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Revisión

Recommendations of the GARIN group for managing non-critically ill patients with diabetes or stress hyperglycaemia and artificial nutrition

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Abstract

Background & aims: **By means of this update, the GARIN working group aims to define its position regarding the treatment of patients with diabetes or stress hyperglycaemia and artificial nutrition. In this area there are many aspects of uncertainty, especially in non-critically ill patients.**

Methods: **Bibliographical review, and specific questions in advance were discussed and answered at a meeting in the form of conclusions.**

Results: **We propose a definition of stress hyperglycaemia. The indications and access routes for artificial nutrition are no different in patients with diabetes/stress hyperglycaemia than in non-diabetics. The objective must be to keep pre-prandial blood glucose levels between 100 and 140 mg/dl and post-prandial levels between 140 and 180 mg/dl. Hyperglycemia can be prevented through systematic monitoring of capillary glycaemias and adequately calculate energy-protein needs. We recommend using enteral formulas designed for patients with diabetes (high monounsaturated fat) to facilitate metabolic control. The best drug treatment for treating hyperglycaemia/diabetes in hospitalised patients is insulin and we make recommendations for adapt the theoretical insulin action to the nutrition infusion regimen. We also addressed recommendations for future investigation.**

Conclusions: **This recommendations about artificial nutrition in patients with diabetes or stress hyperglycaemia can add value to clinical work.**

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Key words: *Diabetes. Stress hyperglycaemia. Enteral nutrition. Parenteral nutrition. Non-critically ill patients.*

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RECOMENDACIONES DEL GRUPO GARIN PARA EL MANEJO DE PACIENTES NO CRÍTICOS CON DIABETES O HIPERGLUCEMIA DE ESTRÉS Y NUTRICIÓN ARTIFICIAL

Resumen

Introducción y objetivos: **En el tratamiento de los pacientes con diabetes o hiperglucemia de estrés y la nutrición artificial existen muchas áreas de incertidumbre, sobre todo en pacientes no críticos. El grupo de trabajo GARIN tiene como objetivo definir su posición en este campo.**

Material y métodos: **Revisión bibliográfica previa y reunión presencial en la que se discutieron y contestaron preguntas específicas sobre el tema.**

Resultados: **Proponemos una definición de hiperglucemia de estrés. Las indicaciones y las rutas de acceso a la nutrición artificial no difieren en los pacientes con hiperglucemia de estrés o diabetes respecto a los no diabéticos. El objetivo debe ser mantener los niveles de glucemia preprandial entre 100 y 140 mg/dl y postprandial entre 140 y 180 mg/dl. La hiperglucemia puede prevenirse a través de una monitorización sistemática de las glucemias capilares y un cálculo adecuado de las necesidades energético-proteicas.**

Recomendamos el uso de fórmulas enterales diseñadas para pacientes con diabetes (alto contenido en grasas monoinsaturadas) para facilitar el control metabólico. El mejor tratamiento farmacológico para tratar la hiperglucemia/diabetes en pacientes hospitalizados es la insulina, aconsejando adaptar la acción teórica de la insulina al régimen de infusión de la nutrición. También realizamos recomendaciones para investigaciones futuras.

Conclusiones: **Estas recomendaciones aportan respuestas concretas sobre cuestiones comunes en la asistencia a pacientes con diabetes o hiperglucemia de estrés y nutrición artificial.**

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Palabras clave: *Diabetes. Hiperglucemia de estrés. Nutrición enteral. Nutrición parenteral. Pacientes no críticos.*

Introduction

Although dietary recommendations have formed part of medicine for many centuries, nutrition has only been considered a scientific discipline for about 200 years, initially starting alongside advances in chemistry when early experiments into nutrient oxidation were conducted.[1] However, the "clinical nutrition" discipline did not emerge until the end of the 1960s when it was proven to be possible to maintain the growth and life of a child by exclusively administering nutrients parenterally.[2] Today, clinical nutrition is a multi-disciplinary area that supports most medical specialties and has come of age by incorporating scientific methodology and evidence-based medicine to establish clinical practice guidelines.[3,4]

Nevertheless, there are still many areas of uncertainty due to it being a relatively young specialty and it being difficult to conduct well-designed studies (observational and/or randomised, prospective clinical trials with a sufficient number of patients) allowing conclusions based on the best available evidence to be reached.

One of these areas is artificial nutrition in patients with diabetes or stress hyperglycaemia in which there are many aspects still requiring clarification, especially in non-critically ill patients. In fact, the latest clinical practice guidelines on the management of hyperglycaemia in non-critical hospitalised patients, published by the U.S. Endocrine Society[5] and the American Society for Parenteral and Enteral Nutrition (ASPEN),[6] only make three evidence-based recommendations on general aspects of care for patients receiving artificial nutrition (enteral or parenteral), which shows the high degree of uncertainty faced by clinicians; the first one[5] also only makes one strong recommendation based in high quality evidence and two weak recommendations based on very low quality evidence and the second one[6] two strong recommendations and it cannot make a recommendation about the third question because of lack of evidence. Also the recent clinical practice guidelines published by the American College of Physicians about use of Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients only makes three recommendations focused on critical patients; the two strong recommendations are about not using intensive insulin therapy and the weaker recommends a target blood glucose level if insulin therapy is used.[7] Also the recent consensus of SEMICYUC-SENPE makes recommendations only centered in critically ill patients.[8]

Therefore, in fields with high levels of uncertainty and low quality evidence, expert consensus or recommendations can add value to clinical work.

