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Original article

Magnitude of gluconeogenesis and endogenous glucose production: are they predictable in clinical settings?



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SUMMARY

Introduction: Regulation of endogenous glucose production (EGP) is essential for glucose homeostasis. It includes gluconeogenesis (GNG) from non-carbohydrate substrates and hepatic glycogenolysis. Both these pathways are dysregulated in acute stress, but the magnitude of this deregulation cannot be assessed in clinical practice. The study aims at identifying clinically available variables predictive of EGP and GNG magnitude by modeling routinely available data.

Methods: This exploratory study is based on the data from the Supplemental Parenteral Nutrition study 2 (SPN2), which measured EGP and GNG at days 4 and 10 in 23 critically ill patients. The correlation between EGP and GNG and 83 potential clinical indicators were explored, using single-stage and multivariate analysis.

Results: On single-stage analysis, the strongest correlations were noradrenaline dose at day 4 with GNG ($R = 0.71$; $P = 0.0004$) and Nutrition risk screening score (NRS) with EGP ($R = 0.42$; $P = 0.05$). At day 10, VO_2 ($R = 0.59$, $P = 0.04$) was correlated with GNG and VCO_2 with EGP ($R = 0.85$, $P = 0.00003$). Cumulated insulin dose between days 5 and 9 was correlated to EGP at day 10 ($R = 0.55$, $P = 0.03$). Our multivariate model could predict EGP at day 4 (VCO_2 , glucose and energy intake) with an error coefficient (e.c.) between 7.8% and 23.4% (minimal and maximal error), and GNG at day 10 (age, mean and basal blood glucose), with an e.c. of 18.5% and 29.9%. GNG at day 4 and EGP at day 10 could not be predicted with an e.c. < 40%.

Conclusion: This preliminary exploratory study shows that GNG and EGP have different predictors on days 4 and 10; EGP is more correlated with the metabolic level, while GNG is dependent on external factors. Nevertheless, a bundle of variables could be identified to empirically assess the magnitude of both values. Our results suggest that a robust model might be built, but requires a prospective study including a larger number of patients.

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1. Introduction

The energy requirements of critically ill patients remain a conundrum and a challenge after four decades of artificial feeding. It still predominantly relies on predictive equations, which have been shown to overestimate patients requirement with potentially deleterious effects [1–3].

The catabolic responses observed in critically ill patients [4] lead to a dysregulated, enhanced systemic production of endogenous substrates. This energy source is not considered by classical energy balance as assessed by the difference between measured energy expenditure (mEE) and exogenous energy supply. Hence, feeding requirements might be over-evaluated. Indeed, a large indirect calorimetry (IC) study including 1109 patients showed that a mean exogenous energy administration corresponding to 75–90% of mEE during the intensive care unit (ICU) stay was associated with the lowest mortality [5]. Further the amount of endogenous substrate

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Abbreviations	
APACHE	acute physiology and chronic health evaluation
BMI	body mass index
CRP	c-reactive protein
EC	Error Coefficient
EGP	endogenous glucose production = sum of glycogenolysis and GNG
EN	enteral nutrition
ESPEN	European society for clinical nutrition and metabolism
GNG	gluconeogenesis
GRa	glucose rate of appearance
IC	indirect calorimetry
ICU	intensive care unit
mEE	measured energy expenditure
NRS	nutrition risk score
SAPS	simplified acute physiology score
SOFA	sepsis-related organ failure assessment score
SPN	supplemental parenteral nutrition
SPN2	Supplemental Parenteral Nutrition study 2

production varies over time in critically ill patients, which changes the exogenous energy required to cover EE.

Blood glucose homeostasis is a priority for the organism. It is achieved by endogenous glucose production (EGP) and exogenous carbohydrate supply (i.e. feeding). EGP relies on glycogenolysis and gluconeogenesis (GNG), the latter taking place in the liver, the kidney, and, to a smaller extent, in the gut.

Current recommendations of the European Society of Clinical Nutrition (ESPEN) are to initiate nutrition therapy within the first 48 h of admission and to increase it progressively over 3–4 days [7]. During this period, EGP is strongly activated [8]. As demonstrated by tracer studies [9], this activation covers around 2/3 of mEE and appears to last until day 10 [10]. However, the amplitude of EGP is variable between patients [6,9,10].

