Surgical Metabolism

The Metabolic Care of the Surgical Patient

Kimberly A. Davis
Stanley H. Rosenbaum
Editors

Second Edition

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Preface

We are delighted to have produced the second edition of our text on surgical metabolism. We continue with our belief, as stated in the first edition, that specialists in the treatment of modern surgical disease must also have a strong understanding of normal metabolism and perturbations induced by surgical interventions.

Our approach is not to follow a traditional systems or organ-based approach but rather to encourage our readers to think of the patients as complex biochemical systems. We intend this work to provide information that supplements the more traditional approaches and provides a detailed overview of the metabolic knowledge needed for surgical practice.

We recognize that the biochemical aspects of modern medicine are advancing so rapidly that it is difficult to keep up even with the best efforts. In this book, some chapters have been updated, and several new chapters have been added. We hope this will help our readers keep pace in this race for state-of-the-art knowledge.

We continue to acknowledge the long-ago trailblazing work of Dr. Francis Moore that represented the birth of the field of surgical metabolism. We also thank our many mentors. Our deep gratitude also goes out to the many contributors whose efforts made this volume possible. We also wish to thank the support we received from our academic chairs at Yale School of Medicine, Dr. Nita Ahuja of the Department of Surgery and Dr. Roberta Hines of the Department of Anesthesiology. Once again, this work could not have been produced without the fine efforts of Ms. Elise Paxson and the rest of the Springer publishing team.

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Abbreviations

A

AACE	American Association of Clinical Endocrinologists
ABW	Adjusted body weight
$AcAc^-$	Acetoacetate
ACEI	Angiotensin-converting enzyme inhibitor
ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
ACTS	Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis Trial
ADA	American Diabetes Association
ADH	Antidiuretic hormone
ADL	Activities of daily living
ADP	Adenosine diphosphate
AKI	Acute kidney injury
AKIN	Acute kidney injury network
AG	Anion gap
AGc	Anion gap corrected
AGI	Acute gastrointestinal injury
AgRP	Agouti-related protein
ALI	Acute lung injury
AMPK	Adenosine monophosphate-activated protein kinase
ANP	Atrial natriuretic peptide
ANS	Autonomic nervous system
AQP	Aquaporin
ARDS	Acute respiratory distress syndrome
ASPEN	American Society for Parenteral and Enteral Nutrition
ATP	Adenosine triphosphate
AUC	Area under the curve

B

β-OHB	β-Hydroxybutyrate
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene

BMI	Body mass index
BMR	Basal metabolic rate
BUN	Blood urea nitrogen

C

cAMP	Cyclic AMP
CARS	Compensatory anti-inflammatory response syndrome
CBG	Cortisol-binding globulin
CCCPG	Canadian Critical Care Practice Guidelines
CCI	Chronic Critical Illness
CCK	Cholecystokinin
CD	Crohn's disease
C/EBP-β	CCAAT-enhancer-binding protein-β
CETP	Cholesteryl ester transfer protein
CGM	Continuous glucose monitoring
CI	Confidence interval
CIF	Chronic intestinal failure
CIP	Critical illness polyneuropathy (CIP)
CLOCK	Circadian locomotor output cycles kaput
CNS	Central nervous system
CoA	Coenzyme A
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase 2
CPAP	Continuous positive airway pressure
CREB	cAMP-responsive element binding protein
CREB/CRTC2	cAMP-responsive element-binding protein-regulated transcriptional coactivator-2
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CPT2	Carnitine palmitoyltransferase 2
CRTC2	CREB-regulated transcription coactivator 2
CRRT	Continuous renal replacement therapy
CT	Computed tomography
CyTOF	Cytometry by time-of-flight

D

DAMP	Damage-associated molecular pattern
DHA	Docosahexaenoic acid
DIC	Disseminated intravascular coagulation
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DS	Degree of substitution
DXA	X-ray absorptiometry