By means of this revision and update, the GARIN (Grupo Andaluz de Reflexión e Investigación en Nutrición) working group aims to define its position regarding the treatment of patients with diabetes and artificial nutrition based on the critical reading of literature and also the experience of group members.

Material and methods

The main objectives of the GARIN group include reflecting on various aspects of clinical nutrition and generating recommendations agreed by consensus. Its members meet once a year in Osuna (Andalusia, Spain) after first systematically reviewing the best available evidence on a pre-agreed specific topic. Initially, a bibliographical review is carried out of the papers published on PubMed regarding enteral nutrition, parenteral nutrition and hyperglycaemia or diabetes: all members review this literature prior to the meeting (two months in advance). The topic was formally presented by the coordinator at the meeting for 45 minutes and then a series of specific questions that were written by the coordinator (GO) in advance (of which all were pre-informed) were discussed for the next four hours. These were answered at the meeting in the form of conclusions. The review of the literature and the answers to these questions are reflected in this article, which has been prepared by the coordinator and then discussed and adopted by all participants.

Review of the literature

Prevalence of diabetes mellitus and hyperglycemia in hospitalised patients receiving artificial nutrition

It is estimated that there are currently 246 million people with diabetes in the world and that this figure will increase over the next few years, reaching 380 million by the year 2025 according to the latest predictions.[9] An ageing population and lifestyle-related factors (changes in diet and increased sedentary lifestyle with consequent weight gain and obesity) are the main factors behind this epidemic.[10,11]

It is estimated that around 14% of the adult population in Spain has diabetes.[12,13] The prevalence of diabetes in the hospital setting is also very high, at about 11%, if data are taken from the administrative databases generated from hospital discharge reports,[13-15] exceeding 21% in the subgroup of patients over the age of 75 years.[14] However, if data are taken from hospital medical charts or prospective studies, the prevalence is higher still, at around 20-30%, while in patients over the age of 65 years or patients admitted to certain departments such as cardiology or cardiovascular surgery, the prevalence is even higher than 30%.[16-18]

The presence of diabetes in hospitalised patients is associated with an increased risk of death during hospitalisation, an increased length of hospital stay (3-4 days on average) and increased costs.[14,15,19]

Stress hyperglycaemia (in patients without diabetes) associated with acute diseases also seems to increase the morbidity and mortality of hospitalised patients [20]. Nevertheless, there are no reliable data regarding the

prevalence of this disorder as different definitions are given in the literature and none are accepted internationally.[21-23]

It is estimated that 8% of hospitalised patients receive some type of artificial enteral feeding support to treat or prevent malnutrition, whether as supplements or complete diets.[24,25] Approximately 2-3% more receives total parenteral nutritional support (TPN) for the same purpose.

Hyperglycaemia is a common complication in hospitalised patients receiving enteral nutrition.[26,27] Nevertheless, the prevalence of diabetes in patients receiving enteral nutrition is unknown. In one study involving an internal medicine department, 34% of patients receiving TEN had blood glucose levels over 200 mg/dl.[28] In another study assessing dependent geriatric patients (with severe cognitive impairment) admitted to long-term care units and receiving enteral nutrition, 50% had diabetes (defined as an HbA1C above 7%) with 44% of them being undiagnosed.[29] In a randomised study comparing two insulin therapy regimens in patients with enteral nutrition and diabetes (defined as two blood glucose levels above 130 mg/dl), half of the 50 randomised patients did not know they had diabetes.[30]

Between 16 and 30% of the subjects randomised to intervention trials comparing intensive and conventional insulin treatment in critically ill patients had diabetes mellitus prior to randomisation.[31-36] Nevertheless, the prevalence of hyperglycaemia or previously diagnosed diabetes in patients receiving TPN treatment, especially in patients from non-critically ill units, has not been well studied. In a series of 50 retrospective cases, Pleva et al. describe rates of hyperglycaemia above 150 mg/dl in more than 90% of patients receiving TPN.[37] Among hospitalised patients receiving TPN in Spain from general wards (not intensive care units), prevalences of hyperglycaemia above 200 mg/dl have been described in 12-27% of patients.[38,39] In a recent study conducted by the Group for the Study of Hyperglycaemia during Parenteral Nutrition of the Area of Nutrition of the Sociedad Española de Endocrinología y Nutrición (Spanish Society of Endocrinology and Nutrition),[40] 51% of patients (non-critically ill) prescribed TPN had some type of glucose metabolism alteration prior to starting TPN (based on blood glucose and glycated haemoglobin values): known diabetes 18%, undiagnosed diabetes 3.8%, stress hyperglycaemia 12.4%, being at risk for the development of diabetes 15%. During the TPN infusion, 80% of patients had at least one capillary blood glucose measurement above 140mg/dl with 51% above 180 mg/dl.

