UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: ENDOCRINOLOGIA

SUPORTE NUTRICIONAL EM PACIENTES HOSPITALIZADOS: REVISÃO SISTEMÁTICA COM META-ANÁLISE DE DIFERENTES REGIMES DE INSULINA PARA TRATAMENTO DA HIPERGLICEMIA E FATORES PROGNÓSTICOS EM PACIENTES CRÍTICOS DE BAIXO PESO

TESE DE DOUTORADO

MARINA VERÇOZA VIANA

Porto Alegre, março de 2018.

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DEDICATÓRIA

À minha família.

"A nossa família sempre é assim, maior que a humanidade. "

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LISTA DE ABREVIATURAS

APACHE II – Acute physiology and chronic health evaluation II

ASPEN – American society of parenteral and enteral nutrition

BMI – Body mass index

DM – Diabetes mellitus

ESICM – European Society of Intensive Care Medicine

ICU – Intensive care unit

MGB – Mean blood glucose

NOS – Newcastle-Ottawa scale

NS – Nutrition support

NUTRIC – Nutritional risk in critically ill

OMS – Organização Mundial da Saúde

RCT – Randomized clinical trial

SAPS 3 – Simplified acute physiology score 3

SCCM – Society of Critical Care Medicine

SD – Standard deviation

SOFA – Sequential organ failure assessment

UTI – Unidade de terapia intensiva

WHO – World Health Organization

Resumo

A terapia nutricional tem um importante papel no cuidado do paciente hospitalizado, reduzindo o consumo muscular e mantendo o estado nutricional do paciente. Em paciente previamente desnutridos, é possível que um suporte nutricional especializado seja ainda mais benéfico.

Pacientes hospitalizados apresentam-se frequentemente com alteração glicêmica, seja por resposta ao estresse ou efeitos adversos de medicamentos e do suporte nutricional. A hiperglicemia, especialmente em pacientes sem diabetes, está associada a piores desfechos. A insulina faz parte do controle glicêmico de pacientes hospitalizados. Contudo, o melhor regime para administra-la ainda não está definido.

Dessa forma, o primeiro estudo dessa tese consiste em uma revisão sistemática de pacientes hospitalizados que recebem suporte nutricional para definir qual o melhor regime de insulina para tratar hiperglicemia desses pacientes. Essa revisão incluiu um total de 17 estudos e 3260 pacientes. Contudo, não foi possível determinar qual o esquema de insulina para controle glicêmico de pacientes hospitalizados sob suporte nutricional.

O segundo estudo dessa tese consiste em uma coorte que avaliou o suporte nutricional em 342 pacientes críticos desnutridos (índice massa corporal < 20 kg/cm^2). O estudo não mostrou associação entre mortalidade intra-hospitalar e suporte nutricional na primeira semana de internação na unidade de terapia intensiva.

Palavras-chaves: terapia nutricional; desnutrição; pacientes críticos; controle glicêmico; insulina.

Introdução

O conceito de desnutrição engloba todos pacientes com algum desequilíbrio nutricional[1]. A desnutrição contribui de forma significativa para o aumento de morbimortalidade, diminuição da qualidade de vida, aumento da necessidade de internação hospitalar e estadia prolongada no hospital[1; 2; 3]. Além disso, essa condição afeta cerca de 50% dos pacientes hospitalizados [3].

Pacientes críticos frequentemente agravam seu estado nutricional devido a resposta inflamatória, estresse metabólico e imobilidade [4]. As evidências atuais sugerem que terapia nutricional precoce (24 a 48 horas) em pacientes admitidos na unidade de tratamento intensivo (UTI) é capaz de alterar desfechos favoravelmente desses pacientes [5]. Contudo, nem todos pacientes críticos terão o mesmo benefício de terapia nutricional especializada. O efeito favorável pode ser mais evidente em pacientes com estado nutricional inadequado quando comparado com pacientes eutróficos [6; 7]. A incapacidade de fornecer um aporte calórico e proteico adequado para os pacientes está associada à perda de massa magra, maior mortalidade e aumento no tempo internação hospitalar [4; 7].

Dessa forma, as diretrizes de nutrição orientam que pacientes hospitalizados em enfermarias incapazes de ter alimentação adequada por via oral (≥60% das necessidades calóricas) por mais de sete a 14 dias devem ser candidatos a suporte nutricional especializado [8]. O aporte nutricional pode ser ofertado nessas condições através de nutrição enteral ou parenteral, variando conforme o caso, porém a via preferencial é a enteral. A via enteral oferece a vantagem de manter a integridade estrutural e funcional do trato gastrointestinal e reduzir a resistência insulínica, além de oferecer um aporte calórico e proteico para manter a massa magra [7].

Em pacientes críticos as atuais diretrizes europeias e americanas de medicina intensiva recomendam o inicio de nutrição enteral precoce (24-48 horas da admissão na

UTI) naqueles pacientes que não podem receber dieta via oral[9; 10]. A recomendação para o momento de inicio da nutrição parenteral em pacientes críticos considera o estado e risco nutricional, sendo sugerido inicio precoce (48-72 horas) naqueles pacientes de alto risco ou desnutridos em que a nutrição enteral não é possível e para pacientes de baixo risco o inicio deve ser após uma semana na UTI [9].

Neste sentido a avalição do risco nutricional nos pacientes críticos torna-se de extrema importância na tomada de decisão. Tradicionalmente, avaliações de risco nutricionais consideram os pacientes críticos como de alto risco, não estratificando, entretanto, esse mesmo grupo de pacientes. Os pacientes de mais alto risco, por exemplo, poderiam se beneficiar de uma tentativa mais agressiva de atingir o alvo calórico, embora este seja ainda um tema controverso [7; 11]. A maioria dos escores de risco nutricional não foram validados na UTI e consideram principalmente o estado nutricional isoladamente do paciente, não considerando a gravidade da situação clínica [7]. O escore NUTRIC foi avaliado em pacientes críticos e leva em consideração a idade, a gravidade da doença (escore APACHE II e SOFA), número de comorbidades, dias de admissão hospitalar prévios à admissão na UTI e nível de interleucina 6 [11]. A adequação do aporte calórico modifica a associação entre o escore e a mortalidade em 28 dias [11].

Além de avaliar o risco nutricional desses pacientes também é importante classificar seu estado nutricional. A Organização Mundial da Saude (OMS) classifica desnutrição no adulto segundo o IMC como leve (IMC 17 – 18,49 kg/m^2) moderada (IMC 16 – 16,99 kg/m^2) e grave (<16 kg/m^2) associado ou não a edema [12]. Contudo em pacientes críticos um índice de massa corporal (IMC) inferior a 20 kg/m^2 já está associada a maior mortalidade, mas não está definido o impacto que a terapia nutricional adequada tem nesses pacientes [13; 14; 15].

Em condição de estresse como a que ocorre no paciente crítico, em especial naqueles com status nutricional alterado associado a baixo peso, o aporte calórico adequado através de suporte nutricional especializado é prioritário. Entretanto, deve ser lembrado que o suporte nutricional nesta população pode estar associado a complicações ou situações de risco, como a hiperglicemia. A hiperglicemia é um evento frequente em pacientes que recebem nutrição especializada, podendo ocorrer em até 30% e 50% dos pacientes em regime de nutrição enteral e parenteral respectivamente [16]. Ainda, a presença da hiperglicemia está associada a uma maior taxa de complicações e mortalidade[8; 17]. A ocorrência de hiperglicemia não se restringe a pacientes com diabetes mellitus. Alguns dados sugerem que os desfechos são piores em pacientes com hiperglicemia durante a internação sem o diagnóstico prévio de diabetes [18]. De fato, a avaliação e manejo adequado, da hiperglicemia em pacientes submetidos a suporte nutricional não deve ser subestimada quando do emprego da terapia de nutrição especializada. Em 2001 o ensaio clínico randomizado em pacientes críticos cirúrgicos mostrou uma redução de mortalidade com controle rigoroso (80-110 mg/dl) quando comparado com controle convencional (180 – 200 mg/dl) [19]. O estudo randomizado multicêntrico NICE-SUGAR mostrou aumento de mortalidade com controle glicêmico rigoroso (81-108 mg/dl) comparado com controle convencional (140-180 mg/dl) [20]. As recomendações atuais quanto ao alvo glicêmico para pacientes consistem em manter valores de glicemia abaixo de 180 mg/dl em paciente críticos e, dessa forma, intervenções devem ter inicio quando glicemia estiver acima de 150 mg/dl [21]. A Sociedade Americana de Endocrinologia sugere para pacientes hospitalizados manter a glicemia entre 100-140 mg/dl antes das refeições e abaixo 180 mg/dl em medida randômica [22].

O controle glicêmico em pacientes hospitalizados passa normalmente por ajustes no conteúdo da dieta e uso de terapias farmacológicas [16; 18]. As dietas enterais para

controle glicêmico apresentam menor quantidade de carboidratos e maior quantidade de gordura monossaturada, fibras e frutose quando comparadas com a dieta enteral padrão [23]. Um ensaio clínico randomizado mostrou que uso de dietas específicas para diabetes estavam associadas a redução da necessidade de insulina, melhor controle glicêmico, redução da taxa de infecção quando comparada com as dietas convencionais [24].

O principal tratamento farmacológico da hiperglicemia em paciente hospitalizados é a insulina. O regime de insulina para pacientes hospitalizados varia de insulina endovenosa contínua, insulina subcutânea de intermediária, longa e rápida e ultrarrápida ação em diferentes esquemas e ajustes, além da prática de acrescentar insulina na nutrição parenteral dos pacientes. A eficácia e segurança desses regimes de insulina ainda não está clara [23].

Diante do exposto os dois artigos que compõe essa tese de doutorado abordam:

- Revisão sistemática com meta-analise sobre o papel de diferentes regimes de insulinoterapia no controle da hiperglicemia associada ao suporte nutricional em pacientes hospitalizados.

- O impacto do suporte nutricional em pacientes críticos de baixo peso na mortalidade intra-hospitalar através de um estudo coorte prospectivo realizado em dois hospitais de Porto Alegre.

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Insulin regimens to treat hyperglycemia in hospitalized patients on nutritional support: systematic review and meta-analyses

Short Title: Insulin regimens to treat hyperglycemia in hospitalized patients

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Abstract

Background- The best insulin regimen to treat hyperglycemia in hospitalized patients on nutritional support (NS) is unclear.

Methods- We searched electronic databases to identify cohort studies or randomized clinical trials (RCTs) in order to evaluate the efficacy of different insulin regimens used to treat hyperglycemia in hospitalized patients on NS on diverse outcomes: mean blood glucose (MBG), hypoglycemia, length of stay in hospital, and mortality.

Results- Seventeen studies from a total of 5,030 were included. *Enteral Group* [8 studies; 1,203 patients using rapid, glargine, NPH, or Premix insulin; MBG 108-225mg/dl; [1]hypoglycemia 0-13%]. In indirect meta-analysis, NPH insulin ranked best for glucose control [MD95%CI= -2.50mg/dl (2.65,-2.35)]. *Parenteral Group* (4 studies; 228 patients using regular and glargine or NPH insulin; MBG 137-202mg/dl; hypoglycemia 0-40%). In meta-analyses comparing regular insulin added to parenteral nutrition bag with glargine, MBG [MD95%CI= -3.78mg/dl (-11.93, 4.37); I^2=0%] or hypoglycemia frequency [RR95%CI=1.37 (0.43,4.32); I^2=70.7%] did not differ. Description of hospital length of stay, and mortality were inconsistent in all groups.

Conclusions- The best insulin regimen to treat hyperglycemia in hospitalized patients on NS has not been established; best results using insulin regimens with NPH in enteral nutrition do not seem to be clinically relevant.

Keywords: nutritional support, hospitalized patients, insulin, glycemic control

1. Introduction

Hyperglycemia is a costly and common health care problem in hospitalized patients with and without diabetes. The risk of hospital complications increases with illness severity and also in patients without a previous history of diabetes [1]. The mechanism underlying hyperglycemia during acute illness is complex and includes the release of counter-regulatory hormones (corticosteroids and catecholamines) and proinflammatory mediators, administration of exogenous corticosteroids, vasopressors, and enteral and parenteral nutrition [2].

The objective of nutritional support, including both enteral and parenteral nutrition, is to prevent the effects of starvation, such as increased risk of death and/or infection, and occasionally to alter favorably the natural course or treatment of a specific disease [3, 4]. Enteral nutrition, whenever possible, is preferred over parenteral nutrition because there are less associated complications, including hyperglycemia, and costs [5].