Full feeding to the target calculated based on predictive equation has been proposed by some authors [11,12] in order to prevent underfeeding. However, in critical illness, contrary to healthy subjects, EGP is not suppressed by feeding or glucose intake after fasting [6]. Hence, overfeeding may occur if endogenous catabolic fluxes are not taken into consideration. This might overwhelm the organism in a situation characterized by major endocrine and inflammatory response, including insulin resistance [12,13]. Hence, the ability to quantify EGP would improve the prediction of extrinsic energy needs, thereby avoiding both under- or over-feeding and their associated complications and mortality [3,14,15]. Isotope tracer methods give reliable estimates, but are expensive, labor intensive and not available in clinical practice [16,17]. No practical tool or biomarker enables the evaluation of the magnitude of EGP at the bedside.

The aim of the study was to assess whether a model based on routine clinical variables related to glucose metabolism could predict the magnitude of EGP and GNG, in order to adapt exogenous nutrition delivery on a daily basis. To test this hypothesis, we retrospectively analyzed data from the 23 patients included in the Supplemental parenteral nutrition-2 study (SPN2) [10] for whom GNG and EGP were measured at day 4 and day 10 after initiation of nutritional support. Our working hypothesis was that there were individual or a bundle of clinically available laboratory or clinical variables sufficient to meaningfully adapt exogenous energy administration.

2. Patients and methods

The study was a post hoc analysis of the SPN2 trial (NCT02022813), a prospective randomized, controlled trial conducted in 23 critically ill patients, between May 2014 and April 2016. The trial was approved by the Commission Cantonale d’Ethique de la Recherche sur l’Etre Humain (CER-VD 371–13).

2.1. Patients

Inclusion criteria were: mechanical ventilation, a functional gut, and, by end of day 3, enteral nutrition (EN) less than 60% of the energy target determined by equation (25 kcal/kg/day). Patients were randomized to either continue receiving EN alone or to receive EN plus supplemental parenteral nutrition (SPN) to cover 100% of mEE from day 4 to day 10. Protein turnover and glucose kinetics were measured at days 4 and 10 [10] (Fig. 1- appendix).

2.2. Glucose kinetics

The complete glucose tracer methods are provided in the appendix. Briefly, tracers were administered on Day 4 and 10 at T0, as a loading dose followed by a continuous infusion. This achieves a near-constant tracer blood level, allowing calculation of the production rate of glucose. The standard formula for the measurement of the rate of glucose appearance in steady state is

$$GRa = \frac{\text{tracer infusion rate}}{\text{plasma glucose isotopic enrichment}}$$

GNG was estimated from ¹³C-glucose synthesis during continuous ¹³C-bicarbonate infusion [10,18]. The labeled glucose enables measuring the fractional contribution of pyruvate carboxylase to the hepatic oxaloacetate flux, and the hepatic pyruvate dehydrogenase.

2.3. Indirect calorimetry

Indirect calorimetry (IC) studies were carried out on Day 4 and 10 during the tracer studies (Quark-RMR, Cosmed, Roma, Italy) lasting 30 min after stabilization. We used crude values to explore the relationship between mEE and nutritional intake. Further, we computed “intrinsic feeding” corresponding to the conversion of measured EGP in energy (assuming 1 g of glucose equals to 4 kcal) (Fig. 1).

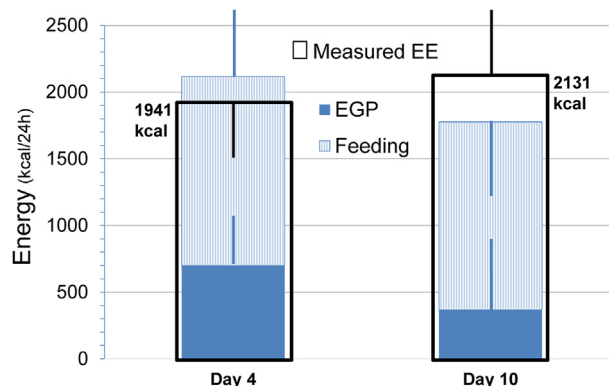


Fig. 1. Mean measured EE compared to the sum of EGP values and extrinsic feeding on Days 4 and 10.

