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POSITION PAPER

ADI-AMD recommendations on insulin treatment during artificial nutrition

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Abstract The prevalence of diabetes in hospitalised patients is not well identified; in 2000, 12.5% of patients discharged from US hospitals were diagnosed as having diabetes. In Italy data are limited; in Campania, these data show a 6% prevalence of diabetes in discharged patients, while in Emilia Romagna it reaches 21%. These data do not consider stress hyperglycaemia. There are in fact three categories of people who may have hyperglycaemia during hospitalisation: those with known diabetes diagnosed before hospitalisation; those with diabetes diagnosed during hospitalisation; and those with stress hyperglycaemia, i.e., hyperglycaemia occurring during hospitalisation, but decreasing at the time of discharge. Observational studies have clearly shown how hyperglycaemia leads to a worsening of prognosis because of increased morbidity and mortality and of longer hospitalisation in cases of known diabetes and of stress hyperglycaemia. Intervention studies have confirmed that strict glycaemic control brings about significant improvement of prognosis, thus the importance of good glycaemic control is recognised today, also for critically ill patients receiving artificial nutrition (AN). In recent years, the interest in prevention of microangiopathic and macroangiopathic complications has shifted the interest toward hyperglycaemic peaks and glycaemic variability, along with the "glycated haemoglobin" factor. In hospitals most patients do not receive adequate nutritional support for their calorie requirements, either for preventing or curing protein-energy malnutrition (PEM). One of the reasons for inadequate treatment is precisely the fear of worsening hyperglycaemia; from this perspective, hyperglycaemia is considered the major obstacle in practising proper nutritional support. On the other hand, the use of AN without adequate insulin therapy may cause serious metabolic decompensation. The ADI-AMD (Italian Dietetics and Clinic Nutrition Association-Diabetologist Association) Diabetes study group (GS) considered it advisable to review the previous recommendations drawn up in 2005. The scientific proof level at the basis of each recommendation was classified according to that provided for by the National Guidelines Plan. The document reports the objectives considered desirable in handling the majority of the patients with hyperglycaemia while receiving AN; comorbidity and other factors connected with the individual case may justify different choices.

Keywords Artificial nutrition · Insulin · Diabetes · Parenteral nutrition · Enteral nutrition

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Introduction

The prevalence of diabetes in hospitalised patients is not well identified; in 2000, 12.5% of patients discharged from US hospitals were diagnosed as having diabetes. Umpierrez reported 26% prevalence of diabetes in hospitalised patients; in this study, an additional 12% of

patients had unrecognised diabetes or stress hyperglycaemia [1]. In Italy data are limited; they go back to the introduction of Diagnosis Related Groups (DRG) into the system and tend to underestimate the prevalence of diabetes since diagnosis is not always included in the Hospital Patient Report (SDO). In Campania, these data show a 6% prevalence of diabetes in discharged patients, while in Emilia Romagna it reaches 21%.

These data do not consider stress hyperglycaemia. There are in fact three categories of people who may have hyperglycaemia during hospitalisation: those with known diabetes diagnosed before hospitalisation; those with diabetes diagnosed during hospitalisation; and those with stress hyperglycaemia, i.e., hyperglycaemia occurring during hospitalisation but decreasing at the time of discharge. A high percentage of hospitalised patients have type 2 diabetes mellitus and show insulin resistance, which influences not only glucidic, but also protein, lipid, water and electrolyte metabolism. A patient receiving artificial nutrition (AN) is often in a "critical situation" as a consequence of the main disease from which he is suffering. Stress induces increased secretion of counterregulatory hormones (mainly epinephrine and cortisol), release of fatty acids from adipose tissue and release of cytokines. These factors influence the worsening of glycometabolic control, through the increase of both peripheral and hepatic insulin resistance. These same factors are also responsible for catabolism increase, reported during stress in diabetics, increasing the risk of malnutrition. Observational studies have clearly shown how hyperglycaemia leads to a worsening of prognosis because of increased morbidity and mortality and of longer hospitalisation in cases of known diabetes and of stress hyperglycaemia. Intervention studies have confirmed that strict glycaemic control brings about significant improvement of prognosis, thus the importance of good glycaemic control is recognised today, also for critically ill patients receiving AN.

In recent years, the interest in prevention of microangiopathic and macroangiopathic complications has shifted interest toward hyperglycaemic peaks and glycaemic variability, along with the "glycated haemoglobin" factor. Glycaemic variability, both postprandial and intradaily, could be a factor involved in formation of reactive oxygen species (ROS), thus increasing oxidative stress. With AN, however, there are not enough studies to indicate the importance of hyperglycaemic peaks and glycaemic variability in the pathogenesis of complications. Nevertheless, it is always advisable to avoid hyperglycaemic peaks as much as possible and to keep glycaemia constant during the day. Due to the same mechanisms that lead to increased glycaemia, a diabetic in a critical situation or with stress hyperglycaemia will more frequently reach a state of malnutrition, which represents a further negative prognostic factor. In hospitals most patients do not receive adequate nutritional support for their calorie requirements, either for preventing or curing protein-energy malnutrition (PEM). One of the reasons for inadequate treatment is precisely the fear of worsening hyperglycaemia; from this perspective, hyperglycaemia is considered the major obstacle in practising proper nutritional support [2, 3]. On the other hand, the use of AN without adequate insulin therapy may cause serious metabolic decompensation.

AMD-SID-Diabete Italia recently proposed to create standards 'with the intent of providing clinics, patients, researchers and all those involved in the treatment of diabetes' with treatment objectives substantiated by a good degree of scientific evidence (upon the basis of which choices can be made for treating the individual diabetic patient), as well as with instruments for evaluating the quality of the cure suitable for the Italian situation [4]. They constitute the scientific reference model for diabetes treatment, regarding both objectives and processes. The project proposes to share common treatment objectives and models for health care in our country with diabetologists and all medical professionals.