The Van den Berghe et al. [6] seminal randomized clinical trial (RCT) conducted in critically ill surgical patients demonstrated that treatment of hyperglycemia by continuous intravenous insulin administration attaining strict glycemic control (80 - 110 mg/dl) reduced morbidity ICU length of stay by five days, and surgical mortality in critically ill patients. Since then, the treatment of hyperglycemia in hospitalized patients has become an important target of clinical care. However, these results were not confirmed in the NICE-SUGAR multicenter study, where increased mortality occurred for ICU patients on strict glucose control using intensive insulin therapy and no reduction on length of stay in hospital was observed[7]. Subsequently, different strategies to reach glycemic control have been proposed for hospitalized patients inside and outside the intensive care unit (ICU).

In general, up to 30% of hospitalized patients received some type of specialized nutritional support [8]. Usually, a high frequency of hyperglycemia is observed in these

patients. Depending on the definition of hyperglycemia, its prevalence varies from 44 to 90% [9] for patients receiving parenteral nutrition and around 40% [10] for patients on enteral nutrition. Clinical societies have different thresholds for hyperglycemia[11, 12]. According to the Americand Diabetes Association, insulin therapy should be initiated for treatment of persistent hyperglycemia starting threshold 180 mg/dL. Once insulin therapy is started, a target glucose range 140-180 mg/dL is recommended for the majority of critically and noncritically ill patients[12]. However, even considering the great number of patients who need to treat hyperglycemia and its associated complications in daily clinical practice, there are no guidelines to recommend the best regimen of insulin therapy to treat hyperglycemia in these patients.

The aim of this study was to evaluate the effect of different insulin regimens used to treat hyperglycemia in hospitalized patients receiving nutritional support - enteral, parenteral, or both - on pre-established outcomes: hyperglycemia, hypoglycemia, hospital length of stay, and mortality.

2. Methods

This systematic review was carried out using a protocol constructed according to the Cochrane Handbook recommendations [13] and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. The study protocol was registered in the PROSPERO International prospective register of systematic reviews (CRD42015015749).

2.1 Data Sources and Searches

We searched databases from Medline, Embase, ISI web of science, ClinicalTrials.gov register, Cochrane, and Scopus, up to March 2017, to identify studies that compared different insulin regimens in hospitalized patients receiving either enteral

or parenteral nutritional support. In addition a manual search was performed in the reference lists of included articles. We contacted the authors by mail if essential data were not clearly described in a study.

The initial search strategy was defined by the following MESH terms: "*Nutritional support"[Mesh] or "Enteral nutrition"[Mesh] or "Parenteral nutrition, Total"[Mesh] or "Parenteral nutrition, Solutions"[Mesh]* combined with "*Insulin"[Mesh] or "Insulin lente"[Mesh] or "Insulin ultralente"[Mesh] or "Insulin regular, human"[Mesh] or "Insulin lispro"[Mesh]* or "*Insulin aspart"[Mesh] or "Insulin shortactig"[Mesh] or "Insulin isophane"[Mesh] "Insulin detemir"[Mesh] or "Insulin long-acting, human"[Mesh]*. All potentially eligible studies were considered for review, regardless of the primary outcome, but limited to English, Spanish, French, or Portuguese language. A manual search was also performed in the reference lists of included articles and in recent reviews about the topic.

2.2Study Selection

All citations retrieved from electronic databases were imported to the EndNote Program. Two reviewers (M.V.V., L.V.V.) independently analyzed the titles and abstracts of every paper retrieved from the literature search to identify potentially eligible studies. All studies that did not meet the inclusion criteria were excluded. The full text of the remaining papers was obtained for further examination. Disagreements were solved by a third reviewer (M.J.A.).

The inclusion criteria for the studies were RCTs and cohort studies that evaluated different insulin regimens in patients receiving enteral, parenteral, or both, nutritional support. We excluded studies if patients were on an oral diet without enteral or parenteral support, or were using antihyperglycemic agents but insulin as the only treatment for hyperglycemia, or if they had no documented hyperglycemia.

2.3 Data Extraction and Quality Assessment

The data of included studies were independently extracted by the same two reviewers using a standardized data extraction form. Extracted data included: first author's name, year of publication, number of participants, details of the study design (i.e., RCT or observational trial), study duration, and patient characteristics (age, sex, body weight, body mass index, severity of illness score, frequency of patients with diabetes, previous use of insulin or oral antihyperglycemic agents, corticosteroid use, reasons for admission (clinical or surgical), hospitalization setting (ward or ICU), mean baseline blood glucose, and presence of renal replacement therapy. The type of insulin therapy, as well the criteria adopted to initiate insulin therapy, total insulin dose, daily insulin units per body weight, and description of nutritional support were recorded. Total energy, macronutrients, and fiber content were also extracted when available. The pre-established evaluated outcomes were: glycemic control, hypoglycemia, hospital length of stay, and mortality. Glycemic control targets and hypoglycemia were defined by each study's authors and this information was extracted.

Direct meta-analyses were performed in Stata and indirect meta-analysis was performed in R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

The methodological quality of all included studies was independently assessed (M.V.V., A.L.J.T.). We used a score based on the Cochrane Collaboration tool to assess risk of bias for RCTs [15] and the Newcastle-Ottawa (NOS) for observational studies [16]. According to the Cochrane Collaboration, biases were classified into six domains: selection, performance, detection, attrition, and reporting[17]. The risk of bias for each domain was classified as high, low, or unclear. Regarding the Newcastle-Ottawa Scale each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the

exposure or outcome of interest. Up to nine stars were awarded for each quality item and served as a quick visual assessment (14).

The quality of the body of evidence of each meta-analysis was assessed by the GRADE [18] approach including factors that may decrease (e.g., methodological quality, directness of evidence, heterogeneity, precision of effect estimates, risk of publication bias) or increase (e.g., large magnitude of effect, reduction or spurious effect due to plausible confounding factors, dose-response gradient) the quality of evidence. Each evaluated factor was rated as high, moderate, low, or very low. Using this approach, we considered a serious risk of bias when an individual study had more than three unclear or high risk of bias and imprecision was defined as a meta-analysis confidence interval > 0.5.

3. Results

We identified 5,039 studies in our database search (**Figure 1**). Of them, 4,885 were excluded based solely on title or abstract, leaving 154 for full text evaluation. From these 154 selected papers, 137 articles were also excluded after full text scrutiny mostly because they used the same regimens of insulin in both arms or due to the absence of a description of nutritional support. Therefore, we included 17 studies (6 RCTs and 11 cohort studies) providing data from 3,260 patients. Clinical trials were heterogeneous in patient populations and there was lack of information on blood glucose variability, duration of blood glucose in target range, caloric and protein intakes and timing of initiation of nutrition therapy preventing from most metanalysis. Most of the patients (n = 2,657) were studied in the ICU. Enteral feeding was the only nutritional support used in eight studies, parenteral nutrition in four, and mixed (enteral plus parenteral) in five.

The studies included in the current systematic review were classified into three groups according to type of nutritional support received by patients: *Enteral Nutritional*

Support Group, Parenteral Nutritional Support Group, and Mixed Nutritional Support Group.

General features of studies, adopted definitions of hyperglycemia and hypoglycemia, type of insulin regimens, data on mean blood glucose (MBG) and hypoglycemia, besides other studied outcomes for each included study are presented in **Table 1** according to the types of nutritional support. The report on outcomes as well as the description or definition of studied variables were not uniform. Mortality was described only in seven studies[19-25] and hospital length of stay in six [20-22, 24, 26, 27]. MBG was described in all but one study [28]. The presence of hypoglycemia in the studies was differently reported: number of events, percentage of events, or number of patients with hypoglycemia. Total energy, macronutrients, and fiber content of administered nutritional support were not reported in most of the studies. Details of insulin regimens and available nutritional support information of included studies are presented as **Supplement Table 1**.

Enteral Nutritional Support Group: Eight studies [19-21, 28-32] evaluated different insulin regimens for glycemic control in patients receiving enteral support **(Table 1A)**. Two RCTs and six cohort studies comprising 1,203 patients were reviewed. Patients' mean age was 64.8 years, 57% were men, BMI ranged from 28-30 kg/m^2, 64% had diabetes. Half of the studies were conducted in ICU settings and three studies did not inform the patients' setting. Glycemic targets and hypoglycemia definitions were heterogeneous: the glycemic target ranged from 70 to 180 mg/dl and hypoglycemia was defined as capillary glucose less than 40 mg/dl in three studies[19, 20, 30], less than 70 mg/dl in three [21, 28, 29] and less than 79 mg/dl in one[31]. Only one study had no definition for hypoglycemia [32]. Only one study in this category presented data about hospital length of stay [20] and three described hospital mortality[19-21]. MBG control

ranged from 108 to 225 mg/dl and was <180 mg/dl in 62.5% of the studies (5 out of 8) in both control and intervention groups. The percentage of hypoglycemia varied from 0 to 9%. The most used insulin regimen to control glucose was sliding scale insulin [19, 31,32]. Regarding enteral support, four studies [19, 20, 31, 32] used special formulas **(Supplementary Table 1A)**.

Figure 2 summarizes the results of the indirect meta-analysis[21, 31, 32] comparing all evaluated insulin regimens. NPH insulin ranked as the best regimen to reduce MBG level (SMD 95%CI): NPH, -2.50 mg/dl (-2.65, -2.35); Premix, -1.21 (-1.53, -0.89), and Glargine+Lispro, -1.23 (-1.41, -1.05) mg/dl as compared to sliding scale rapid insulin regimen. There was no difference between Premix and Glargine+Lispro insulin regimens.

Parenteral Nutritional Support Group: Four studies [22, 26, 33, 34] evaluated different insulin regimens for glycemic control in parenteral support **(Tables 1B)**. Two RCTs and two cohort studies comprising 228 patients were reviewed. Mean age was 60.7 years, BMI 23.5-27.7 kg/m^2, and 40% of the patients had diabetes. One study was conducted exclusively in an ICU setting [26], two studies included exclusively ward patients [33, 22], and one study included patients from ICU and ward settings [34]. Glycemic targets and hypoglycemia definitions were heterogeneous in these studies: the maximum glycemic target ranged from 140 to 180 mg/dl and hypoglycemia was defined as glucose less than 80 mg/dl in two studies and around 70 mg/dl in two others. MBG ranged from 137 to 173 mg/dl in the intervention and from 142 to 202 mg/dl in the control groups. The percentage of hypoglycemia varies from 3 to 40% in the intervention groups and from 0 to 29% in the control group. MBG was <180 mg/dl both in control and intervention groups, except in one study [22].

RCTs compared subcutaneous insulin glargine with regular insulin added to the parenteral nutrition bag [26, 34]. Meta-analyses did not demonstrate differences in MBG [SMD 95%CI = -3.78 mg/dl (-11.93, -4.37); I^2=0%] or frequency of hypoglycemia [RR 95%CI = 2.48 (0.61, 10.10); I^2=45.6%] between the two insulin regimens **(Figure 3, Panel A1 and A2**).

Mixed Nutritional Support Group (enteral plus parenteral): Five studies [23-25, 27, 35] evaluated different insulin regimens for glycemic control in mixed (parenteral plus enteral) nutritional support (**Table 1C**). Two RCTs and three cohort studies comprising 1,829 patients were reviewed. All studies were conducted in the ICU. One study was conducted exclusively with patients with acute kidney failure [27] and one study excluded patients with diabetes [23]. Mean age was 50.5 years, BMI 25.7-27 kg/m^2 and 18% of patients had diabetes. Glycemic targets and hypoglycemia definitions were diverse: the maximum glycemic target ranged from 80 to 180 mg/dl and hypoglycemia was defined as glucose less than 40 mg/dl in three studies[24, 25, 27]. MBG ranged from 106 to 145 mg/dl in the intervention and from 107 to 133 mg/dl in the control groups. Hypoglycemic events varied from zero to less than 1% in the included studies. In all studies MBG was lower than180 mg/dl.

Three studies compared computer based protocols with standard protocols for hyperglycemia control (one RCT and two cohort studies) [24, 25, 35]. The RCT [24] protocol took into account several variables (patient profile at admission, blood glucose, insulin dose, nutrition, and steroid medication) and was not comparable to cohort study protocols. A meta-analysis of cohort studies [25, 35] demonstrated that the MBG value was higher in paper based than computer based protocols [MD 95% CI = 5.41 (1.40, 9.40); $I^2$0%]. Descriptions of hypoglycemic events were not comparable in studies.

3.1 **Quality evaluation**

Individual quality of RCTs revealed a low risk of bias for most evaluated domains, except performance (bias for most of studies (**Supplementary Table 2**). For observational studies, Newcastle-Ottawa Scale scored moderate (4 -7 stars out of 9) **(Supplementary Table 3)**.

The GRADE quality of evidence for systematic review was evaluated **(Supplementary Table 4)**. In the indirect meta-analysis of the insulin regimens used to treat hyperglycemia in patients on enteral support the GRADE score evidence was considered very low, due to indirectness of the comparison and small number of studies. The quality of direct meta-analyses of insulin regimens on parenteral nutrition support was moderate both for MBG and frequency of hypoglycemia events. The quality of evidence was also low for meta-analysis of MBG of insulin based protocols regimens in mixed nutritional support.

