



FACULTY OF MEDICINE

Efficacy of including an insulin bolus
calculator to reduce the number of severe
hypoglycaemia episodes in patients with type
1 diabetes mellitus treated with multi-daily
insulin injections

A randomized, controlled, open-label clinical trial

END OF TERM PROJECT

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My diabetes is such a central part of my life... it did teach me discipline... it also taught me about moderation... I've trained myself to be super-vigilant... because I feel better when I am in control.

Sonia Sotomayor

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1. ABSTRACT

Background: Severe hypoglycaemia (SH) is a major complication in patients of diabetes mellitus treated with insulin analogues and insulin secretagogues. SH events leads patients to uncomfortable situations, low quality of life rates and the continue feeling of fear of been hurt or injured during SH events. Patients with type 1 diabetes mellitus (autoimmunity destroys pancreas beta-cells completely and there are lack of endogenous insulin) are the more affected by it because normally it have to be treated with intensive multi-daily injections of insulin. New devices have been developing during last years, they are called insulin bolus calculators (IBC) and they have demonstrated to be useful increasing the metabolic control of diabetes patients and quality of life of them. Those devices have already been matched with continuous glucose infusion pumps but only a few built-it glucometers are available nowadays.

Objective: evaluate if insulin bolus calculators included in glucometers can reduce the incidence and number of severe hypoglycaemia in patients with type 1 diabetes in front of patients with type 1 diabetes treated with classic therapy with carbohydrates counting method and multi-daily insulin injections.

Design: The study will be a multicentre, centralized randomization, controlled open-label clinical trial. The patients will be randomly divided in three groups.

Intervention: Insulin bolus calculator (Accu-Chek Aviva Expert), smartphone APP(Social diabetes) and carbohydrates counting method and multi-daily injection, one intervention per group and all during a period of 1 year.

Subjects of the study: men and women (≥ 18 - ≤ 50 years old) who had been diagnosed of T1DM at least 1 year before the beginning of this study with recurrent hypoglycaemia events and a punctuation greater than 28 at FH-15 test.

Keywords: hypoglycaemia; programmable implantable Insulin Pump; insulin infusion system; blood glucose self-monitoring; type 1 diabetes mellitus; Life quality; telemedicine; cell phones.

2. ABBREVIATIONS

- **AF:** Application form
- **APP:** Application
- **CC:** Carbohydrate counting
- **CGM:** Continuous glucose monitoring
- **CHO:** Carbohydrates
- **CSII:** Continuous subcutaneous insulin infusion
- **DQOL:** Diabetes quality of life
- **FH-15:** Fear of hypoglycaemia scale
- **FoH:** Fear of hypoglycaemia
- **HUDJT:** Hospital Universitari Doctor Josep Trueta
- **GH:** Growth hormone
- **GS:** Glucose sensor
- **ICS:** Institut Català de la Salut
- **IBC:** Insulin bolus calculator
- **IG:** interstitial glucose
- **SC:** subcutaneous
- **SGM:** self-glucose monitoring
- **SH:** Severe hypoglycaemia
- **T1DM:** Type 1 diabetes mellitus
- **T2DM:** Type 2 diabetes mellitus

3. INTRODUCTION

3.1 Diabetes Mellitus as a chronic disease: classification and epidemiology

Diabetes mellitus (DM) is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycaemic control. It is very important to give to patients self-management education to prevent acute complications and reduce long-term conditions.(1)

In Spain, the total prevalence of DM adjusted for age and sex was 13,8% (2)

Diabetes can be classified into four clinical categories:

-Type 1 diabetes (T1DM) (due to b-cell destruction, usually leading to absolute insulin deficiency)

-Type 2 diabetes (T2DM) (due to progressive insulin secretory defect on the background of insulin resistance)

Other specific types of diabetes due to other causes, e.g., genetic defects in b-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/ AIDS or after organ transplantation)

- Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes)

Although, some patients cannot be clearly classified.(1)

Symptoms of marked hyperglycaemia include: polyuria, polydipsia, weight loss, sometimes with polyphagia and blurred vision. When it is chronic, impairment of growth and susceptibility to certain infections can appear.(3)

3.2 Type 1 diabetes mellitus (T1DM)

It is defined as immune-mediated diabetes. A cellular-mediated destruction of the B-cells of the pancreas produce decreased levels of insulin and start of status of hyperglycaemia.

There are several antibodies (islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2B) which are markers of the immune destruction. Usually, one or more of these antibodies are present in 85-90% of individuals when fasting hyperglycaemia is initially detected (3).

T1DM constitutes about 10 - 15 % of total diabetes rates and its incidence has been increasing worldwide at an alarming rate of 3-5 % per year(4)

3.2.1 Complications

○ Complications of the disease

T1DM is associated with poor glycaemic control an increased risk of microvascular and macrovascular comorbidities (sight-threatening retinopathy, renal failure and coronary disease), as neurological complications(4–6).

Intensive versus conventional glycaemic control results in a reduction of microvascular but also macrovascular complications(4,5), so intensive treatment is getting more important during last times.

○ Complication of T1DM treatment: Hypoglycaemia

The most common complication of surviving T1DM was hypoglycaemia [5] and it is the major side effect of glucose-lowering therapies (6).

The American Diabetes Association (ADA) defines it as "any abnormally low plasma glucose concentration that exposes the subject to potential harm", and proposes a threshold of $<70\text{mg/dl}$ ($<4\text{mm/L}$) (1,7). Another accepted definition of Canadian Diabetes Association is the development of autonomic or neuroglycopenic symptoms, a low plasma glucose level ($<4.0\text{ mmol/L}$ for patients treated with insulin or an insulin secretagogue) and symptoms responding to the administration of carbohydrate. The severity of hypoglycaemia is defined by clinical manifestations (8) .

The Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) as other amount of studies demonstrated that intensive treatment associates with a considerably increased rate of hypoglycaemia(4,5). It is frequent in people treated with insulin and is more common in T1DM than T2DM(6). The prevalence of hypoglycaemia is about 7,1% in T1DM patients(7).

It can be classified as being biochemical, symptomatic or both, based on the presence or absence of symptoms and corroborative glucose monitoring results. Symptoms can be divided into autonomic or neuroglycopenic (Table1)

Symptoms of hypoglycaemia

| Neurogenic (autonomic) | Neuroglycopenic |
|------------------------|--------------------------|
| Trembling | Difficulty concentrating |
| Palpitations | Confusion |
| Sweating | Headache |
| Anxiety | Dizziness |
| Hunger | Weakness |
| Nausea | Drowsiness |
| Tingling | Vision changes |
| | Difficulty speaking |

Table 1: Hypoglycaemia symptoms. Adapted from (1,7,8)

More important is the classification about the severity of the event, adjudged by the need for external help or assistance (1,7,8)(Table 2)

Severity of hypoglycaemia

Mild: Autonomic symptoms are presents. The individual is able to self-treat.

Moderate: Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.

Severe: Individual requires assistance of another person. Unconsciousness may occur. Plasma glucose is typically very low(<2.8 mmol/L)

Table 2: Classification of hypoglycaemia according to their symptoms (8)

With incidences of approximately 2 per patient per week for mild (i.e. self-treated) hypoglycaemia, and 0.1-1.5 per patient/year for severe hypoglycaemia (SH)(4) and a prevalence between 30-40% of severe hypoglycaemias(9), hypoglycaemia is both the main limitation in achieving glycaemic targets and the main side effect of intensified insulin therapy in T1DM. It produce reluctance to initiate or intensify the therapy(6). Moreover, rates of severe hypoglycaemia have not generally diminished despite the introduction of insulin analogues and advances in glucose monitoring (4,6,7)

So, hypoglycaemia has a significant burden as it can engender fear and anxiety, disrupt sleep and adversely affect domestic and social life in addition to worsen the microvascular and macrovascular complications

produced by hyperglycaemia(6,8). Retrospective studies even show a decrease in intellectual performance linked with frequent severe hypoglycaemia (more or at less 5 episodes since diagnosis).

It effects on psychological facts too, knowing as the most important impaired sleep quality and fear of hypoglycaemia.(6–8)

For example, nocturnal hypoglycaemia is a major limiting factor on attaining near-normal glycaemic control in patients with T1DM and it is emotionally burdensome for patients and caregivers alike (10). The appearance of **fear of hypoglycaemia** (FoH) is very frequent, and patients prefer to maintain their levels of blood glucose greater (they do not want to intensify the therapy) in order to avoid it, so it is an important limiting factor (10). As FoH has developed into one of the best problems for the treatment and especially with a decrease in life quality, even particular questionnaires are developed to estimate how much it affects to T1DM patients. Clarke questionnaire (to assess hypoglycaemia awareness)(11) and HFS-II (to quantify the fear)(12) are the most used as it is translated and validated in other languages. Fear of Hypoglycaemia 15-item scale (FH-15) is a new measure that explores specific FoH in adult patients with T1DM and it have demonstrated a good reliability and validity, so it may be used more than HFS-II because it is shorter and easier to apply(13). However, FH-15 is not already traduced and validated in any other language than English. All this test normally are done with Diabetes quality of life test (DQOL) which assess various facts that can affect to diabetes mellitus patients life and it is designed, especially, for T1DM patients(even though it is not focused on hypoglycaemia like the others). That test is already translated and validated in many languages because it have demonstrated a very good reliability and it is easy to perform(14,15).

In addition, it is more convenient to avoid overtreatment of hypoglycaemic reactions since this often leads to unstable blood glucose levels and prolonged hyperglycaemia, making difficult insulin dosages an starting a vicious-circle(5). To treat hypoglycaemia it have to be used oral carbohydrates or parenteral drugs as IV dextrose or glucagon (contra regulatory hormone) (5,6)

Hypoglycaemia is also a burden on healthcare resources and on society as a consequence of the direct costs of its treatment and the indirect costs associated with lost productivity, considered the most expensive aspect of treating severe hypoglycaemia the hospital admission and inpatient care (6). Social aspects affected by hypoglycaemia are: impact on employment, productivity, impact on driving, accidents and impact on exercise practice (where are a higher risk of developing hypoglycaemia especially during and after perform it)(7,16)

For all of that reasons, hypoglycaemia is much more than an acute complication of diabetes or an uncomfortable symptom, it fits the bio-psychosocial model of disease, as it has significant biological, psychological social effects(1,3–8,10–13,16,17)

3.3 New technologies in order to get better

In order to control their blood glucose, T1DM patients self-manage multiple daily injections (MDI) of rapid-/short-acting insulin or use insulin pumps (continuous subcutaneous insulin infusion (CSII)).

Until the first “smart” insulin pump (Deltec Cozmo®(Smiths Medical MD)) was available at 2002, it has incorporated a system which estimates insulin doses by counting carbohydrates and using insulin-to-carbohydrate ratios (number of grams of carbohydrate that would be covered by 1 unit of insulin) along with correction factors (a ratio used to calculate how much 1 unit of insulin will lower and elevated blood glucose value)(18). That system is called insulin bolus calculators (IBC). Currently, IBC are available integrated in insulin pumps and works like a form of software applications which even have the possibility to download their data to smartphones (19).

Indications of treatment with an insulin pump are incapacity for obtaining normoglycemia although MDI, recurrent hypoglycaemia, unawareness of hypoglycaemia and patients treatment preference(20).

Even everything seem advantages(improved blood sugar control, insulin availability and convenience, use of multiple basal rates, flexibility and freedom, reduction of hypoglycaemia events, etc.) some patients prioritize the disadvantages (remembering to give insulin boluses with food intake, weight gain, skin infections, infusion site locations and set changes, psychological factors) (21). As patients can decide about their treatment, some of them prefer to use MDI method. Moreover, in randomized controlled trials HbA1C levels are often not so different comparing subjects treated with CSII and MDI(22).

In intensive insulin treatment (MDI and CSII) treatment is important to manage it as well as possible nutrition facts. In last few years, carbohydrate counting (CC) has played an important role (22). The quantity of carbohydrates (CHO) in a meal is the major nutritional determinant of postprandial glucose levels so monitoring (CHO) intake patients are able to calculate pre-meal insulin doses in order to control postprandial glucose excursions. Normally, patients are trained how to evaluate the CHO content of the meal in grams or in food choices (portions of 10 or 15g of CHO)(23).

Even though this method seems easy, more facts, as the correction factor (CF) and insulin-to-carbohydrate ratio (ICR), are parameters that have to be considered in the insulin bolus calculation. Although it are

patient specific empirically estimated parameters, for most people bolus equations are complex, difficult and time consuming to solve by mental calculation. That difficulties produce miscalculations resulting in much cases as lack of glycaemic control(19).

For those facts, new technological devices have been developed during last times because the need of making easier and safer T1DM treatment. We mentioned that CSII pumps have already beneficiate of IBC incorporated in their structure and after some preliminary experiences it is now available for MDI therapy(22).

