Comparative analysis between the therapy of sliding scale insulin and basal-bolus insulin in a hospital emergency

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A mi mujer Elisabet, quien siempre estuvo a mi lado día y noche.

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ABBREVIATIONS

HA1C: Glycosylated Hemoglobin

ADA: American Diabetes Association

AMI: Acute Myocardial Infarction

BBI: Basal-Bolus Insulin

CREC: Clinical Research Ethics Committee

DM: Diabetes Mellitus

GAD: Glutamic Acid Decarboxylase

HLA: Human Leukocyte Antigen

HUMT: Hospital Universitario Mutua Terrassa

IFG: Impaired Fasting Glucose

IGF: Insulin-like Growth Factor

IGT: Impaired Glucose Tolerance

IU: International Units

MODY: Maturity Onset Diabetes of the Young

NOAD: Non-insulin Antidiabetics

OGTT: Oral Glucose Tolerance Test

SOCMUE: Sociedad Catalana de Medicina de Urgencias y Emergencias

SSI: Sliding Scale Insulin

TDID: Total Daily Insulin Dose

WHO: World Health Organization

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ABSTRACT

TITLE: Comparative analysis the therapy of sliding scale insulin and basal-bolus insulin in a hospital emergency

BACKGROUND: Diabetes mellitus (DM) is a chronic metabolic illness with a high prevalence in our population, approximately 13,8% has a DM background and 6% of them haven't been diagnosed yet. In the emergency services, about 30-40% of patients are diabetic regardless of the reason for consultation. On many occasions, the control of blood glucose is not appropriate, as it has been proven in various studies in which blood sugar level has kept over 140 mg/dl. This situation worsens the prognosis, increases medical complications, and lowers the survival rate of diabetic patients.

That's why it is necessary to stablish protocols that have scientifically proven a good control of blood sugar levels. In Cataluña, the Catalan Society of Urgencies and Emergencies diabetes group (SOCMUE in its Spanish acronym) developed a protocol based on the usage of insulin in a basal-bolus regimen.

This scientific society and several groups of experts recommend the usage of this protocol in the insulinisation of the hospitalized diabetic patient. However, the traditional treatment based on a sliding scale of rapid insulin depending on the blood sugar level after each main meal is still being used.

OBJECTIVE: This intervention study intends to analyse and compare the effectiveness of the traditional treatment (ISS) instead of the protocol proposed by the SOCMUE using as reference population patients treated in the emergency services of the University Hospital Mutual of Terrassa.

STUDY DESIGN AND METHODS: This intervention study will be conducted in a 3 month period. The first month the blood glucose control will be analysed with Insulin Sliding Scale therapy. The second month. The second month nurses and doctors will be trained in the use of basal bolus insulin (BBI) therapy in the emergency services. The last month the blood glucose control will be analysed again after using the BBI therapy. The sample selection will be conducted using a consecutive, non-probabilistic type model, in which all patients fulfilling the required criteria will be selected in a determined period of a month per group.

KEYWORDS: Diabetes Mellitus; Insulin; Emergency services protocols; Insulin Sliding Scale; insulin Basal Bolus; diabetic patient; glycemia; control of blood glucose; hyperglycemia.

1. INTRODUCTION

Diabetes Mellitus is an illness with a high prevalence in our population. A study carried out with a representative sample of the Spanish population, with more than five thousand participants from different Spanish territories, determined that DM prevalence reaches 13.8%[(1)], growing higher with age. Moreover, based on growth projections by the WHO, DM with be the seventh cause of mortality on 2030 [(2)].

Diabetes affects the life quality of patients due the complications it causes in specific organs, often in a silent way and showing up in advanced stages. In addition to promoting the occurrence of cardiovascular risk factors such as hypertension or hyperlipidaemia. [(3)]

It is also necessary to assess the costs arisen from diabetes in order to be aware of the importance of a proper control and treatment. A study called CODE-2 was carried out in Spain with the intention of estimating the direct and indirect costs stemmed from the treatment of type 2 diabetic patients, using as a representative sample of the patients treated in primary care. The annual cost by patient obtained by this study resulted in 1.305,15.-€. However, the cost was even higher, a 64.5% rough total of the cost, in those patients with complications, as opposed to a 13,7% estimated total of the cost of a diabetic patient without complications.[(4)]

That is why an optimal control of diabetic patients is necessary, as to improve both complications, risk factors, survival rate, hospitalisation in emergency and wardrooms and, therefore reducing the costs. To that effect, the emergency service is a good start for the aforementioned control.

Emergency services are, on many occasions, the entry point of diabetic patients into the health system, through it, they arrive with urgent medical situations in which glycemia is frequently out of control, often due to the illness responsible for said visit to the emergency services. This is why emergency services must carry a proper control of blood sugar levels, as alterations in the levels of sugar in blood are frequent, even in those patients with a good domestic control of glycemia.[(5)]

A Catalan guide on the handling of glycemia in emergency services has been recently developed by the Catalan Society of Urgencies and Emergencies diabetes group (SOCMUE) and it was introduced in the XXIV Catalan National Congress on Emergency Medicine held in Reus on April 2017. This guide proposes and action protocol for glycemia control in emergency services based on the consensus achieved by different Spanish scientific associations that want to stop using the actual insulinisation treatment, based on an insulin sliding scale, to develop a more physiological treatment called bolus-basal.[(6)]

1.1. Definition of diabetes mellitus

Diabetes is defined as a metabolic disorder with multiple causes, characterized by chronic hyperglycemia alongside metabolic alterations of carbohydrates, proteins and fats caused by defects in the secretion of insulin and/or its action. Chronic hyperglycemia, characteristic of this illness, is associated to damage, dysfunction or failure of multiple organs, specially the eyes, kidneys, nervous system, hearth and blood vessels.[7][8]

1.2. Classification

Diabetes is classified at an international level since 1977, as proposed by an experts committee of the American Diabetes Association (ADA) in type 1 and type 2 diabetes, gestational diabetes and more specific kinds; as type MODY (maturity onset diabetes of the young) amongst others. [9]

Due being the most prevalent and of higher relevance, the following paragraphs will only describe type 1 and 2 diabetes.

1.2.1 Type 1 Diabetes Mellitus:

It is characterized by the destruction of beta cells from the pancreatic islets, and therefore there exists an absolute deficit in the secretion of insulin and a higher prevalence of ketoacidosis. Following ADA most recent recommendations, in 2017 three levels can be distinguished based on autoimmunity, glycemia, and symptoms shown by the patient (table 1). [9]

	STAGE 1	STAGE 2	STAGE 3
STAGE CRITERIA	autoimmunity	autoimmunity	new-onset hyperglycemia
	normoglycemia	dysglycemia	symptomatic
	presymptomatic	presymptomatic	
DIAGNOSTIC CRITERIA	Multiple autoantibodies	Multiple autoantibodies	clinical symptoms
	No IGT or IGF	dysglycemia; IFG and/or IGT	diabetes by standard criteria
		FPG 100-125 mg/dl 2h PG 140-199 mg/dl	
		A1C 5.7-6,4% or >10% increase in A1C	

Table 1 States of diabetes type 1 according to the American Diabetes Association 2017 (ADA)

Even so, in a more general sense type 1 DM may be divided between those immune-mediated and idiopathic.