2.4. Data extraction and verification

Data from the SPN2 study were completed with extractions from the computerized patient record (MetaVision®, iMDsoft, Tel Aviv, Israel) to provide additional clinically available input data.

2.5. Model derivation

2.5.1. Working definition

The multivariate and single-stage analysis are based on output and input variables, which are described below.

2.5.1.1. Output variables. The output variables, i.e. those that should be predictable from available clinical variables; EGP and corrected GNG, at day 4 et 10, and the difference (delta) between the 2 respective values.

2.5.1.2. Input variables. Altogether 38 clinical variables and 7 scores and demographic variables were considered at day 4 and 10, and, resulting in 83 variables;

- Demographic variables

Age, sex, weight, Body Mass Index (BMI).

- Severity scores

Simplified Acute Physiology Score (SAPSII) [19], Acute Physiology And Chronic Health Evaluation (APACHEII) [20], Sepsis-related Organ Failure Assessment Score (SOFA) [21], Nutrition Risk Screening score (NRS) [22]. All these scores are used on a daily base in the ICU.

- Blood glucose

In the ICU, blood glucose determinations are generally repeated several times within 24 h. In the present study, additional values are available from the tracer study; A) basal blood glucose, taken before the isotope tracers infusions. B) Average blood glucose of the whole day C) Blood glucose at the beginning of the isotope tracer infusions. D) Average of the last 2 values at the end of the tracer infusion. E) The mean the first and 2 last two blood glucose values during the tracer study. Of note the tracer study includes a glucose infusion which alters the basal glucose values.

- Medications with a direct effect on glucose metabolism

Insulin (UI/kg/24 h) needed for a target blood glucose between 6 and 8 mmol/l (average dose per day, on study day 4, 5, 6, 7, 9, 10), catecholamines (dobutamine, norepinephrine in mcg/kg/24 h), methylprednisolone (mg/kg/24 h).

- Cortisol level

The analysis was completed on the frozen sample of the SPN2 study.

- Inflammatory variables

Leucocyte count, C-reactive protein (CRP: 6am values), patient's temperature (mean of the 6hr tracer study).

- Nutrition parameters

Type of nutrition (enteral versus enteral with supplemental parenteral nutrition), energy balance [23], energy target, delivered carbohydrates (g/kg/day), lipids (g/kg/day), and proteins (g/kg/day).

- Calorimetry

VO₂ (mL/kg/min), VCO₂ (mL/kg/min), and respiratory quotient.

- Blood gases

PaCO₂, lactate.

In a final stage, we assessed the impact of the differences between variables at days 4 and 10 delta values (Δ).

2. Single-stage analysis: Correlation coefficients

First, we assessed the correlation between each input and output variables. In this single-stage analysis, “1” corresponds to a perfect correlation, “-1” to an inverse perfect correlation while 0 means absence of correlation (Table 3). We report separately correlations with coefficients >0.4 (Table 4). We verified the P value (Pearson) with IBM SPSS Statistics®.

3. Multivariate analysis

Details of the model and its equations are provided in the Appendix. The working method is a multivariate analysis, using a combination of 2,3 and 4 input variables (see definition above) and linking it with one output variable (definition above). The hypothesis was that the model could link input and output variables (Fig. 2 in Appendix). For each of these “links”, the error coefficient (e.c.) was calculated, along with the number of samples used, the idea behind being that an e.c. of zero would link perfectly the chosen input variables with an output variable. To calculate e.c., the correlation of the input and output variables were calculated on all samples (Σ) minus one. The difference between the prediction of all the samples (Σ) and the excluded one was used to calculate e.c. Each sample was once excluded to calculate one e.c. for each “link”.

An uncertainty value was arbitrarily fixed for each variable (see appendix for details). This resulted in two error values for each calculation, corresponding to the plus and minus range (Table 5).

3. Results

3.1. Patients

The characteristics of the 23 patients of the SPN2 trial are reported in Table 1: there was no difference at baseline between the two original groups EN and SPN. The patients started with similar energy deficit on day 4 with a median (IQR) cumulated energy balance of -3788 (-4428,-3033) kcal, with similar median energy intakes day 4 (1294 (896,-1617) kcal). Energy delivery increased in the SPN group by protocol, resulting in significantly different energy balances on day 10 (Table 1 and Appendix Table 2-complement).