1.3.1 Insulin bolus calculator (IBC)

Insulin pumps and some glucose meters already incorporate IBC to help users to simplify CC (24). A bolus calculator is a device used to calculate insulin dosages for correction of out-of-target glucose and/or intake of COH.

To calculate appropriate bolus doses, IBC requires accurate settings for the insulin-to-carbohydrate ratio (grams of ingested carbohydrates that are covered for one unit of insulin), glucose correction factor, duration-of-insulin action, and correction factor (or target). The IBC include an algorithm in their software that use all that settings plus the patients inputs (and in some IBC historical data input)(25). The tuning of the bolus calculator parameters depends on various factors such as: time of the day, physical activity level, hormonal cycles, psychological stress, alcohol and illness. Therefore, it is important to adapt parameters to these situations and re-adjust them over time(24).

Current literature has shown that integration of IBC may help individuals to meet prandial insulin dosages requirements, improve postprandial glycemic excursions, and achieve optimal glycemic control(25).

Studies of an advanced automated IBC with integrated blood glucose meter have been published during last years. The first publication was a 16-week randomized, controlled pilot study (the BolusCal Study) demonstrated a change in HbA1C from 8.9% to 8.1% in patients using the BC and this improvement was maintained 1 year after the device was implemented in their therapy(19,26). Another study called the ABACUS trial had similar results. It included either T1DM than T2DM patients and the sample size was greater. The result was that significant more patients in the BC group achieved an HbA1C reduction of more than 0.5%(27). Finally, another study recently published and made at Navarra highlights the importance of including a IBC into MDI therapy(but the conclusion is that IBC have a better effect on HbAc1 in people treated with CSII)(28).

However, much of the studies related with the IBC and its capacity to control blood glucose levels are applied to pumps and not to IBC incorporated in a glucose meter system (18,19,29).

Another fact studied about IBS is their effect on hypoglycaemia. As fear of hypoglycaemia is an important factor that conditions life of T1DM patients (it affects their quality of life and their metabolic control of the disease), IBS seemed to be a possible solution of that.

Ziegler et al (27) used a 45-item questionnaire to know how the fear of hypoglycaemia descends on T1DM patients treated with MDI therapy plus a IBN incorporated in their glucometer (they use ACCU-CHEK® Aviva Expert). Results of the survey suggested that the use of bolus advisor may alleviate some of the fears and inconvenience associated with MDI therapy. There was a reduction of fear of hypoglycemia, increased confidence in bolus calculation and a sense of increased flexibility. Moreover, the majority of patients felt more comfortable using IBC because it was easier than manual bolus calculation.

Even though, data are contradictory about hypoglycemic events. A 1-year open-label, randomized, controlled trial 123 adult type 1 diabetes patients randomized on a 1:1 basis to either an ABC or control group found that more severe hypoglycemia events appear among ABC users ($P = 0.04$). However, a recent study, where an insulin support decision algorithm was tested both in subjects with type 1 and type 2 diabetes, rather supports the idea that the frequency of hypoglycemia is lower among patients using an IBC(30). A study published during last year (3 of June 2015) is the only study which takes in consideration the number of severe hypoglycemia events making a comparison between CSII and MDI with a bolus calculator. The result was that CSII don't have any severe hypoglycemia event while in MDI group one patient suffered it ($N=60$)(28). All the latest studies have used Accu-Chek® Aviva Expert from Roche more than Freestyle Insulinx® from Abbott, the two glucometer with a IBC-built-in system currently available at Europe(22,26–28,31).

In conclusion, although some more studies may demonstrate that IBC reduces the incidence of severe hypoglycemia, the results are few and contradictory.

1.3.2 Smartphone applications (APP)

Nowadays, software applications for smartphones to assist the diabetes patient in CC and bolus calculation have long since surpassed the realization of studies testing application safety, reliability and clinical efficacy. Patients can download applications, either free or at very low cost that provides insulin dosing

advice even though they have not been approved for the corresponding regulatory authority. This leaves the health care provider with the challenge to work with that may potentially cause harm to patients. Some recent reviews are done about the most used APPs but there is not much information about it.

At 2013, the first smartphone application received approval for insulin dose management. The software include an IBC plus a telemedicine component which allows for communication between patient and health provider (many apps have this function).

A positive fact of smartphone APP, demonstrated in a randomized clinical trial comparing a patient group using CC method and a patient group using an approved APP, was the significant difference between the increase scores in quality surveys (DTSQ) of APP group in front of CC group. However, there was not difference between HbA1c improvements in two groups(19). A study which evaluate several Android APP concluded that diabetic patients consider easy of use and direct communication with the glucometer the most important features of the APP(32).

Taking into account those studies, smartphone APPs may be a good tool for increase comfort of diabetic patients although we do not have much information about safety conditions. Moreover, as we said, unless APPs has an IBC system included we cannot know if it works equal as IBC included in glucometers.

3.4 Justification

Several studies talk about the influence of having severe hypoglycaemia events in patient's quality of life. An incidence on 1.5 SH events/year for patients treated with MDI therapy are reviewed, placing it as the most frequent complication of insulin treated patients(4). The inconvenient of that is not only because of the psychological stress that can produce as it can be physically harmful for the patients producing fallings, driving accident, etc. (5–7,10,11,16). Moreover, the treatment of it when an event appears has a rebound effect on blood glucose levels, leading to hyperglycaemia and difficulties on insulin dosage(5,6) . For all these reasons, SH events have to be taken in consideration as a real complication of diabetes, more often presented in T1DM (6) an a solution of that uncomfortable situation.

The main objective of this clinical trial is to evaluate if insulin bolus calculators included in glucometers can reduce the incidence and number of severe hypoglycaemia in patients with type 1 diabetes in front of patients with type 1 diabetes treated with classic therapy with carbohydrates counting method and SC intensive insulin therapy(MDI)(19,26–28,30). The introduction of and IBC into MDI therapy has shown a

beneficial effect on T1DM patients increasing their control in HbAc1 levels (19,25–28) and in consequence, better control and incidence in microvascular and macrovascular complications derived of hyperglycaemia(4–6). Moreover, several studies have demonstrated the use of IBC included into the glucometer can decrease the fear of having an hypoglycaemia event, one of the most conditioning factors of lacking of good treatment and metabolic control in that patients. As we said, FoH decreases the quality of life of MDI treated diabetic patients, so the decrease of that perception may lead to better HbaC1 controls. There is lack of studies measuring the hypoglycaemia events in patients using IBC with their glucometer.

Other new telemedicine tools are appearing, the smartphone APPs. There are not so many studies available, but some currently have been accepted by medical community(19,32).

For these reasons, we want to determinate if there is a real decline in the number of severe hypoglycaemia events in patients using those new devices (IBC) which seems to be a good innovation in diabetes care and how it affects in the quality of life of patients. A comparison with a smartphone APP will be done to try to find a difference or not between this technological devices.

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5. HYPOTHESIS

5.1 MAIN HYPOTHESIS

The use of insulin bolus calculator (IBC) in glucometers reduces the incidence of severe hypoglycaemia in T1DM patients.

6. OBJECTIVES

6.1 MAIN OBJECTIVE

The main aim of this study is to evaluate if insulin bolus calculators included in glucometers can reduce the incidence and number of severe hypoglycaemia in patients with type 1 diabetes in front of patients with type 1 diabetes treated with classic therapy with carbohydrates counting method and subcutaneous intensive insulin therapy (MDI).

6.2 SECONDARY OBJECTIVES

1. Evaluate if insulin bolus calculator can reduce the incidence of severe hypoglycaemia in front of patients using a smartphone APP.
2. Assess if the inclusion of an IBC in the management of T1DM patients with severe hypoglycaemias will reduce the subjective feeling of fear of having another event of it.
3. Evaluate if insulin bolus calculator can improve the quality of life of patients with T1DM compared with carbohydrate counting method and SC insulin treatment.
4. Evaluate if the inclusion of an IBC can reduce the incidence of mild-moderate hypoglycaemia in patients with T1D.

7. METHODS

7.1 STUDY DESIGN

The study will be a multicentre, centralized randomization, controlled open-label clinical trial.

The study will be conducted in six hospitals belonging to Institut Català de la Salut (ICS): Hospital Universitari Doctor Josep Trueta de Girona (HUDJT), Hospital Universitari Vall D'Hebron (HUVH), Hospital Universitari de Bellvitge (HUB), Hospital Universitari Germans Trias i Pujol (HUGTP), Hospital Universitari de Tarragona Joan XXIII (HUTJ) and Hospital Universitari de Arnau de Vilanova de Lleida. HUDJT will be the coordinator center.

The patients will be randomly divided in three groups (1:1:1 ratio). The first group will use classic carbohydrates counting method. The second group will use the insulin bolus calculator included in their glucometer. The third group will use the smartphone APP to measure the carbohydrate intake. The randomization will be performed with a randomized electronic procedure (see interventions).

Then, the groups will be stratified according to the time duration between the diagnosis of the disease (T1DM) and the present, also in three groups (>1 year with T1DM, >5 years with T1DM and >10 years with T1DM). During the follow-up of all three groups, a strict metabolic control will be done (accepting as a good metabolic control a HbA_{1c} under 8%, trying to get as close as possible to 7.5%) to try to avoid a bias.

All three groups will have the same insulin therapy regime:

- Rapid-acting insulin (Humalog Kwipen-Lispro 100u/ml) three times per a day. It has to be injected before meals (pre-prandial).
- Long acting insulin (Lantus Solostar 100u/ml) 1-2 hours before going to bed.

The self-glucose monitoring will be done by a glucometer at least 3 times a day (prior to meals and when they suspect low blood glucose; occasionally postprandially, at bedtime and prior to exercise).

7.2 SUBJECTS OF THE STUDY

The patients of the study would be men and women (more than 18 years old and less than 50) who had been diagnosed of T1DM at least 1 year before the beginning of this study.

The estimated time of recruitment is 1 year. They will be recruited when they visit outpatient clinic of one of the six involved centres and complete all the following inclusion and exclusion criteria.

7.2.1 Inclusion criteria

1. Patients diagnosed of type 1 diabetes mellitus.
2. Age between 18 and 50 years.
3. Patients with frequent (defined as more than 5 episodes since diagnosis) episodes of severe hypoglycaemia and recurrence of it episodes (defined as at least 1 episode a month of SH with a good adherence of insulin therapy).
4. Patients with a FH-15 score equal or greater than 28 (cut-off score measure of specific fear of hypoglycaemia), knowing hypoglycaemia as a conditioner of their quality of life.
5. Patients with, at least, more than 1 year since the diagnosis of T1DM (debut).
6. Patients with moderate diabetes control (considered a moderate control a HbAc1 <8 %)
7. Signed informed consent
8. Patients who has an smartphone (with Android or IOS software)

7.2.2 Exclusion criteria

1. Type 2 DM, LADA diabetes, MODY and other types of diabetes.
2. Comorbidities that can effect blood glucose levels:
 - a. Cardiac insufficiency.
 - b. Other endocrine disease: Hypo/Hyperthyroidism, Addison's disease, GH deficiency, hypopituitarism.
 - c. Insulinoma.
 - d. Renal failure.
 - e. Severe hepatic dysfunction/ Hepatic failure
3. Current acute comorbidity: sepsis, cancer, burns.
4. Occurrence of chronic hyperglycaemic complication during the study
5. Psychiatric disease (diagnosed at clinical history)
6. Use of other Drugs that can affect the glycaemic control (corticoids, beta-blockers, diuretics, adrenalin, oestrogens, sulfonylureas, thyroid substitute hormones...)
7. Use of illicit drugs

8. Alcohol consumption (not more than 3-4 units of alcohol/day for men and 1-2 units of alcohol/day for women).
9. Performance of high intensity exercise (>70% VO₂ max or doing aerobic exercise for more than two consecutive days)
10. Difficult life situation (psychological stress)
 - Loss of a close person
 - Job loss
 - Economic problems
11. Low sociocultural level

7.2.3 Subjects withdrawal criteria

1- Patient decision: the subject can withdraw his/her consent to participate in this study at any time and for any reason and they will be considered as a dropout. At patient request, all previously added data will be destroyed from the study database.

Withdrawal of patients from this study is not predicted to be huge because of the short study duration and the interventions seems to be not much difficult for patients who live with diabetes every day. Even though, subjects withdrawn from the trial will not be replaced.

2- Investigator decision: each investigator participating in this study can consider the convenience of withdrawal of a patient in case of she or he do not lead the instructions of the study (correct carbohydrate counting method, correct use of SC insulin).

7.2.4 Protocol withdrawal criteria

- Belatedly identified violation of the inclusion and/or exclusion criteria.
- A failure to complete the protocol requirements.
- Any severe adverse event, unacceptable health risk or consequence for the participant derived from this study (for example, appearance of more episodes of hypoglycaemia, extreme glucose excursions, etc.).