E

ECF	Extracellular fluid or Enterocutaneous fistula
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
EEG	Electroencephalogram
EEN	Early enteral nutrition
EMA	European Medicines Agency
EMPD	Electromagnetically guided placement devices
EN	Enteral nutrition
EPA	Eicosapentaenoic acid
ERAS	Enhanced recovery after surgery
ESPEN	European Society for Clinical Nutrition and Metabolism
ESRD	End-stage renal disease

F

FABP	Fatty acid-binding protein
FAO	Food and Agriculture Organization of the United Nations or Fatty acid oxidation
FATPs	Fatty acid transport proteins
FDA	US Food and Drug Administration
FFA	Free fatty acid
FFAR3	Free fatty acid receptor 3
FFM	Fat-free mass
FGF	Fibroblast growth factor
FHH	Familial hypocalciuric hypercalcemia
FM	Fat mass
FOS	Fructooligosaccharides
FOXO1	Forkhead box protein 1

G

GALT	Gut-associated lymphoid tissue
GCS	Glasgow Coma Scale
GDE	Glycogen-debranching enzyme
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GI	Gastrointestinal
GIF	Gastrointestinal failure
GIP	Glucose-dependent insulinotropic polypeptide
GIT	Gastrointestinal tract
GLIM	Global Leadership Initiative on Malnutrition
GLP	Glucagon-like peptide
GnRH	Gonadotropin-releasing hormone

GP	Glycogen phosphorylase
GRV	Gastric residual volumes
GOS	Galactooligosaccharides
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation

H

H2RA	H2-receptor antagonist
HCAR2	Hydroxycarboxylic acid receptor-2
HCMA	Hyperchloremic metabolic acidosis
HDACs	Histone deacetylases
HDL	High-density lipoprotein
HEI	Healthy Eating Index
HES	Hydroxyethyl starch
HHS	Hyperosmolar hyperglycemic state
HF	Heart failure
HMGB1	High-mobility group box1
HPN	Home parenteral nutrition
HRV	Heart rate variability
HSL	Hormone-sensitive lipase
HSP	Heat shock proteins
HTS	Hypertonic saline

I

IABT	Intra-aortic balloon pump
IAH	Intra-abdominal hypertension
IBW	Ideal body weight
IC	Indirect calorimetry
ICAM	Intracellular adhesion molecule
IEF	Immune-enhancing formula
IL	Interleukin
IADL	Instrumental activities of daily living
ICF	Intracellular fluid
ICM	Ischemic cardiomyopathy
ICU	Intensive care unit
I-FABP	Intestinal fatty acid-binding protein
I-FALD	Intestinal failure-associated liver disease
IGF	Insulin growth factor
iNOS	Inducible NO synthase
IP	Inducible protein
IV	Intravenous(ly)

K

KIM-1	Kidney injury molecule-1
KLF	Kruppel-like factor

L

L-FABP	Liver-type fatty acid-binding protein
LAMP-2	Lysosome-associated membrane protein 2
LCT	Long-chain triglycerides
LDL	Low-density lipoprotein
LE	Lipid emulsions
LH	Luteinizing hormone
LIS	Lung Injury Score
LMF	Lipid-mobilizing factor
LODS	Logistic organ dysfunction system
LPS	Lipopolysaccharide
LR	Lactated Ringer's
LRS	Lactated Ringer's solution
LV	Left ventricular

M

MACE	Major adverse cardiac events
MALT	Mucosa-associated lymphoid tissue
MAP	Mean arterial pressure
MAS	Magic-angle spinning
MAS-NMR	Magic-angle spinning NMR spectroscopy
MCP-1	Monocyte chemotactic peptide
MCT	Medium chain triglycerides
MDSC	Myeloid-derived suppressor cell
MI	Myocardial infarction
MIF	Macrophage migration inhibitory factor
MIP	Macrophage inflammatory protein
MNA-FF	Mini-Nutritional Assessment-Full Form
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
MS	Mass spectrometry
α-MSH	α-Melanocyte-stimulating hormone
MRI	Magnetic resonance imaging
MSR	Macrophage scavenger receptor
MST	Malnutrition Screening Tool
mTORC1	Mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1
MUST	Malnutrition Universal Screening Tool