3.2. Glucose kinetics

As reported in Table 2, EGP decreased over time, while GNG remained stable.

3.3. Energy fluxes

The sum of extrinsic (feeding) and intrinsic (EGP + GNG) energy production is close to mEE (Fig. 1). This results in a 272 ± 829 kcal/day overfeeding at day 4, and -69 ± 1308 kcal/day at day 10.

Table 1
Patients characteristics upon admission, and on days 4 and 10.

	Units	Day 1	Day 4	Day 10
Patients	N	23		
Age	years	64.13 (61.5–72.5)		
Gender	M/F	*19/4		
Weight	kg	80.43 (67–94.5)		
Body mass index	kg/m ²	27.25 (24.65–30.3)		
Ideal body weight	kg	66.83 (65–71.5)		
NRS	points	4.13 (3–5.5)		
APACHE II	points	22.78 (18.5–26)		
SAPS II	points	49.87 (37.5–59)		
SOFA	points	9.52 (7–11)	8.61 (6–10)	5.75 (3–7.25)
mEE	kcal/kg/d		24.19 (21.2–27.5)	25.52 (22.9–28.4)
Energy Intake	kcal/24 h		1294.4 (895.5–1617)	1850.6 (1604–2074.5)
Cumulated Energy balance ^a in EN group	kcal		-3448 (-4063–2796)	-6050 (-10'637–4830)
Cumulated Energy balance ^a in SPN group			-2741 (-3130–2406)	-3416 (-4027 -2336)
Basal Blood glucose	mmol/L		8.13 (6.25–9.1)	7.48 (6.6–7.9)

Data as medians (IQR25–75). Abbreviations: NRS= Nutrition Risk Screening, APACHE II = Acute Physiology And Chronic Health Evaluation II, SAPS II = Simplified Acute Physiology Score II, SOFA = Sequential Organ Failure Assessment, mEE = mean energy expenditure.

^a Cumulated from admission.

Table 2
The magnitude of EGP and GNG changed over time: EGP was superior to GNG on day 4, but both values were equivalent on Day 10.

	Units	Day 4	Day 10
EGP	mg/kg/min	1.65 (1.19–2.10)	1.11 (0.54–1.41)
	g/24 h	208 (166.9–240.7)	147.8 (87.8–160.1)
GNG	mg/kg/min	1.12 (0.59–1.35)	1.11 (0.57–1.64)
	g/24 h	121.9 (78.1–179.1)	112.8 (38.9–159.3)
mEE	kcal/d/kg	24.19 (21.24–27.53)	25.52 (22.95–28.45)
Glucose Intake	mg/kg/min	1.20 (0.83–1.72)	2.06 (1.60–2.24)
GRa	mg/kg/min	2.93 (2.30–3.27)	2.80 (2.36–3.06)
Plasma glucose	mmol/L	7.60 (6.65–8.60)	7.46 (6.90–8.00)
Plasma cortisol	nmol/L	667.17 (340.5–696.5)	520.48 (418.5–651.5)

Data as means (IQR25–75). Abbreviations: EGP = Endogenous Glucose production, GNG = Gluconeogenesis, mEE = mean energy expenditure, GRa = Glucose rate of appearance.

3.4. Single-stage analysis: correlation coefficients

In our first single stage analysis, we found no direct correlation between our input and output variables (Table 3a,b), except for noradrenalin dose and GNG at day 4 (R = 0.71 p < 0.0004), NRS and EGP at day 4 (R = 0.42; p < 0.05), VCO₂ and EGP at day 10 (R = 0.85, p < 0.00003), mean days 5–9 insulin delivery and EGP at day 10 ((R = 0.55, p = 0.03), and finally VO₂ (R = 0.59, p = 0.04) and VCO₂ (R = 0.54; p < 0.03) with GNG at day 10.

Table 4 summarizes correlation coefficients >0.4 already shown in Table 3a–b, with the p values according to Pearson.

This shows that each output has different indicators, which change over time.

On day 10, EGP is strongly correlated with VCO₂ (R 0.85, P < 0.000), followed by the insulin dose, and respiratory quotient), while it is negatively correlated with blood glucose in the beginning of tracers. GNG is strongly correlated with VO₂ and VCO₂, to a lesser degree to insulin dose, while it is negatively correlated to noradrenaline and methylprednisolone dose.