4. Discussion

This systematic review included 17 studies, six RCTs and 11 cohort studies, design to evaluate diverse insulin regimens used to treat hyperglycemia and comprised 3,260 hospitalized patients receiving enteral, parenteral, or mixed nutritional support. MBG ranged from 106 to 225 mg/dl and frequency of hypoglycemia from 0 to 40%. Taking into account the type of administered nutritional support, we performed some direct or indirect meta-analyses. These comparisons allowed us to demonstrate that in patients on enteral support the MBG was lower with NPH insulin than with sliding scale insulin, Premix, or Glargine+Lispro regimens (indirect meta-analysis). On the other hand, for parenteral nutrition support, the reduction of hyperglycemia did not differ when insulin was added to the parenteral nutrition bag or with subcutaneous insulin glargine use. Lastly, for hyperglycemic patients on mixed nutritional support insulin regimens using computer based protocols seemed to promote more MBG reduction than paper

protocols. Hypoglycemia could be compared only in patients on parenteral nutrition in whom hyperglycemia was treated using regular insulin added to the parenteral nutrition bag or with subcutaneous insulin glargine and no difference was observed between these insulin regimens. However, regardless of the insulin regimen used, there was only a small, not clinically significant, reduction in MBG.

Hyperglycemia in critically ill patients may be an adaptive response to spare glucose to brain, erythrocytes and injured tissues; although the benefits of this response may be outweighed by detrimental effects over the long term[36].Hence, there is still some controversy about the degree of glycemic control in hospitalized patients, especially in ICU settings [6, 7]. Most critical care and endocrinology societies nowadays endorse a random glucose value below 180 mg/dl (4, 30) as the target for hospitalized patients. In our systematic review, there was a great variability in glycemic target even within the nutritional categories; however, in most studies (76%) MBG values were in agreement with current recommendations. This MBG goal was reached irrespective of the insulin regimen used to treat hyperglycemia. Only in four studies, three conducted in ICU settings, the target of strict glucose control was less than 110 mg/dl [19, 24, 25, 32] but MBG reached this goal only in half of them [19, 24]. Actually the differences between MBG reductions of insulin interventions were lower than 6 mg/dl. This small difference in MBG would require a very large study to show a clinical benefit. Therefore, it should be emphasized that although our results on glucose control were statistically significant, there is no clinical relevance.

A post hoc analysis of the NICE-SUGAR trial revealed that hypoglycemia was strongly associated with mortality [37] and guidelines recommend that insulin infusion programs have to be coordinated with nutritional support intervention to minimize the risk of both hyperglycemia and hypoglycemia [11]. In this sense severe hypoglycemia,

defined as blood glucose lower than 40 mg/dl [38], is the most feared adverse effect related to insulin treatment. Therefore, the choice of insulin regimen should also be based on the absence of harmful effects. From the total of 17 included studies only six [20, 24, 25, 27, 30, 41] reported data on severe hypoglycemia and its frequency varies from 0 to 2.8%. Moreover, in the current systematic review the definition of hypoglycemia was heterogeneous and unclear in most studies. We could only compare the frequency of hypoglycemia in two studies [26, 33] conducted in patients on parenteral nutrition and there was no difference in hypoglycemic events.

Our systematic review had some limitations even though we have performed a comprehensive search and detailed data extraction strictly following all current recommended guidelines [14, 15, 40]. It was not possible to compare most of the studies due to their methodological differences, unclear or different outcomes definitions, or even missing data. The quality of included studies was moderate and most of them were observational. Very few studies evaluated mortality and hospital length of stay and, therefore, these outcomes could not be compared. Heterogeneity of insulin regimens did not allow us to perform direct comparisons for other pre-determined outcomes. The differences among the individual studies are likely to be important. The type of patients (medical, surgical) and the place where the studies occurred (ICU or ward) differed significantly and this might influence the optimal glycemic target. Lack of clinical outcomes could have been attributed to heterogeneity in patient population between studies, differing populations whereby benefit from level of glycemic control may be different, blood variability, hours/day in target blood glucose range, caloric and protein intakes, and timing of initiation of nutrition therapy. Also, samples with diverse characteristics, such as patients with or without diabetes, were studied together. The possible influence of this heterogeneity on our results is unknown since sensitivity

analyses were not allowed due to the characteristics of these studies. Lastly, nutritional support was heterogeneous even within the same category and poorly described and this might be potential confounder factor.

According to our systematic review studies comparing different insulin regimens to treat hyperglycemia in hospitalized patients requiring nutritional support are heterogeneous. Our best results on reduction of MBG obtained by insulin regimens using NPH in enteral nutrition or rapid insulin computer based protocols in mixed nutritional support were not clinically relevant. Additional RCTs, with focus on hard outcomes and severe hypoglycemia, beyond hyperglycemia per se, are needed. Possible, the best choice might be the less expensive insulin regimen with less associated hypoglycemia events. However, until now it has not been feasible to establish the best insulin regimen to treat hyperglycemia in hospitalized patients on nutritional support.

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Figure Legends

Figure 1. Flow diagram of literature search to identify studies evaluating different insulin regimens to treat hyperglycemia in hospitalized patients on nutritional support.

Figure 2 – Forest plot (indirect meta-analysis, random-effect model) of rapid insulin sliding scale (RISS), NPH, Premix, Glargine+Lispro insulin regimen effects on mean blood glucose (mg/dl) in hospitalized patients on enteral support.

Figure 3 - Forest plots (meta-analyses, random-effects models) of the effect of different insulin regimens on mean blood glucose and on the frequency of hypoglycemia in parenteral nutrition support (Panel A1 and A2)

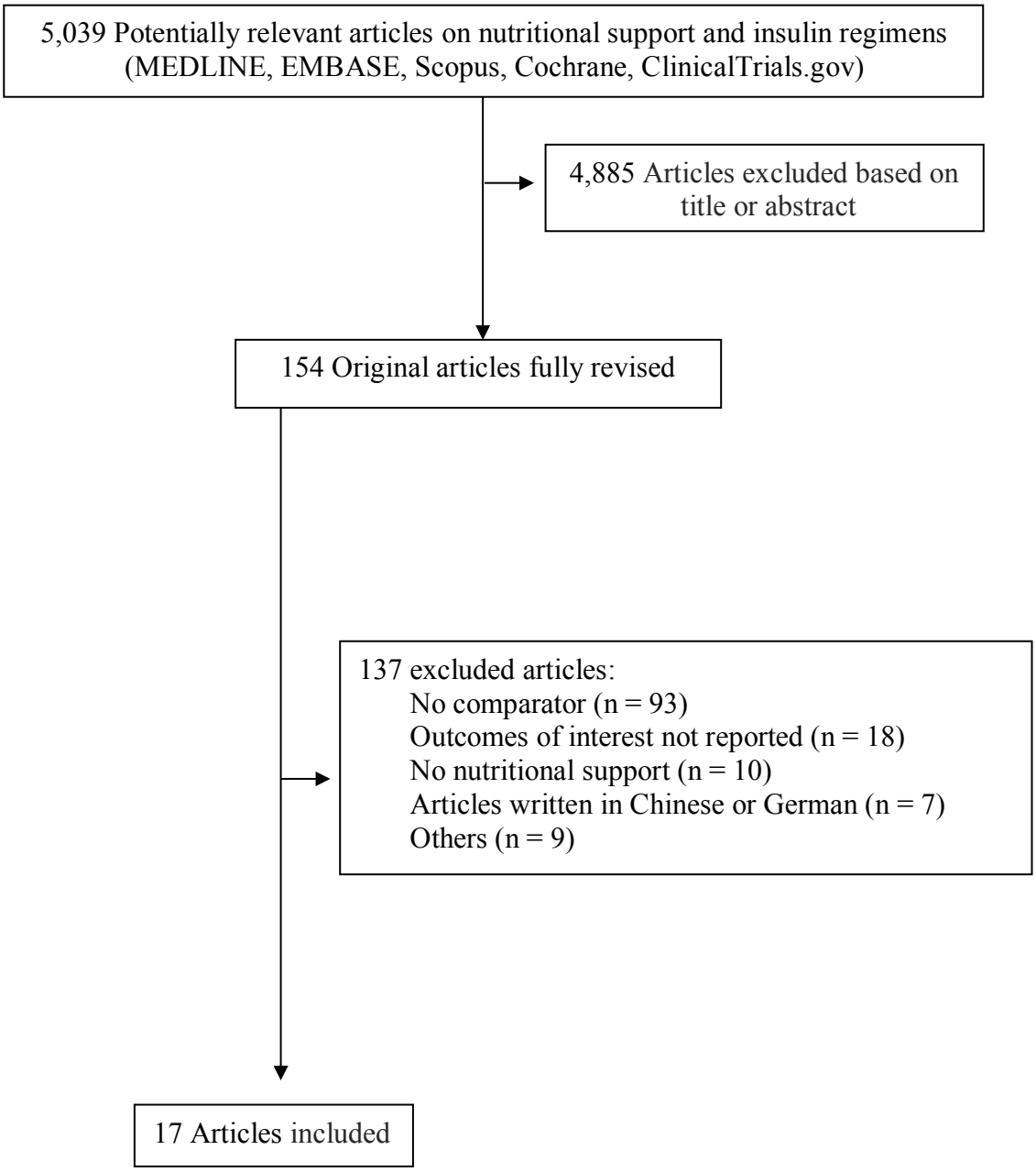

Figure 1. Flow diagram of literature search to identify studies evaluating different insulin regimens to treat hyperglycemia in hospitalized patients on nutritional support.

Table 1: General characteristics of studies included in the systematic review

Author Year	Study and Patients Characteristics	Main Outcomes Definitions	Insulin Regimens	Mean blood glucose *Significance between interventions*	% of Hypoglycemia Events *Statistical significance between interventions*	Other Outcomes *Statistical significance between interventions*
A. ENTERAL NUTRITION						
Randomized Control Trials						
Korytkowski 2009	n = 50 Age = 65 years Male = 30 (60%) DM = 50 (100%) BMI = 28 kg/m^2 ICU = none Ward = 50 (100%) Follow-up = 6 ± 2.2 days	**Glycemic target** 100 - 180 mg/dl **Hypoglycemia** <70 mg/dl	**Intervention 1** **(n = 25):** sliding-scale regular insulin **Intervention 2** **(n = 25):** insulin glargine plus sliding scale regular insulin	**Intervention 1** 160.2 ± 28.8 mg/dl **Intervention 2** 165.8 ± 28.8 mg/dl P = 0.71	**Intervention 1** 1.1% **Intervention 2** 1.3% P = 0.35	Hospital LOS: NA Hospital Mortality: NA
Leelarathna 2013	n = 24 Age = 60.5 years Male = 18 (75%) DM = 11 (46%) BMI = 27.45 kg/m^2 ICU = 24 (100%) Ward = none Follow-up = 48 hours	**Glycemic target** 108 - 144 mg/dl **Hypoglycemia** <40 mg/dl	**Intervention 1** **(n = 12):** fully automated IV regular insulin **Intervention 2** **(n = 12):** IV sliding- scale regular insulin	**Intervention1** 142 (133 - 148) mg/dl **Intervention 2** 164 (150 - 234) mg/dl P = 0.001	**Intervention** 0% **Intervention 2** 0% P = NS	Hospital LOS: NA Hospital Mortality: NA
Cohort Studies						
Grainger 2007	n = 52 Age = 67.5 years Male = 26 (50%) DM = 36 (69%) BMI = 29 kg/m^2 ICU = 52 (100%) Ward = none Follow-up = maximum 21 days	**Glycemic target** 80 - 140 mg/dl **Hypoglycemia** <79 mg/dl	**Intervention** **(n = 28):** glargine and lispro insulins **Control** **(n = 24):** preprandial insulin	**Intervention** 148 ± 51.4 mg/dl **Control** 225 ± 72 mg/dl P <0.0001	**Intervention** 4.1% **Control** 1.7% P = 0.02	Hospital LOS: NA Hospital Mortality: NA