The standards, however, do not face the problem of treatment of hyperglycaemia in patients receiving AN; for this reason the ADI-AMD (Italian Dietetics and Clinic Nutrition Association-Diabetologist Association) Diabetes study group (GS) considered it advisable to review the previous recommendations drawn up in 2005 [5] using a methodology analogous to that of the standards and entirely accepting what the standards propose.

The scientific proof level at the basis of each recommendation was classified according to that provided for by the National Guidelines Plan (Table 1, www.pnlg.it). The document reports the objectives considered *desirable* in handling the majority of the patients with hyperglycaemia while receiving AN; comorbidity and other factors connected with the individual case may justify different choices. Furthermore, the recommendations do not intend to preclude more in-depth evaluations or the treatment of patients by other specialists when necessary. The study group believes that the care of a diabetic receiving AN requires continuous research in order to develop increasingly safe and efficient protocols for glycaemia management. These recommendations are addressed to all doctors who are involved in managing patients with hyperglycaemia during AN (clinical nutritionists, diabetologists, intensive care specialists, surgeons, etc.) so as to share a common protocol which can clearly be modified on the basis of local needs. For more detailed information, please refer both to the previously mentioned guidelines and to references in the individual sections.

Table 1 Proof levels and strength of the recommendations (www.pnlg.it)

Proof types	
I	Proofs obtained from several controlled randomised clinical studies and/or from systematic revisions of randomised studies
II	Proofs obtained from a single randomised study of adequate design
III	Proofs obtained from non-randomised cohort studies with concurring or historical checks or of their metanalysis
IV	Proofs obtained from retrospective studies, case-control type, or their metanalysis
V	Proofs obtained from a series of cases without a control group
VI	Proofs based on the opinion of authoritative experts or of committees of experts as indicated in guidelines or consensus conferences, or based on opinions of members of the work team responsible for these guidelines
Strength	
A	The carrying out of that particular procedure or diagnostic test is highly recommended. It indicates a special recommendation supported by good quality scientific proof, even if not necessarily type I or type II
B	There are doubts as to whether that particular procedure or action should always be recommended, but it is deemed that it should be closely considered
C	There is considerable uncertainty for or against the recommendation to carry out the procedure or action
D	The carrying out of the procedure is not recommended
E	It is strongly recommended that the procedure NOT be carried out

Methodology

The ADI-AMD Group Recommendations of 2005 and the SINPE (Italian Society of Parenteral and Enteral Nutrition) 2002 guidelines [6], which deal specifically with the topic of hyperglycaemia during AN, are actually followed in Italy. In the international literature this problem is faced in an ambiguous manner. There are many protocols for insulin treatment of hyperglycaemia in critical hospitalised patients, whereas the same thing cannot be said for patients in stabilised AN or for those who are not in intensive care [7–13]. The considerable variability of intravenous insulin infusion protocols (IIP) has been reported recently, with little attention being given to this problem [14]. The ADI-AMD study group (GS) analysed the data found in the literature as well as previous recommendations and, during the meeting/debate, an agreement was reached among members of the GS expressing the premises for new recommendations (R) and an equivalent number of keynotes (K). The ADI-AMD group, composed of S. Leotta, G. Marelli, M. Parillo, M. Tagliaferri, F. Tomasi and C. Tubili, was joined by four clinicians with experience in insulin treatment during AN: F. Cortinovis, G. Fatati, L. Fontana and E. Mirri. The limited group consensus conference method was chosen for the final writing of the document.

The process

The process leading to these recommendations was as follows:

- The project was commissioned by the National Board of Directors of the ADI and AMD, which requested a revision and update of the 2005 Recommendations;
- In order to guarantee better effectiveness in applying the document, a group of experts in diabetes and AN with *proven clinical experience* was created. These experts were asked:
  (a) to investigate the new evidence on protocols for intensive insulin treatment regarding patients with hyperglycaemia receiving AN;
  (b) to reflect on its use three years after the 2005 ADI-AMD recommendations for stabilised patients;
  (c) to define the proof levels and the strength of the new ADI-AMD recommendations; and
  (d) to evaluate integration with treatment standards.
- The Editing Group is composed of ten diabetes and AN experts, two of which – G. Fatati and E. Mirri – represent the Coordination Committee.

Indications for artificial nutrition

R: AN is a therapeutic procedure for patients for whom oral nutrition is not practicable and/or is not sufficient to satisfy protein-energy requirements or is contraindicated. Proof Level I, Strength A

R: The main objectives of nutritional therapy are prevention and treatment of malnutrition and protein-energy support in hypercatabolism conditions. Proof Level I, Strength A

R: Enteral Nutrition (EN) should be considered as a first choice before Parenteral Nutrition (PN). PN is used when EN is not practicable or is insufficient to satisfy requirements. Proof Level I, Strength A

K: A candidate for AN must be considered in critical condition.

K: AN significantly improves the prognosis in many disease situations, reducing morbidity and mortality and improving the clinical course and quality of life.