A) Immune-mediated:

It affects 5-10% of diabetics, also known as insulin-dependent, or juvenile onset diabetes since, as we have already stated, it implies an autoimmune destruction of ß pancreatic cells. It tends to happen on childhood and adolescence, but it may happen at any age, even in the eight or ninth decade of life. Generally speaking, the rate of ß cells destruction is higher in children than in adults, in whom it tends to be slower.

The destruction tracers are the antibodies against the cells from the islets and insulin, the GAD antibody (glutamic acid decarboxylase) (GAD 65) and the IA-2 and IA-2ß tyrosine phosphatase antibody, are present in 80-95% of fasting hyperglycaemic individuals. The immune self-destruction of ß cells is also related to little defined environmental factors

Some patients, mostly children and teens, may show ketoacidosis as a first manifestation of the illness. Other show moderate hyperglycemia while fasting, which may rapidly change into severe hyperglycemia and/or ketoacidosis, moreover when an infection or other situations predisposing to hyperglycemia are present. When it manifests in adults they mainly have a sufficient residual secretion of ß cells, which allows the prevention of ketoacidosis for many years even though this people become insulin-dependent and are at risk of ketoacidosis.[8]

As this type is greatly influenced by the patient's autoimmunity they are also highly prone to other autoimmune disorder: Grave's disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac disease, autoimmune hepatitis, myasthenia gravis or pernicious anaemia.[7]

In short, this kind of diabetes is characterized by:

- A sudden start, normally before age 30.
- Propensity towards ketoacidosis.
- Not caused by obesity, though its presence does not exclude its diagnosis.
- The presence of autoimmune processes in its aetiology.
- The presence of other autoimmune illnesses, though they may not be present.

B) idiopathic

Some types of DM 1 have no differential diagnosis. Some patients have a permanent insulin deficit and are prone to ketoacidosis but have no evidence of autoimmunity. Only a minority of type 1 diabetes patients fit into this category and many are of African or Asiatic heritage.

This type of diabetes is characterized by:

- A strong hereditary component.
- Lacking immunological evidence of ß cells autoimmunity.
- It isn't related to HLA
- The need for an insulin-based treatment might be imminent.

Patients with this kind of diabetes suffer from episodic ketoacidosis and show different degrees of insulin in between episodes.

1.2.2 Type 2 Diabetes Mellitus [9]

It is the most prevalent kind of diabetes, as it has a prevalence of 90-95%. This type of diabetes is related to age, obesity and physical inactivity. It's caused by the association of resistance to insulin and a secretion of diminished insulin. It is possible for one of both to prevail, but both insulin resistance and diminished insulin must always be present.

Patients suffering from type 2 diabetes mellitus have a slow development of the illness and scarce symptomatology that goes undetected for various years. This situation frequently causes them to be diagnosed in later stages in which they already have complications when diagnosed.

It is characterized by:

- A progressive start, usually after age 40.
- It isn't common for it to cause ketoacidosis, though it may appear if there is an associated pathology that bolsters its emergence.
- It is associated to obesity and physical inactivity. It has been also related to intrauterine growth retardation as an environmental factor.
- It often affects one's progeny, though the genetic component is complex and hasn't been properly defined nor fully discovered yet.

2. JUSTIFICATION

Focusing on hospitals' emergency departments, around 30-40% of patients treated in emergency services have diabetes[10], and 25% of patients hospitalized in internal medicine services do so too (many of whom proceed from the emergency services).[11] In most cases, the reason for their visit is not diabetes but another breakthrough illness or the medication used for an acute pathology that, often, unbalances the underlying diabetic illness, disrupting capillary glycemia. At the same time hyperglycemia, and mainly sustained hyperglycemia, increases the risk of suffering illnesses related to target organs as the heart, kidney, nervous system and immune system. [12][13]

A study carried out in the emergency service of Santa Creu i Sant Pau Hospital from Barcelona and published in 2017 in which they analysed the glycemia control on diabetic patients hospitalized on a 4-month period, determined that blood glucose control isn't optimal, since 70% of analysed patients had glycemia over 140 mg/dl (Table 2). Moreover, 25% of patients with hyperglycemia had no treatment for glycemia control. Only 17% were controlled for glycemia using the basal-bolus insulin protocol backed by Spanish and American scientific societies as the protocol of choice.[14] [15]

Variable		N (%)
Average age		77.9 (11.8)
Women		80 (56.3)
Men		62 (43.7)
Glycemia	80-140	42 (29.6)
	141-200	52(36.6)
	201-250	33 (23.2)
	>251	15 (10.6)
Treatment	Any	64 (45.1)
	Insulin sliding scale	53 (37.3)
	Insulin basal-bolus	25 (17.6)

Table 2: Results of the study on Diabetes in emergency services: evaluation of monitoring and installed treatments

This makes us reflect on the inadequate control of glycemia carried out in hospitals' emergency services and the need for the instalment of a protocol followed by all professional who intervene in the blood glucose control of diabetic patients.

This ends up resulting in a worsening of the patient's prognosis, making it necessary for the patient to be hospitalized, therefore increasing the risk of hospitalization, of a longer duration too, for diabetic patients compared with the rest of the population. Which in consequence entails a higher health spending. Moreover, diabetic patients have a higher risk of mortality, being cardiovascular complications the leading cause of death and bronchopneumonia the main infectious complication for these patients. [16]

Furthermore, many patients going to the emergency services aren't diabetic but get diagnosed with hyperglycemia. This is called stress hyperglycemia. It refers to that hyperglycemia (>126 mg/dl when fasting or > 200 mg/dl in a routine check) that shows up in a patient that's in critical condition or hospitalized by an illness, not necessarily critical, without a background of type I or type II diabetes, that disappears once the acute process is under control. We can rely on haemoglobin HbA_{1c} to detect stress hyperglycemia on those undiagnosed diabetic patients with an incorrect control of glycemia in an acute moment. [9] [17]

It is mainly caused by two mechanisms present on the critical or hospitalized patient:

- An increase of counter-regulatory hormones (catecholamine, glucagon, cortisol…)
- A systemic inflammatory response as part of the pathological process, with an increasing hyperglycemia as the inflammatory response becomes worst. As a consequence of the systemic inflammation there is a neuroendocrine response, that releases pro-inflammatory cytokines, tumour necrosis factor-alpha (TNF-A) and interleukins 1 and 6 (IL 1-IL6) mainly, that stimulate hepatic glycogenesis and glycogenolysis [18].

This finally results in a hyperglycemia due to:

- An increase of plasma glucose emanated from glycogenesis and glycogenolysis on a hepatic level.
- Peripheral resistance to insulin action, mainly due to the inhibition of the insulin-dependent glucose transporter GLUT-4, present in adipose tissue and striated and cardiac muscle.

Referring to particular pathologies, it has been demonstrated that stress hyperglycemia in patients who suffered from an acute myocardial infarction (AMI) is associated to an increase on complication rates due to a higher risk of suffering from cardiac insufficiency or even cardiogenic shock [19]. Therefore, hyperglycemia can be an effective tool in the prediction of prognosis, as it has shown to be effective as a morbidity and mortality tracer during the time of a chronic or acute illness.

