patients often reported a dislike of using tablets, disbelief that they have been diagnosed with diabetes and dissatisfaction with metformin treatment due to the gastrointestinal (GI) side effects associated contributed to non-adherence (36, 37). One in ten patients using metformin experience gastrointestinal side effects including flatulence, diarrhoea, nausea, abdominal pain, and bloating (38). As a result, many patients fail to adhere to treatment recommendations.

Polypharmacy has been identified as a major barrier contributing to medication adherence. Patients with T2DM often have comorbidities leading to more medications

being prescribed to treat their concurrent illnesses (39). This can lead to complex medication regimes and subsequently result in non-adherence. Pasina et al., examined the

effects of polypharmacy and found that 55.1% of patients receiving polypharmacy reported non-adherence, and only 28% of patients understood the basis for their medications (40). Similarly, Claxton et al., conducted a review illustrating a significant inverse relationship between the prescribed number of doses and medication adherence (41). This clearly shows the importance of developing new, simple regimes to improve glycaemic control.

**PREVALENCE OF CAM THERAPY**

Experts have acknowledged the need to help patients achieve targets via lifestyle modification and improvement of first-line treatment.

The average one-year prevalence of use of complementary alternative medicine in the population (CAM) was 41.1% (42). It has also been estimated that the annual UK expenditure on CAM is up to £1.6 billion per year, illustrating the popularity and frequent use of CAM (43). This is a phenomenon that has been recognised over the globe and notably examined in a US study that showed among patients with diabetes 57% reported use of one or more CAM therapies, and a further 35% reported using CAM specifically as a treatment for their diabetes (44).

Alqathama et al., conducted a cross-sectional survey examining the effects of herbal medicines in Saudi Arabia, which has the seventh-highest rate of diabetes globally (45). The authors reported that 68% of patients with T2DM used herbal remedies frequently; however, 71.4% did not inform practitioners that they were consuming herbs. A further 54% strongly believed that the herbal medicine was effective as a treatment for T2DM. A similar study investigating the use of herbal medicines in the Pakistani community was conducted in Bradford, England (46). The study found that 66% of participants preferred using herbal medicine compared to conventional medicine which not only illustrates the increasing popularity of herbal medicines but highlights the limited knowledge on the effectiveness of herbal medicines, their benefits, potential adverse events, and pharmacological reactions.

Parallelly, there is an array of clinical studies, largely unnoticed, that have shown the anti-diabetic efficiency of common spices and food products (see Annex 1: Booklet for Health

Professionals). The available spices and food products that have been proven by at least one robust randomized controlled trial to be anti-diabetic are **Aloe vera, Astragalus, Bitter melon, Black cumin, Cinnamon, Fenugreek, Ginger, Nettle, Psyllium fiber.**

**RATIONALE OF THE STUDY**

Persons suffering from chronic illnesses, including DM worldwide, are known to resort to remedies based on folklore. Herbal treatment, cellular nutrition, and faith therapy are among the therapies used by those with diabetes to manage their ailment.

In line with this, many patients with diabetes prefer to use traditional medicine, but the effectiveness of providing information on the rational use of plant foods with known hypoglycaemic properties is largely unknown.

Diabetic patients often do not reach desired blood glucose control despite advice on lifestyle changes and standard medication. In parallel, in recent years, an array of clinical studies has shown the anti-diabetic effect of common spices and food products. These studies have gone largely unnoticed. Thus, the research question is: Can diabetes control by improved by advising patients to use what they like within a list of validated food products with hypoglycaemic effects?

**OBJECTIVES**

To evaluate the impact on glycaemic control of advice on the use of clinically validated spices and food products against diabetes, in terms of preparation and dosage.

**Hypothesis:** This approach might be associated with a fair adherence to the intervention (thanks to its “user-friendly” aspect) and an improvement in diabetes control.

**METHOD**

**Trial design**

The project will be run as a series of randomized controlled trials (RCT), which will evaluate the effectiveness of the intervention in real-life routine practice conditions. RCTs are designed with 2 arms: “usual care + choice of hypoglycaemic food/spices” *versus*

“usual care”. Usual care means: advice on lifestyle and standard medication if applicable. The ratio between the intervention group and the control group will be 1:1.

In Iraq, the study is designed as a 3-arms RCT, with the 3rd arm being “usual care + olive leaf decoction” (see Iraqi protocol for more details).

After a run-in period of 2 weeks, the trial will be led over 12 weeks (enough time to be able to see a change in terms of HbA1c and if not possible, fasting blood glucose FBG only).

**Program sites**

Ethiopia, Thailand, Serbia, Iraq, the UK, etc.