AN is a therapeutic technique for patients for whom oral nutrition is not practicable and/or is not sufficient to satisfy protein-energy requirements or is contraindicated. For these patients, nutritional therapy is indicated in the prevention and treatment of malnutrition (condition of functional and structural alteration and alteration of organism development resulting from imbalance between requirements, intakes and utilisation of nutrients, such as to bring about an excess of morbidity and mortality or an alteration of life quality) and in satisfying the increased protein-energy requirements typical of hypercatabolism i.e., metabolic response to stress secondary to pathological events, such as polytraumas, sepsis, major surgery, characterised by accentuated muscular proteolysis and visceral protein depletion [15, 16]. Patients receiving AN must be considered in critical condition, as suggested by the Guidelines Committee of the American Intensive Care Society, which includes 'serious nutritional disturbances requiring nutritional support' among the characteristics of criticalness on par with the following disease conditions: haemodynamic instability; respiratory insufficiency with or without the need for mechanical ventilation; acute neurological insult and endocranial hypertension; acute renal insufficiency; life-threatening endocrine and/or metabolic disorders; overdose; drugs and poisonings; coagulation disorders and serious infections [17]. AN significantly improves the prognosis in many disease situations with a reduction of morbidity and mortality [18], and improvement of clinical course [19] and of quality of life [20]. In particular, the review by Stratton et al. pointed out the great benefits of EN: in 12 RCTs (600 subjects) mortality was reduced (23% *vs.* 11%), in 17 RCTs (749 subjects) there was a reduction in total complications (48% *vs.* 33%) and in 9 RCTs (442 subjects) a reduction in infective complications were reported (46% *vs.* 23%). These results are correlated with the increase in nutritional intake and the regaining of weight [21]. EN is defined as the procedure that makes it possible to convey nutrients into the digestive canal (stomach, duodenum or jejunum) by means of probes and PN is the procedure for administering nutrients into a vein (in a peripheral or central vein) [22, 23]. EN is the first choice before PN, as it is more physiological, burdened by fewer side effects and less expensive [24–27]. PN is used when EN is not practicable or is insufficient for satisfying the subject's requirements. Conditions of anatomical-functional inability of the digestive tract are contraindications to the use of EN. In particular, clinical situations of intestinal insufficiency secondary to short intestine syndrome or severe enteropathy, intractable vomiting, paralytic ileum or conditions of mechanical occlusion or severe intestinal ischaemia, and lastly the presence of high output jejunal or ileal fistulas favour the use of PN [23, 24]. Both EN and PN require precise monitoring protocols, as various types of complications are possible: metabolic (common to EN and PN), gastrointestinal and mechanical secondary to EN and, lastly, connected with access to the central vein for PN [24].

Artificial nutrition and hyperglycaemia (PN *vs.* EN: the incretin effect)

The plasmatic concentrations of glucose depend on the balance of the amount of glucose reaching the organism following intestinal absorption and glucose produced *de novo*. In basic conditions of fasting, glycaemia reflects the production of glucose by glycogenolysis and glyconeogenesis; these processes occur mainly in the liver, but also in the kidneys [28] and possibly in the intestines. In the postprandial period the absorption of glucose through the intestines is responsible for most of the concentration of circulating glucose, while hepatic glyconeogenesis is suppressed. In critical patients there is a state of hepatic insulin resistance, such as to make physiological suppression ineffective: consequently there is increased endogenous production of glucose which is added to that absorbed intestinally. Glucose metabolism does not depend only on the alimentary availability of glucose, but also on the administration method, especially in regard to AN. Oral nutrition provokes the secretion of a multitude of gastrointestinal hormones, which, besides modulating gastrointestinal motility, gastric secretion, production of pancreatic juice and gall bladder contraction, also allow better and faster metabolism of absorbed glucose by stimulating insulin secretion [29]. In the early 1900s Moore et al. hypothesised that the duodenum released a factor stimulating pancreatic secretion [30]. Later, La Barre and Still first used the term "incretin" to indicate the intestinal hormonal activity that could act on the secretory activity of the endocrine pancreas [31]. The most important among these hormones is glucagon-like peptide-1 (GLP-1), which above all regulates postprandial hyperglycaemia, because of its effect on stimulating the releasing of insulin from beta cells and inhibiting the glucagon being released from the alpha cells [32]. EN provides a greater insulinotrophic stimulus than the parenteral administration of an isoglycaemic preparation: this is an effect that we can define as incretinic [33]; it is shared evidence that patients receiving PN require greater amounts of insulin to obtain good glycaemic control compared to patients nourished enterally. Long-term PN is a real risk for diabetic disease in children with a negative history of diabetes [34]. Lastly, in patients affected by pancreatitis, EN allows better glycometabolic control compared to those treated with PN [35]. These

observations can be most likely explained by the effect of incretin-mediated insulin secretion connected with EN and not found in PN [36].

The objectives of glycometabolic control during artificial nutrition and the risks of hypoglycaemia

R: The normalisation of glycaemia levels using intensive IIP improves clinical results in patients in a critical condition. Proof Level II, Strength B

R: The reaching of "near normal" glycaemia targets must be gradual: even in intensive care it must be achieved in 6–24 h, so as not to increase the risk of hypoglycaemia. Proof Level VI, Strength B

R: Glycemia values ≤140 mg/dl are indicated for patients in critical conditions in intensive medical and surgical care. Proof Level II, Strength B

R: The desirable values for hospitalised non-critical patients are <126 mg/dl with an empty stomach and <180 mg/dl postprandial or random. Proof Level VI, Strength B

R: Glycaemia values <140 mg/dl are sufficient for patients in the coronary ward regardless of whether or not they have a history of diabetes. Proof Level VI, Strength B

R: For patients with coronary heart disease hospitalised but not in intensive care, a target of <180 mg/dl is recommended. Proof Level VI, Strength C

K: Hyperglycaemia is an important adverse prognostic factor, for both diabetics and non-diabetics.

K: Patients with stress hyperglycaemia must be studied after the acute event in order to verify the level of metabolic disorder, checking fasting glycaemia, HbA1c and possibly OGTT.

K: Patients receiving AN hospitalised in ordinary conditions or in assisted-living accommodations or in home care, in stable clinical conditions, may be treated with the same standards as those in non-critical conditions.

K: Glycaemic variability is an important prognostic factor for patients in a critical condition.