Chase 2008	n = 784 Age = 64 years Male = 479 (61%) DM = 133 (17%) BMI = NA ICU = 784 (100%) Ward = none Follow-up = NA	**Glycemic target** 72 - 108 mg/dl **Hypoglycemia** <40 mg/dl	**Intervention** **(n = 371):** Specialized Relative Insulin Nutrition Tables (SPRINT) protocol (IV insulin) **Control** **(n = 413):** variety of s.c. insulin sliding scales	**Intervention** 108 ± 28.8 mg/dl **Control** 129 ± 43.2 mg/dl P <0.01	**Intervention** 2.8% **Control** 1.2% P <0.01	Hospital LOS: NA Hospital Mortality: (categorized by length of ICU stay) **Intervention** 20.6 - 26.3% **Control** 27.4 - 34.4%
Cook 2009	n = 159 Age = 68.5 ± 12.8 years Male = 77 (48.4%) DM = 54(40%) BMI = NA ICU = NA Ward = NA Follow up = NA Retrospective	**Glycemic target:** 80 -110 mg/dl **Hypoglycemia:** NA	**Intervention 1** **(n = 31):** s.c. insulin aspart sliding-scale **Intervention 2** **(n = 52):** NPH insulin sliding-scale every 4 hours **Intervention 3** **(n = 76):** NPH insulin sliding-scale every 6 hours	**Intervention 1** 156 **(**153 - 161) mg/dl **Intervention 2** 134.7 (133 - 137) mg/dl **Intervention 3** 133.7 (132 - 135) mg/dl P <0.01 (1 vs. 2 or vs. 3) P = 0.41 (2 vs. 3)	**Intervention 1** 0.7% **Intervention 2** 1.36 % **Intervention 3** 0.9% P = 0.03 (1 vs. 2) P = 0.25 (1 vs. 3) P = 0.16 (2 vs. 3)	Hospital LOS: NA Hospital Mortality: NA
Hsia 2011	n = 22 Age = 23-68 years Male = NA DM = 22 (100%) BMI = NA ICU = none Ward = 100% Follow up = 72 hours Retrospective	**Glycemic target:** 140 - 180 mg/dl **Hypoglycemia:** <70 mg/dl	**Intervention 1** **(n = 8):** basal/bolus glargine/lispro **Intervention 2** **(n = 8):** premixed insulin 70/30 twice daily **Intervention 3** **(n = 6):** premixed insulin 70/30 3 times daily	**Intervention 1*** 24% **Intervention 2*** 22% **Intervention 3*** 69% **% of BG values in thetarget range* P <0.01	**Intervention 1** 5.4% **Intervention** 2.1% **Intervention 3** 1.4% P = 0.07 (1 vs. 2 vs. 3)	Hospital LOS: NA Hospital Mortality: NA

Dickerson 2013	n = 66 Age = 58 years Male = 17 (25%) DM = 37 (56%) BMI = 30 kg/m^2 ICU = 66 (100%) Ward = none Follow up = 7 days Retrospective	**Glycemic target** 70 - 148 mg/dl **Hypoglycemia** <40 mg/dl [41](41)(41)(41)(41)(41)	**Intervention 1** **(n = 32):** continuous IV regular insulin infusion therapy **Intervention 2** **(n = 34):** supplemental intermittent IV regular insulin therapy	**Intervention 1** 125 ± 11 mg/dl **Intervention 2** 133 ± 14 mg/dl P <0.01	**Intervention 1*** 9% **Intervention 2*** 9% ** % of patients with any hypoglycemic event* P = NA	Hospital LOS: **Intervention 1** 41± 27 days **Intervention 2** 39 ± 28 days P = NS Hospital Mortality: **Intervention 1** 3.2% **Intervention 2** 13.3% P = NS
Murphy 2014	n = 46 Age = 74.8 years Male = 27 (58.6%) DM = 46 (100%) BMI = NA ICU = NA Ward = NA Follow up = over 40 days Retrospective	**Glycemic target** NA **Hypoglycemia** <72 mg/dl	**Intervention 1** **(n = 18):** premixed insulin 70/30 **Intervention 2** **(n = 13):** short acting s.c. insulin before each feed plus Glargine insulin at night **Intervention 3** **(n =15):** long acting analogue insulin	**Intervention 1** 227 ± 97.3 mg/dl **Intervention 2** 225 ± 76 mg/dl **Intervention 3** 218 ± 90 mg/dl P = 0.46	**Intervention 1*** 4% **Intervention 2*** 0% **Intervention 3*** 7% **% hypoglycemia during feeding* P = 0.004	Hospital LOS: Over 40 days for the 3 groups Hospital Mortality: **Intervention 1** 3 (16,7%) **Intervention 2** 4 (30.8%) **Intervention 3** 5 (33.8%) P = NA

B. PARENTERAL NUTRITION

Randomized Trials

Hakeam 2015	n = 67 Age = 58 years Male = 28 (42%) DM = 55 (82%) BMI = 27.7 kg/m^2 ICU = None Ward = 67 (100%) Follow up =NA	**Glycemic target** 140 -180mg/dl **Hypoglycemia** <70 mg/dl	**Intervention** **(n = 35):** Glargine insulin at night **Control** **(n = 32):** Regular insulin added to parenteral nutrition	**Intervention** 136.8 ± 39.6 mg/dl **Control** 148 ± 37.8 mg/dl P = 0.39	**Intervention*** 5.7% **Control*** 6.25% **% of patients with hypoglycemia* P >0.1	Hospital LOS:NA Hospital Mortality: NA
Oghazian 2015	n = 42 Age = 56.1 years Male = 26 (43%) DM = 0 BMI = 23.5 kg/m^2 ICU = 100% Ward = None Follow up = NA	**Glycemic target** 110 - 180 mg/dl **Hypoglycemia** <700 mg/dl	**Intervention** **(n = 21):** Glargine insulin **Control** **(n = 21):** Regular insulin added to parenteral nutrition bag	**Intervention** 140 ± 19 mg/dl **Control** 142 ± 15 mg/dl P = 0.741	**Intervention*** 19 % **Control*** 0% **% of patients with hypoglycemia* P = 0.107	Hospital LOS: **Intervention:** 37 days **Control:** 37 days Survival to hospital discharge: NA

Cohort Studies

Jakoby 2012	n = 48 Age = 58.5 years Male = 21 (43.8%) DM = 16 (33.3%) BMI = NA ICU = 10 (20.8%) Ward = 38 (79.1%) Follow up = NA Prospective	**Glycemic target** 140 mg/dl **Hypoglycemia:** <80 mg/dl	**Intervention** **(n = 22):** insulin doses based on carbohydrate delivery (regular insulin in parenteral nutrition bag and NPH) **Control** **(n = 26):** ad hoc insulin management (NPH, glargine, etc)	**Intervention** 138 ± 37 mg/dl **Control** 159 ± 46 mg/dl P <0.0001	**Intervention*** 3% **Control*** 1% **Number of glycemic events <40 mg/dl* P = 0.12	Hospital LOS: NA Hospital Mortality: NA

Neff 2014	n = 53 Age = 68 years Male = 30 (56.6%) DM = 18 (33.9%) BMI = 27 kg/m^2 ICU = None Ward = 53 (100%) Follow up = NA Retrospective	**Glycemic target** 72 - 180 mg/dl **Hypoglycemia** <72 mg/dl	**Intervention** **(n = 32):** IV insulin protocol **Control** **(n = 21):** individually prescribed s.c. insulin supplemental scales (basal + rapid acting analogues)	**Intervention** 173 ± 37 mg/dl **Control** 202 ± 48 mg/dl P = 0.009	**Intervention*** 40 % **Control*** 29% * *% of patients with any hypoglycemic event* P = 0.19	Hospital LOS: **Intervention** 61± 49 days **Control** 43 ± 35 days P = 0.08 Survival to hospital discharge: **Intervention** 77% **Control** 67% P = 0.2
			C. MIXED NUTRITIONAL SUPPORT			
			Randomized Trials			
Holzinger 2004	n = 40 Age = 54.5 years Male = 27 (67.5%) DM = none BMI = 26.2 kg/m^2 ICU = 40 (100%) Ward = none Follow-up = 9 ± 4,5 days	**Glycemic target:** NA **Hypoglycemia:** NA	**Intervention** **(n = 20):** low dose continuous IV insulin (1 IU/h) **Control** **(n = 20):** placebo	**Intervention** 131 ± 39 mg/dl **Control** 128 ± 30 mg/dl P = NS	**Intervention** 0% **Control** 0% P = NS	Hospital LOS: NA Hospital Mortality: **Intervention** 5 (25%) **Control** 6 (30%) P = NS
Van Herpe 2013	n = 300 Age = 63.5 ± 14.5 years Male: 181 (60%) DM = 64 (21.3%) BMI = 27.7 ± 5.15 kg/m^2 ICU = 300 (100%) Ward = none Follow-up = 14 days	**Glycemic target** 80 - 110 mg/dl **Hypoglycemia** <40 mg/dl	**Intervention 1** **(n = 149):** algorithm guided IV insulin **Intervention 2** **(n = 151):** nurse-directed IV insulin	**Intervention 1** 106 ± 9 mg/dl **Intervention 2** 107 ± 11 mg/dl P = 0.36	**Intervention1** 0% **Intervention2** 6 (0.1%) P = 0.015	Hospital LOS: **Intervention 1** 16 (10-33) days **Intervention 2** 14 (9-27) days P = 0.24 Hospital Mortality: **Intervention 1** 19 (12.8%) **Intervention 2** 10 (6.6%) P = NS
			Cohort studies			

Thomas 2005	n = 891 Age = 51.4 years Male = 458 (56%) DM = NA BMI = NA ICU = 891 (100%) Ward = none Follow up = NA Retrospective	**Glycemic target:** maximum 128 mg/dl **Hypoglycemia:** <50 mg/dl	**Control** **(n = 288):** No protocol **Intervention 1** **(n = 502):** Protocol- IV insulin **Intervention 2** **(n =101):** modified protocol of IV insulin	**Control**: 131 ± 32.4 mg/dl **Intervention 1:** 118 ± 28,8 **Intervention 2:** 111.6 ± 23.4 P = NA	**Control*** 1 **Intervention 1*** 13 **Intervention 2*** 6 **Number of hypoglycemic events* P = NA	Hospital LOS: NA ICU Mortality: **Control:** 76 (26%) **Intervention 1:** 125 (25%) **Intervention 2:** 27 (27%) P = NA
Dortch 2008	n = 552 Age = 41years Male = 391 (71%) DM = 40 (7.2%) BMI = NA ICU = 552 (100%) Ward = none Follow-up = NA	**Glycemic target:** 80-110 mg/dl **Hypoglycemia:** <40mg/dl	**Intervention** **(n = 243):** IV insulin computerized protocol **Control (n = 309):** paper-based IV insulin protocol	**Intervention** 116 ± 37 mg/dl **Control** 120 ± 37 mg/dl P< 0.001	**Intervention** 0.54 % **Control** 0.23% P <0.001	Hospital LOS: NA Hospital Mortality: **Intervention** 33 (13.6%) **Control** 51 (16.5%) P = 0.4
Dickerson 2014	n = 46 Age = 68 years Male = 38 (82.6%) DM = 20 (43.5%) BMI = 33 ± 8.5 kg/m^2 ICU = 46 (100%) Ward = none Follow-up = 7 days	**Glycemic target** 150-180 mg/dl **Hypoglycemia** <40 mg/dl	**Intervention 1** **(n = 21):** Former protocol **Intervention 2** **(n =25):** New protocol	**Intervention 1** 145 ± 10 mg/dl **Intervention 2** 133 ± 14 mg/dl P <0.001	**Intervention1** 0.35% **Intervention 2** 0% P = 0.005	Hospital LOS: **Intervention 1** 38±26 days **Intervention 2** 44 ± 35 days P = NS Hospital Mortality: NA

BMI = body mass index; DM = diabetes mellitus; ICU = intensive care unit; IV = intravenous; NA = not available; LOS = length of stay, NS = not significant; s.c. = subcutaneous Data are shown as mean ± SD; median (interquartile range)

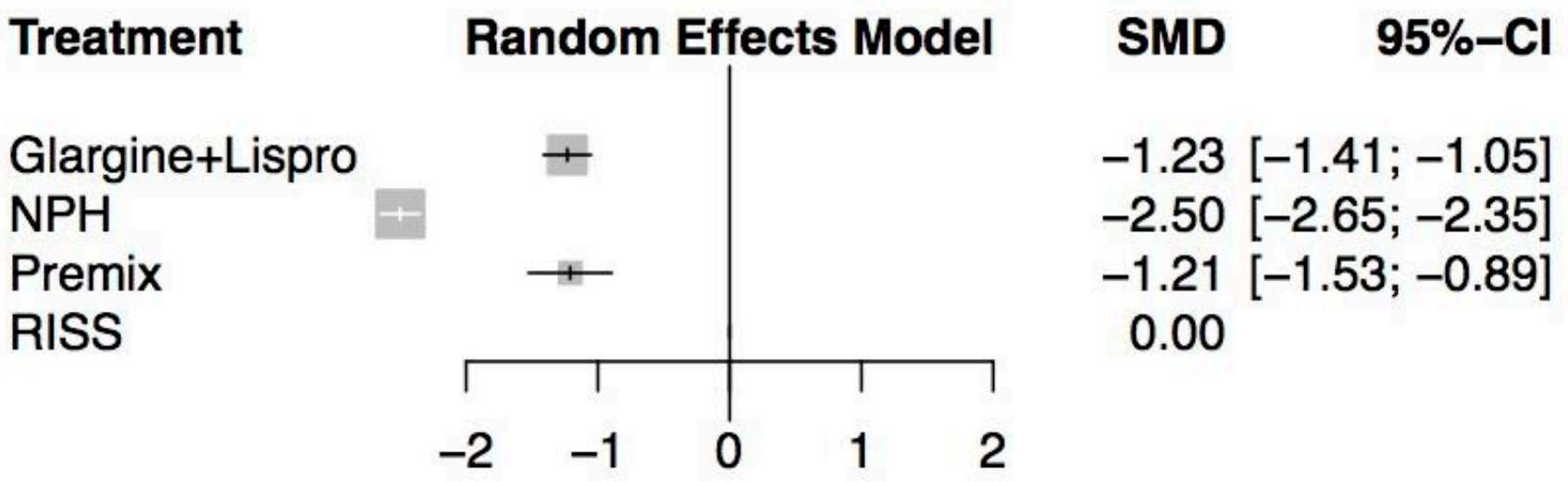

Figure 2 – Forest plot (indirect meta-analysis, random-effect model) of rapid insulin sliding scale (RISS), NPH, Premix, Glargine+Lispro insulin regimen effects on mean blood glucose (mg/dl) in hospitalized patients on enteral support.