Effects of hyperglycaemia on the outcome of hospitalised patients

Short-term hyperglycaemia in hospitalised patients has been related to an increased susceptibility to infections and other alterations, such as increased oxidative stress, increased hypercoagulability, dyslipidemia, etc., resulting in a secondary increase in morbidity, mortality and generated costs.[25] This increase in complications and mortality has been observed with different clinical conditions (myocardial infarction, strokes, trauma, coronary bypass, COPD, elderly patients, etc.).[41]

Experimental data are currently available on potential mechanisms from observational and intervention clinical studies that support the fact that hyperglycaemia per se, in addition to being a marker of illness severity, causes major adverse effects that affect the prognosis of hospitalised patients, including increased mortality, rates of infection and length of hospital stay. Some studies also suggest that stricter control of blood glucose levels in critically ill patients with and without diabetes could improve their prognosis.[5,18,26,42]

In the case of patients receiving TPN (both in critically ill and non-critically ill patients), it seems that hyperglycaemia per se, possibly independently of the previous presence of diabetes, could worsen the prognosis of patients by increasing morbidity and mortality (increased cardiac, infectious and septic complications, renal failure, etc.), especially if not associated with insulin therapy.[26,43-49]

Objectives of hyperglycaemia treatment in non-critically ill patients

Until the beginning of the 21st century, it was generally accepted that blood glucose levels of hospitalised patients should be kept within safe limits between 150 and 250 mg/dl. However, following the first papers published by the Van den Berghe group in ICU patients,[36] this concept was rethought and substituted by another concept supporting a more active approach in order to achieve better glycaemic control. Therefore, over recent years, the management of hyperglycaemia during hospitalisation has become particularly relevant with recommendations being established that suggest that the objective of glycaemic control during hospitalisation should be to normalise blood glucose levels.[18,26,42]

Nevertheless, the treatment of hyperglycaemia with the objective of normalising blood glucose levels has had contradictory results in the literature, especially in critically ill patients, the area where most randomised and controlled trials have been conducted. Therefore, studies by Van den Berghe in critically ill patients showed a reduction in mortality in surgical patients assigned to intensive IV insulin treatment (objective 80-110 mg/dl) compared to conventional treatment (starting infusion with blood glucose levels above 220 mg/dl with the objective of 180-200 mg/dl).[36] The same group managed to replicate results (lower mortality) in critically ill patients in ICUs, but only in those patients receiving treatment for more than 3 days.[35] However, other randomised, multi-centre studies in critically ill

patients comparing intensive and conventional treatment (generally with stricter control in the conventional group than in studies conducted by Van den Berghe) have not been able to replicate the same results (no reduction in mortality has been observed and in some cases an increase in mortality has even been noted, possibly related to hypoglycaemia).[31-34]

Although there is a huge debate in the literature[41,48,50-52] regarding the disparity between results in the different papers on intensive treatment, part of the effects could be due to the nutritional therapy used in the different studies (higher parenteral infusion rate of glucose and nutrients in the Van den Berghe studies compared to the others).

In a recent systematic review and meta-analysis on the use of intensive insulin therapy (with an approximate treatment objective of 140-180 mg/dl) in non-critically ill patients, a reduced risk of infections and a tendency towards a higher incidence of hypoglycaemia compared to patients treated with conventional insulin therapy was observed.[53]

After initially adopting the objective of normoglycaemia, clinical practice guidelines and consensus currently recommend maintaining a pre-prandial glucose level of less than 140 mg/dl and a glucose level of 180 mg/dl at all other times in most "non-critically ill" patients.[5,18] Objectives may vary based on the clinical situation (with objectives being less strict, for example, in patients with a short vital prognosis or a high risk of hypoglycaemia).

Indications for artificial nutrition in patients with diabetes

Indications for artificial nutritional support in patients with diabetes are no different from those for patients without diabetes. Enteral nutrition is indicated in those patients that cannot, should not or do not want to meet adequate nutritional requirements by oral intake and who have a functioning, accessible gastrointestinal tract.

Between 5 and 8% of hospitalised patients receive some type of artificial enteral feeding support, either as supplements or complete diets.[25] If we apply the actual hospital diabetes prevalence rates, we can estimate that 1-2% of hospitalised patients are diabetic and receive some type of enteral artificial nutritional support.

The prescription of home enteral nutrition (HEN) is also gradually increasing.[54] The main indications for the use of HEN[54,55] are neurological alterations preventing swallowing and neoplasms, which are more common conditions in adults of advanced age. This means that the prevalence of diabetes in patients prescribed home enteral nutrition is potentially very high.

TPN is prescribed to approximately 1-3% of hospitalised patients (based on their complexity) and has proven to be effective and safe for restoring or maintaining the nutritional status of patients who cannot ingest or tolerate food via the digestive tract.[56]

However, as mentioned above, both parenteral and enteral nutrition increase the risk of hyperglycaemia regardless of the previously diagnosed presence of diabetes[28,40,44,49,57] and therefore strategies should be implemented to prevent deleterious effects on the outcome of patients, including the prevention and adequate treatment of this complication.

Treatment of hyperglycaemia/diabetes and enteral nutrition

Selection of enteral formulas in diabetes/hyperglycaemia

"Standard" commercial formulas used in enteral nutrition have a high carbohydrate content (about 50%), a low-moderate lipid content (about 30%) and contain no dietary fibre. These liquid formulations seem to increase the glycaemic and insulin response more in healthy people or patients with diabetes mellitus when compared with a similar intake of nutrients from a mixed meal. Although any formula can be used in patients with diabetes, adjusting the insulin therapy as required, enteral formulas designed specifically for patients with diabetes and stress hyperglycaemia have been marketed over recent years to reduce glycaemic response and also improve lipid profile and other cardiovascular risk factors.[25]

All formulas "for diabetes" contain sources of carbohydrates with a low glycaemic index, such as non-hydrolysed starch or modified maltodextrin. Although the addition of fructose is currently a matter of debate, most add this nutrient in moderate-low amounts. Likewise, all diabetic formulas add fibre, almost always with a high proportion or exclusive content of fermentable ("soluble") fibre, which is associated with an improved glucose and lipid profile.[58-62]