3.5. Multivariate analysis: modelisation

We collected combinations of up to 4 input variables for each output variable, giving 280'000 results for each of the 4 output variables. Table 5 presents the results of the models with an error coefficient below 40%. Note that the maximum patient sample is not 23 because all input variables are not always available.

The model could correlate several input to output variables.

EGP on day 4 was best estimated using a combination of VCO₂, glucose intake, and energy intake. EGP on day 10 and GNG on day 4 are poorly predictable with this model. GNG on Day 10 is approached by the combination of energy balance and VO₂.

3.6. Evolution between day 4 and 10, delta values (Δ) to predict day 10 outputs

A complete table of delta value (Δ) is available in appendix (see Fig. 3).

- Leukocyte count (Δ) and EGP (Δ); R = 0.70, P < 0.04
- RQ (Δ) and EGP (Δ); R = -0.70, P < 0.05
- Methylprednisolone (Δ) and GNG at day 10; R = 0.62 and P < 0.01.

4. Discussion

In this exploratory analysis, we attempted to identify predictors of EGP and GNG in critically ill patients based on routinely available parameters using single-stage and multivariate analysis. The main findings are that: 1) EGP and GNG on day 4 have different determinants, EGP depending on energy metabolism and GNG on neuroendocrine factors, and 2) that GNG equals EGP on day 10 and is the abnormal component of EGP in these patients as previously shown by our group [24,25]. GNG at day 10 is proportional to VO₂, VCO₂ and metabolic factors, possibly due to inflammation and mEE dependent on inflammation as well.

Searching for EGP predictors in diabetes patients, investigations have produced several models. Dala Man et al. [26] proposed a model in which the EGP in the liver is described by two differential equations [27]. The model's inputs were mean insulin, portal insulin and blood glucose concentrations, and the EGP was extrapolated with precision for both normal and type 2 diabetes subjects. More recently, Van Stee et al. described a mathematical procedure to calculate glucose dynamics, based on Dala Man's first equations [27]. Their aim in diabetic patients was to estimate diurnal EGP dynamic directly from plasma glucose, insulin and Insulin Secretory Rate (ISR), gathered from 3 consecutive meals. This method is not applicable in critically ill patients receiving continuous feeding.

The patients included in the present investigation were severe critically patients receiving mechanical ventilation and complex ICU therapies: they were fed using standard techniques (EN, PN or their combination) and enrolled because they encountered the

Table 3

a) Coefficient correlation (R) between output variables (EGP and GNG) and input variables at day 4. **b)** Coefficient correlation between output variables (EGP and GNG) and input variables at day 10. Same color code Color code; green for perfect positive correlation (+1), red for perfect negative correlation (-1), yellow when no correlation can be seen (0).