Parenteral Nutritional Support

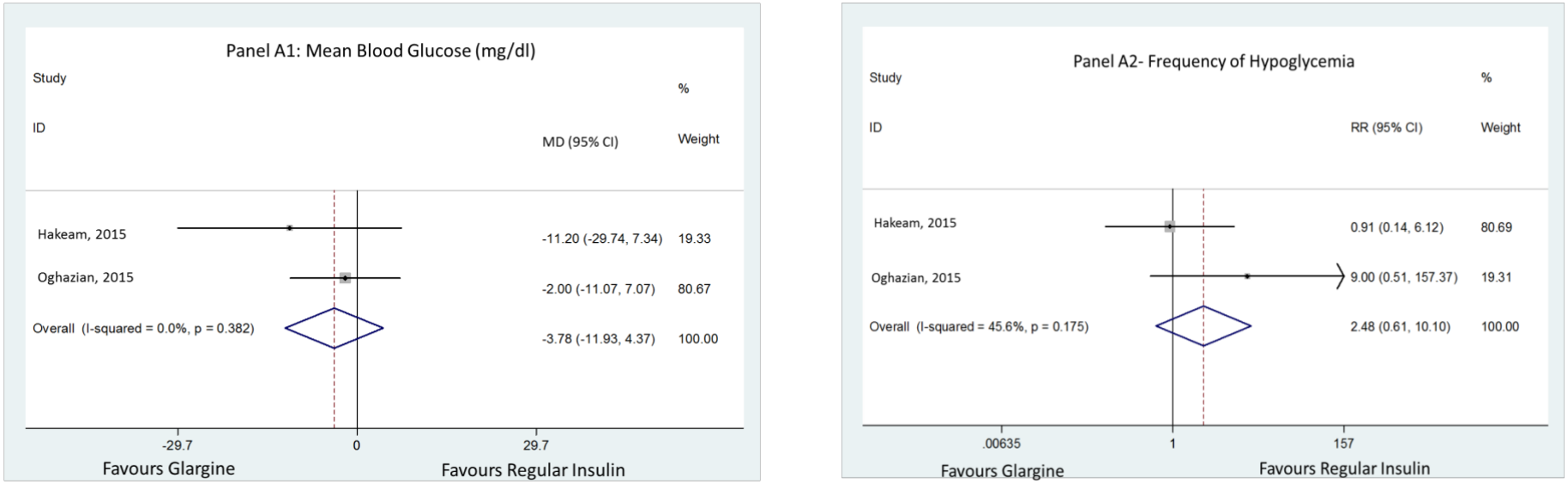

Figure 3 -Forest plots (meta-analyses, random-effects models) of the effect of different insulin regimens on mean blood glucose and on the frequency of hypoglycemia in parenteral nutrition support (Panel A1 and A2).

Table S1. Characteristics of insulin regimens and nutritional support in the studies included in the systematic review.

Author, Year	Insulin Regimen 1	Insulin Regimen 2	Insulin Regimen 3	Nutritional Support
		ENTERAL NUTRITION		
		Randomized Control Trials		
Korytkowski 2009	Sliding scale regular insulin every 4-6 h according to bedside glucose monitoring. NPH insulin was added if persistent glucose>180 mg/dl	Insulin glargine plus sliding scale regular insulin	None	No protocol. % of total energy: CHO 34-65% The majority of patients received formulas using ≥50% CHO
Leelarathna 2013	Fully automated IV regular insulin: sc continuous glucose monitoring systems, computer running a model predictive control algorithm, and two syringe pumps (one with insulin solution and the other with 20% dextrose infusion)	Local insulin therapy paper-based protocol: glucose goal values: 72-360 mg/dl. Insulin infusion titrated according to bedside glucose monitoring. Hourly infusion rates adjusted by the attending physician if glucose was outside target	None	Local protocol. One patient received both enteral and parenteral nutrition. Mean Energy: 63.2kcal/h Mean CHO: 7.5 g/hour
		Cohort Studies		
Grainger 2007	Fixed dose of glargine insulin and variable doses of lispro insulin. Daily glargine according to BMI: <30 kg/m^2 - 10 UI; ≥30 kg/m^2 - 20 UI. Baseline lispro dose according to BMI and CHO feeding: <30 kg/m^2,1UI for every 15g of CHO; BMI ≥30 kg/m^2, 1 UI for every 10g of CHO. Baseline lispro titrated according to glucose monitoring.	Preprandial insulin prescribed by the house-staff physician.	None	Two feeding formulas: TwoCal HN (standard formula): 200kcal/100ml, protein 8.35 g/100ml, CHO 21.9/100ml; Nepro (renal failure): 200kcal/ml, protein 7 g/100ml, CHO 22.27g/100ml. Energy needs were estimated on actual body weight depending on BMI. Tube feeding was given by bolus every 4 h. No continuous drip-enteral feeding
Cook 2009	SC sliding scale of aspart insulin. Insulin titrated according to: UI of insulin = (BG - 100)/20	NPH insulin sliding scale every 4h. Insulin titrated on daily basis according to predefined table.	NPH insulin sliding scale every 6h. Insulin was titrated daily according to predefined table.	Continuous enteral feeding using 9 different types of formulas. Energy goal: all patients received at least 70% of calculated basal energy expenditure.
Hsia 2011	Basal bolus glargine/lispro. Lispro administered as needed at 6h intervals if BG >180 mg/dl.	Premixed insulin 70/30 twice daily. Lispro administered as needed at 6h intervals if BG >180 mg/dl.	Premixed insulin 70/30 3 times daily. Lispro administered as needed at 6h interval if BG >180 mg/dl.	Primary team and nutritional service decided about type of enteral nutrition and caloric content Continuous enteral feeding. CHO: 45- 65% of total energy.

Dickerson 2013	Transition from continuous IV regular human insulin to s.c. NPH insulin using intermittent IV supplemental regular insulin. Initial NPH dose: 30%-50% of continuous insulin in the previous 24h, divided into 2 separate doses and given every 12 h.	Transition from IV intermittent regular human insulin to s.c. NPH using intermittent IV supplemental regular insulin. NPH insulin therapy added to preexisting intermittent corrective IV regular insulin approach.	None	"Diabetic" enteral formula (lower in CHO and higher lipid content) or specialized (glutamine/ω3 fatty or fluid restricted) Continuous enteral nutrition..
Murphy 2013	A 70/30 premixed human insulin was prescribed at beginning of the feed.	Short acting s.c. insulin before each feed plus glargine insulin at night.	Once or twice daily prescription of long acting insulin analogue	All patients were fed with a standard 1kcal/ml formula to meet nutritional requirements Nutrition support according to insulin regimen: continuous enteral feed over 20h or intermittent bolus feeding lasting over 4h
PARENTERAL NUTRITION				
Randomized Control Trials				
Hakeam 2015	Glargine insulin was initiated in a dose equal to 80% of the total insulin received through rapid insulin sliding scale (RISS) on the previous day; thereafter, adjustments were based on laboratory MBG: 141-216 mg/dl: 40% of total RISS; >216 mg/dl: 60% of total RISS; <70 mg/dl: next insulin dose reduced by 50%	Regular insulin added in PN solution in a dose equal to 80% of the total insulin received through rapid insulin sliding scale on the previous day; adjustments were based on laboratory measured BG: 141- 216 mg/dl: 40% of total RISS; >216 mg/dl: 60% of total RISS; <70 mg/dl: next insulin dose reduced by 50%	None	Individualized PN formula in a 2-in-1 fashion through a central IV line. PN target goal was achieved on day 3, providing macronutrients based on: 1.5 g/kg for amino acids; 2 mg/kg/min, for dextrose; and 168-240 mL for lipids. All PN started at 21:00 at 50ml/h. Caloric characteristics ~20kcal/kg.
Oghazian 2015	In the glargine insulin group dose was 80% of total daily dose of regular insulin used in PN solution on the day prior to randomization. Glargine insulin was administered 2h before next PN infusion.	If BG was already in 151 to 199 mg/ dl range, 0.15 units of insulin per gram of dextrose were added on the 1st day; if BG measured on the day before starting PN was 121-150, 100-120, and <100 mg/dl, 10, 5, and 0 units of insulin per gram of dextrose were added in PN bag, respectively. If needed, regular insulin was also administered s.c. to correct any glucose values >150 mg/dl according to a correctional insulin dosing protocol (correctional protocol provides 2 units of regular insulin for every 50 mg/ dl of blood glucose over 150 mg/dl. Subsequently, 70-100% of the correctional insulin dose is added to the next day PN solution.		PN provides approximately 40–60% of calculated daily energyy requirement of CHO during the first 24h (150 to 250g of dextrose) and is then promoted to the desired goal during the next 24 hours. IV amino acid and fat emulsion are started from day 1 based on individualized requirements.
Cohort Studies				

Jakoby 2012	For patients without diabetes, insulin was started as 1U/20 g CHO. Prandial regular insulin was administered in PN (2/3 of total insulin) and basal NPH insulin (1/3 of total insulin) in 4 equal sc doses at 6-hour interval. For patients with diabetes and initial BG measure <200 mg/dl, prandial insulin was administered as 1U/10 g CHO and basal insulin as NPH 0.15U/kg/day in 4 doses of 6h-hour interval. For patients with diabetes and initial BG >200 mg/dl prandial regular insulin was 1U/5 g CHO and basal NPH insulin was 0.25U/kg/day. Insulin adjustments followed a predefined protocol.	Patients who met the eligibility criteria and were managed before the implementation of insulin protocol and treated with sliding scale insulin	None	Nutrient content of PN and infusion rates were left at the discretion of the pharmacist. Patients were excluded if >10% of daily CHO was delivered through the alimentary tract.
Neff 2014	Patients with hyperglycemia while on PN were started with a IV insulin protocol.	Patients with hyperglycemia were individually prescribed s.c. insulin with no standardized dose. Patients received a mixture of rapid acting insulin analog and basal insulin.	None	Not described
		MIXED NUTRITIONAL SUPPORT		
		Randomized Control Trials		
Holzinger 2004	Patients received a continuous infusion of 1UI/h of insulin during 24 hours.	Patients received a saline infusion of 1ml/h during 24 hours.	None.	All patients received artificial nutrition continuously via parenteral and/or enteral routes during the study. Daily energy needs were calculated as 25 kcal per kg of total body weight.
Van Herpe 2013	The insulin dosage is guided by software. The model comprises information regarding patient profile (reason for ICU admission, BMI, history of diabetes, severity of illness) and other variables such as BG, insulin dose sequence, and steroid medication).	The insulin dosage is defined by a paper guideline.	None.	Patients received dextrose 5% 30-40 ml/h as long as 7 days after ICU admission. Enteral nutrition was started when possible, and if enteral nutrition was insufficient at 7 days in ICU, PN was initiated on day 8 to reach energy goal.
		Cohort studies		
Thomas 2005	No standardized doses of insulin. The resident prescribed an insulin sliding scales to achieve blood glucose control.	Insulin protocol that used a calculator to define insulin dose.	Modified web-based insulin protocol: amount was increased by an extra 1U/h above the values produced by the old protocol when BG was >130 mg/dl plus a bolus of 2U of insulin.	Feeding protocol: a daily intake of approximately 1800 calories.
Dortch 2007	BG was managed with an automated nurse driven, computer based protocol. The bedside nurse enters the BG, the primary source of glucose and method of glucose measurement. The computer software calculates the recommended insulin dose .	BG was manually managed by nurse driven, paper based protocol. The nurse calculated the recommend dose of insulin according to an algorithm.	None	Primary glucose source, consisting of dextrose containing fluids that delivered a partial CHO supply of 5-10g/h. As soon as possible PN, combined PN and enteral or enteral feeding was instituted. Enteral feeding the preferred support nutrition.