That said, several studies conducted with critical patients in ward and intensive care units evaluating the consequences of an intensive treatment of stress hyperglycemia, as opposed to another group of patients in which a more conservative control is taken, have shown that mortality and stay in intensive care units is similar. In addition, the group treated with a more intensive insulin therapy has had more episodes of hypoglycemia.[13] That is the reason why, knowing this information, it would be convenient to consider the bolus-basal therapy as a more physiological option for these patients.

This is why a badly controlled hyperglycemia is a clear tracer for severity and a worst prognosis. In consequence we have to act on diabetic patients, mainly when they access the emergency services, where an optimal and early control of hyperglycemia is decisive to improve the prognosis and termination of the pathology that has motivated their visit to the hospital's emergency services, which would reduce the economic costs and the morbidity and mortality of this population.

The object of this study will be conducted in the emergency service of the University Hospital Mutual of Terrassa, where they are controlling the glycemia of diabetic patients who access the emergency service using insulin sliding scales (Table 3), which is discouraged with an A degree of evidence, following the recommendations published in January 2017 in the guidelines *of American Diabetes Association*. [9]

Blood Glucose Level, mg/dL	Human Insulin, IU[a]
0-80	0
81-100	0
101-150	0
151-200	2
201-250	4
251-300	6
301-350	8
351-400	10
>401	12

Table 3: example of sliding insulin scale depending on blood glucose

Therapy based on insulin sliding scales consists on the administration of predetermined amounts of short acting insulin in situations of hyperglycemia, increasing the amount of insulin to be administrated depending on the glycemia (they are generally increased by 2 IU of insulin with each increase of 50 mg/dl of plasmatic glucose). [20] [21]

Insulin sliding scales aren't recommended for several reasons: [6]

- They aren't physiological, as they only try to correct hyperglycemias and, in many cases, this regime remains unaltered along the whole hospitalization.
- They don't prevent hyperglycemias but treat them when they show up, so, when hyperglycemia manifests, there has already been a negative effect on comorbidities associated to it, and once hyperglycemia has settled, glycemia control becomes more difficult.
- They don't take into account the patient's sensitivity to insulin, if he or she still is under the effect of a different insulin taken prior to hospitalization, of the patient's diet or weight.
- It has been associated to a control that's more likely to cause hyperglycemia.

A Catalan guide on the Handling of glycemia in emergency services has been recently developed by the Catalan Society of Urgencies and Emergencies diabetes group (SOCMUE) and it was introduced in the XXIV Catalan National Congress on Emergency Medicine held in Reus on April 2017. This guide proposes and action protocol for glycemia control in emergency services based on the consensus achieved by different Spanish scientific associations, included in a document titled "*tratamiento de la hiperglicemia en el hospital*" (*treatment of hyperglycemia in hospital*).

In this Catalan guide, it is proposed the handling of the diabetic patient using insulin in a bolus-basal regime. This therapy tries to simulate as physiologically as possible the insulin secretion in a non-sick patient. Understanding the physiological insulin secretion process is needed for that.

Insulin is secreted in two ways at the same time: (figure 1)

- 50% of insulin release is done in a constant way, to then metabolize the glucose obtained from glycogen in glycogenesis and glycogenolysis during fastening.
- The other 50% is secreted as peaks depending on carbohydrates ingested in one's diet.

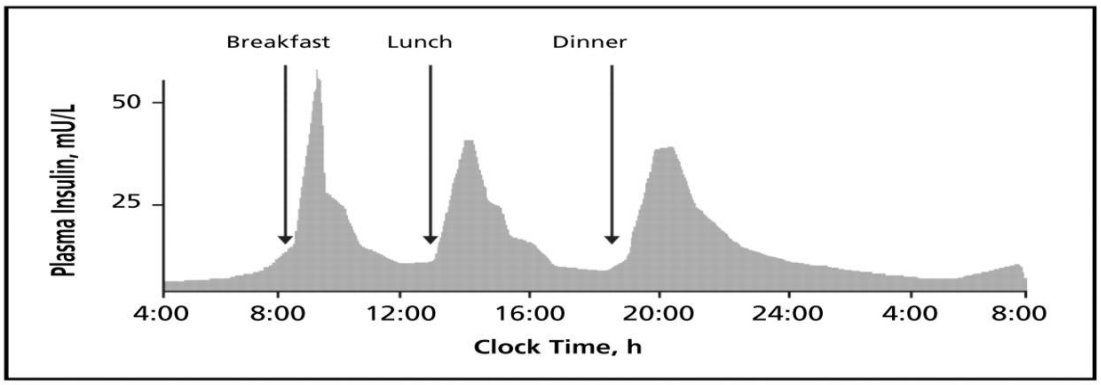


Figure 1: physiological insulin secretion

That said, to carry out the recommendations of the Catalan guide on the Handling of glycemia in emergency services it's necessary to initially calculate the total daily insulin dose (TDID) and afterwards distribute it in between basal and postprandial insulin. To calculate the TDID an algorithm is used depending on the glycemia when arriving into the emergency services and the background treatment had, always removing oral antidiabetics, as shown on figure 2. [(6)]

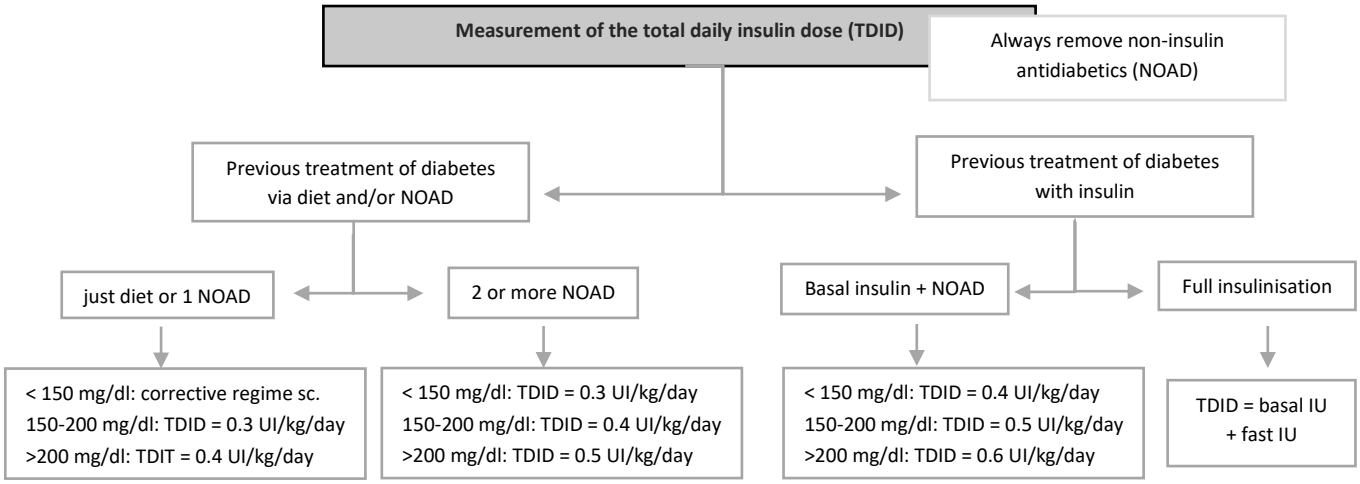


Figure 2 Measurement of the total daily insulin dose based on the protocol created by the Catalan Society of Urgencies and Emergencies diabetes group (diabetes SOCMUE)

Once the amount if insulin required by the patient is measured it is necessary to differentiate the situations in which a person has an oral intake or is in an absolute diet, a common situation in hospital's emergency services. Acting as follows:

A. In the event of an oral intake, 50% of the TDID is administered as basal insulin, trying as far as possible for it to be done in a single dose. The other half must be administered as rapid insulin distributed in equal parts before daily main meals. To adjust the dose of fast insulin as much as possible IU may be added or taken depending on the weight and glycemia prior to the intake, taking after the recommendations of the SOCMUE following the corrective regime shown on table 4.