A			B		
	EGP (mg/kg/min)	GNG (mg/kg/mn)		EGP (mg/kg/min)	GNG (mg/kg/mn)
EGP (mg/kg/min)	1.00	0.43	EGP (mg/kg/min)	1.00	0.06
GNG corr	0.43	1.00	GNG corr	0.06	1.00
Blood glucose mmol/l	0.07	-0.03	BG mmol/l	-0.21	-0.33
Basal BG	0.11	-0.08	Basal BG	-0.25	0.35
BG beginning perfusion	0.24	-0.23	BG beginning perfusion	-0.47	0.08
BG end of perfusion	0.34	0.35	BG end of perfusion	0.26	0.08
Mean BG during perfusion	0.36	0.06	BG during perfusion	-0.29	-0.05
mEE (CALO)	-0.30	-0.16	mEE (CALO)	-0.18	0.30
V02 mL/mn/kg	0.04	0.05	V02 mL/mn/kg	-0.15	0.58
VCO2 mL/mn/kg	0.30	0.17	VCO2 mL/mn/kg	0.85	0.54
RQ	0.14	-0.23	RQ	0.53	-0.04
Energy/24H	-0.32	-0.10	Energy/24h	0.04	0.08
Energy/24h/kg (ideal)	-0.26	-0.16	Energy/24h/kg (ideal)	0.12	-0.08
Energy balance D3	0.10	-0.09	Energy balance D9	0.06	-0.01
Energy target reached	0.10	0.11	Energy target reached	-0.03	0.12
Glucose G/24h	-0.34	-0.09	Glucose G/24h	0.11	0.01
Glucose G/24h/kg (ideal)	-0.28	-0.15	Glucose G/24h/kg (ideal)	0.08	-0.13
Protein G/24h	-0.17	-0.06	Protein G/24h	-0.23	0.03
Protein G/24h/kg (ideal)	-0.13	-0.12	Protein G/24h/kg (ideal)	0.00	-0.14
Lipid G/24H	-0.28	-0.11	Lipid G/24h	-0.16	-0.03
Lipid G/24h/kg (ideal)	-0.25	-0.17	Lipid G/24H/kg (ideal)	-0.08	-0.11
Age	0.25	0.02	Age	0.34	-0.01
IBW	-0.16	0.10	IBW	-0.20	0.02
BMI	-0.31	-0.09	BMI	0.11	-0.17
SAPSII	0.14	0.24	SAPSII	0.10	0.06
SOFA D1	0.18	0.11	SOFA	-0.08	0.29
NRS	0.42	-0.16	NRS	0.10	-0.15
APACHE II	0.26	0.06	APACHE II	-0.08	0.19
Insulin/kg 24h	0.21	0.14	Insulin/kg 24H	0.36	-0.13
Methylpred/kg 24h	0.34	-0.19	Insulin/kg D5-9	0.55	0.19
Noradrenaline/kg 24h	0.26	0.71	Methylpred/kg24H	-0.17	-0.42
Noradrenaline/kg/1:10-4	0.20	0.45	Nor24H	0.12	-0.49
Dobutamine/kg 24h	0.31	-0.37	PaCO2	0.32	-0.67
PaCO2	0.34	0.37	Lactate	-0.20	-0.13
Lactate	-0.25	-0.07	Leukocytes	-0.19	0.03
Leukocytes	0.01	-0.19	CRP	0.24	0.22
CRP	0.05	0.32	Temperature	0.09	0.35
Temperature	-0.31	-0.12	Cortisol	-0.08	0.05
Cortisol	0.25	0.35			

Table 4

Correlation Coefficient (R) and P value according to Pearson (P) on selected input variable. R: Color code; green for positive correlation (+1), red for negative correlation (-1), yellow when no correlation can be seen (0). P: value p < 0.05 appear in red characters. Abbreviations: NRS = nutrition risk score, BG b.p. = blood glucose before tracers perfusion, RQ = respiratory quotient, Nor = noradrenaline, Dobu = dobutamine, methylpredn = methylprednisone.

		NRS	BG b.p.	VO2	VCO2	RQ	Insuline D5-9	Nor D4	Nor D0-4	Nor D10	Dobu D4	Methylpr edn D10
				mL/kg/m	mL/kg/m							
EGP D4	R	0.42	0.24	0.04	0.30	0.14	N/A	0.26	0.20	N/A	0.31	N/A
	P	0.05	0.27	0.87	0.19	0.56	N/A	0.23	0.35	N/A	0.15	N/A
GNG D4	R	-0.16	-0.23	0.05	0.17	-0.23	N/A	0.71	0.45	N/A	-0.37	N/A
	P	0.50	0.34	0.86	0.49	0.36	N/A	0.00	0.05	N/A	0.11	N/A
EGP D10	R	0.10	-0.47	-0.15	0.85	0.53	0.55	N/A	N/A	0.12	N/A	-0.17
	P	0.66	0.05	0.58	0.00	0.03	0.03	N/A	N/A	0.67	N/A	0.52
GNG D10	R	-0.15	0.08	0.59	0.54	-0.04	0.27	N/A	N/A	-0.49	N/A	-0.42
	P	0.54	0.78	0.04	0.03	0.89	0.27	N/A	N/A	0.05	N/A	0.11

Table 5

Multivariate analysis results; EGP at day 10 and GNG at day 4 could not be predicted with an error <40%. The multiple regression that are shown are those where the minimal and maximal errors are smallest.