- Apparition of intolerable clinical symptoms that cannot be explained by DM (onset of a new disease, comorbidity, etc).

7.3 SAMPLE SIZE AND SELECTION

Accepting an alpha risk of 0.05 and a beta risk of 0.1, with an incidence of 30-40% of severe hypoglycaemias in patients with T1DM population (we selected a 35%), in a two-sided test, **241** exposed subjects and **241** in the non-exposed are necessary to recognize as statistically significant a relative risk greater than or equal to 0.6.

It has been anticipated a drop-out rate of 5%. Sample size is obtained by GRANMO power calculator with the use of POISSON approximation.

Non-exposed group is considered to be the control group using classic carbohydrate counting method. There are two exposed groups, the groups using the IBC and the group using the smartphone app. Two groups will have the same sample size.

So, the total amount of participants needed for the study is **723**.

This is a consecutive and competitive non-probabilistic sampling. Centers will compete for subject inclusion until completion of the estimated sample size. Patients will come to Endocrinology outpatient clinic of one of the six involved centres as they would normally do.

An Information sheet (Annex 1) for participants of the project will be given to the candidate and if the patient agrees with it, he or she will sign the informed consent form (Annex 2).

7.4 INTERVENTIONS

7.4.1 Randomization

All patients will be randomized by a statistical specialist after they will be selected at hospital, once they meet the established criteria, have given their informed consent and they had learned to make a correct carbohydrate counting method (all patients included in the study will do it during 1 month) controlled with a glucose sensor. Patients will be randomly assigned to each group using the software SPSS.

They will be included in one of the following 3 groups:

- First group: they will continue with the carbohydrate counting method.
- Second group: they will use the Accu-Chek® Aviva Expert (Roche) insulin bolus calculator.
- Third group: will calculate their carbohydrate intake with the Social Diabetes® smartphone APP.

Assignments will be known by the investigation team as it is an open-trial but nobody in the team will have decided in which approach the patient should have been included. Is correct to perform it as an open-label clinical trial because we are comparing very similar treatments to determine which is most effective (we are only including new gadgets to the same treatment).

A numeric code will be assigned to each patient (obtained by a number code generator) in order to respect the confidentiality of personal data.

7.4.2 Description of interventions

Carbohydrate counting (CC) method and SC insulin therapy

As the quantity of CHO in a meal is the major nutritional determinant of postprandial glucose levels, patients are taught how to evaluate the CHO content of the meal. That study wants to make a comparison between the accuracy of CC and two devices at time to decide the insulin bolus needed, evaluated as the quantity of severe hypoglycaemia events and its repercussions into patients life quality.

For that reason, it is necessary that the patients learn how to do it as well as possible to avoid bias. To get it, during the first month of the study, they will have two appointments with the team of certified diabetes educators.

CC consists in counting the amount of CHO in a meal in grams. To make easier that process, it has been developed a system of portions of 10 grams (g) of COH (in some other counties are used 15g as a portion). It consists in dividing the food in portions that contribute 10g of COH. For example, a portion of weighted cooked rice correspond a 38g of rice which means that quantity of rice have 10g of COH. Patients will have to look to the nutrition facts table of the food (where the total quantity of carbohydrate is written) to estimate it or there are several information tables where the most common food appears.

Diabetes educators will teach the patients about how to do it at the first appointment. A table of equivalencies will be given (Annex 3) to them and they will review it method during the second appointment.

All patients, as we said before, will have the same intensive insulin regime. Those regimes try to mimic the normal secretion of insulin of the body. It can be done with CSII pump or, in that case, it is done by MDI. It is necessary one dose of basal insulin (long-acting) and one bolus dose of insulin before each meal (rapid-acting).

Patients will use:

- Rapid-acting insulin (Humalog Kwikpen-Lispro 100u/ml) three times a day. It has to be injected before meals (pre-prandial).
- Long acting insulin (Lantus Solostar 100u/ml) 1-2 hours before going to bed.

Therapy will be adjusted from the start and during the study with the intention to control chronic hyperglycaemia events (controlled testing HbaC1 levels and trying to keep it <8% during all the study) in order to avoid withdrawing patients from the study.

[Continuous glucose monitoring \(CGM\) system and glucose sensor](#)

During the first month of the study and simultaneously with the carbohydrate counting method plus SC insulin treatment, patients will use a glucose sensor (GS), a system of continuous glucose monitoring. The function of that is to control if there is a good control of glucose levels (huge variations during the day and during the month, with the intention to evaluate if the method of carbohydrate counting is been did well) and to evaluate the presence of hypoglycaemias (all of that, mild-moderate-severe).

Continuous glucose monitoring (CGM) provides real time glucose readings, throughout day and night, allowing diabetes patients to see their glucose levels.

That device consists of 3 parts:

- Small sensor that measures glucose levels just underneath the skin (into interstitial liquid).
- Transmitter that is fastened on top of the sensor and sends data wirelessly to the receiver
- Receiver that displays glucose trends in an easy way to understand it's by the patient.

Glucose sensor is a little part of the device. Is like a thin needle inserted just under the skin where it remains in place for several days, detecting glucose into interstitial fluid.

After looking for many CGM systems, we had decided the study will use **FreeStyle Libre (ABBOTT)**. A little GS (35 mmx 5 mm) collects and stores glucose levels during day and night and patients only have to scan it to know their current glucose levels, levels of the last 8 hours and a tendency arrow indicating where glucose levels go. It is no necessary to calibrate it (other CGM systems need several calibrations by pricking the fingertips). Moreover, it is easy to wear because patients can get a shower, do exercise or swim with that device and the scanning can be made through clothes (it only takes 1 second at a distance of 1 to 4 cm). The sensor remains during 14 days (then it have to be changed) at the posterior site of the arm (more information about the device at <http://www.freestylelibre.es/>) (Annex 4).

Taking this information in consideration, every patient will need his or her CGM kit. Taking into account that the patients need the device during 1 whole month and Freestyle Libre GS have to be changed every 14 days, the patients will need 2 GS (in the initiation kit are included).

The kit will be given to patients when they came for the first appointment with diabetes educators when CC class finishes. The first GS can be added. Educators will teach them about how to use it, how they have to change the GS and advising them to scan the GS at least 4 times a day, highlighting the necessity to make one scanning when they get up and before going to bed (because Freestyle Libre have a memory of 8 hours). They have to download the information from the lector to the computer using enabled by FreeStyle Libre software (available for PD and MAC) (Annex 5).

[Study management and devices](#)

This part takes place at the second part of the study. Patients had been completed a month with classic carbohydrate counting and with CGM. Now is when the randomization takes place into three groups.

First group: they only will continue with classic carbohydrate counting method, without CGM. The CGM system was used to control if there was a good fulfilment of carbohydrate counting method, how patient's levels of glucose change during the day according to their activity (diet, exercise, during night) and the most important, the number of hypoglycaemia during that year are registered.

Second group: That group will include in their therapy **Accu-Chek® Aviva Expert** (Roche) (glucometer with a built-in-system IBC) (Annex 6). They will use it the same way they were using the glucometer (before meals and before going to bed) to calculate the amount (bolus) of insulin to inject themselves. They have to use it too when suspect a hypoglycaemia event. IBC take in consideration some "health events" like performing

exercise, stress, illness or menstrual period for women to increase the accuracy of the bolus dose. The option to add customizable reminders may be useful to accomplish these measurements. Furthermore, a “limit of awareness” of hypoglycaemia can be introduced, and when the patient’s blood glucose is below the inferior accepted limit a warning message will appear with the quantity of COH the patient have to eat for return to normoglycemic levels (for more information about the device go to <https://www.accu-chek.es/es/atencionalcliente/productguides/metersystems.html>).

That recommended dose is calculated automatically by the device in function of the following information:

- IBC configuration values
- Result of current glycaemia
- The amount of carbohydrate quantified for a meal
- Level of descending glycaemia due to anterior correction doses.
- The influence of last meal on glycaemia level

Third group: will use the same SC treatment but they will use a smartphone APP to calculate the carbohydrate intake and the insulin dose. They will use Social Diabetes APP. That app is completely developed in Barcelona and had won the price of best Spanish app into the category of mHealth of 2012 World Summit Award Mobile. It is easy to use app with the function of bolus calculator and carbohydrate counting and it is approved to be safe in front of other apps (it is already accredited by *Junta d’Andalusia* for medical use). There is Social Diabetes for iTunes and Social Diabetes for Android Play Store, so there is no problem of what type of smartphone’s operative system uses each patient (more information: <https://www.socialdiabetes.com/es>). (Annex 7)

All three groups have to record in a diary their blood glucose levels as they do normally for the regular reviews with the endocrinologist. The most important thing they have to do is to record when (day/hour) they have a hypoglycaemia, if it was severe (need to be helped by others ;), the situation in that moment (exercise, resting, during night, etc.) and the blood glucose levels if it’s possible.

7.5 VARIABLES

7.5.1 Independent variable

The independent variable of this study is the different method to decide the amount of insulin bolus of each patient:

- Classic carbohydrate counting(CC) method (control group)+MDI therapy.
- Use of insulin bolus calculator (Accu-Chek® Aviva Expert (Roche))
- The APP for smartphones (Social Diabetes®)

It will be treated as a nominal qualitative variable. It will be measured as proportions or percentages.

7.5.2 Dependent variable

It will be the number of episodes of severe hypoglycaemia (measured in each group), which is defined as a symptomatic hypoglycaemia (considered as a clinical syndrome documented by Whipple's triad: symptoms consistent with hypoglycaemia, a low plasma glucose concentration, and relief of those symptoms when the plasma glucose concentration is raised) which requires the assistance of another individual in patients with high risk of it because recurrence (defined as at less 5 episodes of hypoglycaemia since the diagnose of T1DM, including, at less, one of this episodes during the last year).

It will be adjusted for sports practice and season of the year because these co-variables can be a confusion variable if it are not taken in consideration.

It is a discrete quantitative variable. It will be measures as a mean.

7.5.3 Secondary dependent variables

- Fear of suffering a hypoglycaemia event measured by Fear of Hypoglycaemia Scale (FH-15). It is a quantitative discrete variable. It will be measures as a mean.
- Quality of life: It will be measure with EsDQOL questionnaire (diabetes quality of life) and administered to patients of all groups. It is a quantitative discrete variable. It will be measured as a mean.

- Number of mild and moderate hypoglycaemia events in patients with T1DM. It will be measured as ordinal numbers (1, 2, 3 events) according to patients logs and blood glucose records in the devices. It is a discrete quantitative variable. It will be measured as a mean.

7.5.4 Co variables

- Age: 18 or older or 35 and younger. Is a quantitative discrete variable. It will be expressed in years.
- Gender: is a dichotomous nominal qualitative variable. It will be assessed by male or female
- Body mass index (BMI): Is a continuous quantitative variable. It will be expressed in kg/m^2 .
- Season of the year: Is a nominal qualitative variable. It will be registered as: Spring, Summer, Autumn, Winter.
- Sport practice: Is a dichotomous nominal qualitative variable. It will be assessed as sport practitioner (equal or more than 2 days/week with duration of at least 30 minutes) and non-sport practitioner (less than 2 days/week).
- Diabetes duration: Is a nominal qualitative variable because we measure it as intervals (year intervals: ≥ 1 year, ≥ 5 years, ≥ 10 years). We will know it by the information in the clinical history.
- Number of severe hypoglycaemias since debut: is a discrete quantitative variable. It will be measured as numbers (1, 2, 3, etc.). That number will be estimated by data included into clinical history.

7.6 MEASURE TOOLS

1. **Fear of Hypoglycaemia Score (FH-15):** it has 15 items evaluated with a 5-point Likert scale with a range of 1-5. Those 5 options are: *Never* [1], *Almost never* [2], *Sometimes* [3], *Almost always* [4], *Every day* [5]. The overall score is calculated with the sum of the numbers of every item. The cutoff score is 28 points, considerations that a global punctuation equal to or greater than 28 points will be classified as having FoH(13,28)(Annex 8)

2. **Diabetes Quality of Life (EsDQOL; Spanish version):** it questionnaire has 43 questions distributed into 4 subcategories: “Satisfaction” (15 questions), “Impact” (17 questions), “Social/vocational concern”(7 questions) and “Diabetes worry”(4 questions). Every question have to be quantified with a 5-point Likert scale:

- “Satisfaction”: the 5 options are Strongly Agree [1], Agree [2], Neutral [3], Disagree [4], Strongly disagree [5]. For example, if in all questions are strongly agree, the patient will have a punctuation of 15.
- “Impact”, “Social/vocational concern” and “Diabetes worry”: the 5 possible answers are *Never* [1], *Almost never* [2], *Sometimes* [3], *Almost always* [4], *Always* [5]. The minimum punctuations of those subcategories are 17, 7 and 4 respectively, which means diabetes performs low impact and little worry into life of diabetes patients.