**Eligibility criteria**

**Inclusion Criteria**: Type 2 diabetes patients with poorly controlled glycaemia, i.e., at least one of the following measurements:

(1) Fasting plasma glucose (FPG) values ≥ 7.0 mmol/L (126 mg/dl), or 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl), or HbA1c > 6.5% (48 mmol/mol); or a random blood glucose ≥ 11.1 mmol/L (200 mg/ dl) (WHO, 2019), despite ≥ 3 months usual care (lifestyle + medication if applicable).

(2) If under medication, the treatment and dosage have not changed for at least the last 3 months and are not planned to change for the next 3 months. If Patients are under insulin, it should be long-acting only and stable for ≥ 3 months. If Patients are under analogue GLP-1, it should be stable for ≥ one year.

**Exclusion criteria:**

1. Severe and unstable complications of diabetes: end-organ damage such as nephropathy, retinopathy, neuropathy, etc.
2. Patients with Rapid Insulin,
3. Any health condition that requires urgent attention,
4. Patients with a cognitive or sensory impairment that may prevent conducting the interview,
5. HbA1c more than 11.5% should not be included,
6. Pregnant women (excluded as a rule because gestational diabetes is different pathology).

**Intervention:**

Abooklet (see Annex 2) with thelist ofcommon food products or common spices, clinically validated against diabetes, with instructions for use, will be presented to the diabetic patient. The selected plants have been assessed as anti-diabetic for humans through at least one fair randomized comparative clinical trial, with a follow-up of several weeks or months. There will be a version of the booklet for health professionals with scientific references (see Annex 1) as well. Booklets will be adapted to the country’s available products and recipes.

A lesson learned with the approach of the Patient & Public Involvement (PPI) led in Oxford is that usual diet advice will have to be provided to all (control and intervention) patients. Thus, Unwin’s table of equivalent teaspoon of sugar as a unit of Glycaemic load is included in both booklets as it is very user friendly. The booklet for patients after having been drafted by the investigators will be then again updated with local patient’s feed-back during a small pilot.

While continuing to take his/her standard medication if any, the patient will be encouraged to follow his/her preferences within the established list of foods and spices: she/he is expected to choose 2 plants from the list and to consume each of them every day during the whole duration of the trial.

For each plant, several recipes are proposed. Recipes are designed so that the product is in the same form as in the reference clinical trial (e.g., a juice with limited heating), to minimize degradation of the active principles.

Patients will also receive information on doses, indicated in the weight unit and their equivalent amount in teaspoons. The use of a teaspoon for measuring doses is acceptable because doses do not need to be extremely accurate – as is the plants are food products with very wide therapeutic margin. It is, however, recommended always to use the same sized teaspoon. All of this is also presented in booklets.

A run-in period will start 2 weeks before (W-2). During this run-in period, patients of the intervention group will be advised to test several plants amongst the ones proposed through shown recipes, maximum of 3 times per week and just for one meal. At the end of the run-in period, patients should have chosen 2 plants that they wish to take every day during the 3 months intervention. To minimize the bias of attention, the control group will be seen and explained the study. The follow-up visits will be performed at 2 and 12 weeks

after the start day of the study. Other intermediate consultations can be done if desired but are not mandatory for the study. At the 1st follow-up visit (after 2 weeks), if fasting BGC did not decrease more than 0,1mmol/L, the patient will be advised to increase the dose of the plants if recommended (see the list below or each monograph in the booklet). If it is not possible to increase the daily dose, the patient will be advised to add a 3rd plant. For both intervention and control groups, FBG will be measured at W-2, W0, W2 and W12, while HbA1c will be measured at W0 and W12.

**Plants for which the dose can be increased, i.e., for which a dose-response effect has been observed or seems to be present when comparing different clinical trials using different dosages:**

**Aloe vera, Astragalus, Fenugreek, Ginger, Psyllium**

Each patient's baseline data will be recorded at inclusion, including what they are taking regularly as traditional medicines for their diabetes. If the patient is already taking one of the plants listed but with a lower dosage, (s)he will be advised to increase the dose up to the recommended dose in the booklet, plus to add 1 more plant. If a patient is already taking one of the listed food products and at a similar dosage as the one recommended in the booklet, s/he will be advised to add from the list 2 other plants in addition to the one s/he is already taking.

At the enrolment visit, patients will also be informed about the signs of hypoglycaemia and hyperglycaemia, and it will be checked that they know how to recognize them and how to act in such cases.

The approach of proposing scientifically validated (as hypo-glycaemic) food products, following patient preferences, is a first, to our knowledge. In case of success, this approach would provide a patient-friendly tool that might increase the effectiveness of overall diabetes control efforts (i.e., usual lifestyle advice and medicines). This approach might also be culturally appropriate and more affordable than standard medication.

**Precautions**

- If a patient has a moderate or severe adverse reaction that is possibly attributed to the used plants, (s)he should be withdrawn from the study and referred to adequate

health facility. If the adverse effect is mild, the patient may be advised to continue with this plant and see if it is transient.