N

NADH/NAD	Nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide (NADH/NAD)
NAG	N-Acetyl-β-D-Glucosaminidase
NF-κB	Nuclear factor kappa B
NGT	Nasogastric tube
NICM	Nonischemic cardiomyopathy
NMR	Nuclear magnetic resonance
NOAC	Novel oral anticoagulant
NO	Nitric oxide
NOS	Nitric oxide synthase
NRS	Nutritional risk screening
Nrf2	Nuclear factor erythroid 2-related factor 2
NSS	Normal saline solution
NUFFE	Nutritional Form for the Elderly
NUTRIC	Nutrition Risk in Critically ill

O

$O2^-$	Superoxide
OKG	Ornithine alpha ketoglutarate
OR	Odds ratio

P

PAF	Platelet-activating factor
PAI	Plasminogen activator inhibitor
PAMP	Pathogen-associated molecular pattern
PCM	Protein-calorie malnutrition
PEM	Protein-energy malnutrition
PICC	Peripherally inserted central catheter
PDH	Pyruvate dehydrogenase
PDK-4	Pyruvate dehydrogenase kinase isozyme 4
PEEP	Positive end-expiratory pressure
PEG	Percutaneous endoscopic gastrostomy
PI3K	Phosphoinositide 3-kinase
PG	Prostaglandin
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1 α
PG-SGA	Patient-Generated Subjective Global Assessment
PICS	Persistent inflammation and immunosuppression
PIF	Proteolysis-inducing factor
PPAR-α	Peroxisome proliferator-activated receptor alpha
PPI	Proton-pump inhibitor

Posm	Plasma osmolality
PN	Parenteral nutrition
PRR	Pattern recognition receptors
PUFA	Polyunsaturated fatty acids
PROPATRIA study	Probiotics in Pancreatitis Trial
PTH	Parathyroid hormone

Q

QoL	Quality of life

R

RAGE	Receptor for Advanced Glycation End Products
RBC	Red blood cell
RBP	Retinol-binding protein
RCT	Randomized controlled trial
RDA	Recommended daily allowance
REDOXS	REducing Deaths due to OXidative Stress trial
RE-ENERGIZE	RandomizEd Trial of ENtERal Glutamine to miniZE thermal Injury trial
REE	Resting energy expenditures
RIFLE	Risk injury failure end-stage renal disease
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RR	Risk ratio
RTA	Renal tubular acidosis

S

SAE	Sepsis-associated encephalopathy
SAFE	Saline versus Albumin Fluid Evaluation
SBE	Standard base excess
SBFT	Small bowel follow through
SBS	Short bowel syndrome
SCCM	Society of Critical Care Medicine
SCFA	Short-chain fatty acid
SCREEN-II	Seniors in the Community: Risk Evaluation for Eating and Nutrition Questionnaire
SGA	Subjective Global Assessment
SHBG	Sex hormone-binding globulin
SIADH	Syndrome of inappropriate antidiuretic hormone
SID	Strong ion difference
SIG	Strong ion gap

SIGN	Scottish Intercollegiate Guidelines Network
sIL-6R	Soluble IL-6 receptor
SILT	Spiral intestinal lengthening and tailoring
SIRS	Systemic inflammatory response syndrome
SIRT3	Silent mating-type information regulator number 3
SNAQ-RC	Short Nutritional Assessment Questionnaire-Residential Care
SNP	Single-nucleotide polymorphisms
SOD	Superoxide dismutase
SOFA	Sequential Organ Failure Assessment
SPN	Supplemental parenteral nutrition
STEP	Serial transverse enteroplasty
sTNF-R	Soluble TNF receptor

T

TAVR	Transcatheter aortic valve replacement
TBG	Thyroid-binding globulin
TBI	Traumatic brain injury
TBSA	Total body surface area
TBW	Total body weight OR total body water
TLC	Total lymphocyte count
TLR4	Toll-like receptor 4
TMAO	Trimethylamine N-oxide
TNF	Tumor necrosis factor
t-PA	Tissue plasminogen activator
TREM-1	Triggering Receptor Expressed on Myeloid Cells
TRH	Thyrotropin-releasing hormone
tRNA	Transfer RNA
TSH	Thyroid-stimulating hormone