Also, most diabetes-specific enteral formulas have increased the percentage of fat (preferably monounsaturated) compared to carbohydrates. In general, post-prandial glycaemic response with a high intake of a formula with a high monounsaturated fat content is lower compared to formulas with a high carbohydrate content as response depends fundamentally on the total carbohydrate content. As the carbohydrate content of the formulas increases, other factors also affect glycaemic response, such as the carbohydrate source or content and the type of fibre.[58,60,62-64]

Diabetes and stress diabetes-specific diets (especially those high in fats) in hospitalised patients (in intensive care or on general wards) reduce blood glucose levels and insulin requirements without modifying aspects such as hospital stay, infectious morbidity or mortality.[65,66] High-fat diets also do not worsen lipid control and even tend to improve it[67] compared to high-carbohydrate diets. The use of a diabetes-specific supplement in outpatients, high in fat when compared to a hyperprotein supplement, reduced medium-term glycaemic

control (HbA1C).[68] Short and medium-term (up to three months) high-fat diabetes-specific diets in tube-fed outpatients also improve metabolic control (blood glucose levels, HbA1C and insulin requirements in some cases) compared to standard formulas (generally with fibre), although they do not modify morbidity.[69-73] These formulas may also reduce glycaemic variability and hypoglycaemia compared to standard formulas, at least in the short term.[71,73-75]

To summarise, it must be highlighted that diets designed for people with diabetes and stress hyperglycaemia (especially those high in monounsaturated fats) are safe and clearly reduce post-prandial blood glucose levels, insulin requirements and, according to some papers, glycaemic variability and medium-term HbA1C without worsening or maybe even improving the lipid profile.

Nevertheless, more randomised and preferably double-blind studies must be conducted that involve more patients, lower rates of withdrawal from the protocol and a longer duration in different clinical situations to assess the efficacy and efficiency (cost/effectiveness) of such diets on metabolic effect and morbidity and mortality in order to be able to give better evidence-based recommendations.

In fact, although there are meta-analysis supporting its use,[62] the recent ASPEN guidelines conclude that there aren't sufficient data to recommend the use of these formulas in hospitalized adult patients with hyperglycemia.[6]

Treatment of hyperglycaemia in patients with diabetes/stress hyperglycaemia and enteral nutrition

To date, only one prospective randomised study has been published that evaluates different insulin therapy regimens in this type of patient.[30] Korytkoswski et al. studied 50 patients, 25 randomised to receive treatment with insulin glargine and regular insulin compared to 25 randomised to sliding-scale insulin with added NPH insulin if poor control persisted. Both strategies showed a similar efficacy and safety in non-critically ill patients receiving enteral nutrition. Half of the patients in the sliding-scale group required added NPH insulin.

Other retrospective studies with a small number of patients have shown the efficacy of the injection of basal-bolus insulin regimens (insulin glargine + rapid-acting insulin), 70% NPH and 30% rapid-acting insulin biphasic insulin mixes (divided into 2 or 3 doses) and NPH insulin sliding-scale regimens (divided into 4-6 doses) in patients receiving continuous enteral nutrition with diabetes.[76,77,78] Although conclusions cannot easily be generalised (due to being retrospective studies with few patients), it seems that the biphasic insulin regimen in three doses or the NPH insulin sliding-scale regimen (four daily injections) could be advantageous for achieving better therapeutic objectives, thus reducing hypoglycaemia. The use of insulin glargine + insulin lispro in patients receiving enteral nutrition in boluses also seems to be effective at controlling hyperglycaemia.[79]

The percentage of hypoglycaemia in most studies conducted with enteral nutrition and insulin therapy varies between 3 and 5%, which is slightly higher than the percentage achieved in other studies in non-critically ill hospitalised patients not receiving enteral nutrition.[80] It must be considered that it is not uncommon for enteral nutrition to be unexpectedly suspended (due to gastrointestinal complications, diagnostic test requirements, accidental feeding tube removal, drug administration, etc.).

The lack of prospective randomised studies involving an adequate number of patients encourages guidelines, reviews and consensuses to make recommendations based not on evidence but on the experience of the different groups.[5,17,75,81]

Therefore, some authors suggest that the administration of lower but more frequent doses of intermediate-acting insulins (NPH, NPL or similar) or regular insulin could reduce the risk of hypoglycaemia and insulin-associated risks and, moreover, reduce the number of injections and controls. Furthermore, intermediate-acting insulins could be more useful when adjusting the dose of enteral nutrition received (since its half-life is shorter), adding regular insulin or rapid-acting insulin analogs as needed.[5,75,77] They could also be used in patients receiving night-time EN infusions in one or two doses. Long-acting insulins (insulin glargine or two doses of insulin detemir) would be reserved for patients with more stable requirements or receiving EN infusion as boluses combined with ultra-fast-acting insulin.[5,17,75] Nevertheless, all imaginable options are possible, especially if the theoretical insulin action is adapted to the enteral nutrition infusion regimen (continuous, bolus, cyclic, nocturnal, etc.).[5]

Treatment of hyperglycaemia in non-critically ill patients receiving TPN

The current discussion in literature regarding intensive treatment with insulin therapy in critically ill patients has been mentioned above. In most of these studies, parenteral nutrition and/or glucose solution infusions are combined with enteral nutrition administering insulin by way of perfusion pumps that are separate from the TPN. However, outside the intensive care units (where the health professional-to-patient ratio is high) or outside the context of clinical trials, the use of protocols for intravenous insulin therapy with separate nutrition infusion is less common, except in cases with very poor metabolic control.