B. If the patient is in an absolute diet, he or she is administered 70% of the TDID as basal insulin applying every 6 hours the corrective regime used in the event of an oral intake of the patient, so defects on the administration of basal insulin can be corrected. Granting in any case and adequate intake of intravenous glucose.

Glycemia before ingestion	< 40 UI/day – weight < 60kg.	40-80 UI/day – weight 60-90kg.	>80 UI/day – weight > 90kg.
<80 mg/dl	-1	-1	-2
80-129	0	0	0
130-149	1	1	1
150-199	1	2	2
200-249	2	3	4
250-299	3	5	7
300-349	4	7	10
>350	5	8	12

Table 4: corrective regime based on the protocol created by the Catalan Society of Urgencies and Emergencies diabetes group (diabetes SOCMUE)

On the other hand, if a patient hospitalized in the emergency service has hyperglycemia, it must be handled in a proper way and following a different regime depending on it being a simple hyperglycemia or it appearing on a critic patient.

We define as simple hyperglycemia the one that's over 140 mg/dl when fasting of over 180 mg/dl in a postprandial intake (always when no data suggesting ketoacidosis, or a hyperosmolar syndrome, appears). Therefore, if hyperglycemia is lower than 350-400 mg/dl it is administered a rapid intravenous insulin bolus following a subcutaneous insulin regime depending on glycemia, always associated to 500cc of a 2h physiological saline solution. If hyperglycemia is over 350-400 mg/dl, an insulin intravenous perfusion is directly initiated at a rate of 6-8 IU/hour, being possible to associate serum therapy with physiological saline solution depending on the patient's hydration. When glycemia is < 250 mg/dl, the perfusion speed has to be lowered to 3-4 IU/hour and dextrose 10% serum associated at a rate of 1000 cc every 24h. In both cases when glycemia is stabilized, and remains under 200 mg/dl, the oral diet must be retaken, and the bolus-basal regime restarted.

Assessing the available bibliography on this topic, both in 2007 and 2011 two random studies have been respectively published in the scientific magazine *Diabetes Care* of the American Diabetes Association (ADA), called RABBIT-2 and RABBIT-2 Surgery. The latest compared the efficiency and security of a basal insulin treatment with glargine insulin bolus once a day and glulisine before meals (n = 140) with rapid insulin in a sliding scale insulin (SSI) 4 times a day (n = 107) in patients with type 2 diabetes mellitus that underwent general surgery. [(22)]

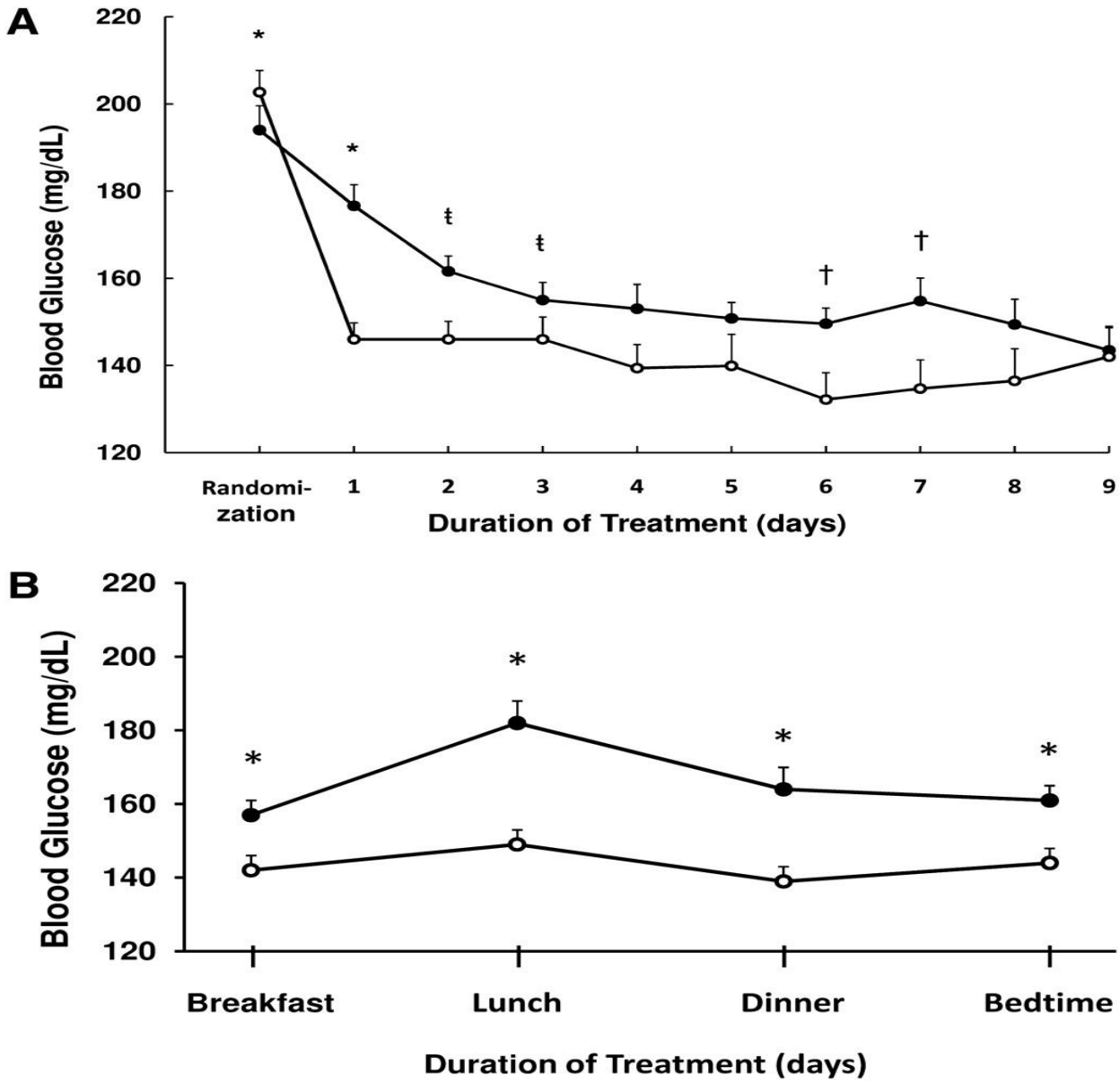


Figure 3

A: Glucose levels during basal-bolus and SSI treatment. Changes in blood glucose concentration after the 1st day of treatment with basal-bolus with glargine once a day plus glulisine before meals (o) and with insulin sliding scale 4 times a day (•)

B: Glucose levels before meals and bedtime premeal and bedtime glucose levels were higher throughout the day SSI group (•) campared with basal-bolus régimen (o).