U

UC	Ulcerative colitis
UCP	Uncoupling protein
UGI	Upper gastrointestinal
uHGF	Urinary hepatocyte growth factor
ULK1	Unc-51 like autophagy activating kinase-1
uNGAL	Neutrophil gelatinase-associated lipocalin
UPS	Ubiquitin-proteasome system

V

VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor

VIP Vasoactive intestinal polypeptide
VLDL Very low-density lipoprotein

W

WHO World Health Organization
WMD Weighted mean difference

Part I

Normal Metabolism

Introduction to Metabolism

1

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Introduction

Metabolism is the combination of reactions and processes necessary to sustain life [1]. These reactions and processes occur within different levels of the living organism. The production and consumption of energy at the cellular level is the basis of life. Maintaining equilibrium between the production and consumption of energy is paramount to survival, and mismatches lead to infection, illness, disability, organ dysfunction, and death. Most metabolic derangements are the result of a disease process, although some can be inborn. Understanding metabolism at the cellular level has helped the scientific community develop methods of maintaining homeostasis and in turn has provided clinicians with therapies to treat patients with disease processes and optimize outcomes.

History of Metabolism

The word *metabolism* is derived from the root "meta" meaning "change" and "ballein" meaning "to throw [2]." From individual metabolic reactions at the cellular level to the metabolic responses of the organism, the scientific community has been studying metabolism for centuries. Santorio Sanctorius is considered the "founding father of metabolic balance studies" in the seventeenth century [3]. He explored insensible loss through perspiration. He documented his weight before and after specific activities in his book *Ars de Statica Medicina* in 1614. Friedrich Wohler published one of the first articles on metabolic pathways, specifically the synthesis of urea in 1828. The discovery of enzymes by Eduard Buchner in the twentieth century preceded the rapid acceleration of biochemical discovery. Landmark discoveries in metabolism include the citric acid cycle, urea cycle, and glyoxylate cycle.

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The understanding of energy metabolism started with Antoine Lavoisier. He focused on heat exchange and developed the first direct calorimeter in the nineteenth century. Subsequently the law of conservation of energy was developed. He discovered that he could directly measure the energy expenditure of an organism by calculating heat dissipation. He demonstrated that "respiration is a slow form of combustion [4]." The development of indirect calorimetry led to a more practical method to obtain the information for resting energy expenditure indirectly from measured oxygen consumption. Liebig, Voit, and Max Rubner were major players in discovering the link between oxygen consumption and metabolism and calculating caloric value of specific energy sources [4]. Modern studies of metabolism involve biotechnology techniques and genomics. Chromatography, X-ray diffraction, nuclear magnetic resonance (NMR) spectroscopy, radioisotope labeling, electron microscopy, and molecular dynamic simulation are all techniques currently used to evaluate metabolic pathways and explore the genetic basis of metabolic disorders.