In 2006, a group of hospital pharmacists in Spain reported that up to 18% of patients with TPN and hyperglycaemia with blood sugar levels above 200 mg/dl were not receiving any insulin treatment and

almost 57% were only receiving such treatment via subcutaneous injection.[39]

However, more recently, in 605 non-critically ill patients receiving TPN under the care of endocrinologists in the Nutrition Units, 71.1% of the cases evaluated were prescribed insulin, with 58.1% of the patients with no glucose metabolism alteration also receiving insulin. In this study, of all the cases treated with insulin (n = 433), intravenous insulin was used in 55% of the cases, added to the TPN bag (36%) or by intravenous perfusion (8.8%). Subcutaneous administration alone was used in 55.1 % of cases.[82]

The use of insulin added to the TPN bag, with adjustments of subcutaneous regular insulin every 6-8 hours (or rapid-acting insulin analogs every 4 to 6 hours), is a common practice in Spain and other countries that often allows reasonable metabolic control to be achieved in patients.[5,38,75,81,83] Nevertheless, there are no randomised studies comparing the efficacy and effectiveness of different insulin therapy regimens in TPN.[83] Although adsorption to the bags is a controversial subject,[84,85] the percentage lost seems to be minimal in ternary mixtures using the new bags. To adjust the insulin therapy, one-half to two-thirds of the subcutaneous units administered the previous day are added to the bag. The mean doses used in patients with known diabetes generally reach 0.7-0.8 IU/kg of bodyweight or 0.3 IU/gram of infused carbohydrate.[38,82] In patients with stress hyperglycaemia, the usual doses range between 0.1 and 0.15 IU per gram of carbohydrate infused via TPN. With this regimen, the risk of hypoglycaemia is low since the insulin perfusion is discontinued with TPN withdrawal.

There are other specific protocols for managing insulin in TPN that have been recently proposed, such as adding regular insulin (2/3 of the calculated dose) to the bag with NPH insulin every 6-8 hours (a total of 1 unit every 5 to 20 grams of carbohydrate based on whether diabetes was previously diagnosed or not and the blood glucose levels at the start) and "basal" insulin in diabetics or corticosteroids at doses of 0.15 to 0.25 IU/kg administered as NPH insulin every 6 to 8 hours. This regimen could be more effective than ad hoc regimens in which insulin was added on demand.[86] Satisfactory results have also been published in short studies or isolated clinical cases with other slow-acting insulins such as insulin glargine or NPL[78,87]. When it is not possible to control hyperglycaemia, the infusion of IV insulin separately from TPN may be necessary.[5]

On the other hand, as was mentioned earlier on, it is fundamental to adequately calculate requirements, not to administer high doses of glucose and to take into account all nutrients supplied (not just from TPN but also including dextrose/glucosaline solutions) in order to prevent and treat TPN-associated hyperglycaemia[83,88-90] as hyperglycaemia and complications would be affected by the total amount of glucose and calories infused.[49,91]

In the case of type 1 diabetes, some authors suggest administering low doses of insulin detemir or glargine to prevent ketoacidosis if TPN is suddenly discontinued.[17]

Although the use of special amino acid (e.g. enriched with glutamine)[92-94] or lipid formulas (based on olive oil or supplemented with omega-3 fatty acids)[83] may be beneficial to prevent or treat hyperglycaemia, there is not sufficient data in the literature to make recommendations.

Conclusions of the Garin Group

After systematically reading the literature and in view of the lack of studies allowing recommendations based upon high-level evidence to be reached regarding the best strategy for preventing and treating patients with diabetes and hyperglycaemia and artificial nutrition, we hereby make the following recommendations based on data from the literature and the group's clinical experience.

Question 1: Is hyperglycaemia and the presence of diabetes a major problem in patients receiving artificial nutrition?

1. Hyperglycaemia in patients receiving enteral or parenteral nutrition is a major problem in both hospitalised patients and outpatients due to its high prevalence and possible consequences in terms of morbidity and mortality, regardless of the pre-existence of glucose metabolism disorders.

2. It is recommended that these patients be monitored by nutritional support teams with specific training in clinical nutrition and diabetology given that it is common that specific hypoglycaemic treatments which can determine the effectiveness of parenteral and enteral artificial nutrition are used.

Question 2: Are the indications for artificial nutrition different in patients with diabetes or hyperglycaemia vs. non-diabetics?

3. The indications and access routes for artificial nutrition are no different in patients with diabetes or stress hyperglycaemia than in non-diabetics. As an exception, in the case of diabetic gastroparesis requiring EN, post-pyloric (non-gastric) enteral access placement is recommended.

Question 3: What is the definition of stress hyperglycaemia and "at risk for the development of diabetes"?

4. In hospitalised patients with unknown diabetes and in the context of an acute disease, stress hyperglycaemia is defined as plasma glucose levels above 126

Table I
Definition proposed for stress hyperglycaemia and "at risk for the development of diabetes" prior to admission

Stress hyperglycaemia	*"At risk for the development of diabetes" prior to admission*
Blood glucose levels ≥ = 126 mg/dl in fasting conditions or ≥ 200 mg/dl at any time	
No known diabetes, in context of hospital admission for acute disease	
HbA1C < 5.7%	HbA1C ≥ 5.7 and < 6.5%
Reassess after 3 months with blood glucose and HbA1C tests	

mg/dl in fasting conditions or above 200 mg/dl at any time with glycated haemoglobin levels below 5.7%. By definition, this increase would be transient (it disappears once the disease causing admission is resolved) then we recommend reassessing metabolic state three months after reaching clinical stability by doing blood glucose and HbA1C tests.