The total punctuation of every subject is the sum of all punctuations. There are not a cutoff score. As low is the total punctuation, less impact into quality of life exercise diabetes(14,28). (Annex 9)

7.7 DATA COLLECTION

Before starting the protocol:

FH-15 test have to be translated and validated in Catalan or Spanish because of it is only validated in English. The research team of HUDJT (performing a revision team) has reviewed the scale and now it have to be translated. Then, two specialized translators (A and B) will do the translation. If there are significant differences between the two translations, translators A and B have to come to term. When there are not significant differences, the scale is given to a third translator (translator C) to do a back translation. With that supplies the revision team will did a translated version of the scale. Then a preliminary adjustment test will be done with 10-15 patients with similar characteristics for two or three members of the team. If there is no problem in that phase, a validation phase composed by two steps will be performed.

To establish the face validity (test is subjectively viewed as covering the concept it purports to measure), two groups should be formed, one for subjects that will be measured by the scale and other for experts who will analyze the scale and dictate whether it really seems to measure what is proposed. To stablish the content validity (evaluation of the various items included in the instrument adequately represent the

domains or factors of the concept to be measured), factorial analysis will be performed. For this type of analysis we will need at least 100 patients in total.

Finally, a statistical comparison with a gold standard scales (for example, HFS-II) will be done. If it is correct, we have the FH-15 translated and validated.

First visit:

Patients will come to Endocrine outpatient in a normal way to check-out DM control. They can have information into their Clinical History about several episodes of hypoglycaemia or severe hypoglycaemias or they can ask for help because they have had new episodes of it. Moreover, they can express their fear of suffering some new episode and how it effects on their daily life.

After a good anamnesis and physical exploration (a nurse will register physical exploration data), when a patient is recognized as a possible partaker into the study (because they seems to complete the study conditions), the physician (part of the work team) will ask to he or she to take part of it giving to them the necessary information. It is important to aware the patients about the possibility to not be chosen for the study (because of inclusion or exclusion criteria).

If the patients want to participate, physician will gave an information sheet (Annex 1) explaining in an easy way how the study is going to be and an Application Form (AF). It will include questions about personal data and all the inclusion and exclusion criteria to be sure if there is some of that (and if some of that are not documented into the clinic history).

Patients have to complete the AF the same day of the visit and it will be evaluated for the physician. The physician will be the responsible to decide if the patients complete all the requirements. The physician can notify to the patient that he or she can join the study during that visit (and the informed consent (Annex 2) will be signed) or during next days with a call (if there is no time during the visit, the informed consent will be signed the first day of the study). If the patient cannot take part because they do not complete the criteria, physician will explain it to them in the most respectful and right way.

Patients will be cited for the start of the study during the following month. All patients will have an appointment with certified diabetes educators at endocrinology day hospital of their Hospital centre for the start of the study.

Starting the study:

The patients who have not signed the informed consent will do. Patients have to know that they can quit the study at any time although they have signed the informed consent.

A team of diabetes educators will train every patient about carbohydrate counting method. They will adjust their MDI insulin therapy too. All patients will have a class about carbohydrate counting (about half an hour per patient) at the outpatient visits of endocrinology day hospital.

In that visit the educator will teach them about how to use the GS (how it has to be changed and treated) and the CGM system (FreeStyle Libre (ABBOTT)). The CGM kit will be given to patients and the first GS added. Educator will advise the patient to scan the GS at least 4 times a day (highlighting the necessity to make one scanning when they get up and before going to bed).

The FH-15 score and the EsDQOL questionnaire will be done at this point of the study to assess the current situation of fear of hypoglycaemia. A laboratory analysis of the levels of HbA_{1c} will be done.

It is important to inform the patient about the necessity of changing the sensor in 14 days.

Controlling the glucose levels:

Patients will return to the endocrine day hospital for a revision of their glucose levels recordings during last two weeks. Educators will check the registers of CGM system to evaluate if the control of that is going well (same or better control than previous) and if there some hypoglycaemia event during it.

The work team will ask to the patient about the carbohydrate counting method. The patient will explain some example and then he or she can ask for help about some problem.

If some patients have problems with the GS the work team will help them.

Patient will return to the hospital two weeks later.

Introducing devices: Randomization:

All patients whom continue into the study will come another time to the hospital. Data of number of hypoglycaemias during that month will be computed. They will be random divided into the three groups of interventions. Each patient will have an identification number to not be identified by their name.

The patients will stop using the CGM system and they will use glucometer normally (the CC group and the Social diabetes APP group; at less 3 controls/day). They will take the determinations into their diary like they did before doing that study. The group with Accu-Chek® Aviva Expert will use it as the glucometer (it is a glucometer with a built-in IBC).

Patients with the IBC and the APP will be trained about how using that. Moreover, they have a manual of use of the IBC (included) and a phone number if they have doubts about it.

It is very important that patients record their number of hypoglycaemias, when (day/hour) it appeared, if it was severe (need to be helped by others), the situation in that moment (exercise, resting, during night, etc.) and the blood glucose levels if it's possible.

FH-15 score and EsDQOL questionnaire will be did another time.

The patient will be cited a year later with the physician. During this year, patients will check of HbaC1 levels at the 4th month and at the 8th month.

Results: Patients of 3 groups will return to the hospital for a last time.

The data of "hypoglycaemia diary" will be computed using Microsoft Excel software.

FH-15 score and EsDQOL questionnaire will be done another time and the value will be computed too (to compare if there is a significant difference between before the CC method, after it and finally after the intervention). Another HbAc1 test will be done.

8. STATISTICAL ANALYSIS

In the univariate analysis, we will define variables as categorical or continuous:

- Categorical variables are gender, season of the year, sport practice, diabetes duration and the method used for estimating the amount on bolus dose. Each categorical variable will be described as percentages and proportions.
- Quantitative variables are age, BMI, total number of severe hypoglycaemias since debut, FH-15 punctuation, EsDQOL punctuation and number of mild and moderate hypoglycaemia events. Each quantitative variable will be described as means +/- standard deviation or median + confidence interval depending on whether or not they are normally distributed.

In the bivariate analysis, the relative risk (RR) will be calculated for each group to analyse our primary objective.

Medians of dependent variable (number of episodes of severe hypoglycaemia) in each group of intervention have to be stratified by the duration of the DM since the debut of it (>1 year, >5 years, >10 years). It will be compared using Mann-Whitney U test.

For the comparison between the independent (method to decide the amount of insulin bolus of each patient) and the secondary dependent variables (fear of suffering a hypoglycaemia event, quality of life and number of mild and moderate hypoglycaemia events), Student's t-test or U-Mann-Whitney will be used as the independent and the secondary dependent variables are quantitative.

In the multivariate analysis, it will be performed a type of probabilistic statistical classification model such logistic regression analysis in order to add the covariates that could skew the main association we want to analyse.

As we said, SPSS software package will be used for statistical analysis and the computed data will be managed with Microsoft Excel program (it is available for Microsoft and Mac)

We will assume a confidence interval of 95% and P value <0, 05 to consider that there is a significance difference.

Missing data: The study requires a strong presence of the patient at the hospital (at least 4 times during 2 months) so it is possible to have dropouts. If this situation occurs, variables will not be collected. Intention-to-treat will be used for missing data

9. ETHICS

This research protocol will be evaluated by the Comitè Ètic d'Investigació Clínica (CEIC) from Hospital Universitari Doctor Josep Trueta and will start after they give their approval.

It is important to take into account that this study will not have any risk for patients. It is a comparison between new devices (Accu-Chek® Aviva Expert insulin bolus calculator and Social Diabetes APP) that can improve the quality of life of patients related with episodes of hypoglycaemia and fear of suffering it, but the control group use the treatment and the management approved by the medical consent.

It means that the only thing this study can conclude is a better and easier way to manage the decision about the amount of insulin bolus according to patient's needs, resulting in less fear of hypoglycaemia, less incidence of severe hypoglycaemias and definitely better quality of life (according to beneficence principle). However, is necessary that the patients understand the information sheet of this clinical trial and sign the informed consent form (written in an understandable language by the patient) to respect the principle of autonomy. As we said before in this protocol, they can decide in any moment to withdraw it.

All basics ethics principles will be respected according to Worlds Medical Association Declaration of Helsinki about ethical principles for medical research involving human subjects.

The patients data collected will follow the Spanish data protection law (Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal), in order to protect the patients' confidentiality. Patients are not identified by their names, but by their unique identification numeric code.

10. STUDY LIMITATIONS

The main limitation of the study is that it is an open-label trial. That means the patient, doctors and the study team will know in which intervention group is the patient include.

It has to be taken in consideration that is a limitation because patients placed in the carbohydrate counting method can think that they have worse conditions into the study in relation with the other two groups. For that reason, patients may want to be changed to other group or may want to withdraw from the study. It is important to inform as good as possible the patients about the aim of the study and doctors have to explain to these patients that they are not able to change patients from one group to another. Furthermore, patients have to know that if they are not taking part in the study, they will also use the carbohydrate counting method.

As the study requires a lot of participation of the patient (they have to go several times to the hospital, understand how to use new devices, etc.) some patients will decide to drop-out the study or do not come to the hospital all times. Before exclude a patient of the study, we will try to phone her or him to come to the appointment. In the other hand, as the study takes a year and a month, patients will not have to come to hospital may be more involved in it.

As the research team is composed for 5 people who can record data in every hospital (30 people in total) because of the large sample size needed, there can be differences between data collection. It is important to train all the team about the correct use of Microsoft Excel (used for data collection) and how to use the devices, the questionnaire and the scale. Moreover, is serious that physicians choose the correct patients to be included in the clinical trial and even though the AF is easy and may help them to do it, inter-observer bias may occur.

To avoid a drop-out at the end of the study (where patients have to give the information about their month using each type of intervention) because patients does not attend to the appointment, the hospital will try to contact them via phone or e-mail during the following days. Intention-to-treat will be used for missing data.

11. WORK PLAN

The research team of every hospital center will be composed by three endocrinologists (EC), 2 diabetes specialist educators (DE) and a statistical specialist (SS). A technical expert from ABBOTT (AT) and a technical expert from ROCHE (RT) will be available during the study. The coordinator center will be Hospital Universitari Doctor Josep Trueta (HUDJT).

The trial has been designed in 5 phases:

1. Phase 1: Coordination (3 months)

Activity 1: The approval of Comitè Ètic d'Investigació Clínica (CEIC) is included into that phase. One EC (EC1) of HUDJT will be the responsible of this.

Activity 2: FH15 test validation in Spanish will be done. There will be a person from HUDJT responsible of it (EC2).

Activity 3: As it is a multicenter study, during that phase all the research team have to meet in order to check the protocol and get acquainted with the interventions. The timeline of the study will be examined and the methods of data collection will be shared. In this period, tasks will be distributed and information sheet, informed consent form and application form will be designed. One more meeting of all the team will be done with AT and RT. They will come one time to train all the team about the use of Freestyle Libre CGM system and Accu-Chek Aviva Expert IBC. That standardized training will minimize the inter-observer variability.

2. Phase 2: Recruitment, interventions and data collection(25 months)

Activity 4: A competitive and consecutive non-probabilistic sampling will be performed at endocrinology outpatient visits of every hospital by the EC. The estimated time of recruitment will be 1 year. Patients will receive the information sheet and informed consent form must be signed. The application form will be given and completed by the patient.

Activity 5: Once the patients are enrolled in the study, the interventions and data collection will be done by DE (except the collection of results, did by EC). During this period, AT and RT will be available to help the research team with any doubt about the devices. Every patient will have a timeline lasting 1 year and 1 month, but the inclusion time of the clinical trial will last 2 year and 1 month because of the lack of possibility to do the study at the same time for all patients and the sample size.

3. Phase 3: Data analysis (3 months)

Statistical analysis will be done by the SS.

4. Phase 4: Interpretation of results (4 months)

The research team will draw conclusions from the obtained results.

5. Phase 5: Publication and dissemination of the research findings(6 months)

The corresponding articles will be written and research findings will be published.

The chronogram is the following:

13. FEASIBILITY

As the clinical trial is performed at Hospital belonging to Insitut Català de la Alut (ICS), most of the members still work there (only the statistical specialist need to be hired and 3 translators have to be hired, because the technical expert from ABBOTT and the technical expert from ROCHE comes from their industry for free).

As the sample size of this study has to be large, we cannot did it in only in one hospital, but that will not a problem.

Endocrinologists and diabetes educators will receive their habitual salaries in the hospital. We only have to pay to the statistic specialist and for the translations and validation of the FH-15 scale. The price of the material is the only problem, but as we said (see budget) it is possible to reduce the price and obtain a viable total budget. Although is an expensive study (all studies which include technological devices may have this problem) it will be important for the health system economics.

In Catalunya, around 0.7%-1% of the population has T1DM. As 7,5 million of people live here, at least 52.633 persons have this illness. To find the main hypothesis relevant, it was estimated that the sample size should be a total of 723 patients. Taking into account that information, it seems that 1 year of recruiting in 6 centers is enough to meet that goal.