This study arrives to the conclusion that the group treated with a basal-bolus regimen has glycemia control (considering as control blood glucose ≤ 140 mg/dl) in 55% of patients, as opposed to a 31% glycemia control in patients treated with Sliding Scale Insulin. This data plays a greater role when related with the first study conducted in 2007 with type 2 diabetic patients hospitalized in general medical wards, which arrived at the conclusion of a 66% glycemia control in the bolus-basal insulin group as opposed to a 38% in the SSI group.[23]

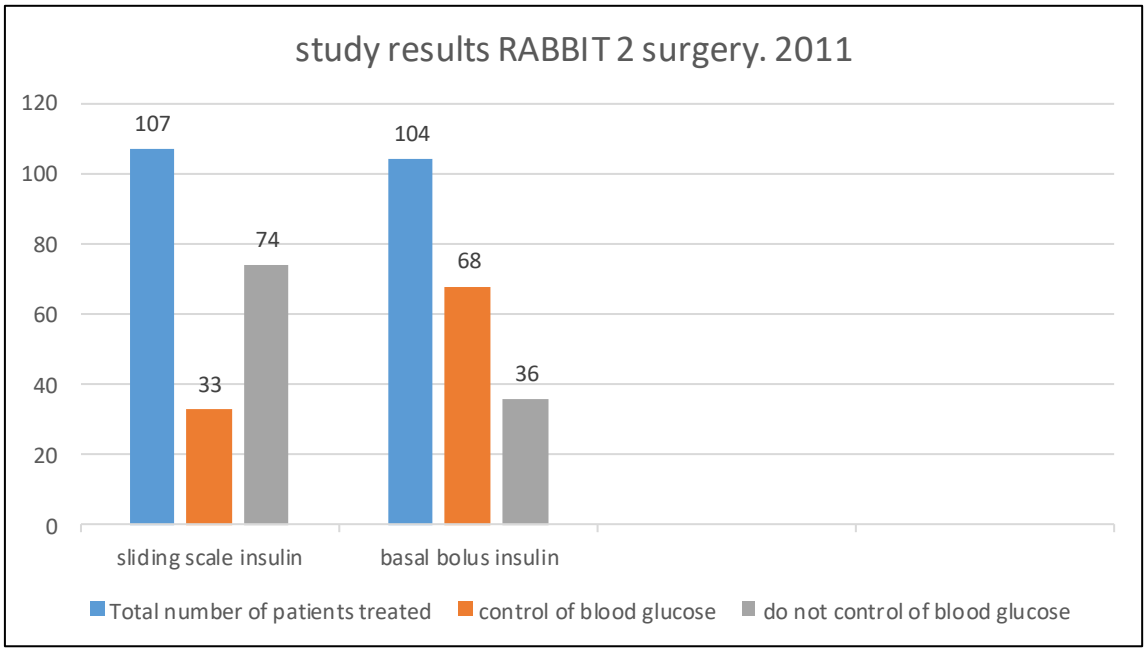


Figure 3: study result RABBIT 2 surgery in 2011.

In addition, the RABBIT-2 Surgery study demonstrated a lower number of postoperative complications and lesser days of hospitalization in wards for critical patients in the group treated with Basal-Bolus Insulin, (Table 5).

	All	SSI	Basal-bolus insulin	*P* value
Wound infections	14	11	3	0.050
Pneumonia	3	3	0	0.247
Acute respiratory failure	6	5	1	0.213
Acute renal failure	15	11	4	0.106
Bacteremia	3	2	1	0.999
Number of patients with complications	35	26	9	0.003
Mortality	2	1	1	NS
Postsurgery ICU admission (%)	16	19.6	12.5	NS
Length of stay (days)				
ICU	2.51 ± 1.90	3.19 ± 2.14	1.23 ± 0.60	0.003
Hospital	6.8 ± 8.9	6.3 ± 5.6	7.23 ± 11.39	NS

Table 5: Complications in the groups of patients treated with SSI versus Basal-Bolus Insulin

That way, this protocol pretends to conduct an interventional study in which it is or not observed the efficiency and benefit of applying the SOCMUE recommendations on the bolus-basal theory instead of the actions practised at the present with the fast insulin sliding scale in the University Hospital Mutual of Terrassa.

3. HYPOTHESIS

The actual handling of glycemia in the emergency services of patients previously diagnosed of diabetes mellitus, o not previously diagnosed but that present hyperglycemias during their stay, when going to an emergency service, isn't optimal.

4. MAIN OBJECTIVE

Analysing if the implementation of a new insulinisation protocol for the diabetic patient, or with hyperglycemia criteria, in the Emergency Service of the University Hospital Mutual of Terrassa (HUMT) improves the early control of glycemia on patients who are hospitalized for more than 24h, related to the fast insulin with sliding scale protocol already used in said hospital.

5. METHODOLOGY

5.1 Design

This intervention study will be conducted in a 3 month period distributed as it follows. During the first month, there will be a compilation of data from patients, which will be included in the study following the inclusion and exclusion criteria in which the glycemia control with a fast insulin mobile regimen was done. Afterwards, all associate and resident doctors in the HUMT's general hospital emergency service will undergo training, which will be included in the monthly mandatory formative sessions. In this training, they'll be taught the theoretical grounds on the bolus-basal insulinisation therapy, as well as practical cases. It is estimated a one-month period for the training of the emergency services facultative team. Next, there will be another data collection, this time using the new insulinisation therapy for another month.

Therefore, there will be two consecutive moments of data collection. This way, the data gathering is prevented from taking place in different moments of the year, so this doesn't affect the variability of data due to affluence or the different characteristics present in the patients that go at different times during the year. Afterwards, the glycemia control from each of these therapies in the studied population will be analysed, and the studies will be published.

To validate the theoretical protocol and the data-gathering questionnaire, there will be a pilot test with a duration of one week, with a data gathering that allows to evaluate if it is possible to achieve the determined sample amount needed within the time proposed for the field research.

5.1.1 Definition of participants:

The size of the sample has been calculated using a public software designed specifically for this function, called *GRANMO* [24]. Using the study with two independent proportions as a guide and taking the RABBIT-2 study as a bibliographic ground to estimate already awaited results that will help to find out the sample size.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 55 patients are required in one group and 55 in the other too, to detect how statistically significant is the difference between both proportions, that is estimated to be at least 0.66 in the group treated with basal-bolus insulin, and 0.38 in the group treated with sliding scale insulin. Estimating at least a 10% loss in patient's follow-up.

An approximation has been done consulting the databases from the emergency service at the Mutua of Terrasa Hospital, and the clinical records in a 24h period following the inclusion and exclusion criteria shown next, resulting in 5 participants in a single day. Estimating this progression, it is expected that during a month, more than the expected 55 participants can be attained. If that happens, there will be no random selection of the accepted participants; instead, all of them will be included to increase the reliability of the study.

Therefore, the sample selection will be conducted using a consecutive, non-probabilistic type model, in which all patients fulfilling the required criteria will be selected in a determined period of a month per group.

5.1.1.1 Inclusion criteria:

The study population are all known diabetic patients that go to the emergency service of the University Hospital Mutual of Terrassa and have to stay longer than 24h, regardless of the reason for consultation, and those who despite not having been previously diagnosed with diabetes, at the moment the arrival or during hospitalization (always > 24h) show high glycemia that requires an insulin treatment, including in this population of patients those who are administered corticosteroids and their glycemia increases as a result.