5. We propose defining hospitalised patients as being "at risk for the development of diabetes" prior to admission when said patients have unknown diabetes and, in the context of an acute disease, have plasma glucose levels above 126 mg/dl in fasting conditions or above 200 mg/dl at any time with glycated haemoglobin levels between 5.7% and 6.5% as having pre-admission glucose metabolism alteration. We recommend reassessing metabolic state three months after reaching clinical stability by performing blood glucose and HbA1C tests.

6. To define both stress hyperglycaemia and being pre-admission "at risk for the development of diabetes", it would be necessary to measure HbA1C in all hospitalised patients with hyperglycaemia (above 126 mg/dl) in order to correctly classify the condition and determine the best possible hypoglycaemic treatment during admission and upon discharge (table I).

Question 4: Are there any proven benefits from strictly controlling blood glucose levels in patients receiving artificial nutrition and what would be the objectives of such controls in non-critically ill patients?

7. Strict blood glucose level control (80-110 mg/dl) is not recommended for ICU patients or non-critically ill patients receiving artificial nutrition. The objectives of metabolic control (during admission), if receiving continuous nutrient infusion, must be to keep blood glucose levels between 140 and 180 mg/dl. In patients receiving discontinuous artificial feeding infusion, the objective must be to keep pre-prandial blood glucose levels between 100 and 140 mg/dl and post-prandial levels between 140 and 180 mg/dl. It is necessary to inform the patient of the importance of taking a series of blood glucose measurements and of starting drug treatment if these limits are exceeded. Insulin therapy must be started in patients with blood glucose levels above 180 mg/dl. We also recommend starting insulin therapy at levels above 140 mg/dl, although therapy can be personalised based on the patient's individual characteristics (risk of hypoglycaemia).

Question 5: Can hyperglycaemia be prevented in patients receiving artificial nutrition?

8. It is recommended that all patients starting artificial nutrition (enteral and/or parenteral), with or without a history of diabetes, have their blood glucose levels monitored initially every 6-8 hours and for at least 24 hours after reaching the total estimated requirements. After this, if blood glucose levels are below 140 mg/dl, the number of controls may be decreased based on the patient's clinical condition (table II).

9. Hyperglycaemia can be prevented in patients receiving artificial nutrition by implementing local protocols that adequately calculate energy-protein needs. It is vital to provide individualised nutritional requirements based on the patient's clinical condition, body composition, age and gender. This implies not giving excess calories to a population that often suffers from obesity. We therefore recommend calculating baseline requirements by applying the Harris-Benedict formula as this includes age as a variable. To calculate the total requirements, we recommend multiplying the baseline energy expenditure (Harris-Benedict) by a stress factor of between 1.1 and 1.3, depending on the condition indicating the use of artificial nutrition (greater requirements are only needed in exceptional cases). We recommend using the real weight in malnourished and normally nourished patients (up to a BMI of 25 kg/m^2) for calculations. Above this limit we recommend using the adjusted weight, taking the weight that would give a BMI of 24 kg/m^2.

10. In all patients receiving artificial nutrition, especially those receiving parenteral nutrition, it is necessary to take into account all glucose administered (including glucose drips) to prevent the deleterious effects of hyperglycaemia.

Table II
Strategies to prevent to hyperglycaemia during artificial nutrition

Monitor capillary blood glucose levels every 6-8 hours when starting artificial nutrition
Strict calculation of energy needs – Hospitalised patients. Harris-Benedict formula * Stress factor (1.1-1.3). Use adjusted bodyweight in patients with BMI > 25 kg/m^2 – Outpatients. Harris-Benedict formula * Physical activity factor, or equations proposed by US National Academy of Sciences.
Take into account all glucose supplies

11. In the case of outpatients, to calculate total energy expenditure we recommend applying the Harris-Benedict formula and multiplying by a coefficient that takes into account physical activity or using the equations proposed by the US National Academy of Sciences (which already include physical activity).[95,96]

12. The estimated protein requirement, in the absence of limiting renal or hepatic disease, will depend on the degree of metabolic stress shown by the patient. General estimates are 1 g/kg/day (in patients with no or minimum stress) and 1.5 g/kg/day (in patients with severe stress), which may be increased in exceptional cases with large additional losses (e.g. large burn areas).

Question 6: In the field of enteral nutrition and hyperglycaemia and diabetes, should diets designed for patients with diabetes be used in the presence of stress hyperglycaemia/ diabetes? What would be the recommended macronutrient composition?

13. In patients with enteral nutrition and stress diabetes, we recommend using diets designed for patients with diabetes and stress hyperglycaemia with a high or moderate monounsaturated fat content to facilitate metabolic control and achieve therapeutic objectives as these formulas have proven to reduce post-prandial blood glucose levels, insulin requirements and, in some papers, glycaemic variability and medium-term HbA1C without worsening or maybe even improving the lipid profile. However, there is no evidence of improvement in morbidity and mortality. We recommend initially avoiding these diets in patients with gastroparesis if enteral nutrition is given via the gastric route. We recommend high-monounsaturated fat formulas that give between 38 and 52% of lipids plus fibre (high proportion of fermentable/soluble fibre) and low glycaemic index/load carbohydrates.