- If any deterioration of the patient's state occurs, linked or not to the intervention, the patient should be referred to the appropriate health service and if needed, withdrawn from the study.

If an increase of the standard medication is required during the intervention, the patient will be thus withdrawn from the study but included in the data analysis as he/she doesn’t meet the inclusion criteria anymore.

**Field work organization**

\* For patients in the “intervention” group: The first encounter will be a health awareness lecture (or video) on the management of hyperglycaemia and the potential benefits of using a selection of validated natural products to lower blood glucose. Following this lecture, participants will receive the patient’s booklet with explanations on how to use the plant and in which daily amount: they are expected to choose 2 plants from the list and to consume them every day during the whole duration of the trial, in addition to their standard treatment if applicable. The patients will prepare the chosen plants according to the proposed recipes and at the daily dose recommended in the booklet. In parallel, they will receive lifestyle and dietary recommendations to be followed during the duration of the study, as well as signs on how to recognize hypoglycaemia / hyperglycaemia and how to handle it.

\* The control group will have a health awareness lecture (or video) on managing hyperglycaemia, and lifestyle and dietary recommendations in-depth to spend equivalent time with the patient to avoid the attention bias in this group. Participants of both groups will continue to take their standard medication and/or traditional medicine, if applicable, during the whole duration of the trial.

**OUTCOMES**

Glycaemia change (measured with FPG and - if available- HbA1c) over 3 months

**Primary outcomes:**

- Percentage of patients in each group reaching a decrease of ≥ 0.5mmol/L in FPG  
- Percentage of patients reaching a decrease of ≥ 0.5 points of percentage from the baseline value in HbA1c; each of these reductions being deemed as clinically significant.

**Secondary outcomes:**

* Mean reduction of FPG and mean reduction of HbA1c e.g., differences between baseline values and values at 3 months.
* Proportion of patient in each group reaching target glycaemia (<7mmol/L for FPG and <7% & ≤6.5% for HbA1c).
* Mean change of weight and mean change of blood pressure e.g., differences between baseline values and values at 3 months.
* Proportion of patients who wish to continue to take the plant after the intervention.
* Assessment of adverse effects.

**Sample size**:

The sample size is calculated based on detecting a statistically significant difference between two proportions with a level of confidence of 95% and a power of 80%. The calculator used is Epitools Epidemiological Calculators, which is based on **STATA** Software (Sergeant, 2018). Thus, 51 patients in each group would allow for detection of a difference of ≥25 points of percentage in the proportion of those with improvement considered clinically significant, e.g., 10% clinically significant improvement in the control group versus 35% in the intervention group. With subsequent corrections to consider potential attrition (20%), the total required sample at inclusion is 124 (62 in each group). In Iraq, the total required sample at inclusion is 222 (74 in each group).

**Randomisation**

A randomisation list will be made by computer-generated sequencing.

As the trial cannot be blinded and to minimize a spill-over effect, patients allocated to the intervention group will have their medical visits at different times or locations than those one in the control group.

**Data collection, Measurements**

Baseline data (FPG, HbA1c (if available), weight and height, BP, patient demographic characteristics and history, medication) for each participant will be taken at the beginning of the study, followed by FPG + a brief questionnaire on clinical progress and adherence.

**Statistical method**

The statistical analyses will be performed on an intention-to-treat basis with Epi Info7 and STATA. Chi-square and Fisher exact tests will be used to compare proportions of participants with clinically significant effects and proportions of participants reaching target value. Mean reductions of continuous variable will be compared with unpaired *t*-test. All statistical tests will be done with a significance level of 0.05. Results of different RCT will be analysed as a meta-analysis.

**Expected results:**

To observe a significant difference in glycaemia reduction in the intervention group compared to the control group.

**Ethical clearance**

The participation in the trial is voluntary and the participants are free to withdraw from the study at any time and without any penalty. Participants will receive an adequate and understandable explanation about the study’s intent, the possible results, their meaning. if they agree to participate, they will then be asked to sign (or fingerprint if appropriate) the informed consent form. All data will be kept confidential. Ethical clearance letters will be obtained from respective regional ethical committees. The protocol is designed to ensure the reliability of data, as well as the patient’s safety at any stage of the comparative study according to the Good Clinical Practices (GCP). The study will be performed in accordance with the Declaration of Helsinki.

**Organization and funding:** Could beorganized as part of a Master or PhD student’s work. Partnership with Antenna Foundation, Geneva.

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**ANNEXES**

Annexe 1: Booklet for health professional: A draft literature review on evidence-based food and herbal products with references.

Annexe 2: Booklet for patients: A description of the therapeutic concept of patient’s choice of evidence-based natural products with hypoglycaemic effect, recipes, and complementary diet advice.