Dickerson 2014	Former algorithm recommending Aggressive titration of insulin infusion to maintain blood glucose100 – 125 mg/dl	New algorithm allowed a slower progression of insulin	None	Patients received continuous enteral feeding or PN. Daily target for caloric intake was 30 to 35 kcal/kg and for protein 0.8 to 1.5 g/kg based on serum urea nitrogen concentration or changes in serum nitrogen concentration between dialysis periods. If enteral or PN was discontinued, to prevent hypoglycemia a 5% dextrose solution was started at the same infusion rate as the feeding formulation.

BG = blood glucose; BMI = body mass index; CHO = carbohydrate; IV = intravenous; PN = parenteral nutrition; s.c. = subcutaneous

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
	Random sequence generation	Allocation Concealment	Blinding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
ENTERAL NUTRITION						
Koritkowski, 2009	Low	uncertain	High	uncertain	low	low
Leelarathna, 2013	Low	low	High	high	low	low
PARENTERAL NUTRITION						
Hakeam, 2015	low	low	high	high	low	low
Oghazian, 2015	low	uncertain	high	uncertain	low	uncertain
MIXED NUTRITIONAL SUPPORT						
Van Herpe, 2013	Low	low	High	low	low	low
Holzinger, 2004	Low	low	Low	low	low	low

Table S2. Quality assessment for randomized studies included in the systematic review.

Table S3. Quality assessment of cohort studies included in the systematic review.

	Selection (max. 4 stars)				Comparability (max. 2 stars)	Outcome (max. 3 stars)			Total stars (max. 9 stars)
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertaining exposure	Outcome of interest not present at the start of the study	Control for possible confounding factors (major ones and any additional ones)	Assessment of outcomes	Adequacy of duration of follow-up	Adequacy of completeness of follow-up	
ENTERAL NUTRITION									
Grainger, 2007	★	★	★	★					**4**
Chase, 2008		★	★	★	★			★	**5**
Cook, 2009	★	★	★	★					**4**
Hsia, 2011	★	★		★			★	★	**5**
Dickerson, 2013	★		★	★			★	★	**5**
Murphy, 2013	★	★		★			★	★	**5**
PARENTERAL NUTRITION									
Jakoby, 2012	★	★	★	★	★	★	★		**7**
Neff, 2014	★	★	★	★			★		**5**
MIXED NUTRITIONAL SUPPORT									
Thomas, 2005	★	★	★	★			★	★	**6**
Dortch, 2007	★	★	★	★			★		**5**
Dickerson, 2014	★	★	★	★			★	★	**6**

Table S4. Quality assessment of systematic review for different insulin regimens used to treat hyperglycemia in patients receiving nutritional support.

Quality Assessments							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention 1	Intervention 2	Relative (95% CI)	Absolute		
A - Enteral Nutrition Group: Sliding Scale Insulin (Intervention 1) compared to NPH, Premix and Glargine+Lispro Insulins (Intervention 2)												
Mean Blood Glucose (Better indicated by lower values)												
3	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	56	135	-	MD 2.5 lower (2.65 to 2.35 lower)[2]	ÅOOO VERY LOW	IMPORTANT
B- Parenteral Nutrition Group: Glargine Insulin (Intervention 1) compared to regular insulin added to parenteral nutrition bag (Intervention 2)												
Mean Blood Glucose (measured with: mg/dl; Better indicated by lower values)												
2	randomized trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	53	-	MD 3.78 lower (11.93 lower to 4.37 higher)	ÅÅÅO MODERATE	IMPORTANT
Hypoglycemia												
2	randomized trials	Serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	RR 1.37 (0.43 to 4.32)	-	ÅÅÅO MODERATE	IMPORTANT
								0%		-		
C- Mixed Nutrition Group: Paper based (Intervention 1) versus computer based protocols (Intervention 2) for IV insulin use												
Mean blood glucose (Better indicated by lower values)												
2	observational studies	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	745	410	-	MD 5.41 higher	ÅÅOO LOW	IMPORTANT

		risk of bias								(1.4 to 9.4 higher)		

[1] It was not possible to make direct comparisons

[2] Results for Best ranked insulin NPH vs. sliding scale insulin

[3] No sliding was possible for interventions and blinding was not reported

Absence of an effect of nutritional therapy on intra-hospital mortality in malnourished critically ill patients

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Word count: 2595

Abstract

Purpose: We assessed the effects of nutrition therapy on mortality for malnourished critically ill patients during the first week of an intensive care unit (ICU) stay.

Methods: This was a prospective, 2-centre, observational study. Patients admitted to ICUs with a body mass index (BMI) < 20 kg/m^2 were included. Two nutritional evaluations were performed: between days 2 and 3 (first evaluation) and between days 5 and 7 (second evaluation) of ICU admission. In the first evaluation, patients were divided into non-fed (without nutritional support) and early-fed (those already receiving nutritional support) groups.

Results: A total of 4236 patients were screened, and the prevalence of undernourished patients was 16.3%. The intra-hospital mortality rate of the 342 included patients was 58.5% (with a median of 21 [11-38.25] days of follow-up). In a time-dependent multivariate Cox regression model [HR, 95%], there was no difference in mortality between groups based on protein intake (0.97 [0.78 -1.20]) adjusted for sequential organ failure assessment (SOFA) score on the day of each evaluation (1.13 [1.10-1.73]) or based on caloric intake (1.00 [0.99-1.16]) adjusted for the SOFA score on the day of each evaluation (1.14 [1.10-1.18]). At the first evaluation, there was no difference in mortality between the early-fed and the non-fed groups after adjusting for SOFA on the day of the evaluation. At the second evaluation, there was no association between mortality and caloric or protein intake after adjusting for the SOFA score. Nutritional therapy was not associated with refeeding syndrome or electrolyte disturbances.

Conclusion: In the first week of an ICU stay for malnourished critically ill patients, nutritional therapy was not associated with in-hospital mortality or refeeding syndrome. Additional studies are needed to determine the optimal nutrition for these patients.

Keywords: malnourishment; critically ill; nutrition support.

(ClinicalTrials.gov number NCT03398343)

Introduction

Undernutrition, defined as a state of altered body composition and body cell mass resulting from a lack of uptake or intake of nutrition that leads to diminished physical and mental function and impaired outcomes from disease [1], affects up to 65% of hospitalized patients[2, 3]. Malnutrition can make a person more susceptible to infection, and infection also contributes to malnutrition, which leads to a vicious cycle[2]. Malnutrition is robustly associated with death in critically ill patients[4]. A body mass index (BMI) lower than 20 kg/m^2 has been associated with poorer survival in critically ill patients, probably because of its role as a marker of nutritional status[5, 6].

Malnourished patients incur higher costs than non-malnourished patients, with an increase ranging between 45% and 102%[7]. Adequate nutritional therapy in hospitalized malnourished patients might be a cost-saving measure, with one study estimating the potential savings to be on the order of 250 million euros per year[8]. Despite this evidence, cohort studies show that nearly 60% of malnourished patients do not receive any nutritional treatments[8, 9].

Nutritional support in critically ill patients aims to reduce catabolism, attenuate muscle wasting and maintain nutritional status[10]. Not all critically ill patients, however, will derive the same benefit from nutritional therapy[10]. Patients with moderate to severe nutrition risk might benefit from more aggressive nutritional therapy[11]. However, they may also have more risk of complications from such therapy, including refeeding syndrome[12]. Most guidelines are unable to define when and how to feed malnourished critically ill patients (Table 1) [13-16]. Whether feeding interventions improve clinical outcomes in patients with pre-existing malnutrition (BMI <20 kg/cm^2) is unknown.

We hypothesized that critically ill patients with malnutrition, determined by a BMI <20 kg/cm^2, would benefit from early feeding and higher protein and caloric intake

during the first week of ICU admission. We evaluated the impact of nutritional therapy on in-hospital mortality in underweight critically ill patients.

Methods

We conducted a prospective, two-centre (Hospital de Clínicas de Porto Alegre and Hospital Nossa Senhora da Conceição), observational study in underweight critically ill patients (Supplemental Figure 1). Between October 2015 and August 2017, all patients admitted to intensive care were screened for study eligibility. Patients with a BMI < 20 kg/m^2 were consecutively enrolled. Exclusion criteria were age less than 18 years, pregnancy, life expectancy less than 24 hours, exclusive oral intake, and exclusive palliative care.

For every included patient, the following data were recorded at ICU admission: age, sex, weight, height, admission category (surgical vs. medical), comorbidities, history of weight loss, primary admission diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score[17], Simplified Acute Physiology Score 3 (SAPS 3)[18], Sequential Organ Failure Assessment (SOFA) score[19], and Nutrition Risk in Critically Ill (NUTRIC) score[20]. Height (actual or estimated) and weight at admission (estimated or actual weight) were used to calculate BMI [i.e., weight (kg)/height (m^2)]. We performed two evaluations to assess protein and caloric intake. The first occurred between days 2 and 3 of ICU admission, and the second occurred between days 5 and 7 of ICU admission. At each evaluation, we recorded the type and amount of nutrition received in the previous 24 hours, non-nutritional calories administered (glucose infusions and propofol), and contraindications for enteral nutrition. We also recorded the use of vasopressor, mechanical ventilation, or renal replacement therapies as well as

serum electrolytes (potassium, magnesium, phosphorus) and the SOFA score at each evaluation. If patients resumed exclusively oral intake, if palliative care was instituted, or if patients were discharged, the second evaluation was not performed. Nutritional support was prescribed by the assistant staff members and usually aimed for a caloric target of 20-25 kcal/kg/day and a protein target of 1.2-1.5 g/kg/day[21].

We followed patients until hospital discharge. During the hospital stay, we assessed the successful weaning of mechanical ventilation (defined as successful extubation for more than 48 hours) and the presentation of refeeding syndrome (defined by the assistant physician and requiring intervention). The primary outcome was in-hospital mortality. Secondary outcomes were the duration of mechanical ventilation, length of ICU stay, and rate of refeeding syndrome.

The study protocol was approved by the ethics committee of the Hospital de Clínicas de Porto Alegre and the Hospital Nossa Senhora da Conceição. This study was registered with ClinicalTrials.gov, number NCT03398343.

Statistical analysis

Statistical analyses were performed using SPSS 20 and R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive data are reported as the mean±SD, median (interquartile range) or frequency (percentage). Non-normally distributed variables were compared using Mann-Whitney U tests. The chi-square test was used to compare categorical variables. To account for changes in the severity of illness, caloric intake, and protein intake over time, we performed a time-dependent Cox regression model analysis with in-hospital mortality as the outcome variable.

For the first evaluation, we divided the sample of patients into those who received

nutritional support, either parenteral, enteral or both (early-fed group), and those who did not receive nutritional support (non-fed group). In the second evaluation, we divided the sample according to protein target (1.3 g/kg/day) and caloric target (20 kcal/kg/day). A Cox regression analysis was performed for both evaluations with in-hospital mortality as the outcome. The analyses of in-hospital survival were adjusted for SAPS3, NUTRIC, and SOFA severity scores on the day of the evaluation.

Results

Patient profiles and overall mortality

Between October 2015 and August 2017, 4236 adult patients were acutely admitted into the ICUs (mean of 193 patients/ month). The prevalence of BMIs lower than 20 kg/m^2 was 16.3%. Figure 1 shows the study diagram. A total of 342 patients were included, of whom 203 (59.4%) were men, 205 (59.9%) had a BMI lower than 18.5 kg/m^2, and 185 (54%) had high NUTRIC scores. The mean SAPS3 score was 68.53±13.9.

The in-hospital mortality rate was 58.5% over a median of 21 (11-38.25) days of follow-up. There was a reduction in SOFA scores (5 [3-8] to 4 [2-6], $p < 0.001$) between the 1st and 2nd evaluations. Moreover, there was an increase in caloric (18.07 [9.84-26.14] to 26.23 [20.50-30.36], $p < 0.001$) and protein (0.89 [0.30-1.40] to 1.42 [1.05 -1.63], $p < 0.001$) intake between the 1st and 2nd evaluations. A univariate analysis performed on the first and second evaluations found no difference between survivors and non-survivors based on protein and caloric intake. A total of 558 evaluations of protein and caloric intake were performed. In time-dependent multivariate Cox regression model [HR, 95%] with mortality as the outcome, there were no differences for protein (0.97 [0.78-1.20]) or caloric intake (1.00 [0.99-1.16]) when adjusted for the SOFA score (1.13[1.10-1.73]). A 100% power was detected in a post hoc analysis for protein and calories.