14. BUDGET

The physician outpatient visits are not included in the budget. Educators will have a little salary because they have three appointments with patients in a short period of time (60€ each one).

We will hire a statistical specialist for make easier and reliable the randomization. He or she will code patients too. The estimated salary will be 30€/hour and more or less 30 hours will be needed. So, the total estimated cost will be 900€.

The translation and the validation require three expert translators. Everyone will have total salary of 600€.

The huge amount of money will be spent in the study material. We need an initiation kit of Freestyle Libre CGM system for every patient. The cost of that is 169,90€. It means 169,90€ per 723 patients, a total of 122.837,7€.

In the other hand, during the second month of the trial timeline, there are 3 groups. The groups that use CC method+ MDI therapy are not included in the budget because they use the treatment provided by the healthcare system. The group that uses the Social Diabetes APP will not be included because the APP is free. Finally, the group which uses Accu-Chek® Aviva Expert has a device of 240€. For 241 patients, the total will be 57.840€. However, many pharmaceutic platforms can reduce the price of its devices. We can contact with Roche enterprises to try to get the devices with lower price (100€ per device, with a total budget of 24.100€). In this study we can demonstrate that IBC reduces the number of hypoglycemia events with their device, so this price can be achieved.

Finally, we need to include the cost of HbAc1 test (the first control will be done with the patient normal analytic control of the year, but the other 3 not. The price at HUDJT is 6,35€ for each measurement. The total cost is 19, 05€ for every patient), the publication costs (about 1000€) and travel expenses disseminating findings (about 1200€).

| | |
|--|------------|
| Personnel costs | |
| Statistical Specialist | 900€ |
| Expert translators | 1.800€ |
| Material costs | |
| Freestyle Libre initiation kit | 122.837,7€ |
| Accu-Chek® Aviva Expert | 24.100€ |
| Laboratory costs | |
| HbAc1 test | 13.773,15€ |
| Publication and dissemination costs | |
| Approximated cost of publication | 1000€ |
| Travel expenses | 1200€ |
| TOTAL = 165.610,85€ | |

15. IMPACT ON THE NATIONAL HEALTH SYSTEM

We have mentioned that hypoglycaemia is also have effect on healthcare resources and on society as a consequence of the direct costs of its treatment and the indirect costs associated with lost productivity, considered the most expensive aspect of treating severe hypoglycaemia the hospital admission and inpatient care (6). Only that is just a good motivation to search for a device that can descend the inhospital costs.

If our study is relevant, all patients treated with MDI therapy will benefit of it. It will lead to a decrease of severe hypoglycaemia events which will need hospital attention. Not only the hospital admission and inpatient care will significant decrease, use of drugs for the treatment of hypoglycaemia and emergency units will be less used. Moreover, patient's productivity will increase and in total numbers will be a positive fact for the society.

16. ANNEXES

16.1 ANNEX 1. INFORMATION SHEET

FULL D'INFORMACIÓ AL PACIENT

Títol de l'estudi: Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

Ens dirigim a vostè per convidar-lo a participar, de manera **completament voluntària**, en un estudi d'investigació que es realitzarà en persones que, com vostè, pateixen diabetis tipus 1. La nostra intenció és que rebí la informació correcta i suficient perquè pugui avaluar i jutjar si vol o no participar-hi. Per això li demanem llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir.

És important que sàpiga que en aquest estudi no se'l sotmetrà a cap nou tractament amb cap nou fàrmac en investigació els efectes del qual no siguin coneguts, ni a cap prova diagnòstica diferent de la que habitualment sol·liciti el seu metge. Tots els fàrmacs que s'utilitzin se li prescriuran seguint les recomanacions actuals de pràctica clínica habitual. No obstant, la legislació espanyola i els principis ètics de confidencialitat exigeixen que vostè conegui els detalls de l'estudi i doni el seu consentiment a participar-hi.

Perquè es realitza aquest estudi?:

Una de les complicacions més freqüents del tractament de la diabetis amb anàlegs de la insulina és l'aparició de hipoglucèmies. Els símptomes solen aparèixer primerament com a tremolors, palpitations i sudoració entre d'altres i de vegades s'agreugen fins a produir símptomes neurològics com confusió, mareig, visió borrosa i fins i tot pèrdua de coneixement.

Quan això succeeix, les anomenem hipoglucèmies greus.

El fet de que es produeixin sovint produeix una por inherent a patir aquests esdeveniments com a conseqüència del tractament, fet que disminueix l'adherència a aquest. Aquesta por acaba conduint a una disminució en la qualitat de vida del pacient ja que l'impedeix fer el seu dia a dia amb normalitat i sense preocupació.

Durant els últims anys s'han inventat i aprovat nous dispositius i eines que poden ajudar a millorar aquestes circumstàncies i per tant la qualitat de vida de qui ho pateix.

Així doncs, hem dissenyat aquest estudi per tal d'avaluar una nova eina que podria disminuir el nombre d'episodis de hipoglucèmia greu i millorar així la seva qualitat de vida.

L'objectiu d'aquest estudi consisteix en avaluar si la introducció d'un dispositiu de càlcul de bolus d'insulina en la gestió del tractament amb múltiples injeccions diàries d'insulina pot reduir el nombre de hipoglucèmies greus associades a aquest tractament en pacients amb diabetis del tipus 1.

A més, es compararà la seva eficàcia amb una nova aplicació per a telèfon mòbil (validada pel seu ús mèdic) amb una funció similar.

El dispositiu de càlcul de bolus d'insulina consisteix en una eina integrada en el seu mesurador de glucosa (el seu glucòmetre) que l'ajudarà a decidir la dosi d'insulina que s'ha de subministrar sense necessitat de que vostè hagi de dur a terme cap mena de càlcul, ja que el dispositiu el realitza per sí sol amb dades prèviament introduïdes i les que vostè anirà introduint cada dia.

Perquè el convidem a vostè?

Vostè té Diabetis tipus 1 i en l'últim any ha patit alguna hipoglucèmia, per tant és adient per participar en aquest estudi que pot millorar la seva qualitat de vida i la d'altres amb circumstàncies similars a la seva.

Què passarà si participo en aquest estudi?

Aquest estudi es tracta d'un assaig clínic on hi hauran 3 grups de estudi. Vostè serà assignat de manera totalment aleatòria a un dels següents:

- Un grup continuarà utilitzant el tractament amb múltiples dosis d'insulina al dia, juntament amb el càlcul de les unitats de carbohidrats ingerits a cada àpat per determinar la dosi a injectar-se, com normalment ho farien.
- El segon grup utilitzarà el dispositiu de càlcul de bolus d'insulina.
- El tercer grup utilitzarà un aplicació per a telèfon mòbil que també s'utilitzarà com a eina de control de la diabetis i presa de decisions respecte la insulina a injectar-se.

Operativa a seguir:

- Tots els participants de cada grup hauran de venir el mateix nombre de visites a l'hospital.
- Durant la primera visita al centre se l'hi demanarà que empleni un formulari per tal de que el metge que li ha ofert participar en aquest estudi pugui avaluar si compleix, finalment, els requisits necessaris. A més, se li preguntarà sobre tot el que pugui ser important per a ser seleccionat o no per l'estudi. Si vostè compleix tots els requisits de l'estudi i firma el consentiment, se li assignarà una cita durant el mes següent amb un educador o educadora especialitzats en diabetis a l'hospital de dia del seu centre.
- La segona visita la realitzarà amb l'educador/a. Li explicarà que durant el primer mes de l'estudi haurà de continuar tractant-se com fins ara i li ajustarà el tractament amb insulina. Les úniques diferències són que vostè haurà d'aprendre a calcular la quantitat de carbohidrats que ingereix en un àpat per tal de poder ajustar correctament la dosi d'insulina que s'haurà d'injectar.
Per això, l'educador/a li ensenyarà a fer-ho i li donarà una taula d'equivalències per tal que li sigui d'ajuda.
- Per tal de controlar de prop com està realitzant aquest procés i per poder tenir dades per avaluar com canvien els seus nivells de glucosa en sang durant aquest mes, se li posarà al braç un sensor de glucosa.
Juntament amb un transmissor i un receptor, conformarà un sistema que memoritzarà de manera contínua el nivell de glucosa. L'educador/a li explicarà com funciona i com l'ha de fer servir. Tingui en comte que és un dispositiu petit que no el molestarà pràcticament gens, és còmode de portar, es pot mullar i el pot fer servir sense problema quan fa esport. L'únic possible inconvenient que pot notar és degut a que porta una petita agulla.
- L'educador/a també l'hi farà dos qüestionari i haurà de fer-se una analítica per a mesurar els nivells de hemoglobina glicada en aquell moment de l'estudi. El tornarà a citar en dues setmanes per comprovar que tot estigui anant bé i l'hi donarà una nova cita al cap de dos setmanes per continuar el seguiment.
- Quan torni a l'hospital, se li assignarà un dels 3 grups que abans hem anomenat. Se li tornaran a realitzar els mateixos qüestionaris que havia fet un mes abans i se li farà una nova analítica per valorar els nivells de hemoglobina glicosilada en sang.

- Haurà d'estar un any tractant-se seguint la metòdica del grup assignat. És important també que sàpiga que durant aquest any haurà d'apuntar al seu diari el nombre de hipoglucèmies que ha patit amb informació sobre quan (dia/hora) han succeït, si ha necessitat l'ajuda de de tercers per a solucionar la hipoglucèmia, què estava fent en aquell moment (esport, descansar, dormint, etc.) i si és possible, els nivells de glucosa mesurats amb el glucòmetre.
- Serà citat per venir després de al cap 4 i 8 mesos per a realitzar-se analítiques per a determinar els nivells de hemoglobina glicada. Se li programarà finalment una cita al cap d'un any amb el seu endocrí.
- Per acabar, anirà a la cita amb el metge on li tornaran a fer els qüestionaris i la prova analítica de la hemoglobina glicosilada. Es recolliran les dades del seu diari per a poder introduir-les a l'estudi.
- Aquí acaba la seva participació en aquest estudi.

Quines són les meves responsabilitats?

- Assistir a totes les visitis quan sigui convenient
- Seguir de manera exacte les indicacions i procediments que l'hi diguin els metges i educadors/res.
- No amagar informació al personal de l'estudi i avisar-los sobre qualsevol problema que presenti durant l'estudi.

Puc retirar-me o canviar d'opinió una vegada iniciat l'estudi?

Sí.

Com ja li hem dit, la seva participació en aquest estudi és totalment voluntària. Vostè pot prendre la decisió d'abandonar l'estudi en qualsevol moment d'aquest i no li afectarà de cap manera a la seva futura atenció sanitària.

Abans de fer-ho només haurà de parlar amb el metge de l'estudi sobre la seva decisió.

També ha de saber que el metge encarregat de l'estudi o els educadors/res poden traure'l de l'estudi en qualsevol moment si es dona de les següents raons : no segueix les normes de l'estudi, no assisteix a les visites programades o apareix alguna raó mèdica que faci necessari que deixi l'estudi.

Participar en aquest estudi em beneficia?

Sí, a vostè i altres.

Els resultats poden ajudar a persones que com vostè pateixen aquest inconvenient derivat de la teràpia amb múltiples dosis diàries de insulina. La quantitat de persones diabètiques tipus 1 al món és gran, pel que podria suposar una millora en la qualitat de vida de molta gent.

Hi ha cap mena de risc en participar en aquest estudi?

No.

Si segueix bé les instruccions no hi ha d'haver cap mena de risc i inconvenient, ja que tots 3 grups realitzen una teràpia aprovada pel consens mèdic.

Que passarà quan finalitzi l'estudi?

Una vegada finalitzat, vostè rebrà la mateixa atenció actual, el que necessiti segons la seva condició sense afectar que vostè hagi participat en aquest.

Hi ha cap mena de compensació econòmica?

No.

Vostè té la oportunitat de poder utilitzar eines cares per les quals no haurà de pagar res de res i seguirà amb un pla de tractament i control de la seva malaltia semblant a l'actual però més intensificat, fet que també l'hi pot suposar un benefici en la seva qualitat de vida.

La informació que proporcioni per a aquest estudi serà confidencial?

Sí.

Totes les dades de caràcter personal i informació recollida o generada durant l'estudi quedaran protegides sota la Llei Orgànica 15/1999 de "Protecció de Dades de Caràcter Personal".

Les dades recollides durant l'estudi estaran identificades mitjançant un codi numèric i només els col·laboradors de l'estudi podran relacionar aquestes dades amb vostè i amb la seva història clínica.

Què passarà amb els resultats de l'estudi?

Una vegada finalitzat l'estudi es preveu poder publicar els resultats, sempre mantenint la confidencialitat de les seves dades.

Alguna cosa més que hagi de saber?