14. In the presence of other underlying concomitant conditions requiring treatment with enteral nutrition and specific formulas (e.g. renal failure, liver failure), treatment according to the main condition will prevail. Choosing between the different preparations will therefore also depend on the clinical situation of the patient in question (presence of malabsorption, severe renal, liver or lung failure, presence of diabetic gastroparesis, site of formula infusion, special requirements, restriction of certain nutrients or volume, etc.). In these cases, compliance with therapeutic objectives will basically depend on the insulin therapy prescribed.

Question 7: What is the best drug treatment for treating hyperglycaemia/diabetes in hospitalised patients and outpatients?

15. In hospitalised patients with stress hyperglycaemia or diabetes, the best treatment is insulin therapy.

16. For outpatients, drug treatment will follow the same recommendations and clinical practice guidelines as all other general patients (with both insulin and oral anti-diabetic drugs being used).

Question 8: What is the best insulin therapy regimen in hospitalised patients and outpatients receiving enteral nutrition?

17. It is not known which is the best insulin therapy regimen in hospitalised patients or outpatients receiving artificial nutrition. We recommend (table III):

a) Basal-bolus regimens in patients receiving enteral nutrition by bolus feeding or gravity. Total initial requirements will depend on previous treatments.
   a) If treated previously with oral anti-diabetic drugs, we recommend estimating the total initial insulin dose between 0.3 and 0.5 U/kg of adjusted bodyweight/day (based on BMI, home treatment, intercurrent processes, admission blood glucose levels and/or corticosteroid prescription).
   b) If treated previously with insulin therapy, the dose will be personalised based on previous doses and clinical condition.
   c) In general, doses with 40% of total insulin as basal insulin and 60% as prandial insulin will be applied (to prevent hypoglycaemia if enteral nutrition is suddenly discontinued). Prandial insulin injections will preferably be ultra-rapid-acting insulin (aspart, lispro or glulisine) injected just before starting the infusion or after completing infusion (if there is a risk of intolerance to prevent hypoglycaemia). The prandial dose will depend on the amount of carbohydrates infused and adjustment based on blood glucose levels prior to infusion.
   d) When starting enteral nutrition or in unstable patients (requiring frequent dose adjustments), we recommend covering baseline requirements with NPH, NPL or detemir. In stable patients or patients receiving enteral nutrition at final doses, insulin glargine may also be used.
b) In patients receiving continuous enteral nutrition, we recommend a baseline insulin regimen of 40% basal insulin and 60% prandial insulin preferably every 8 hours with rapid-acting insulin (regular) as nutritional insulin in three equal parts (every 8 hours) + adjustment regimen (based on pre-injection blood glucose levels). Basal insulin may be insulin glargine once a day, detemir twice a day, NPH or NPL 2-3 times a day or NPH or NPL insulin mix two or three times a day. Dose calculation will be similar to that described above.
c) In patients receiving cyclic (e.g. night-time) feeding, we recommend using a medium-acting basal insulin (NPH, NPL or Detemir) injected a

Table III
Approach to insulin therapy in control nutrition (EN)

	Basal	*Prandial*	*Adjustment regimen*
Continous EN	40% Glargine (one a day) Detemir (twice a day) NPH, NPL (2-3 times a day)	60% Every 8 hours In 3 equal parts 1st option: Regular insulin	Based on capillary blood glucose levels Same insulin as prandial
Bolus or gravity EN	40% When starting EN or stable patients ➔ NPH, NPL or detemir Stable patients or patients receiving EN at final dose ➔ can also use glargine	60% Rapid-acting insulin analogs (lispro, aspart, glulisine) according to amount of carbohydrates infused	Same insulin as prandial (base on capillary blood glucose levels prior to infusion)
Cyclic EN	Medium-acting insulin (NPH, NPL or detemir) 30-60 minutes before infusion		At the start and every 4-8 hours according to capillary blood glucose levels Regular or rapid-acting insulin analogs

Calculation of total initial insulin requirements. According to previous treatment:
With oral anti-diabetic drugs: 0.3-0.5 U/kg adjusted bodyweight/day (based on BMN, home treatment, admission blood glucose levels, intercurrent processes, corticosteroids).

half hour to an hour before starting infusion + adjustments, if required, with regular or ultra-rapid-acting insulin on starting the infusion and every 4-8 hours according to controls.

Question 9: In the field of parenteral nutrition and hyperglycaemia and diabetes, what proportion of macronutrients would be best?

18. There are no specific studies regarding the best proportion of macronutrients to prevent hyperglycaemia in patients with diabetes or stress hyperglycaemia. However, if total requirements are estimated according to the recommendations given above, the proportion of carbohydrates and lipids for infusion will be adequate. After estimating total calories, we recommend calculating amino acid requirements and subtracting the resulting calories from the total. The remaining calories (non-protein) will then be divided between carbohydrates and lipids in percentages that may range between 60% carbohydrates and 40% lipids to a maximum of 60% lipids and 40% carbohydrates (if there is a greater risk of hyperglycaemia or hyperglycaemia cannot be controlled). Either way, this calculation procedure entails infusing 2-4 grams/kg of bodyweight/day of carbohydrates and 1-1.3 g/kg of bodyweight/day of lipids (we recommend not exceeding 1.5 grams of lipids per kg/day, especially in severely ill patients).

Question 10: In the field of parenteral nutrition and hyperglycaemia and diabetes, what type of macro- and micronutrients would be best?