First evaluation: non-fed versus early-fed

In the first evaluation, 62 (18.13%) patients did not receive nutritional support (non-fed group). The remaining 280 patients received nutritional support (early-fed group) as follows: 272 (79.5%), enteral support; 5 (1.5%), total parenteral nutrition; and 3 (0.9%), supplemental parenteral support. The caloric target of 20 kcal/kg/day was achieved by 149 (43.6%) patients, and the protein target of 1.3 g/kg/day by 109 (31.9%). Table 2 lists the characteristics of all study patients and compares the non-fed group and the early-fed group. Sixty-eight patients had some contraindications for enteral feeding, mainly haemodynamic instability (37 patients). Figure 2 – Panel A shows the four Cox regression models used to assess the relationship between nutritional support (early-fed versus non-fed groups) and in-hospital mortality. A post hoc analysis detected a power of 99% for the model adjusted for SOFA scores on the day of the evaluation.

Second evaluation: protein and caloric intake

A total of 216 patients completed the second evaluation; of these, 10 (4.6%) did not receive nutritional therapy, 202 (93.5%) received enteral nutrition, 1 (0.5%) received parenteral nutrition, and 3 (1.4) received both parenteral and enteral nutrition. The caloric target of 20 kcal/kg/day was achieved by 163 (75.5%) patients, and the protein target of 1.3 g/kg/day by 126 (58.6%) at the second evaluation. The relationship between protein intake, caloric intake and in-hospital survival at the second evaluation was evaluated with different models (Figure 2 - Panel B and Panel C). The protective effect of achieving the nutritional support target was lost when data were adjusted for SOFA score on the day of the second evaluation.

Secondary outcomes

In the first evaluation, there were no differences in the duration of mechanical ventilation therapy or the length of ICU stay between the non-fed and the early-fed groups. In a Cox regression model, protein intake at the second evaluation was not associated with successful weaning. There was also no association between protein intake at the second evaluation and being discharged alive from the ICU. There was a total of 6 (1.8%) patients diagnosed with refeeding syndrome, but we found no association between this diagnosis and the number of calories received.

Discussion

This study was designed to address a real-life dilemma: how to feed underweight critically ill patients. In this prospective observational study, which is, to our knowledge, the largest cohort study of underweight critically ill patients, we demonstrated that there was no difference in in-hospital mortality based on the timing of the initiation of nutritional support or the amount of energy and protein provided during the first week of ICU stay when adjusted for the severity of the illness on the day of the evaluation.

The optimal timing, amount, and route of nutritional support in critically ill patients are controversial, especially in underweight patients[12, 22], mainly because underweight patients have been underrepresented or excluded from previous studies[23-26]. Our data support the findings of previous randomized studies that have demonstrated no clear benefits from increasing enteral feeding during the first week of an ICU stay in a different set of patients[27, 28]. However, our study diverges from previous observational and randomized trials for other reasons. First, we evaluated caloric and protein intake at two distinct periods of time, and second, we adjusted the effect of

nutritional support based on the severity of the illness at the day of the evaluation. Most observational studies have used the mean caloric and protein intake over time and adjusted these values based on the illness severity scores calculated at the time of admission[29-31]. This approach does not consider dynamic changes in the severity of an illness, which might influence nutritional intake. We demonstrated that there was a significant difference in in-hospital mortality between the non-fed and early-fed groups based on protein intake at the second evaluation after adjusting for SAPS3, but this difference was lost when adjusting for the SOFA score at the day of the evaluation. This finding may be especially important since we had 157 (45.9%) patients using vasopressor therapy at the first evaluation and 55 (25.5%) at the second evaluation. Although observational data show that it is safe to start enteral feeding while patients are receiving vasopressor therapy[32-34], the recent NUTRIREA-2 trial showed that this combination can lead to a greater risk of digestive complications[35]. Unfortunately, we did not measure these complications.

Even though we could not establish the benefit of nutritional support in malnourished patients, it should be emphasized that there was no harm in enhancing nutritional therapy in the first week. We did not observe a difference in the incidence of refeeding syndrome and electrolyte disturbances based on nutritional support, which may be a major concern in this population[36].

To identify malnourished patients, we used a BMI lower than 20 kg/m^2, which has been associated with poorer survival rates in critically ill patients than higher BMIs[5]. We are aware of the limitations of using BMI to estimate body fat and lean mass at the individual level. It is possible that some of the included patients had a higher lean body mass composition but were not malnourished[37]. However, we have other clinical data in addition to the BMI values that support the claim that the vast majority of the

patients included in this study were undernourished: 33.9% of the patients had a history of prior weight loss, 79.2% of the patients had temporal muscle wasting, and 79.8% of the patients had pre-existing illness, all of which corroborate the diagnosis of malnourishment in the patients evaluated in our study.

Our study has some limitations. First is the observational design of the study. Observational data, particularly in the field of ICU nutrition, should be interpreted with caution, since the clinical course can affect nutritional intake more than nutrition can affect outcomes[35]. However, we attempted to minimize this interference by adjusting the findings based on the severity of the illness at the time of the patient's evaluation rather than on admission scores. Second, there were very few patients who received parenteral nutrition. Although this precludes any conclusions regarding the possible benefits of early parenteral nutrition or supplemental parenteral nutrition in this population, it is a finding that is consistent with a reduction in the prescription of parenteral nutrition[38] and the guidelines that favour early enteral nutrition[14, 21]. Moreover, recent randomized trials have failed to show a benefit of parenteral nutrition over enteral nutrition[22, 35].

The existing guidelines do not provide recommendations for malnourished critically ill patients based on sound evidence[16, 21] because of a lack of available data. Although we cannot provide definitive answers on how to nourish critically ill underweight patients, our study certainly helps to fill this evidence gap by providing new and important guidance for this population. Additionally, by showing no harm from withholding nutritional support in these patients, this study contributes to the future directions of nutrition research and to the inclusion of this specific group of patients in future randomized trials.

Conclusion

Enhanced nutritional therapy in the first week of an ICU stay for malnourished critically ill patients was not associated with better in-hospital survival or changes in complications such as refeeding syndrome and electrolyte disturbances in the current study. Further studies are needed to establish how to optimize nutrition for these patients.

Figure Captions:

Supplemental Fig. 1 shows the study design and logistics

Fig. 1 shows the screening, assessments and follow-ups included in the study and the reasons for exclusion

Fig. 2 shows different Cox regression models. From right to left: no adjustment and adjusted for SAPS3, NUTRIC and SOFA scores at the day of the evaluation. Panel A shows the models for the non-fed group at the first evaluation. Panel B shows the models for ≥ 20 kcal/kg/day group at the second evaluation. Panel C shows the models for ≥ 1.3 g/kg/day group at the second evaluation.

Table 1. Guideline recommendations for nutritional support in malnourished patients

Guideline (Society)	Year	Recommendation	Observation
Management of severe malnutrition: a manual for physicians and other senior health workers (WHO)[13]	1999	Recommends a caloric target of 35-40 kcal/kg/day	Not specific for critically ill patients.
Early enteral nutrition in critically ill patients (ESICM)[14]	2017	No specific recommendation for previous malnutrition	Suggests an individualized approach that considers clinical evolution and comorbidities.
Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient[15] (ASPEN/SCCM)	2016	Recommends advancing enteral feeding towards goal as quickly as tolerated over 24-48 hours and achieving more than 80% of the estimated or calculated goal energy and protein intake within 48-72 hours. When enteral nutrition is not feasible, suggests initiating exclusively parenteral nutrition as soon as possible following ICU admission.	Suggests monitoring refeeding syndrome.
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock[16] (SCCM/ESCIM)	2017	Suggests considering initiating parenteral nutrition early when enteral feeding is not feasible.	States that there is a lack of evidence with malnourished patients since they are either excluded or rarely represented in trials.

WHO – World Health Organization; ASPEN – American Society of Parenteral and Enteral Nutrition; SCCM – Society of Critical Care Medicine; ESCIM – European Society of Critical Care Medicine.