És important que tingui en compte que ni vostè ni ningú de l'equip de investigació pot determinar en quin dels tres grups de mètode de tractament es trobarà vostè ni el poden canviar de grup un cop assignat. Per això, li demanem que tingui en compte que li podria tocar el grup número 1, on el tractament continuaria sent igual que el que realitza ara però millor ajustat i controlat, el que seria útil per a vostè al saber calcular de manera precisa la quantitat de bolus d'insulina que s'ha de punxar.

Amb qui puc contactar?

Si està interessat en col·laborar en aquest estudi o té qualsevol dubte referent al que li hem explicat pot trucar a la Dra. Serra al 669267703 o al metge que li hagi entregat aquest full d'informació.

Si decideix col·laborar en l'estudi, recordi signar el consentiment tal com li hem explicat.

Gràcies per haver llegit aquesta sol·licitud de col·laboració.

16.2 ANNEX 2. INFORMED CONSENT

FULL DE CONSENTIMENT INFORMAT AL PACIENT

TÍTOL DE L'ESTUDI: Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

- He llegit el Full d'Informació per al Pacient i el formulari de Consentiment Informat. Entenc que podré conservar una còpia d'ambdós.
- He entès el Full d'informació al Pacient
- Tinc la oportunitat de fer qualsevol tipus de pregunta i obtindrà una resposta satisfactòria.
- He entès que la meva participació és totalment voluntària i que puc abandonar l'estudi en qualsevol moment per qualsevol raó i sense que em suposi cap mena de conseqüència en la meva futura atenció sanitària.
- Dono permís al personal de l'estudi perquè consulti la meva història clínica amb finalitats de verificació de dades i la meva informació recopilada durant l'estudi. Sempre en conformitat amb la Llei Orgànica 15/1999, del 13 de desembre, sobre protecció de dades de caràcter personal.
- Finalment, estic d'acord en participar en aquest estudi:

Nom del participant

Nom de l'investigador

DNI

DNI

Firma

Firma

Data:

► Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

16.3 ANNEX 3. CARBOHYDRATE COUNTING METHOD HELP TABLE

(From Fundación para la Diabetes (<http://www.fundaciondiabetes.org/>) materials and means)

10 grams of CHO = 1 portion

Glycaemic index (velocity of increase of glycaemia for every type of food)

- Red: High (equal or more than 70)
- Orange: Moderate (between 56-69)
- Green: Low (55 or less)

TABLA DE RACIONES DE HIDRATOS DE CARBONO



| LÁCTEOS | | | | | CEREALES Y DERIVADOS, HARINAS, LEGUMBRES Y TUBÉRCULOS | | | | | ALIMENTO | | | | | ALIMENTO | | | | |
|----------------------------------|--------------------------------|---|-----------------------------------|------|---|--------------------------------|----------------------------|-----------------------------------|------|--|--------------------------------|-----------------------------|-----------------------------------|------|---------------------------------|--------------------------------|--------------------------------|-----------------------------------|------|
| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (%) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. | ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (%) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. | ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (%) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. | ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (%) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. |
| Cuajada | 200 | Unidad (125ml) | 0,8 | 35 | Arroz, crudo | 13 | | | | Cuscús, crudo | 15 | | | | Juías blancas, cocido | 50 | Plato grande (300g) | 6 | 35 |
| Flan | 50 | Unidad (125g) | 2,5 | | Arroz, cocido | 38 | Plato grande (230g) | 6 | 70 | Cuscús, cocido | 65 | | | | | Plato mediano (200g) | 4 | | |
| Helado de crema | 50 | Bola mediana (100g) Tarrina individual (150ml) | 3 | 80 | Arroz integral, crudo | 13 | Guarnición (75g) | 2 | | Fideos de arroz, tipo Udon, cocido | 50 | | | | | Guarnición (100g) | 2 | | |
| Helado de hielo | 50 | Unidad (100ml) | 2 | 65 | Arroz integral, cocido | 40 | Plato grande (240g) | 6 | | Fideos de soja, cocido | 40 | | | | Lentejas, crudo | 20 | | | |
| Helado sin azúcar añadido | 100 | Unidad (100ml) | 1 | 35 | Arroz hinchado para desayuno | 12 | | | 85 | Galleta tipo Digestiva | 16 | Unidad (11g) | 0,7 | 65 | Lentejas, cocido | 50 | Plato grande (300g) | 6 | 35 |
| Kéfir | 200 | Unidad (125ml) | 0,5 | 35 | Arroz salvaje, crudo | 13 | | | | Galleta tipo María | 15 | Unidad (7g) | 0,4 | 70 | | Plato mediano (200g) | 4 | | |
| Leche desnatada | 200 | Vaso o taza (200ml) | 1 | 30 | Arroz salvaje, cocido | 34 | | | 35 | Galleta tipo Príncipe | 14 | Unidad (15g) | 1 | 70 | | Guarnición (100g) | 2 | | |
| Leche semidesnat. | 200 | Vaso o taza (200ml) | 1 | 30 | Avena, crudo | 17 | | | | Galleta Sin Azúcar | 18 | Unidad (7g) | 0,3 | 50 | Maíz en lata | 50 | Lata pequeña (150g) | 3 | 85 |
| Leche entera | 200 | Vaso o taza (200ml) | 1 | 30 | Avena, cocido | 34 | | | 40 | Garbanzo, crudo | 20 | | | | Maíz en lata sin azúcar añadido | 90 | Lata pequeña (150g) | 1,5 | |
| Leche condensada | 20 | Cucharada sopera (20g) | 1 | | Avena copos | 15 | | | 40 | Garbanzo, cocido | 50 | Plato grande (300g) | 6 | | Maíz tostado (quicos) | 20 | Boisa pequeña (40g) | 2 | |
| Leche en polvo | 25 | Cucharada sopera colmada (25g) | 1 | 30 | Boniato | 50 | Pequeño (80g) | 1,6 | | Guisantes congelados, frescos, de lata | 100 | Plato mediano (400g) | 4 | 35 | Mijo, crudo | 15 | | | |
| Nata líquida | 300 | Botellín o brick (200ml) | 0,7 | 0 | Cebada, crudo | 14 | Mediano (160g) | 3,2 | | Harina de trigo o maíz | 15 | Cucharada sopera rasa (14g) | 1 | 78 | Mijo, cocido | 53 | | | 70 |
| Natillas | 50 | Unidad (125ml) | 2,5 | | Cebada, cocido | 42 | Grande (320g) | 6,4 | | Harina de centeno | 17 | Cucharada sopera rasa (14g) | 0,8 | 45 | Müesli | 15 | | | 85 |
| Pêfit suisse | 70 | Unidad (55g) | 0,8 | 40 | Centeno, crudo | 15 | | | | Harina de soja | 70 | Cucharada sopera rasa (14g) | 0,2 | 25 | Pan blanco o integral | 20 | Barra de 1/4, unos 3 cm (20g) | 1 | |
| Queso fresco | 250 | Tarrina individual (70g) | 0,3 | 35 | Centeno, cocido | 38 | | | 45 | Hojaldre crudo | 30 | | | | Pan de centeno | 20 | Barra de 1/4 entera (180g) | 9 | 70 |
| Quesos de pasta, semis o curados | No variable | | | 0 | Cereales desayuno | 15 | | | 77 | Hojaldre horneado | 24 | | | | Pan de hamburguesa o Frankfurt | 18 | Panecillo restaurant. (60g) | 3 | |
| Yogur natural entero o desnat. | 200 | Unidad (125ml) | 0,5 | 35 | Cereales desay., rios en fibra tipo All-bran, óptima | 20 | | | 50 | Juías blancas, crudo | 20 | | | | Pan de molde | 20 | | | 85 |
| Yogur desnat. sabores o fruta | 125 | Unidad (125ml) | 1 | 35 | | | | | | | | | | | Pan de tripo integral | 23 | Rebanada (25g) | 1,2 | 85 |
| Yogur entero, sabores o fruta | 70 | Unidad (125ml) | 1,5 | 35 | | | | | | | | | | | Pan de tripo integral | 23 | Unidad (50g) | 4,5 | 85 |
| Yogur líquido | 70 | Unidad (200ml) | 3 | 40 | | | | | | | | | | | Pan de tripo integral | 23 | Unidad pequeña (55g) | 3 | |
| Yogur tipo Actimel | 100 | Unidad (84ml) | 1 | 35 | | | | | | | | | | | Pan rallado | 15 | Cucharada sopera colmada (23g) | 1,5 | 70 |
| Yogur tipo Actimel 0% | 200 | Unidad (84ml) | 0,5 | 35 | | | | | | | | | | | | | | | |

Elaborado por Serafin Murillo, Asesor en Nutrición y Deporte de la Fundación para la Diabetes
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► Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

TABLA DE RACIONES DE HIDRATOS DE CARBONO

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|------------------------------------|--------------------------------|-------------------------------|-----------------------------------|------|
| Pan tostado o biscote | 15 | Unidad (10g) | 0,8 | 70 |
| | | Unidad mini (3,3g) | 0,25 | |
| | | Tostada canapé (2g) | 0,15 | |
| | | Krispoll (12,5g) | 0,8 | |
| Pan en bastoncitos | 15 | 3 unidades (15g) | 1 | 70 |
| Pasta alimenticia, crudo | 15 | | | |
| Pasta alimenticia, cocido | 50 | Plato grande (300g) | 6 | 50 |
| | | Plato mediano (200g) | 4 | |
| | | Guarnición (100g) | 2 | |
| | | | | |
| Pasta al huevo, crudo | 16 | | | |
| Patata cocida, hervida | 50 | Plato grande (300g) | 6 | 66 |
| | | Plato mediano (200g) | 4 | |
| | | Guarnición (100g) | 2 | |
| Patata, horno o asada | 35 | | | |
| Patatas fritas | 30 | Guarnición (60g) | 2 | 70 |
| | | Porción hamburguesería (120g) | 4 | |
| Patatas chips | 20 | Bolsa pequeña (30g) | 1,5 | 95 |
| Puré de patatas, copos | 15 | | | 90 |
| Puré de patatas, elabor. con leche | 80 | | | 80 |
| Quinoa, crudo | 19 | | | |
| Quinoa, cocido | 48 | | | 35 |
| Sémola de trigo, crudo | 14 | | | |
| Sémola de trigo, cocido | 90 | | | 67 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|-------------------------|--------------------------------|----------------------------|-----------------------------------|------|
| Soja seca, crudo | 30 | | | |
| Soja seca, hervido | 100 | | | 15 |
| Sushi | 45 | Pieza pequeña (20g) | 0,5 | 42 |
| | | Pieza grande (40g) | 0,9 | |
| Tapioca, crudo | 12 | | | |
| Tapioca, cocido | 33 | | | 84 |
| Trigo sarraceno, crudo | 14 | | | |
| Trigo sarraceno, cocido | 42 | | | 40 |
| Trigo tierno, crudo | 16 | | | |
| Trigo tierno, cocido | 39 | | | |
| Yuca, cocido | 33 | | | 56 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|-----------------------|--------------------------------|--------------------------------|-----------------------------------|------|
| Coco fresco | 30 | Tajada mediana (35g) | 1 | 45 |
| Coco seco | 18 | Cucharada colmada (20g) | 1 | 45 |
| Dátil | 15 | Unidad (12g) | 0,7 | 70 |
| Frambuesa | 150 | Puñado, con mano cerrada (20g) | 0,2 | 25 |
| | | | | |
| Fresones | 200 | 8 unidades grandes (200g) | 1 | 25 |
| Granada | 70 | Unidad mediana (175g) | 2,5 | 35 |
| Grosella | 200 | Puñado, con mano cerrada (20g) | 0,1 | 25 |
| | | | | |
| Grosella negra | 140 | Puñado, con mano cerrada (20g) | 0,2 | 15 |
| | | | | |
| Higos | 100 | Unidad mediana (50g) | 0,5 | 35 |
| Kiwi | 100 | Unidad mediana (100g) | 1 | 50 |
| Limón | No valorate | | | |
| Litchi | 70 | 6 unidades (70g) | 1 | 50 |
| Mandarina | 100 | Unidad mediana (100g) | 1 | 30 |
| Mango | 100 | Unidad mediana (200g) | 2 | 50 |
| Manzana | 100 | Unidad mediana (200g) | 2 | 35 |
| Manzana asada | 50 | Unidad mediana (120g) | 2,5 | 35 |
| Melocotón | 100 | Unidad mediana (200g) | 2 | 35 |
| Melocotón en conserva | 50 | Una mitad (50g) | 1 | 35 |
| Melón | 200 | Un tajada mediana (200g) | 1 | 60 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|-----------------|--------------------------------|--------------------------------|-----------------------------------|------|
| Aguacate | Libre | | | 10 |
| Albaricoque | 150 | Unidad mediana (50g) | 0,3 | 30 |
| Arándano | 100 | Puñado, con mano cerrada (20g) | 0,25 | 25 |
| Castaña cruda | 30 | Unidad (10g) | 0,3 | 65 |
| Castaña tostada | 25 | Unidad (3g) | 0,3 | 65 |
| Cereza | 100 | 12 unidad. (100g) | 1 | 25 |
| Chirimoya | 50 | Unidad mediana (200g) | 4 | 35 |
| Cinuela | 100 | 2 unidades (100g) | 1 | 35 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|---------------------|--------------------------------|--------------------------------|-----------------------------------|------|
| Membrillo | 150 | Unidad mediana (350g) | 2,5 | 35 |
| Membrillo, dulce de | 20 | | | 85 |
| Moras | 150 | Puñado, con mano cerrada (20g) | 0,15 | 25 |
| Naranja | 100 | Unidad mediana (200g) | 2 | 35 |
| Nectarina | 100 | Unidad mediana (100g) | 1 | 35 |
| Níspero | 100 | Unidad mediana (33g) | 0,3 | 55 |
| Pera | 100 | Unidad mediana (200g) | 2 | 30 |
| Papaya | 125 | Una tajada (250g) | 2 | 65 |
| Paraguay | 100 | Unidad mediana (100g) | 1 | 35 |
| Piña | 100 | 2 rodajas (100g) | 1 | 45 |
| Piña en conserva | 85 | 2 rodajas (100g) | 1,2 | |
| Piña en su jugo | 60 | 2 rodajas (100g) | 1,6 | 80 |
| Plátano | 50 | Unidad pequeña (100g) | 2 | 60 |
| Sandía | 200 | Una tajada grande (200g) | 1 | 75 |
| Uva | 50 | 12 unidad. (100g) | 2 | 45 |