For patients with undiagnosed diabetes with hyperglycemia, the criteria proposed by the ADA in its last 2017 revision will be followed, to diagnose diabetes mellitus. [9]

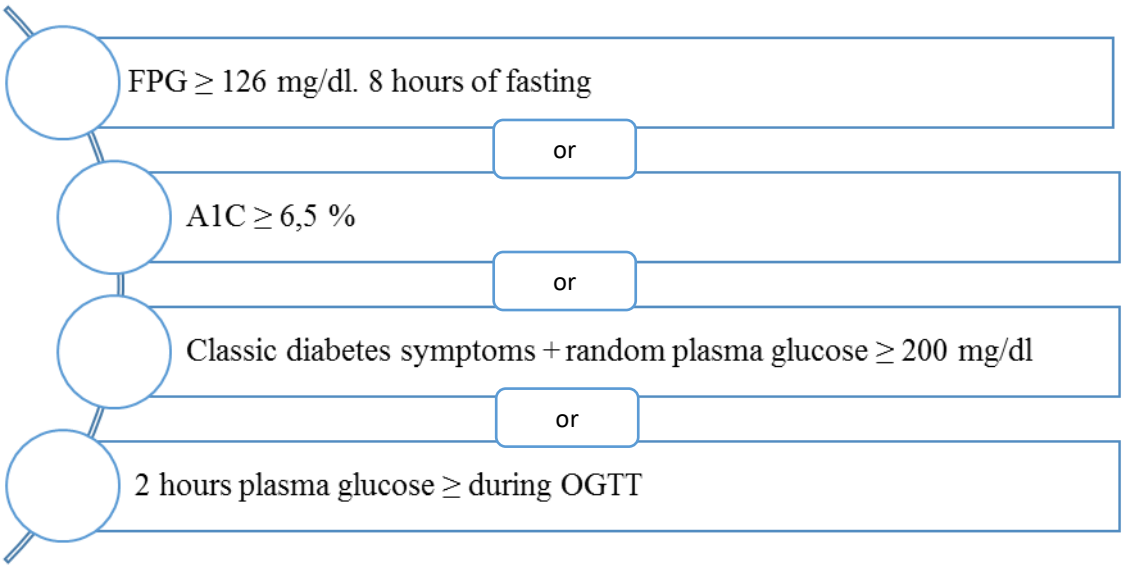


Figure 4: Criteria for the diagnosis of diabetes. American Diabetes Association. 2017

5.1.1.2. Exclusion criteria:

- Negative to participate in the study, either due to non-compliance with it or for not obtaining an informed consent.
- Staying for less than 24h in the emergency service.
- Critical or severe clinical state.
- Aged under 18 years old.

5.1.2. Variables

Dependent variables

Dependent variables are defined as the optimal control of glycemia, considering a blood glucose level of 80-130 mg/dl following the latest recommendations made by the American Diabetes Association

So, to consider an optimal blood glucose level control, both for the sliding scale insulin therapy as for the basal-bolus insulin therapy, at least two consecutive determinations ranging 80-130 mg/dl are required.

Independent variables

- Age
- Sex
- Type of diabetes
- Previous insulin or oral intake treatments
- Previous pathology different to diabetes
- Treatment with corticoids
- Presence of hypoglycemia
- Presence of stress hyperglycemia
- Absolute diet with serum therapy

5.1.3. DATA GATHERING AND ANALISIS

Data gathering will be made by previously trained staff using a formulary that collects all dependent and independent variables (annex 1). In the emergency unit where this study via protocol will be conducted, values on blood glucose level will be collected every 6 hours to all diabetic patients, patients with corticoids and those to whom a high hyperglycemia is detected in a blood analysis. This way the information is directly obtained from the patient's clinical records, using the clinical course of the doctor and the infirmary registry.

The collection of the data will be done by the infirmary staff hired to this effect. These professionals will revise the patients in the emergency services that comply with the inclusion criteria on a daily basis and will make them sign an informed consent to include them in the study. When the patient accesses the study, the nurse will collect its data from its clinical record, including the blood glycemia levels during his/her stay.

Therefore, during the first 24 hours on stay, the patient would have had at least 4 determinations for blood glucose level done to them, of which 2 consecutive ones must be within the optimal range to consider an optimal glycemia control.

Once the required data is gathered, they will be introduced into a database in a computer program designed to determine, rapidly, if a good glycemia control has been achieved.

6. ETHICAL ISSUES

This theoretical protocol will be evaluated by the Clinical Research Ethics Committee of the University Hospital Mutual of Terrassa. This CREC will have to give its approval to start the intervention study in the emergency service at the same hospital. This way, the protection of the rights and safety of the participant is guaranteed during it.

On the other hand, permission and compliance will be asked to the management, medical and emergency infirmary boards.

Patients will be evaluated before their inclusion to verify they comply with the inclusion and exclusion criteria. A member of the research team will ask the patient to participate in the study, explaining its nature, justification, risks, and benefits, as well as answering all questions the patient may have about it. Once the information is given, he or she will be handed the informed consent formulary, to sign it before the data collection. This informed consent will be written in the language of the country where the study is being conducted, and is shown in annex 2.

The patients on the first group treated with sliding scale insulin will be asked to sign the informed consent when they comply within the inclusion and exclusion criteria, since only data from their clinical records will be taken and they'll not be receiving a treatment different from the other patients'.

However, the second group treated with basal-bolus insulin will be asked for the informed consent for every diabetic patient arriving into the emergency services and of any patient being treated with insulin, as to start the basal-bolus insulin treatment regardless of them staying less than 24h in the emergency services. This way when they comply with the requirement of being hospitalized for more than 24h, they will have already given their informed consent. They'll be informed that, if they aren't finally included in the study due to exclusion or inclusion criteria, or by decision of the patient himself, their personal and medical data will be removed from the database.

An adequate management of the data is guaranteed at any given time, protecting data as it's mandatory per Spanish legislation, particularly the Personal Data Protection Act (LOPD) 15/1999 of 13th December.

7. EXECUTION PLAN

This intervention study will be conducted along a 1-year period that will run from 2018 to 2019. In this activity period they'll follow the order given in the schedule shown in annex 3, and it will be led by a main investigator, Asier Juan Quiles, who at the moment of designing this project is a medical student cursing his last year and advised by Dr. Juan José Cara Lozano, associate doctor of the emergency service of the University Hospital Mutual of Terrassa. Both are the leading investigators responsible for the study design and submission to the Clinical Research Ethics Committee, as well as the data analysis and publication of results.

The collaboration of a computer technician is required for the design and development of a database and a software to analyze it in a fast and comfortable way. An external human resources company will be required too in order to select the adequate infirmary professionals for data collection.

On the other hand, the training of doctors and nurses on the protocol, working in the emergency services of the University Hospital Mutual of Terrassa, will be done by Dr. Juan José Cara, who will also participate in the project as one of the main investigators and is one of the leading authors of the Basal-Bolus Insulin protocol by the diabetes SOCMUE group.

8. PUBLICATION AND POPULARIZATION OF RESULTS

A scientific article will be prepared with the results obtained and will be disseminated by the University Hospital to the doctors and nurses, so that they can have all the results and carry out the protocol that has obtained the best result.