"Hyperglycaemia" is defined as a fasting or postprandial (or random) blood glucose level higher than levels established on the basis of the behaviour of this variable in healthy people. The scientific societies working with diabetes have included the *American Diabetes Association* (ADA) indications, which set the upper limit of the normal glycaemia range at 100 mg/dl [37]. Glycaemia above 126 mg/dl, confirmed in at least two surveys, allows a diagnosis of diabetes; values between 100 and 126 mg/dl indicate an alteration of the glucidic metabolism (Impaired Fasting Glucose – IFG) [38]. The postprandial values measured 2 h after a meal generally do not go above 140 mg/dl in healthy people. Hyperglycaemia is frequently found in hospitalised patients (up to 38%), especially in those with serious illnesses that evoke a response from stress [39, 40]. About one third of the people with hyperglycaemia do not report a previous clinical history of diabetes; it is prevalent in 25–50% of those with acute coronary syndrome upon admission [40]. Hyperglycaemia is an important adverse prognostic factor, for both diabetics and non-diabetics [41, 42]. In patients with acute myocardial infarction (AMI), the adverse prognostic effect of hyperglycaemia is also seen from 1 to 6 months after discharge [43, 44]. Hyperglycaemia has a proinflammatory role documented by the high levels of cytokines, and adhesion and metabolic molecules of the NO that are found in this condition; insulin therapy not only corrects hyperglycaemia, but also has an anti-inflammatory role on its own, reducing the levels of the previously mentioned indexes [45]. There is no unanimous definition in the literature of the glycaemic levels that define this condition; therefore, in patients with traumas, targets of 150 mg/dl [46, 47] or 139 mg/dl [48] have been suggested and, in those in intensive therapy, 125 mg/dl [49]. Patients with stress hyperglycaemia must be studied after the acute event with fasting glycaemia, HbA1c and possibly with OGTT [50]. It is likely that the targets must be differentiated for diabetics and non-diabetics who show stress hyperglycaemia, given the adaptation of tissues to hyperglycaemia in the former and the different threshold of the hyperglycaemic response to stress. In a metanalysis the risk of mortality at the hospital is about 4 times greater in non-diabetics hospitalised for AMI whose glycaemia is above 110 mg/dl [41]; for diabetics, however, values >180 mg/dl upon hospitalisation are associated with a 70% increase in mortality [42]. In a post hoc analysis of patients in medical and surgical ICUs, which had confirmed the reduction in mortality and morbidity with intensive insulin therapy and strict glycaemic control, no benefits regarding mortality were observed among those with a history of diabetes, especially if treated with an oral hypoglycaemic drug [51]. The glycaemic target is still being debated, but it is probable that "universal" optimal levels for different types of subjects do not exist, in light of the possible risks of an

aggressive therapeutic approach. In order to make the results assessable, it is necessary to unify the standardised parameters for good glycometabolic control. To this aim, the definition of glycaemic control in 6 levels proposed by Finney [10, 52] can be used, which includes:

- hypoglycaemia: <80 mg/dl
- aggressive control: 80–110 mg/dl
- acceptable control: 111–144 mg/dl
- intermediate control: 145–180 mg/dl
- poor control: 181–200 mg/dl
- hyperglycaemia: >200 mg/dl

The monitoring of glycaemia in patients in a critical condition must be done with glucometers validated in the ICU setting, so as to avoid errors, especially in regard to hypoglycaemia. Subcutaneous sensors for interstitial glucose that provide readings in real time may be helpful in the prevention of hypoglycaemia [53, 54]. The normalisation of glycaemia levels using intensive insulin infusion protocols (IIP) improves clinical results in patients in a critical condition in Intensive Care [42, 47, 54–56]. In this type of subject glycaemic control should therefore be aggressive [57]. The reaching of this objective in clinical practice exposes one to a higher risk of hypoglycaemia: in Leuwen's studies the subjects under strict glycaemic control had an increase of 0.8–5.1% in instances of hypoglycaemia [42, 56]. An increase in episodes of hypoglycaemia with a consequential increase of risk and of cardiovascular events was reported in the Intensive Care Trauma [52] and especially in Cardiology [58, 59] wards, and requires 2–6 times more work from nurses than a less aggressive approach [60–63]. The more or less early start of AN and administration protocols followed at the different Centres (timing of the start and supplementing PN and EN) play an important role. In reports on strict glycaemic control, EN was begun as soon as the haemodynamic stabilisation of the subjects was obtained, with parenteral integration/substitution in case of insufficient supply [51]. The target of 80–110 mg/dl is indicated by the ADA for patients in critical conditions [64]. Higher values (<140 mg/dl) could be sufficient for patients in the Coronary Ward regardless of whether or not they have a history of diabetes. Nevertheless, the optimisation of glycaemia must be attempted, even if the benefits of this approach have not yet been completely documented [50, 65]. In DIGAMI 2 the intensive intervention protocol did not succeed in reaching the pre-established aggressive targets and did not bring about an improvement in the prognosis compared to a less aggressive approach [66]. In individual Hospital situations, a less aggressive approach can therefore be recommended initially (acceptable: 111–144 mg/dl according to Finney), which in the Stanford Project was shown to be effective in reducing mortality (–29.3%) and morbidity in Intensive Care Unit patients suffering from various diseases [55]. In any case, reaching "near normal" glycaemic targets must be gradual: even in intensive care it must be achieved in 12–24 h, because a more rapid correction can increase the risk of hypoglycaemia [51]. The implementation of therapeutic protocols in the individual wards, moving them from more conservative values to 80–110 mg/dl, as recommended by the ACE and ADA, must be done gradually, setting intermediate goals (90–119 mg/dl) and prudently increasing (40%) the boluses of insulin being used, following the experience of Yale [67]. In The *NICE-SUGAR Study* international, randomized trial, investigators found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per decilitre [68]. In this trial, more patients in the intensive-control group than in the conventional-control group were treated with corticosteroids, and the excess deaths in the intensive-control group were predominantly from cardiovascular causes. The importance of glycaemic variability in hospitalised subjects has also been emphasised [69, 70]: its measurement by means of the standard deviation or other ad hoc indexes (lability index, hyperglycaemic index [71]) is an important prognostic factor in patients in a critical condition. According to the ADA, the optimal values for non-critical inpatients are <126 mg/dl at fasting and <180–200 mg/dl postprandial or random [64]; the ACE sets them at <110 mg/dl preprandial and <180 mg/dl postprandial [57]. For coronary disease patients hospitalised in non-intensive conditions, a target of <180 mg/dl is recommended [50]. With non-critical patients, the main obstacles in reaching optimal glycaemic targets are: metabolic repercussions from stress and from the main disease, irregularity of mealtimes, insufficient nutritional intake, hypoglycaemia and inappropriate correction of too high or too low values ("sliding scales") [72]. Even though hospitalised patients receiving AN must be considered by the same standard as patients in critical condition [65], a majority of them, hospitalised in ordinary conditions or in assisted-living accommodation or in home care, in stable clinical conditions, may be treated with the same standards as those in non-critical conditions. It is to be hoped that every centre will use a standardised intensive IIP. The essential characteristics of this protocol must provide for as optimal a glycaemic control as possible and have practical means available, making constant use possible. In the literature there are examples of extremely complex experiences and of others that are simpler to implement [68, 73, 74].