Elaborado por Serafin Murillo, Asesor en Nutrición y Deporte de la Fundación para la Diabetes
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TABLA DE RACIONES DE HIDRATOS DE CARBONO

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|------------------------------|--------------------------------|----------------------------|-----------------------------------|------|
| Apio | 300 | | | 15 |
| Apio-nabo | 500 | Guarnición (125g) | 0,25 | |
| Berenjena | 300 | Unidad grande (300g) | 1 | 20 |
| | | Guarnición (125g) | 0,4 | |
| Berro | No valorate | | | 15 |
| Berza | No valorate | | | 15 |
| Borrajá | No valorate | | | 15 |
| Brócoli | 300 | Plato grande (300g) | 1 | 15 |
| Calabacín | 300 | Unidad grande (300g) | 1 | 15 |
| Calabaza | 200 | | | 75 |
| Cardo | 300 | | | 15 |
| Cebolla | 150 | Unidad mediana (150g) | 1 | 15 |
| Cebolla frita en aros | 100 | | | |
| Champiñón | No valorate | | | 15 |
| Col ácida | No valorate | | | 15 |
| Col Bruselas, Coliflor | 300 | Plato grande (300g) | 1 | 15 |
| Escarola | No valorate | | | 15 |
| Espárrago blanco en conserva | 300 | Unidad (100g) | 0,3 | 15 |
| Espárrago verde | No valorate | | | 15 |
| Espinaca | No valorate | | | 15 |
| Grelos | No valorate | | | 15 |
| Judía verde | 250 | Plato grande (250g) | 1 | 30 |
| Lechuga | 300 | Ración individual (70g) | 0,25 | 15 |
| Lombarda | No valorate | | | 15 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|-----------------------|--------------------------------|----------------------------|-----------------------------------|------|
| Nabo | 300 | Unidad (100g) | 0,3 | 30 |
| Palmitos | 200 | Unidad (25g) | 0,1 | 20 |
| Pepino | 300 | Unidad mediana (150g) | 0,5 | 15 |
| Pimiento rojo/verde | 300 | Unidad mediana (150g) | 0,5 | 15 |
| Puerro | 300 | Unidad mediana (75g) | 0,25 | 15 |
| Rábano | 300 | 5 unidades medianas (100g) | 0,3 | 15 |
| Remolacha | 150 | | | 30 |
| Repollo | 300 | Guarnición (125g) | 0,4 | 15 |
| Ruibarbo | No valorate | | | 15 |
| Setas | 300 | Plato grande (200g) | 0,7 | 15 |
| Soja en brotes | 300 | | | 15 |
| Tomate | 300 | Unidad mediana (150g) | 0,5 | 30 |
| Zanahoria | 150 | Unidad mediana (70g) | 0,3 | 30 |
| Zanahoria hervida | 200 | Unidad mediana (70g) | 0,5 | 85 |
| Zanahoria en conserva | 225 | | | |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|------------------|--------------------------------|--------------------------------|-----------------------------------|------|
| Aceituna | 250 | Una tapa (12 unidad. o 30g) | 0 | 15 |
| Albaricoque seco | 15 | Unidad (5g) | 0,3 | 35 |
| Almendra | 150 | Puñado, con mano cerrada (20g) | 0,1 | 15 |
| Almendra tostada | 140 | Puñado, con mano cerrada (20g) | 0,1 | 15 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|--------------|--------------------------------|--------------------------------|-----------------------------------|------|
| Avellana | 150 | Puñado, con mano cerrada (20g) | 0,1 | 15 |
| Cacahuete | 100 | Puñado, con mano cerrada (20g) | 0,2 | 15 |
| Cinuela pasa | 15 | Unidad (8g) | 0,5 | 40 |
| Dátil seco | 15 | Unidad (10g) | 0,7 | 70 |
| Higo seco | 15 | Unidad (8g) | 0,5 | 40 |
| Nuez | 300 | Puñado, con mano cerrada (20g) | 0 | 15 |
| Piñón | 300 | Puñado, con mano cerrada (20g) | 0 | 15 |
| Pipas | 80 | Puñado, con mano cerrada (15g) | 0,2 | 35 |
| Pistacho | 80 | Puñado, con mano cerrada (20g) | 0,2 | 15 |
| Sésamo | 100 | Cucharada soperá rasa (12g) | 0,1 | |
| Uva pasa | 15 | Puñado, con mano cerrada (20g) | 1,25 | 85 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (g) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | i.g. |
|---|--------------------------------|----------------------------|-----------------------------------|------|
| Bebida refrescante tipo cola o sabores light o sin azúcar | No valorate | | | 0 |
| Bebida de cacao | 100 | Vaso o brick de 200cc | 2 | |
| Bebida de soja | 250 | Vaso o brick de 200cc | 0,8 | 30 |
| Bebida energética | 80 | Lata de 250cc | 3 | 70 |
| Bitter | 100 | Vaso o botellín de 200cc | 2 | 70 |
| Cava brut | No valorate | | | 0 |
| Cava seco o semisecco | 250 | Copa (100cc) | 0,4 | 0 |
| Cerveza | 250 | Vaso o caña de (200cc) | 0,8 | 110 |
| | | Tercio o mediana (330cc) | 1,3 | |
| Cerveza light | 300 | Jarra (600cc) | 2 | 110 |
| | | Vaso o caña de (200cc) | 0,7 | |
| Cerveza sin alcohol | 250 | Tercio o mediana (330cc) | 1,1 | 110 |
| | | Jarra (600cc) | 1,7 | |
| Destilados (ginébra, whisky, ron, vodka) | No valorate | Vaso o caña de (200cc) | 0,8 | 0 |
| | | Jarra (600cc) | 2 | |
| Gaseosa | No valorate | | | 0 |
| Horchata | 75 | Un vaso (200cc) | 2,6 | |
| Horchata light | 300 | Un vaso (200cc) | 0,7 | |
| Licor de melocotón o manzana | 30 | Un chupito (30cc) | 1 | |

Elaborado por Serafin Murillo, Asesor en Nutrición y Deporte de la Fundación para la Diabetes
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► Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections



TABLA DE RACIONES DE HIDRATOS DE CARBONO

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (*) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. |
|--|--------------------------------|----------------------------|-----------------------------------|------|
| Mosto | 70 | Una copa (100cc) | 1,4 | |
| Sangría | 100 | Un vaso (200cc) | 2 | |
| Sidra | 200 | Una copa (100cc) | 0,5 | 0 |
| Tónica | 100 | Un vaso o botellín (200cc) | 2 | 70 |
| Vermut | 75 | Una copa (100cc) | 1,3 | |
| Vino blanco o tinto | No valorable | | | 0 |
| Vino dulce | 75 | Un chupito (30cc) | 0,4 | |
| Zumo de fruta comercial | 100 | Un vaso o brick (200cc) | 2 | 60 |
| Zumo de fruta natural o "sin azúcar añadido" | 250 | Un vaso o brick (200cc) | 0,8 | 45 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (*) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. |
|------------------------------|--------------------------------|--------------------------------|-----------------------------------|------|
| Bollería, en general | 20 | | | 70 |
| Cruasán | 20 | Unidad (60g) | 3 | 70 |
| Cacao en polvo | 12 | Cucharada postre (8g) | 0,7 | |
| | | Cucharada sopera (20g) | 1,7 | |
| Cacao en polvo sin azúcar | 22 | Cucharada postre (8g) | 0,4 | |
| | | Cucharada sopera (20g) | 0,9 | |
| Calamares a la romana | 120 | 4 unidades | 1 | |
| Canelones con bechamel | 100 | 3 unidades (250g) | 2,5 | |
| Caramelo | 12 | Unidad (5g) | 0,4 | 70 |
| Chocolate blanco o con leche | 17 | Pastilla (8g) | 0,5 | |
| | | Tableta individual (30g) | 1,7 | 70 |
| Chocolate negro | 25 | Pastilla (8g) | 0,3 | |
| | | Tableta individual (30g) | 1,2 | 20 |
| Churros | 25 | 2 unidades (25g) | 1 | |
| Crema de cacao | 25 | Cucharada sopera colmada (25g) | 1 | 65 |
| Crema de cacahuete | 100 | Cucharada sopera colmada (20g) | 0,2 | 40 |
| Crema pastelería | 40 | Cucharada sopera colmada (20g) | 0,5 | |
| Croquetas | 50 | 3 unidades (80g) | 1,8 | |
| Donut | 23 | Unidad (56g) | 2,5 | 75 |
| Empanadilla de carne | 50 | 2 unidades (80g) | 1,6 | |
| Ensalmada | 23 | Unidad (70g) | 3 | |
| Fructosa (edulcorante) | 10 | Cucharada sopera (20g) | 2 | 20 |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (*) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. |
|----------------------------------|--------------------------------|---------------------------------------|-----------------------------------|------|
| Gazpacho comercial | 150 | Vaso (200cc) | 1,3 | |
| Gelatina comercial | 62 | Unidad (125cc) | 2 | |
| Glucosa (líquida o en pastillas) | 10 | Pastilla pequeña (2,5g) | 0,25 | 100 |
| | | Pastilla normal (5g) | 0,5 | |
| | | Gel deport (40g) | 2,5 | |
| Golosinas | 18 | | | 70 |
| Ketchup | 50 | Sobre (8g) | 0,2 | 65 |
| Lasaña | 100 | Plato restaurant. (200g) | 2,7 | |
| Levadura | 130 | | | |
| Magdalena | 25 | Unidad (50g) | 2 | |
| Mazapán | 25 | Unidad (35g) | 1,4 | |
| Merengue | 11 | | | |
| Mermelada | 20 | Cucharada sopera (25g) | 1,25 | 65 |
| Mermelada light | Ver etiqueta | | | 30 |
| Miel | 13 | Cucharada sopera (18g) | 1,3 | 65 |
| Mostaza | No valorable | | | |
| Palomitas | 20 | | | 65 |
| Pastel de chocolate | 25 | Porción (100g) | 4 | |
| Pastel de crema | 35 | Porción (100g) | 2,8 | |
| Pepinillos en vinagre | No valorable | | | |
| Pizza | 40 | Triángulo (100g o 1/4 parte de pizza) | 2,5 | |
| | | Media pizza (200g) | 5 | 45 |
| | | Pizza individual (400g) | 10 | |

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (*) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. |
|------------------------------------|--------------------------------|----------------------------|-----------------------------------|------|
| Regaliz | 15 | Unidad (8g) | 0,5 | |
| Salsa barbacoa | 100 | 3 cuchar. soperas (50g) | 0,5 | |
| Salsa bechamel | 100 | 3 cuchar. soperas (50g) | 0,5 | |
| Salsa boloñesa | 150 | 5 cuchar. soperas (75g) | 0,5 | |
| Salsa carbonara | No valorable | | | 0 |
| Salsa de tomate comercial | 100 | 3 cuchar. soperas (50g) | 0,5 | |
| Salsa de soja | No valorable | | | 0 |
| Sucedáneo de café, tipo EKO | No valorable | | | |
| Surimi (palitos de cangrejo) | 100 | Barrita (20g) | 0,2 | |
| Tarta de manzana | 25 | Porción (100g) | 4 | |
| Tofú | No valorable | | | |
| Tortilla de patatas | 120 | Tapa (100g) | 1 | |
| Turrón tipo Alicante | 25 | 1/6 tableta (50g) | 2 | |
| Turrón tipo Jijona | 25 | 1/6 tableta (50g) | 2 | |
| Vinagre | No valorable | | | |
| Vinagre tipo Módena (caramelizado) | 15 | Cucharada sopera (15g) | 1 | |