The study will also be presented at medical congresses, mainly at the congress that the SOCMUE carries out every year in Catalonia, since this is the scope of the study and the reference population. Valuing the possibility of publishing the results in scientific journals.

9. BUDGET

Budget of the intervention study

Human Resources			
Collaborator	**Functions to be performed**	**Number of people and estimated hours**	**Cost**
Investigator	Selection of participants according to inclusion and exclusion criteria and clinical characteristics of the patient. Data and statistical analysis. Publication and dissemination of results.	1 person / 300 h.	18 €/h.
Nurse	Performance of glycemia by capillary blood sample and data collection.	2 people / 360 horas per person	15 €/h.
Professor	Teaching of the bolus-basal protocol.	1 person / 12 h.	20 €/h.
Computer specialist	Design and creation of databases and analysis software.	1 person / 40 h.	12 €/h
The cost has been calculated in relation to the estimated hours each professional will be doing.			
Human Resources Total			**16.920 €**
Material Resources			
Material	**Specify amount**	**Unitary cost**	**Total**
Office material	Stationery, didactic material, costs of printing and reproduction of materials (manuals, reports)	250 €	**250** €
Accu – Chek glucometer	2 units	41.50 €	83 €
Test strips for the glucose meter	8 units	28 €	224 €
Laptop	1 unit	500 €	500 €
TOTAL MATERIAL RESOURCES			**1.057 €**
Dissemination of the results			
	Approximate price per person.	**People**	**Total**
Registration and accommodation of scientific congresses	**600** €	**2**	**1200** €
Moving to the congress holding place	**200** €	**2**	**600** €
Allowances during meetings and dissemination of the project.	**150** €	**2**	**300** €
TOTAL			**2.100** €
TOTAL PROJECT COST			**20.077** €

10. ANNEXES

ANNEX 1: DATA COLLECTION TEMPLATE

ANNEX 2: INFORMED CONSENT

ANNEX 3: SCHEDULE

ANNEX 4: TRIPTYCH OF BASAL BOLUS INSULIN THERAPY

1. DATA COLLECTION TEMPLATE

NHC: Edad: Sexo: Masculino ☐ / Femenino ☐

UNIDAD MÉDICA RESPONSABLE: Medicina ☐/ Cirugía ☐/ Traumatología ☐/ Ginecología ☐

Paciente diabético conocido con descompensación diabética:	SI	NO	Valor
· Glicemia al ingreso	☐	☐	☐
· Tipo de Diabetes Mellitus	1☐	2☐	
· Mayor valor de glucemia durante el ingreso			☐
· Dieta absoluta con sueroterapia	☐	☐	
· ¿Solicitada HBa1 al ingreso?	☐	☐	
· ¿Utilizada pauta móvil de insulina?	☐	☐	
· ¿Utilizada protocolo bolo basal correctamente?	☐	☐	
o ¿Suspensión de ADOS?	☐	☐	
o ¿Cálculo DTID?	☐	☐	
o ¿Revisión y reajuste en 24h.?	☐	☐	
· Control óptimo de la glicemia **(80-130)**	☐	☐	☐
· ¿Se han producido hipoglicemias?	☐	☐	☐
· ¿Ha sido necesario utilización de BIC de insulina?	☐	☐	

Valor de las glicemias	
1º	
2º	
3º	
4º	
5º	
6º	

Paciente diabético no conocido con descompensación diabética:	SI	NO	Valor
· Glicemia al ingreso	☐	☐	☐
· Mayor valor de glucemia durante el ingreso			☐
· Dieta absoluta con sueroterapia	☐	☐	
· ¿Solicitada HBa1 al ingreso?	☐	☐	
· ¿Utilizada pauta móvil de insulina?	☐	☐	
· ¿Utilizada protocolo bolo basal correctamente?	☐	☐	
o ¿Suspensión de ADOS?	☐	☐	
o ¿Cálculo DTID?	☐	☐	
o ¿Revisión y reajuste en 24h.?	☐	☐	
· Control óptimo de la glicemia **(80-130)**	☐	☐	☐
· ¿Se han producido hipoglicemias?	☐	☐	☐
· ¿Ha sido necesario utilización de BIC de insulina?	☐	☐	

Valor de las glicemias	
1º	
2º	
3º	
4º	
5º	
6º	

Paciente diabético conocido o no con descompensación diabética corticoidea:	SI	NO	Valor
· Glicemia al ingreso	☐	☐	☐
· Tipo de Diabetes Mellitus	1☐	2☐	N/C ☐
· Mayor valor de glucemia durante el ingreso			☐
· Dieta absoluta con sueroterapia	☐	☐	
· ¿Solicitada HBa1 al ingreso?	☐	☐	
· ¿Utilizada pauta móvil de insulina?	☐	☐	
· ¿Utilizada protocolo bolo basal correctamente?	☐	☐	
o ¿Suspensión de ADOS?	☐	☐	
o ¿Cálculo DTID?	☐	☐	
o ¿Revisión y reajuste en 24h.?	☐	☐	
· Control óptimo de la glicemia **(80-130)**	☐	☐	☐
· ¿Se han producido hipoglicemias?	☐	☐	☐
· ¿Ha sido necesario utilización de BIC de insulina?	☐	☐	

Valor de las glicemias	
1º	
2º	
3º	
4º	
5º	
6º	

2. INFORMED CONSET

Consentimiento informado para participantes del ensayo clínico "análisis de la terapia móvil insulina vs terapia bolo basal en el servicio de urgencias del Hospital Univertitario Mutua Terrassa"

El objetivo de este documento es informar a los participantes de este estudio en qué consiste la investigación, que se hará con sus datos una vez recopilado y cuál será el rol de los participantes.

La presente investigación es conducida por Asier Juan Quiles, estudiante de Medicina de la Universidad de Girona y tutorizada por Juan Jose Cara Lozano, médico adjunto del servicio de Urgencias Médicas del HUMT.

El objetivo de este estudio es identificar cual es la mejor terapia de insulinización de los pacientes que acuden a las urgencias del hospital Universitario Mutua Terrasa, para ello necesitamos recopilar datos de los pacientes diabéticos o no diabéticos pero con criterios de hiperglicemia y en tratamiento con insulina durante su ingreso en urgencias.

Si usted accede a participar en este estudio, se le pedirá su conformidad para recopilar información de su historia clínica referente a sus antecedentes médicos, edad, valor de la glucemia durante el ingreso, pruebas de laboratorio y valores solicitadas.

Debe saber que se le pude incluir en una de las dos terapias de insulinización que se están analizando, en función de la fase del estudio en la que se encuentre en el momento de su participación y que se utilizarán insulinas que ya están aprobadas y utilizadas en la práctica médica, pero con pautas diferentes. Esto puede provocar mal control de la glucemia o incluso hipoglicemias.

La participación es este estudio es estrictamente voluntaria y sin ninguna aportación económica. La información que se recoja será confidencial y no se usará para ningún otro propósito fuera de los de esta investigación.

Si tiene alguna duda sobre este proyecto, puede hacer preguntas en cualquier momento poniéndose en contacto con el investigador principal, Asier Juan Quiles o el Dr. Juan Cara del servicio de urgencias del Hospital Universitario Mutua Terrassa. Igualmente, puede retirarse del proyecto en cualquier momento sin que eso lo perjudique en su atención médica.