When and how to begin artificial nutrition

R: As a rule, AN should be started only when glycaemia is ≤200 mg/dl in the absence of ketonuria or complications such as dehydration or hyperosmolarity. Proof Level V, Strength B

K: The induction of AN must be slow and gradual, especially for the quota of glucose. The protein-energy requirement of a diabetic patient is not different from that of non-diabetics.

As a rule, AN should be started only when glycaemia is ≤200 mg/dl in the absence of ketonuria or complications such as dehydration or hyperosmolarity [75]. The induction of AN must be slow and gradual, especially for the amount of glucose. Therefore, after the patient's requirements have been calculated, it starts the first day with an amount not more than half of the established dosage and, monitoring the individual response, it is increased each day until reaching the target dosage within 3–7 days. The protein-energy requirement of a diabetic is not different from non-diabetics. If the energy expenditure is not measured (indirect calorimetry), the basic energy expenditure (BEE) can be estimated with the Harris–Benedict formula:

Men: 66.5+[13.75↔att. weight (kg)]+[5↔height (cm)]–[6.75↔age (years)]
Women: 655+[9.56↔att. weight (kg)]+[1.85↔height (cm)]–[4.67↔age (years)]

The increase in the energy expenditure due to a situation of acute stress must also be considered (from 10% to 30% following surgery, 10% to 40% with polytrauma, 10% to 60% with serious infections and sepsis, to more than 100% for extensive burns). In these conditions, the use of AN is aimed at satisfying the increased energy needs and limiting the loss of nitrogen. Therefore the energy requirement must be corrected, multiplying by the activity or pathology coefficients or by those for the illness according to the chart given below.

Activity FACTORS: Complete rest 1.00; Awake in bed 1.10; Walking 1.25–1.50
Pathology FACTORS: Malnourished 1.00; Elective surgery 1.10; Complicated surgery 1.25; Trauma or sepsis 1.25–1.50

As a rule glycaemia should be monitored with a glucometer: every 2–3 h to start with, then, after having completed AN induction and checking the patient's tolerance, at longer intervals, but following a regular schedule defined according to the protocol established (but at least 3–4 readings a day) for the 24-h period. Self-checking is a fundamental element in reaching glycometabolic balance. Patients in intensive care or in situations of intercurrent metabolic instability require more frequent checks [75].

Enteral nutrition

Enteral nutrition (EN) is suitable for all those patients who cannot eat adequately, and it must be the first option chosen when the gastrointestinal tract is "functional" and "practicable". This holds true also in conditions of hyperglycaemia/diabetes. EN may be difficult to carry out in the presence of gastroparesis – a clinical condition easily found in diabetics – which, if not diagnosed, can lead to complications that are sometimes serious, such as "ab ingestis" in unconscious patients. Gastroparesis is secondary not only to autonomic neuropathy, but may also depend on hyperglycaemia and as such may be reversible. Exactly what mechanism correlates glycaemic values, and especially hyperglycaemia, to the motor function of the stomach is not known at present: anomalies in the nervous, humoral and cell pathways have been hypothesised [76]. Clinically, gastroparesis appears with an early sense of satiety, nausea and vomiting that can be treated with drugs such as prokinetics, and the administration of nutrients past the stomach, by means of a nasojejunal probe or by jejunostomy. Besides the difficulties connected with the administration of the mixture, these conditions bring about a difficult glycometabolic compensation connected with the unpredictable absorption of the mixture [77, 78]. This necessitates stricter glycaemic control.

Parenteral nutrition

Parental nutrition (PN) must be used when there is a contraindication to the use of EN or if EN is impracticable. The proportioning of the energy quota of the nutritional mix (glucose/lipids ratio) calls for a slight reduction in the amount of glucose: the intake of glucose for diabetics with glycaemic compensation and stable from a clinical viewpoint must not be more than 4–5 g/kg/day compared to 6–7 g/kg/day for non-diabetics, so as not to exceed the oxidative capacities of glucose; the intake of lipids should be 1.0–1.5 g/kg/day. PN must guarantee nonetheless at least 100–150 g of glucose/day, and the intake of glucose can be increased by 50 g/day in relation to the glycaemic compensation, until reaching the target dosage. In cases in which there is a strong reaction to stress, resulting from acute serious pathologies that bring about a state of hypercatabolism, in diabetics the glucose quota should be reduced due to the lower ability to utilise carbohydrates.

A more or less normal protein intake is generally recommended, equal to 0.8–1.2 g/kg of ideal weight [75].

Use of disease-specific formulas in enteral nutrition

R: Diet formulas specific for the disease must be used for diabetics receiving EN. Proof Level I, Strength A

K: Concerning the specific diet formulas available, preference should be given to those with the following characteristics: low carbohydrate content, low glycaemic index, high fat content, especially monounsaturated fatty acids (MUFA), significant amount of fructose and fibre.