19. There are no data in the literature specifically evaluating these aspects. However, based on physiopathological studies, the use of glutamine or lipids based on olive oil or supplemented with omega-3 fatty acids in patients with increasing metabolic stress could be a reasonable option.

Question 11: What is the best insulin therapy regimen in non-critically ill hospitalised patients with diabetes/hyperglycaemia receiving TPN?

20. We recommend adding regular insulin to TPN bags with a subcutaneous regular (not rapid-acting insulin analogs) insulin regimen every 6-8 hours based on capillary blood glucose levels, with adjustments above 140 mg/dl. In all cases, if the therapeutic objectives are not achieved, the equivalent of 2/3 of the subcutaneous rescue insulin dose required the previous day will be added daily to the bag (table IV). We have applied the following assumptions:

a) No known diabetes and blood glucose levels prior to starting the TPN infusion above 140 mg/dl or no clinical condition commonly associated with hyperglycaemia (severe acute pancreatitis, concomitant use of corticosteroids): start with 1 IU/10 g of glucose in the TPN. Alternative: start with 0.25 IU/kg of adjusted bodyweight.
b) Known diabetes without insulin therapy: start with 1 IU (low stress) to 2 IU (high stress or corticosteroids) for every 10 g of glucose in the TPN.
c) Known diabetes undergoing home treatment with insulin: start with 2 IU per 10 g of glucose or 0.5 IU/kg of bodyweight. As an alternative, start with half (if low stress) to 2/3 (if high stress) of previous outpatient requirements in the bag.

Table IV
Approach to insulin therapy in parenteral nutrition

Parenteral nutrition in hospitalised patients:
– Add regular insulin to TPN bags in combination with subcutaneous regular (not rapid-acting insulin analogs) insulin regimen every 6-8 hours based on capillary blood glucose levels, with adjustments above 140 mg/dl.
– Add the equivalent of 2/3 of subcutaneous rescue insulin dose required the previous day every day
– In cases of uncontrolled hyperglycaemia, separate intravenous insulin infusions from TPN may be required.
Recommended initial insulin dose:
– Unknown diabetes and prior blood glucose levels > 140 mg/dl or no clinical condition commonly associated with hyperglycaemia (severe acute pancreatitis, corticosteroids): start with 1 IU/10 g glucose in TPN, or start with 0.25 IU/ kg adjusted bodyweight.
– Known diabetes without insulin therapy: start with 1 IU (low stress) to 2 IU (high stress or corticosteroids) for every 10 g glucose in TPN.
– Known diabetes receiving home insulin therapy: start with 2 IU/10 g glucose or 0.5 IU/kg of bodyweight, or start with 50-66% of previous outpatient requirements in bag.
In patients with type 1 diabetes, in addition to insulin placed in bag and adjustment regimen, inject 0.05-0.1 IU/kg bodyweight of subcutaneous basal insulin.
Home parenteral nutrition and cyclic infusion: Medium-acting basal insulin (detemir or similar) prior to infusion. Add adjustment regimen if required.

21. In patients with type 1 diabetes, in addition to the insulin placed in the bag and the adjustment regimen, we recommend injecting between 0.05 and 0.1 IU/kg of subcutaneous basal insulin (to prevent ketoacidosis if the TPN infusion is suddenly discontinued). We recommend a preferable use of insulin glargine (once a day) or detemir (once or twice a day) in these cases.

22. In patients receiving home parenteral nutrition and cyclic infusion, subcutaneous insulin may achieve reasonable control of TPN-associated hyperglycaemia in non-diabetic patients. We recommend a dose of detemir prior to infusion.

23. If metabolic objectives are not achieved with the usual regimen, continuous insulin infusion using separate infusion pumps from TPN would be proposed.

Question 12: What would your future investigation recommendations be in the field of diabetes/ hyperglycaemia and artificial nutrition?

24. It is necessary to expand on studies assessing the prevalence of glucose metabolism alterations (diabetes and stress hyperglycaemia) in patients receiving both parenteral and enteral artificial nutrition (in different clinical situations, both hospitalised and as outpatients).

25. It is necessary to assess the physiopathological determining factors of stress hyperglycaemia and, at a clinical level, the natural history of this condition, with it being necessary to reassess the persistence of long-term glucose metabolism alterations after acute processes in order to reclassify patients. Considering these data, a consensus should be reached regarding diagnostic criteria for stress hyperglycaemia and other glucose metabolism alterations.

26. More studies are required in non-critically ill hospitalised patients in order to define glycaemic control objectives by evaluating morbidity, mortality and efficiency criteria.

27. Prospective clinical studies must be conducted to compare the use of different enteral nutrition formulas in patients with diabetes and/or stress hyperglycaemia. These must include more patients, lower protocol withdrawal rates, longer duration (especially in outpatients), be randomised and preferably double-blind in different clinical situations and should assess the efficacy and efficiency (cost/effectiveness) of such formulas on metabolic effect and morbidity/mortality in order to be able to make evidence-based recommendations.

28. It is necessary to conduct clinical trials comparing different insulin therapy regimens in both enteral and parenteral nutrition and different clinical scenarios, assessing not only metabolic control parameters but also their effect on morbidity and mortality.

29. Studies assessing the role of other aspects of the treatment of patients receiving artificial nutrition with hyperglycaemia should be conducted (such as the addition of micronutrients, drug nutrients, glutamine, whey proteins, omega-3 fatty acids, etc.).

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All authors contributed to the conception and design of the study, drafting of the manuscript and critical revision thereof.

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None of the authors has any conflict of interest to disclose.

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