Le agradecemos su participación.

Acepto participar voluntariamente en esta investigación. He sido informado/a del objetivo del estudio y de la finalidad de los datos que se recopilarán de mi historia clínica, los cuales serán utilizados estrictamente para este estudio siendo tratados de una manera confidencial y conforme a la ley de protección de datos.

He sido informado de que puedo hacer preguntas sobre el proyecto en cualquier momento y que puedo retirarme del mismo cuando así lo decida, sin que esto acarree perjuicio alguno para mi persona ni sobre atención médica recibida.

Recibo una copia de este consentimiento informado, sabiendo que puedo pedir información sobre los resultados de este estudio cuando éste haya concluido.

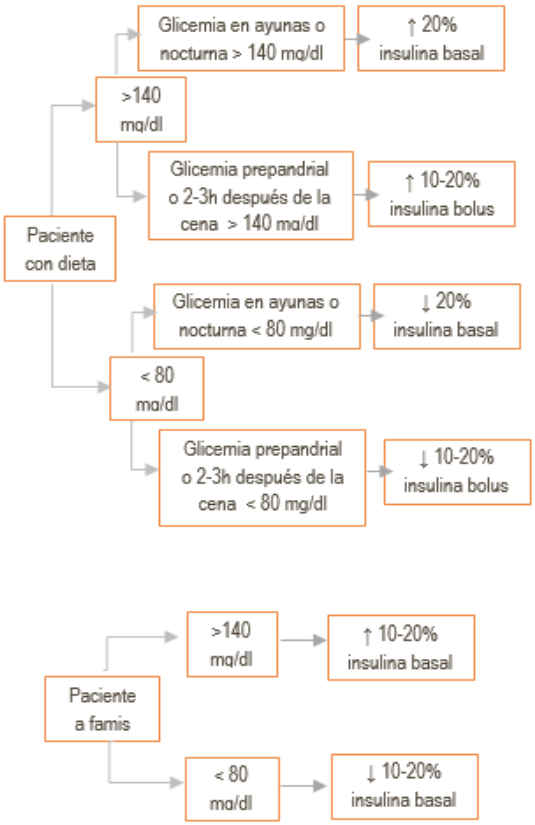
Nombre del Participante Firma del Participante Fecha

3. SCHEDULE

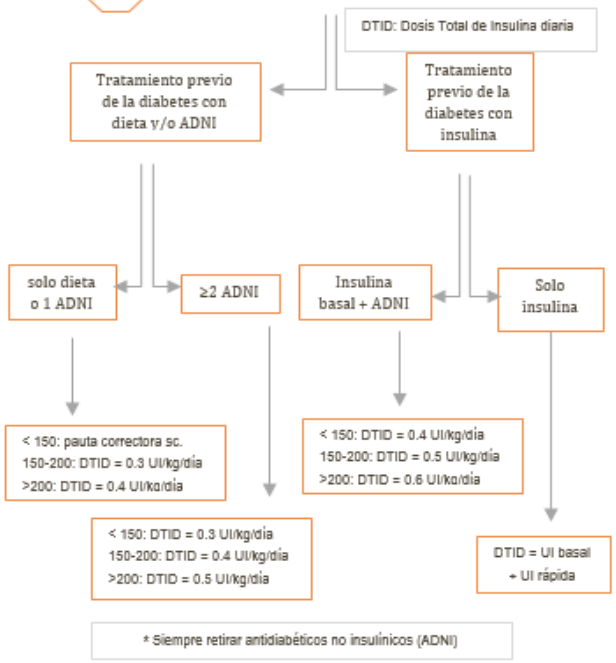
SCHEDULE													
Activity	**professional**	2018					2019						
		August	September	October	November	December	January	February	March	April	May	June	July
Bibliographical review and analysis of the information	Principal investigators												
Defining problems and objectives													
Desing of data collection and specifics software for the database	Principal investigators + IT employ												
Presentation to the CEIC HUMT.	Principal investigators												
Selection of the nursing staff necessary to obtain the collection data	Personal of humaan resource												
Data collection 1st group: Sliding Sacale Insulin	Nurse												
Training for emergency professionals	Teaching staff												
Data collection 2nd group: Basal-Bolus Insulin	Nurse												
Analisys of the information	Principal investigators												
Publication of results and preparation of scientific article													
Dissemination of the results in the HUMT and scientific dissemination congresses													

4 . TRIPTYC OF BASAL BOLUS INSULIN THERAPY

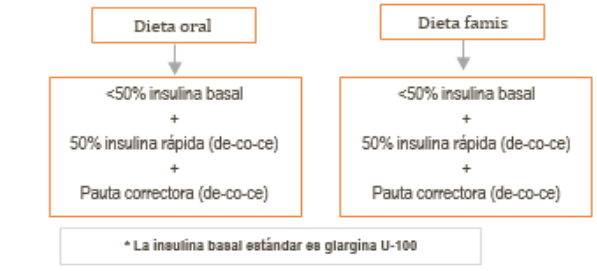
3 REAJUSTE DOSIS DE INSULINA



1 Calculo DTID



2 DISTRIBUCIÓN DTID



TERAPIA DE INSULINIZACIÓN BOLUS-BASAL EN URGENCIAS

Servicio General de Urgencias

MútuaTerrassa

Pauta correctora

Glicemia previa	< 40 UI/día peso <60kg.	40-80 UI/día peso 60-90kg.	>80 UI/día peso >90kg.
<80 mg/dl	-1	-1	-2
80-129	0	0	0
130-149	1	1	1
150-199	1	2	2
200-249	2	3	4
250-299	3	5	7
300-349	4	7	10
>350	5	8	12

Tratamiento de la hiperglicemia simple

Descarta siempre cetoacidosis y síndrome hiperosmolar

Glucemia < 350-400 mg/dl

Bolus insulina rápida i.v.

- 200-250 mg/dl: 4UI
- 251-300 mg/dl: 6UI
- 301-350 mg/dl: 8UI
- 351-400mg/dl: 10UI

+

500 cc SF en 24h

Glucemia > 350-400 mg/dl

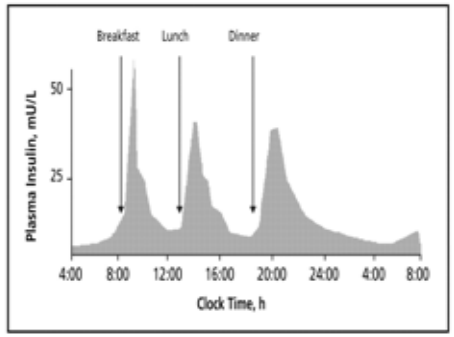
Iniciar Perfusión de insulina i.v a 6-8

Cuando glicemia < 250 mg/dl disminuir ritmo de infusión al 50% + Glucosado 10% 100cc/24h.

Control glicemia cada hora. Cuando glicemia < 200 mg/dl estable pasar a dieta oral + inicio de insulina s.c. con terapia bolo-basal.

¿Cómo se secreta la insulina de manera fisiológica?

- El 50% de la liberación de insulina se hace de manera constante.
- El 50% restante se secreta en forma de picos en función de los hidratos de carbono que se ingieran en la dieta.



Utilizamos una terapia similar a la secreción fisiológica de insulina, la terapia de insulinización bolus-basal

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