As is well known, the standard formula mixtures that can be used in EN generally contain fairly high amounts of low-molecular-weight carbohydrates (especially maltodextrin), along with a modest fat and fibre content. The speed at which these carbohydrates are absorbed, following the rapid gastric emptying consequent to their ingestion, brings about an inevitable and considerable increase in postprandial glycaemia, and this may in turn put diabetics at risk of a dangerous metabolic disequilibrium, particularly in the case of critical patients. In order to avoid this eventuality, the industry has developed diet formulas specifically for diabetes. At present there should no longer be any doubt that the use of disease-specific formulas is always preferable for diabetics, even though some important scientific societies such as the ADA have not yet expressed themselves clearly [79]. This assumption has emerged from two reviews on the topic [80, 81], was reasserted in the Guidelines of the Italian Parenteral and Enteral Nutrition Society [82], and was further and fully confirmed recently by Elia et al. [83] who, in a weighty metanalysis, analysed 23 studies on oral supplementation and nutrition by probe, comparing the effects of these preparations with those of standard mixtures on glycaemia and lipid levels, the nutritional state, the necessity of medicines, quality of life and mortality. The diabetes-specific formulas were shown to be more effective than the standard formulas in inducing a lesser increase in postprandial glycaemia, in limiting the glycaemic peak and in reducing the area underneath the glycaemic curve. At the same time, higher concentrations of HDL cholesterol and lower concentrations of triglycerides were seen with the use of these formulas. Lastly, the metanalysis showed a lower incidence of infections in the urinary tract, pneumonia and fever episodes in diabetics nourished with specific formulas. It should be remembered, however, that diabetes-specific diet formulas may be divided into essentially two groups. The first group includes formulas in which the quota of carbohydrates, though quantitatively similar to those of standard formulas, does not consist of maltodextrin, but is based instead on tapioca starch and fructose. These formulas also contain large quantities of water-soluble fibres (partially hydrolysed guar gum) in order to slow down the absorption of the carbohydrates. The second group instead includes formulas with low carbohydrate content (30–40%) and low glycaemic index: the carbohydrates are represented by modified tapioca starch, classic or modified maltodextrins, fructose and maltitol, depending on the different formulas available. These formulas also have a high fat content (40–50%), with a large share (over 50%) of MUFA, fibre (soy polysaccharides) and fructooligosaccharides. A recent RCT comparing two formulas, one from the first group and one from the second [84], aimed at evaluating the respective effects on glycaemic control and blood lipids over time, demonstrated that the one with low carbohydrate and high fat content, especially MUFA, did not cause any variation in glycaemia and triglycerides compared to basal values, whereas the formula with a normal, though qualitatively modified carbohydrate content and rich in water-soluble fibres causes them to rise after a while. The different result with the use of a formula from the second group is likely due to its high MUFA content and its low glycaemia index [85].

Enteral nutrition and insulin treatment

R: Insulin treatment must be chosen in relation to the EN administration method. Proof Level V, Strength B

R: If EN mixtures are administered continuously, a long-acting analogue can be used to correct hyperglycaemia. Proof Level V, Strength B

R: In the case of cyclic EN that requires a time of 10–12 h, such as the nocturnal type, intermediate-acting insulin can be used with a small dosage of rapid insulin. Proof Level V, Strength B

R: If an intermittent method is used, an insulin plan with boluses or basal bolus must be utilised. Proof Level V, Strength B

K: The continuous low flow of EN mixtures is preferable also in patients with hyperglycaemia.

K: The use of a peristaltic pump reduces to a minimum the risk of glycaemia oscillations.

There are no comparable clinical trials that examine different insulin treatment strategies in patients with hyperglycaemia receiving EN [86–88]. The insulin treatment is related to the EN method used:

Continuous nutrition provides for the administration of the prescribed volume of mixture at constant speed over a 20–24 h period and is the most advantageous and effective method, as it reduces the speed of gastric filling and decreases the gastrointestinal side effects. The subcutaneous model most commonly used in this case is still basal insulin two times a day every 12 h. A small dosage of ready insulin at the start of EN may be useful. The use of long-acting subcutaneous analogues must be considered appropriate: insulin glargine can be administered once daily [89–94]. The initial insulin dosage in patients previously treated with other methods and stabilised can be calculated considering at least the average of the insulin given in the two preceding days [92]. Some authors recommend starting with a reduced dosage of long-acting analogue, gradually correcting hyperglycaemias with rapid insulin and progressively adjusting the dosages [88]. The risk of long-acting analogue, if high dosages are used, could be hypoglycaemia when EN is interrupted for technical reasons connected with nutrition or with the main disease. The use of a peristaltic pump, which reduces the risk of hypoglycaemia to a minimum, and careful monitoring of glycaemias when EN is suspended are sufficient for avoiding possible problems [88]. The necessity of washing the nasogastric tube (SNG) with 20–30 ml of water every 8–12 h, as is commonly recommended to avoid occlusion of the lumen [93], is not considered an obstacle to the use of a long-acting analogue.

Cyclic or nocturnal enteral nutrition. In the case of cyclic EN that requires a time of 10–12 h, such as the nocturnal type, intermediate-acting insulin can be used with a small dosage of rapid insulin. As an alternative, slow analogues can be used. Some subjects could benefit from premixed insulins [94].

Nutrition in boluses. If an intermittent method is used, which provides for the dividing of the total quantity of mixture into equal portions administered several times per day for a period of 20–30 minutes, an insulin plan with boluses or basal bolus must be utilised, making this method very similar to normal alimentation. The dosages would be calculated checking glycaemia before starting EN and two hours after finishing [88, 94].

Parenteral nutrition and insulin treatment

R: PN should be begun with a glucose quantity not less than 100–150 g/day, using 0.1 units of insulin per gram of infused glucose. Proof Level V, Strength B

R: The insulin requirement is established on the basis of the subject's clinical and glycometabolic characteristics. Proof Level V, Strength B

R: For a stabilised patient receiving TPN who uses a peristaltic pump for 24 h, a subcutaneous long-acting insulin analogue may be used. Proof Level V, Strength B

K: Diabetics receiving PN can easily become hyperglycaemic. It is necessary to adjust the insulin treatment rather than to reduce the AN.