Supplemental Figure 1. Study design and logistics

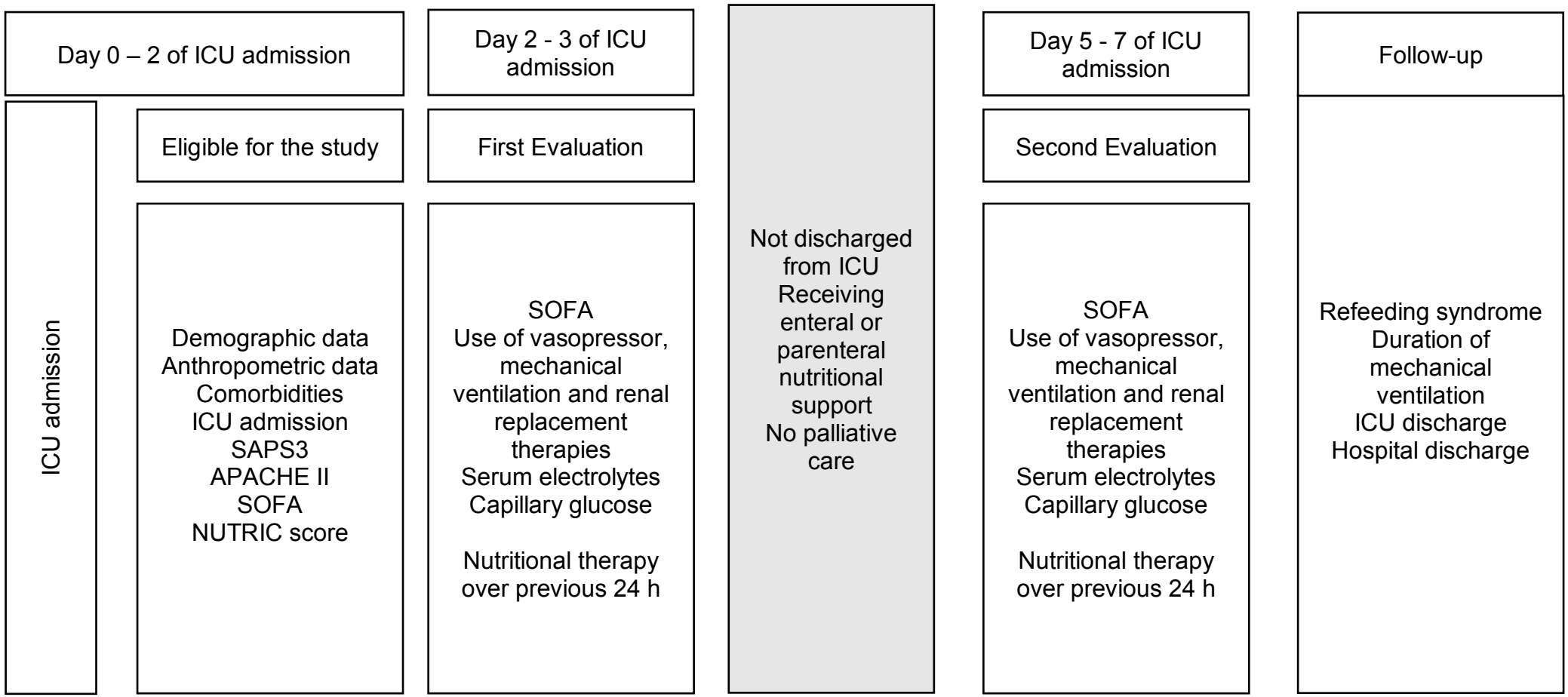


Figure 1. Screening, assessments and follow-ups included in the study

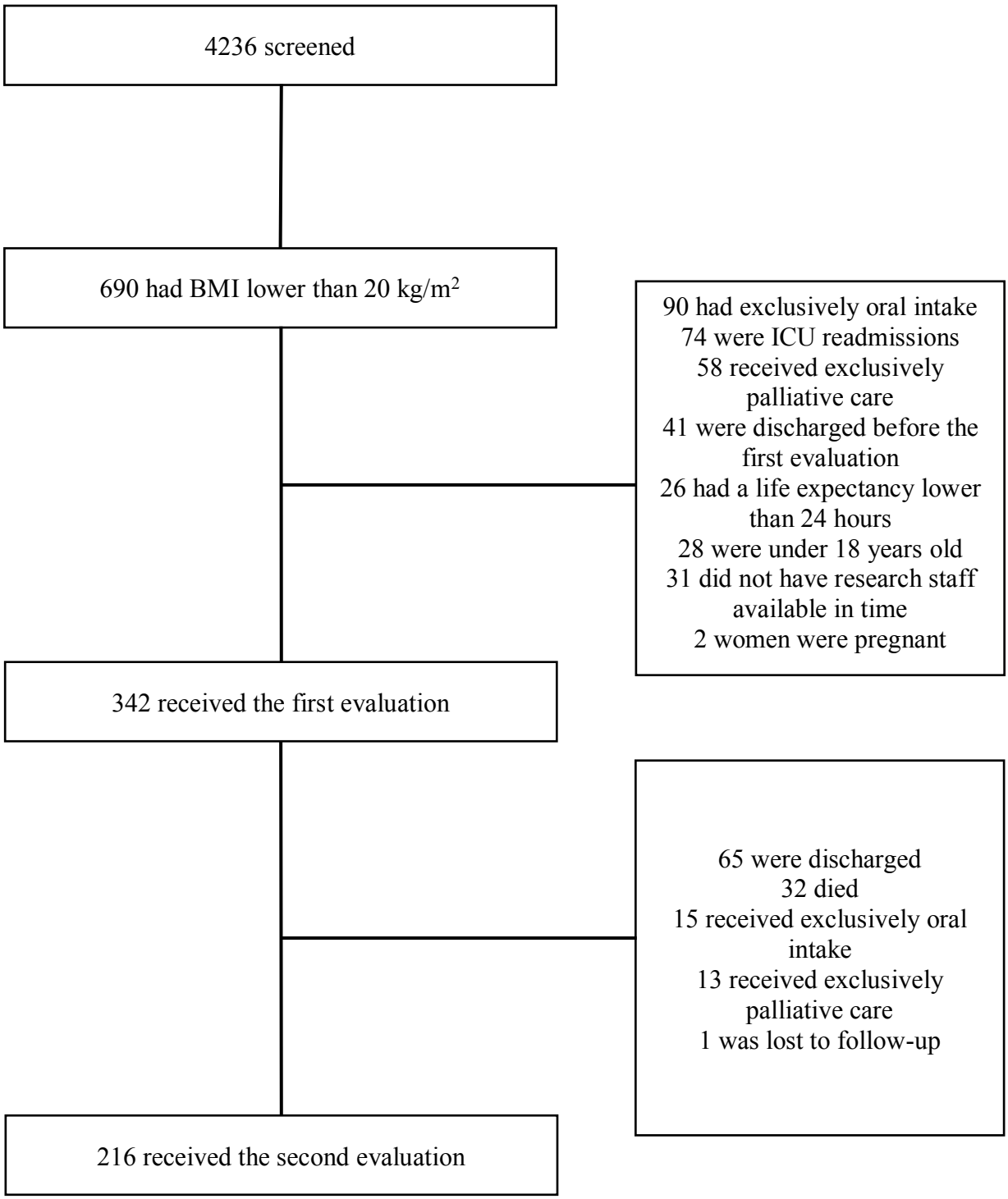


Table 2. Patients characteristics and outcomes at the first evaluation based on nutrition support

	Non-fed group n = 62	Early-fed group n = 280	P
Age (years)	54.63±17.55	53.89±17.28	0.762
Men (%)	34 (54.8)	169 (60.4)	0.423
Weight (kg)	47.69±7.95	47.91±8.13	0.852
BMI (kg/m^2)	18.09[16.68 -19.12]	18.07[16.33-19.12]	0.778
History of weight loss prior ICU admission (%)	21 (33.9)	95 (33.9)	0.517
Temporal muscle wasting (%)	31 (59.4)	152 (54.4)	0.489
Pre-existing illness at ICU admission			
Chronic renal failure (%) Cardiac failure (%) Respiratory (%) Cancer (%) Liver disease (%) Acquired immunodeficiency syndrome (%)	4 (6.5) 5 (8.1) 5 (8.1) 16 (25.8) 10 (16.1) 13 (21)	18 (6.4) 21 (7.5) 58 (20.7) 55 (19.6) 12 (4.3) 70 (25)	0.995 0.885 0.020 0.279 0.001 0.503
Medical diagnosis at ICU admission	46 (74.2)	255 (91.1)	<0.001
Days in hospital prior to ICU admission	3.5[1-13.25]	4[1-12]	0.685
NUTRIC	5[4-6.25]	5 [3-6]	0.035
SAPS3	70.60±16.66	68.26±12.75	0.266
SOFA at admission	7 [5-11]	6 [4-8]	0.022
Main reason for ICU admission			
Respiratory failure Sepsis Neurological Cardiovascular Major surgery	15 (24.2) 25 (40.3) 3 (4.8) 6 (9.7) 12 (19.4)	122 (43.7) 85 (30.5) 39 (14) 14 (5) 14 (5)	<0.001
SOFA at first evaluation	7 [4-11]	5[2-7]	<0.001
At first evaluation			
Vasopressor (%)	43 (69.4)	114 (40.7)	<0.001
Renal replacement therapy (%)	25 (40.3)	44 (15.7)	<0.001
Mechanical ventilation (%)	51 (82.3)	222(79.3)	0.598
Potassium at first evaluation (mEq/L)	3.99±0.71	4.02±0.71	0.724
Magnesium at first evaluation (mg/dl)	2.06±0.59	2.05±0.48	0.892
Phosphorus at first evaluation (mg/dl)	2.97±1.02	3.16±1.44	0.420
Outcomes			
Refeeding syndrome (%)	0 (0)	6 (2.3)	0.261
Duration of mechanical ventilation	7[4-12.5]	8 [4-15]	0.806
Length of ICU stay (days)	8 [5-16.25]	10 [6-17.75]	0.182
Length of hospital stay (days)	17 [7.75 – 29]	22 [12-40.75]	0.021
ICU mortality (%)	30 (48.4)	103 (36.8)	0.090
Hospital mortality (%)	44 (71)	156 (55.7)	0.027

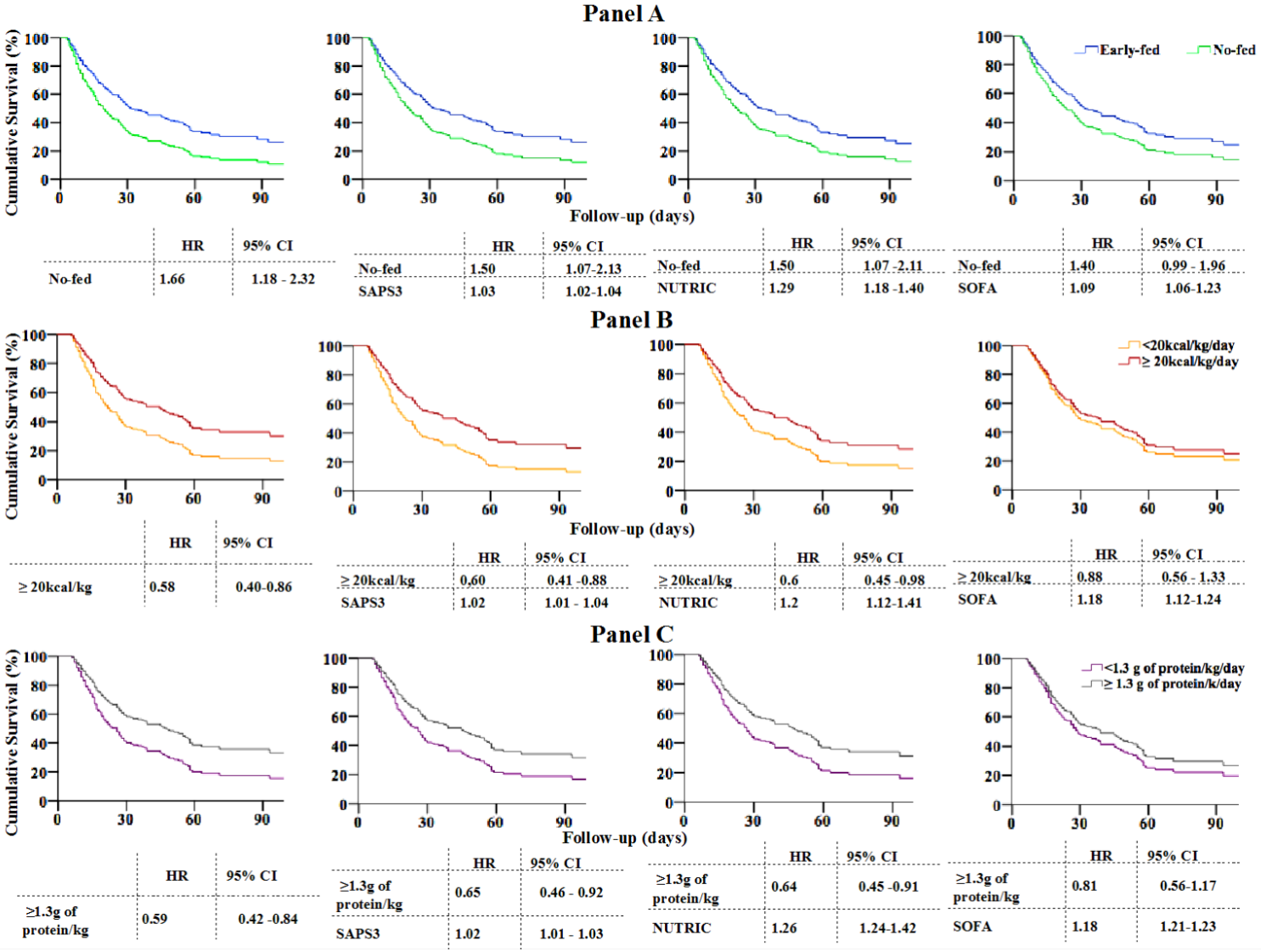
Values are means ± SD; median [interquartile ranges] or numbers (%). BMI – body mass index; ICU – intensive care unit; NUTRIC – nutrition risk in critically ill; SAPS – simplified acute physiology score; SOFA – sequential organ failure assessment

Table 3. Patients characteristics and outcomes at the second evaluation based on protein and caloric target

	< 1.3 g/kg/day n = 90	≥ 1.3 g/kg/day n = 126	p	< 20 kcal/kg/day n = 51	≥ 20 kcal/kg/day n = 165	p
SOFA	5[3-8.5]	3[2-5]	<0.001	5 [3-9]	3[2-6]	0.001
Vasopressor	34 (38.2)	21 (16.5)	<0.001	25(49)	30(18.2)	<0.001
Renal replacement therapy (%)	30 (33.3)	19(15.1)	0.002	15(29.4)	34(20.6)	0.189
Mechanical ventilation (%)	72 (80.0)	84 (66.7)	0.031	42(82.4)	114(69.1)	0.065
Refeeding syndrome (%)	3 (3.4)	3(2.5)	0.691	1(2)	5(3.1)	0.691
Potassium (mEq/L)	4.07±0.85	4.05±0.73	0.334	3.94±0.74	4±0.75	0.218
Magnesium (mg/dl)	2.10±0.43	2.09±0.51	0.775	2.13±0.44	2.08±0.49	0.551
Phosphorus (mg/dl)	3.06±1.74	2.87±1.14	0.155	3.10±0.44	2.08±0.49	0.551
Duration of ventilation (days)	7[4-14]	10[6-18.25]	0.001	11[7-19]	11[6-20]	0.845
Length of ICU stay (days)	7.5[5-13.25]	15[10-23]	<0.001	12[9-22]	15[10-23]	0.126
Length of hospital stay (days)	17[9-29]	29[17-53.75]	<0.001	20[14-30]	28[16-49]	0.012
ICU mortality (%)	43(47.8)	44(34.9)	0.058	24(47.1)	63(38.1)	0.259
Hospital mortality (%)	61 (67.8)	73 (58.3)	0.142	36(70.6)	98(59.4)	0.159

Values are means ± SD; median [interquartile ranges] or numbers (%).SOFA – sequential organ failure assessment. ICU – intensive care unit

Figure 2: Cox Regression Model for intrahospital mortality in underweight critically ill patients



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PERSPECTIVAS

O primeiro artigo dessa tese consiste de uma revisão sistemática sobre diferentes regimes de insulina no tratamento da hiperglicemia em pacientes hospitalizados sob suporte nutricional. Não foi possível, contudo, determinar qual regime é mais eficiente e seguro. Novos estudos, especialmente ensaios clínicos randomizados de boa qualidade, são necessários para definir qual a melhor forma de tratar essa complicação do suporte nutricional especializado.

Já o segundo trabalho avaliou o impacto do suporte nutricional em pacientes críticos desnutridos em mortalidade intra-hospitalar. Nesse estudo de coorte não houve benefício em uma terapia nutricional mais agressiva na primeira semana de internação com relação a mortalidade intra-hospitalar. As possíveis complicações da terapia nutricional, como distúrbios eletrolíticos e síndrome de realimentação, também não ocorreram de forma mais frequente naqueles que iniciaram precocemente o suporte nutricional. Esse resultado traz maior segurança para inclusão desses pacientes em futuros estudos de nutrição em paciente crítico. No passado, pacientes desnutridos foram excluídos de estudos por acreditar que teriam maior benefício da terapia nutricional.

Também com objetivo de esclarecer melhor o benefício da terapia nutricional e suas complicações temos dois projetos em andamento. O primeiro uma análise secundária do banco de dados dos pacientes desnutridos para avaliar se a hiperglicemia nessa população também está associada a maior mortalidade e qual sua associação com o suporte nutricional. O segundo consiste no seguimento de um ano dos pacientes desnutridos através de ligação telefônica para avaliar se a terapia nutricional na primeira semana de UTI afeta a funcionalidade desses pacientes em longo prazo.