OTROS

| ALIMENTO | GRAMOS EN UNA RACIÓN DE HC (*) | MEDIDA HABITUAL DE CONSUMO | RACIONES DE HC EN MEDIDA HABITUAL | I.G. |
|----------------------------------|--------------------------------|-----------------------------------|-----------------------------------|------|
| Azúcar blanco | 10 | Cucharada postre (8g) | 0,8 | 70 |
| | | Cucharada sopera (20g) | 2 | |
| | | Sobre (8g) | 0,8 | |
| Azúcar moreno | 10 | Cucharada postre (8g) | 0,8 | 70 |
| | | Cucharada sopera (20g) | 2 | |
| | | Sobre (8g) | 0,8 | |
| Barrita energética (de cereales) | 20 | Unidad (25g) | 1,25 | 70 |
| Bizcocho o melindro | 20 | Unidad comercial individual (25g) | 1,25 | 65 |

(*) CANTIDAD DE ALIMENTO (GRAMOS) QUE CONTIENE 1 RACIÓN DE HIDRATOS DE CARBONO (HC)

10 GRAMOS DE HIDRATOS DE CARBONO (HC) = 1 RACIÓN DE HC

I.G. = ÍNDICE GLUCÉMICO DE CADA ALIMENTO
ROJO: Elevado (70 o más)
NARANJA: Moderado (55-69)
VERDE: Bajo (55 o menos)
 Los alimentos que en la tabla aparecen sin ningún valor en la casilla de I.G. es porque se desconoce la información de ese alimento en cuestión.

Elaborado por Serafín Murillo, Asesor en Nutrición y Deporte de la Fundación para la Diabetes
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► Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

16.4 ANNEX 4: FreeStyle Libre

- Glucose sensor FreeStyle Libre (ABBOTT)



- Lector FreeStyle Libre (ABBOTT)



► Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

16.5 ANNEX 5. FREESTYLE LIBRE COMPUTER SOFTWARE

Visualización del patrón de glucosa

29 de enero de 2014 - 11 de febrero de 2014 (14 días)

CONFIGURACIÓN DE TOLERANCIA DE GLUCOSA BAJA: Medio

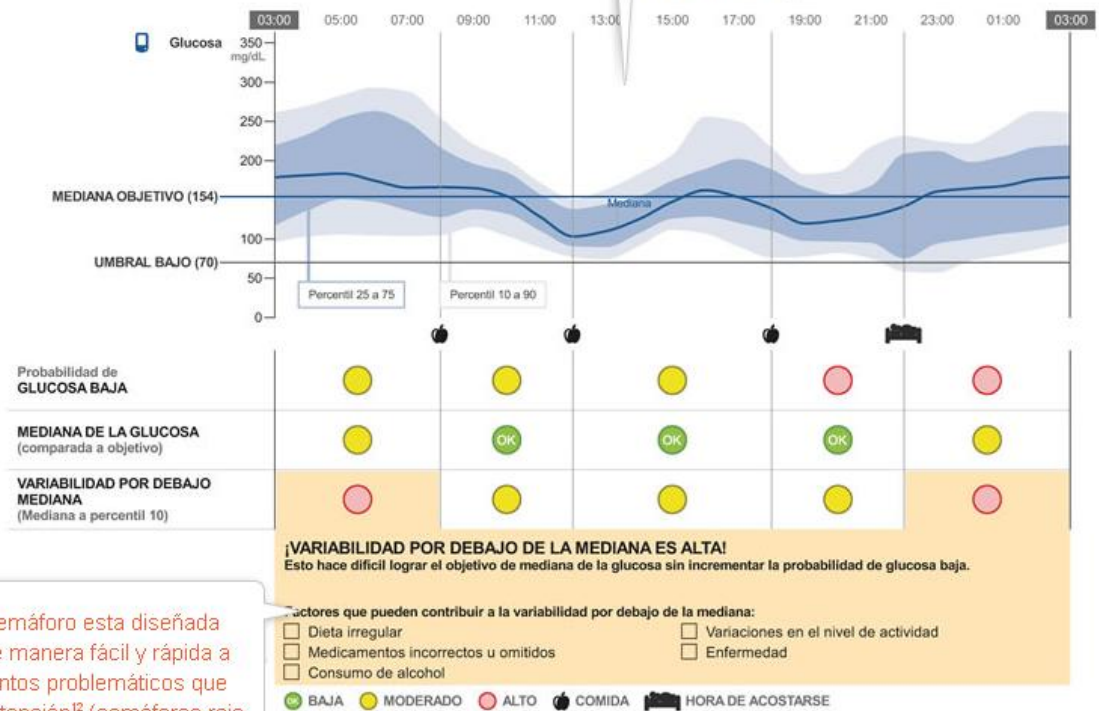
CONFIGURACIÓN DE MEDIANA OBJETIVO: 154 mg/dL (A1c: 7,0% o 53 mmol/mol)

El Perfil Ambulatorio de Glucosa organiza los datos de glucosa en percentiles¹¹ a lo largo del día.

Esta es una foto de un día tipo que muestra las tendencias de hipo e hiperglucemia.

FreeStyle Libre 

A1c estimado 7,1% o 54 mmol/mol



La gráfica tipo semáforo esta diseñada para ayudarle de manera fácil y rápida a identificar los puntos problemáticos que requieren más atención¹² (semáforos rojo y amarillo)

- ▶ Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

16.6 ANNEX 6: ACCU-CHEK® AVIVA EXPERT (ROCHE)



► Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

16.7 ANNEX 7: SOCIAL DIABETES APP

The screenshots illustrate the app's interface for user configuration and data monitoring. The first three screens show the initial setup process, including selecting diabetes type (Type 1 or Type 2) and configuring personal information such as weight, height, and birth date. Subsequent screens show the configuration of glucose ranges (very low, low, high, very high) and postprandial levels, as well as settings for insulin pump use and bolus calculator preferences. The final three screens display monitoring features, including a weekly glucose control chart, a table of recent glucose readings with associated carbohydrate intake, and a summary of glucose control metrics over the last month.

| Glucosa | Ayer | Semana | Mes |
|----------------|----------|--------|--------|
| Valores medios | 0 | 0/0 | 0/0 |
| Último mes | Desayuno | Comida | Cena |
| Valores medios | 0/0 | 0/0 | 0/0 |
| Hipoglucemias | 0 (0%) | 0 (0%) | 0 (0%) |

| Categoría | Contador | Porcentaje |
|-----------|----------|------------|
| Muy bajo | 1 | 1 (17%) |
| Bajo | 1 | 1 (17%) |
| Normal | 2 | 2 (33%) |
| Alto | 1 | 1 (17%) |
| Muy alto | 1 | 1 (17%) |

16.8 ANNEX 8: FEAR OF HYPOGLYCEMIA SCALE (FH-15)

Appendix B

The FH-15 Scale

1. How often do you fear not recognizing the symptoms of hypoglycemia?
 2. How often are you afraid of not knowing what to do in the event of hypoglycemia?
 3. How often are you afraid of having hypoglycemia at work?
 4. How often are you afraid of having hypoglycemia outside of a hospital/health care setting?
 5. How often are you afraid of having hypoglycemia while alone?
 6. How often do you avoid social situations (meetings, outings, etc.) due to fear of having a hypoglycemic episode?
 7. How often do you stop doing things you used to do for fear of having a hypoglycemic episode?
 8. How often do you have hypoglycemia that makes you unable to drive or use machinery?
 9. How often you have hypoglycemia that makes you unable to work?
 10. How often do you have hypoglycemia that interferes with your leisure activities?
 11. How often do you have hypoglycemia that interferes with your family life?
 12. How often do you have hypoglycemia that interferes with your social life?
 13. How often do you worry about losing consciousness due to hypoglycemia?
 14. How often are you afraid of falling asleep for fear of having hypoglycemia at night?
 15. How often are you afraid of taking a trip/holiday for fear of experiencing hypoglycemia?
- Response options are 1 (*Never*), 2 (*Almost never*), 3 (*Sometimes*), 4 (*Almost always*), 5 (*Every day*).

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- Efficacy of including an insulin bolus calculator to reduce the number of severe hypoglycaemia episodes in patients with type 1 diabetes mellitus treated with multi-daily insulin injections

16.9 ANNEX 9. ESDQOL QUESTIONNAIRE

| ANEXO 1 | EsDQOL modificado |
|--|----------------------|
| Satisfacción | |
| 1. ¿Está usted satisfecho con la cantidad de tiempo que tarda en controlar su diabetes? | |
| 2. ¿Está usted satisfecho con la cantidad de tiempo que ocupa en revisiones? | |
| 3. ¿Está usted satisfecho con el tiempo que tarda en determinar su nivel de azúcar? | |
| 4. ¿Está usted satisfecho con su tratamiento actual? | |
| 5. ¿Está usted satisfecho con la flexibilidad que tiene en su dieta? | |
| 6. ¿Está usted satisfecho con la carga que supone su diabetes en su familia? | |
| 7. ¿Está usted satisfecho con su conocimiento sobre la diabetes? | |
| 8. ¿Está usted satisfecho con su sueño? | |
| 9. ¿Está usted satisfecho con sus relaciones sociales y amistades? | |
| 10. ¿Está usted satisfecho con su vida sexual? | |
| 11. ¿Está usted satisfecho con sus actividades en el trabajo, colegio u hogar? | |
| 12. ¿Está usted satisfecho con la apariencia de su cuerpo? | |
| 13. ¿Está usted satisfecho con el tiempo que emplea haciendo ejercicio? | |
| 14. ¿Está usted satisfecho con su tiempo libre? | |
| 15. ¿Está usted satisfecho con su vida en general? | |
| Impacto | |
| 16. ¿Con qué frecuencia siente dolor asociado con el tratamiento de su diabetes? | |
| 17. ¿Con qué frecuencia se siente avergonzado por tener que tratar su diabetes en público? | |
| 18. ¿Con qué frecuencia se siente físicamente enfermo? | |
| 19. ¿Con qué frecuencia su diabetes interfiere en su vida familiar? | |
| 20. ¿Con qué frecuencia tiene problemas para dormir? | |
| 21. ¿Con qué frecuencia encuentra que su diabetes limita sus relaciones sociales y amistades? | |
| 22. ¿Con qué frecuencia se siente restringido por su dieta? | |
| 23. ¿Con qué frecuencia su diabetes interfiere en su vida sexual? | |
| 24. ¿Con qué frecuencia su diabetes le impide conducir o usar una máquina (p. ej., máquina de escribir)? | |
| 25. ¿Con qué frecuencia su diabetes interfiere en la realización de ejercicio? | |
| 26. ¿Con qué frecuencia abandona sus tareas en el trabajo, colegio o casa por su diabetes? | |
| 27. ¿Con qué frecuencia se encuentra usted mismo explicándose qué significa tener diabetes? | |
| 28. ¿Con qué frecuencia cree que su diabetes interrumpe sus actividades de tiempo libre? | |
| 29. ¿Con qué frecuencia bromean con usted por causa de su diabetes? | |
| 30. ¿Con qué frecuencia siente que por su diabetes va al cuarto de baño más que los demás? | |
| 31. ¿Con qué frecuencia come algo que no debe antes de decirle a alguien que tiene diabetes? | |
| 32. ¿Con qué frecuencia esconde a los demás el hecho de que usted está teniendo una reacción insulínica? | |
| Preocupación: social/vocacional | |
| 33. ¿Con qué frecuencia le preocupa si se casará? | |
| 34. ¿Con qué frecuencia le preocupa si tendrá hijos? | |
| 35. ¿Con qué frecuencia le preocupa si conseguirá el trabajo que desea? | |
| 36. ¿Con qué frecuencia le preocupa si le será denegado un seguro? | |
| 37. ¿Con qué frecuencia le preocupa si será capaz de completar su educación? | |
| 38. ¿Con qué frecuencia le preocupa si perderá el empleo? | |
| 39. ¿Con qué frecuencia le preocupa si podrá ir de vacaciones o de viaje? | |
| Preocupación relacionada con la diabetes | |
| 40. ¿Con qué frecuencia le preocupa si perderá el conocimiento? | |
| 41. ¿Con qué frecuencia le preocupa que su cuerpo parezca diferente a causa de su diabetes? | |
| 42. ¿Con qué frecuencia le preocupa si tendrá complicaciones debidas a su diabetes? | |
| 43. ¿Con qué frecuencia le preocupa si alguien no saldrá con usted a causa de su diabetes? | |