K: Additions to the bag must be made in aseptic conditions.

K: Only those medicinal products whose compatibility has been documented may be mixed.

Diabetics receiving PN can easily become hyperglycaemic; it is necessary to adjust insulin treatment rather than to reduce AN [95–97]. The adequate treatment of hyperglycaemia favours muscle amino-acid and protein metabolism [98, 99]. The data in the literature on PN testify to the initial infusion of a quantity of glucose that avoids overfeeding. It is advisable to begin with a quantity not less than 100–150 g/day, and in relation to the glycaemic compensation the intake of glucose can be increased by 50 g/day. In patients with a negative diabetes history, but who have shown two consecutive glycaemic values of 120 mg/dl, and in diabetic patients, one can start with 0.1 units of insulin per gram of infused glucose and 0.15 units when the glycaemia is above 150 mg/dl. Type 2 diabetics and obese patients may need 0.2 units of insulin for each gram of glucose, whereas for type 1 diabetics and thin patients the insulin requirement may go down to 0.5 units per gram of glucose. If glycaemias are too high (above 144 mg/dl) in 24 h, adjustments may be made by infusing a quota of regular insulin greater by 0.05 units per gram of glucose [100, 101]. An insulin infusion separate from the PN bag is initially advisable; 50 units of regular insulin can be diluted in 49.5 ml of saline solution and infused by means of a syringe pump. If a syringe pump is not available, it is recommended that an infusion set with a device for regulating the flow that shows approximate millilitre per hour values be used. In stabilised patients doing PN with a peristaltic pump, a subcutaneous long-acting insulin analogue can be used [95, 102, 103] with single or double administration [96]. There are limited reports of the possible use of insulin lispro in suspension together with subcutaneous protamine sulfate in double administration [104]. The pharmaceutical industry, which supplies three- (or two-) compartment "all-in-one" bags, advises against any modifications to the bags unless done in aseptic, controlled and validated conditions, preferably under a laminar flow hood, and only medicinal products whose compatibility has been documented should be added. As regards the addition of

insulin, only regular human insulin is compatible with PN formulas [105].

Transition from intravenous infusion to subcutaneous insulin therapy for patients receiving AN

R: The transition from intravenous infusion to subcutaneous insulin therapy must be done according to validated protocols. Proof Level II, Strength B

R: The transition from intravenous infusion to subcutaneous insulin therapy must take place in conditions of glycaemic stability. Proof Level V, Strength B

R: Subcutaneous insulin requirements must be calculated taking into account the quantity administered intravenously in the last 24 h (calculated also according to time fractions if necessary) in conditions of glycaemic and nutritional stability. Proof Level II, Strength A

R: In order to correctly determine the dosage of insulin to be administered subcutaneously during the transition period, glycaemia must be closely monitored and the total dose of insulin must be revised daily. Proof Level VI, Strength B

K: In long-term AN, transition from intravenous to subcutaneous insulin therapy is recommended.

In hospitalised patients in various situations, such as AMI, stroke, heart surgery, hospitalisation in intensive care or that require AN therapy, a large number of clinical studies and guidelines suggest the use of intravenous insulin infusion therapy in the acute stage for a more rapid and effective control of glycaemic values, followed by continuation of the insulin therapy administered subcutaneously. Studies conducted on diabetic patients with AMI have indicated the usefulness of continuing insulin treatment following the acute event with refracted subcutaneous administrations. For example, in the DIGAMI (*Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction*) study [106] conducted in Sweden in 1990–1993, a reduction in mortality of 30% one year after the infarction was demonstrated in the group treated with intravenous insulin and glucose in the first 24 h and, subsequently, with a subcutaneous multiple injection therapy for at least 3 months. The benefit in terms of survival continued even years later [106]. Furthermore, in a population of 7049 patients with critical illnesses, Egi et al. [107] observed that glycaemic variability was a predictive factor regardless of in-hospital mortality. One of the tasks of a correct insulin therapy, both intravenous and subcutaneous, is therefore to effectively control glycaemic variability especially regarding the range of glycaemic values. A common problem in the studies on critical patients with intravenous insulin infusion therapy was the management of the transition from the initial intravenous infusion to the subsequent subcutaneous insulin therapy. When the IIP was interrupted with the clinical improvement of the patient and the start of oral nutrition, a rise in glycaemia values or actual hyperglycaemia was observed in the majority of studies. In Goldberg et al.'s 2004 study [108], for example, which presented the initial results of the "Yale insulin infusion protocol", at the end of insulin infusion glycaemia values rose from the target of 100–139 mg/dl to average levels of 178 ± 57 mg/dl in the first 12 h and to average values of 200 ± 70 mg/dl in the next 12 h. In discussing their work, Goldberg et al. recognised the necessity for studies aimed at developing protocols for the transition from insulin infusion to the subcutaneous therapy, designed to minimise this "rebound" effect. There are few examples in the literature of protocols and experiences for the switch from intravenous to subcutaneous insulin therapy. Almost all of the studies evaluated critical patients hospitalised in intensive care wards. In 2004 Bode et al. [109] devised a protocol for the conversion from infusion to subcutaneous insulin therapy that based the calculation of the insulin dosage to be administered subcutaneously on the amount of insulin administered intravenously in the last 6 h, projected over 24 h, and then reducing it by 20% in order to cautiously limit the risk of hypoglycaemia. The total daily dosage of insulin thus calculated was then divided into two quotas: 50% for covering the basal insulin requirement utilising a long-acting insulin analogue in a single administration (glargine) and 50% in the form of boluses with the three main meals, utilising an ultrarapid-acting (lispro) insulin analogue, dividing the dosage into 20% for breakfast, 40% for lunch and 40% for supper. The authors suggest making the transition to subcutaneous insulin therapy at the time of the first evening meal, administering the first insulin glargine dose two hours before mealtime. Thus at suppertime the intravenous infusion of insulin was interrupted and the prandial dose of insulin was given.