Output	Used samples	Minimal error	Maximal error	Uncertainty	Used input
EGP (mg/kg/mn) D4	15	7.8	23.4	5	VCO ₂ mL/mn/kg Glucose g/24 h Energy kcal/24 h
EGP (mg/kg/mn) D4	14	9.6	22.1	5	VCO ₂ mL/mn/kg Glucose G/24 h/kg113W Energy kca1/24 h/kg1BW Methylprednisone mg/kg/24 h
GNG (mg/kg/mn) D4	20	35.8	45.2	5	Mean blood glucose mmol/L Basal blood glucose mmol/L Age
EGP (mg/kg/mn) D10	15	45.2	49.1	5	VO ₂ mL/mn/kg 010-04 Age
GNG (mg/kg/mn) D10	10	18.5	29.9	5	Leukocytes count G/1 VO ₂ mi/kg/mn
GNG (mg/kg/mn) D10	13	28.8	37.2	5	Energy balance 010-04 VO ₂ mi/kg/mn Energy/24 h/kg 18 W

Abbreviations. IBW = Ideal body weight. Used sample = number of patients with complete data. Uncertainty refers to the mean of uncertainty in input variables (see method).

typical enteral feeding challenges. The specificity was that, by study design, due to the use of indirect calorimetry overfeeding was avoided in SPN patients while some degree of underfeeding was present in those on pure EN. The cohort is therefore representative of most ICU patients during the first 10 days after ICU admission. Overfeeding has been shown to occur later in the stay [28]. Fig. 1 shows that some degree of overfeeding occurred on Day 4 due to an elevated EGP and GNG.

Because glucose metabolism is cornerstone to survival, our study focused on glucose and not on proteins or lipids. A constant glucose supply to the brain and other glucose-requiring tissues is dependent on an endogenous glucose production, which is the sum of two biochemical processes, i.e. glycogenolysis and GNG, the latter occurring in the liver, the kidney, and the gut. Blood glucose is often described as the balance between its hepatic production on one hand, and its extra-hepatic use through oxidation and lactate production on the other hand. The real situation is far more complex, since glucose production is autoregulated; a lactate perfusion can stimulate GNG, without raising net glucose production. This is done through an increased glycogen synthesis and a decreased glycogenolysis. In fact, GNG and glycogenolysis determine the hepatic glucose-6-P pool, while the net glucose production is being regulated at the glucokinase/glucose-6-phosphatase cycle. In this regard, glucokinase activity is mainly dependent on (portal) blood glucose level, maintaining it in a relatively narrow range, while glucose-6-phosphatase is regulated by glucagon and other inflammatory mediators. Therefore, the liver plays a central role in blood glucose control by regulating glucose production and glucose/insulin dependent extrahepatic glucose disposal.

The EGP is higher than normal at both days 4 and 10 due to its impaired suppression [24,25]. At day 4, EGP is fueled by both glycogenolysis and gluconeogenesis, with a major contribution of the latter. At day 10, EGP and GNG estimates are similar, indicating that EGP is entirely fueled by GNG. This also implies that GNG is the component of EGP which is abnormal/insulin resistant in these patients.

4.1. Single-stage analysis

Most of the clinically available single indicators are non-contributory as predictors. The single-stage analysis shows that EGP is dependent on VO₂ and VCO₂, i.e. on energy metabolism, while GNG is dependent on pharmacological agents. The EGP at day

4 is correlated to the NRS ($R = 0.42$, $P < 0.05$), which is consistent with the fact that nutritional screening catches a metabolic risk [7,29]. The NRS score has been shown to be associated with poor outcome when values are >5 points [30]. In the present patients, high NRS is correlated to a raised EGP at day 4, indicating a greater deregulation of homeostatic mechanisms. This correlation does not persist at day 10. Regarding GNG, at day 4, it is strongly correlated to the total dose of noradrenaline of the last 24 h ($R = 0.70$, $P < 0.01$), while the cumulated dose of the 4 previous days matters less ($R = 0.45$, $P < 0.05$).

In addition to having different predictors, EGP and GNG determinants seem to be submitted to a time effect: the associated variables are not the same on Day 4 and day 10.

At day 10, EGP is correlated to VCO₂ ($R = 0.85$, $P < 0.001$), respiratory quotient ($R = 0.53$, $P = 0.03$), and doses of insulin perfused on the last four days ($R = 0.55$, $P < 0.03$). GNG at day 10 also correlates with VO₂ ($R = 0.59$, $P < 0.04$) and VCO₂ ($R = 0.54$, $P < 0.03$), and negatively with doses of norepinephrin and methylprednisolone delivered the same day. In other words, the higher the dose, the lower the GNG.

Critical illness is a stress condition characterized by elevated cortisol values, which it contributes to dysregulation of glucose metabolism [31]. Measured cortisol concentrations presented a wide dispersion on both days, and no correlation with EGP or GNG could be found. One possible explanation is that the hypercortisolemia associated to critical illness is not due to stress-induced activation, but rather to a reduced cortisol metabolism with a diminution of its breakdown, as Boonen and al showed [31]. Consequently, cortisol value cannot be correlated linearly with stress.

In summary, the determinants of GNG and EGP are different; EGP is more related values retrieved by indirect calorimetry i.e. to the metabolic level. GNG seems rather correlated by external factors, like medication (noradrenalin, methylprednisolone).

4.2. Multivariate analysis

Multivariate analysis shows that, with a very limited number of subjects, a model based on routinely available clinical variables can predict GNG, with little sensitivity, however. This is nonetheless quite promising since the prediction of GNG may allow prediction of endogenous energy input, and thus improve prescription of exogenous energy intake.

This approach is purely practical and does not provide useful information of pathophysiological factors. For instance, the fact that EGP on day 10 is correlated with insulin does not mean that insulin is involved in the stimulation of EGP, but instead that high insulin doses identify a subset of patients with dysregulated glucose homeostasis and that such patients are likely to have, through a variety of mechanisms (stress, inflammation, hemodynamic disturbances) a stimulation of EGP.

These predictors may nonetheless be useful in clinical practice, since the objective is not to accurately assess EGP or GNG magnitude nor the pathogenic factors leading to their dysregulation, but merely grossly assessing the degree of impairment of EGP and GNG suppression which should be taken into consideration for nutritional supplies.

4.3. Limitations and strengths

The low number of patients is a limitation but is compensated for by the high quality of the metabolic data. Limitation comes from the statistical manipulation of the data and their extrapolations, and the high number of data used. Due to the limited number of patients we could not make a separate analysis of the predictors of EGP between the patients fed enterally or with SPN on Day 10. Further, data mining exposes to false positive results, depending on the power of the model. To avoid this bias, we worked with 22 patients to test the model on the remaining 23rd patient. With this method, we had a prediction reliability between 92.2 and 76.63% for EGP at day 4 (Table 4). Although promising, it requires testing in higher numbers of patients. The prediction was less reliable at day 10, also because the input variables were fewer, some of the patients being already discharged from the ICU.

A weakness is an inversion in the relationship between norepinephrine and EGP/GNG; the correlation between GNG and norepinephrine is first positive on Day 4 ($R = 0.71$; $P = 0.0004$). The correlation thereafter becomes negative on Day 10 ($R = -0.49$; $P = 0.05$). Explanations include a lower number of patients on norepinephrine on day 10 ($n = 21$ patients on day 4 versus $n = 5$ on day 10). In addition, the doses were inferior on day 10. It might also be a statistical coincidence, the correlation being less powerful on day 10.

The originality of the study stands in the use of multivariate analysis based on clinically available data. But not all available input variables could be used in the mathematical model: the correlation coefficient calculation requires a real number, so gender cannot be used in this method. The other constraint is that the mean value cannot be zero (see equation). For this reason, dobutamine at day 10 could not be used for the calculations, being rarely required at this stage.

5. Conclusion

The present exploratory multivariate model showed a statistically significant relationship between a set of clinical variables and EGP: although prediction is not highly sensitive at this stage, we propose that the present model be tested in future studies. The bundle of variables differed on days 4 and 10. No simple predictor could be identified. A larger study is needed to further develop the prediction model and assess its practical implications in terms of individual energy needs.

This initial exploratory study indicates that GNG is the abnormal component of EGP. In the future, the search for EGP predictors could focus on fewer variables (VO_2 , VCO_2 , noradrenalin, insulin and NRS score). The design of such a study may be greatly simplified by measuring only EGP on day 10 at relatively low cost.

Author contribution

IU, LT and MMB conceived the study; IU, MH and MMB extracted the data; MH and MMB did the statistical outwork; IU and MMB generated the figures; IU, LT, AS and MMB generated the first draft of the manuscript; all contributed to critically develop it.

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Conflicts of interest

The authors have no conflict of interest to declare related to the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cnu.2021.05.016>.

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