Furnary and Braithwaite [110] used a protocol for conversion from intravenous infusion to subcutaneous insulin therapy in which the calculation of the insulin requirement was estimated over a time period of 6–8 h and then projected over 24 h. The total quota of insulin was initially administered in the form of insulin glargine for 80% of the total and subsequently, through a daily revision of the insulin dosage, brought to a final distribution of about 50% basal insulin and 50% insulin with meals. Intensive monitoring of glycaemia (preprandial,

postprandial after 2 h, bedtime and 3 a.m.) and the daily revision of the dosage of insulin to be administered were used as fundamental elements for a correct transition. The authors also state that the conversion protocol should be adjusted on the basis of the patient's clinical situation. For example, patients with renal insufficiency have a higher prandial insulin requirement (70%) and lower basal insulin requirement (30%).

In the study by Schmeltz et al. [111], 75 subjects hospitalised and receiving insulin infusion therapy were randomised to receive 40%, 60% and 80% of their total daily insulin requirement calculated on the basis of the requirement of the last 6 h of infusion, in the form of insulin glargine at the time of the transition to the subcutaneous insulin regimen. The study results showed a higher percentage of capillary glycaemia values in the declared range of 80–150 mg/dl in the first 24 h after the transition in the group that used 80% of the daily insulin requirement in the form of insulin glargine.

In a randomised study done in 2005, Bode et al. [112] assessed the safety and effectiveness in type 1 diabetics of the transition from continuous insulin infusion with insulin lispro in CSII to a subcutaneous insulin regimen with insulin lispro and glargine. The study results demonstrated that insulin glargine administered subcutaneously as basal insulin guarantees the control of glycaemia overlapping treatment with CSII, and that the recommended dosage of insulin glargine to be administered subcutaneously is equal to the total basal dosage administered with CSII.

In the work by Marelli et al. [113], the results of the conversion from insulin infusion to subcutaneous therapy were evaluated in a population of diabetics with acute coronary syndrome. The daily insulin dosage was calculated in relation to the quantity of insulin administered intravenously in the last 12 h and projected over 24 h, after at least 24 h of stabilised glycaemia values. Parallel with the insulin infusion, these subjects were also given an IV administration of glucose, corresponding to the quantity of carbohydrates furnished by the diet after one acute event. The variations between the calculated dosages and those actually administered upon discharge were limited to about 30%, with a low incidence of hypoglycaemia. Special attention should be given to the possible hypoglycaemias that these transition protocols could bring about. Generally, in almost all of the cases the significant hypoglycaemias were not very common. In any case, effective protocols for the treatment of hypoglycaemia should be prepared and utilised.

Appendix: Pharmaceutical problems

(With the collaboration of Dino Miceli, Sandro Pertini Hospital)

There are basically two therapeutic possibilities available to doctors prescribing total PN bags today:

(1) the use of pre-prepared bags produced by the pharmaceutical industry; and
(2) the prescription of personalised bags to be prepared at the hospital pharmacy.

The pre-prepared bags produced by the pharmaceutical industry are characterised mainly by having two compartments (amino acids sol./glucose sol.) or three compartments, commonly called "all-in-one" (glucose sol./ amino acids sol./lipids sol.), separated by a partition that is broken at the time of use. Some formulas do not contain electrolytes. They have the advantage of being ready to use, with a long storage life and stability, and are available on the market in different formulas, with different calorie contents. They usually have a storage life of 24 months at room temperature (25°C). In Italy, pre-prepared bags are produced by three pharmaceutical companies: Fresenius Kabj, Baxter and B Braun. Each of these produces lines of bags with average coverage of the necessary calorie intake. The data sheet gives the maximum documented compatibility values for oligoelements and vitamins. The quantity of all electrolytes is assessed on the basis of the relative data sheets, which indicate the maximum concentration in the bag that ensures its stability. The data sheets do not give information on the addition of drugs or insulin. It is possible to add, as described in the data sheet, only those medicines or nutritional solutions whose compatibility has been documented, which is available upon request for the different additives and the storage life of the mixtures thus obtained. Additions must be made aseptically. After infusion, any unused portions must be discarded [114]. Any substance must be added in aseptic, controlled and validated conditions, preferably under a laminar flow hood.

Moreover, as regards the choice of insulin, only regular human insulin is compatible with PN formulas; other insulin types, such as NPH, ultra-slow, slow, lispro, aspart and glargine are not compatible [115]. Personalised bags fall within the exclusive activity of pharmacies according to the dictates of the *Official Italian Pharmacopeia, XI edition*, which assimilates the mixture, dilution and division done for each person, by medical prescription, to a magistral formula [116]. Mixing operations can be done manually or with the use of a filling device, with a positive advantage in terms of precision and speed. In both cases, the preparation must be done in a suitable controlled contamination environment, under a horizontal laminar flow hood. Bags prepared in the pharmacy allow greater personalisation and, therefore, greater compliance with the substrates administered for the therapeutic necessities. They are less stable than industrially prepared bags; however, they are suitable for the normal needs of a health care structure

[114]. The subsequent addition of drugs or insulin to bags prepared in the pharmacy according to the guidelines requires the supervision of the pharmacist, and in any event the presence of these substances changes the stability and storage life of the bag [117]. There are several studies in the literature on drugs administered in PN mixtures; it seems difficult, however, to be able to predict the stability or the interactions of these molecules in complex mixtures such as these, which may contain as many as fifty components [118–120]. The literature recommends extreme caution in the addition of either drugs or insulin [121]. Insulin tends to adhere to the walls of the bags and of the infusion set, thus resulting in incorrect amounts [122–129]. Therefore it is advisable not to add insulin and drugs to nutrition bags, but to administer them separately, so as to avoid interactions and to be certain about the dosage.

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