The Hierarchy of Metabolism

The Mitochondrial Level

Mitochondria are complex double-membrane-bound organelles that play the leading role in cellular metabolism. They are the main energy source in almost all eukaryotes. Mitochondria are composed of five components with unique functions: an outer membrane, intermembrane space, inner membrane, cristae, and matrix space. The outer membrane contains enzymes, which lengthen fatty acids and participates in oxidation and degradation. It also associates with the endoplasmic reticulum membrane where calcium signaling facilitates the transfer of lipids. It contains porins, which make it highly permeable to all molecules. The intermembrane space contains a different protein composition than cytosol. For example, cytochrome C is in the intermembrane space. The inner membrane has five functions: oxidative phosphorylation, generation of adenosine triphosphate (ATP), regulation of metabolite transportation, protein import, and mitochondrial protein modification. The inner membrane has a high protein to phospholipid ratio, and almost all ions and molecules require transporters to cross over the matrix. The electron transport chain sets up a membrane potential across the inner membrane. Cristae are made of abundant inner mitochondrial membranes. This increases the surface area to produce more ATP. Cells that have more demand for ATP, i.e., muscle cells, contain a higher ratio of inner membrane/outer membrane, more cristae, and more mitochondria. The matrix contains most of the protein in the mitochondria. Enzymes, ribosomes, transfer RNA (tRNA), and copies of the mitochondrial DNA genome are within the matrix. Metabolic processes, such as oxidation of pyruvate and fatty acids and citric acid cycle, all take place in the matrix. Damage or dysfunction of mitochondria presents as a neurological or endocrine disorder [5]. Examples include Friedrich's ataxia, Alzheimer's disease, diabetes mellitus, autism, etc.

The Cellular Level

Cellular metabolism is a combination of chemical reactions that occurs to maintain life. Cellular metabolism is divided into two types: anabolism and catabolism. Anabolism is "building" and catabolism is "breaking down." The balance between anabolism and catabolism creates homeostasis. Depending on the needs and stress of the body at the time, it can be in an anabolic or catabolic state. It involves a complex sequence of controlled biochemical reactions creating metabolic pathways. One chemical is transformed into another through the actions of an enzyme. Enzyme regulates pathways in response to changes in the cellular environment. The needs of the cell dictate the flow of biochemical reactions. Glycolysis is an example of a chemical reaction where a substrate is converted into a product through ten steps. In the last step of glycolysis, phosphoenolpyruvate, the substrate, is converted into ATP and pyruvate, the products, by an enzyme called pyruvate kinase. The enzyme acts by transferring a phosphate group from one sub-

strate to another, i.e., adenosine diphosphate (ADP). Temperature, pH, availability of substrates, and cofactors modify the functionality of an enzyme [6]. This is the mechanism behind why patients with physiologic stress develop metabolic derangements.

The Organ Level

Each organ has its own unique metabolic profile [7]. In this section, the metabolic profile of each organ is reviewed. The brain utilizes glucose as its main energy source unless the body enters the later stage of starvation. The brain relies on a continuous source of glucose. In the resting state, the brain uses up to 60% of the total body glucose. The majority of this is used to power the Na^+-K^+ membrane potential and synthesize neurotransmitter synapses to propagate nerve impulses [7].

Very little is known about the role of the lung in metabolism. De novo fatty acid synthesis takes place in the lung as well as several other reactions mainly involving lipid esterification and the synthesis of phosphatidylcholine and prostaglandins. These components of surfactant are made at the gestational age of 24 weeks but not functional until week 34–36 [8]. Surfactant decreases the surface tension of the alveoli.

The liver is the main organ that provides fuel for peripheral organs including the brain and muscle. It is the main center for metabolism and controls the metabolite level in the blood [7]. Sixty-seven percent of carbohydrates are absorbed by the liver. The remaining glucose is absorbed by other tissues. A process called glycogenesis occurs. Glucose is converted into glucose-6-phosphate by hexokinase and glucokinase; then it is converted into glycogen. Glycogen is stored in the liver for later use when blood glucose levels decrease. Glycogen is broken down into glucose through gluconeogenesis in the liver, which then is released into the blood. If the body enters late starvation stage, lactate and alanine from muscle, adipose tissue, and exogenous amino acids become the main precursors for gluconeogenesis [7].

Lipids are also metabolized in the liver. Most fatty acids are absorbed by the liver. In a plentiful state, fatty acids are esterified and secreted into the blood in very low-density lipoprotein (VLDL), but in times of starvation, the liver converts fatty acids into ketone bodies [7].

Amino acid metabolism occurs in the liver as well. Amino acids are the main source for protein synthesis and anabolism. Alanine and aspartate aminotransferases (ALT and AST) are released in the blood stream and indicate liver damage. Catabolism of amino acids results in nitrogen products which are processed into urea. 20–30 g/day of urea is secreted from the liver. This process removes ammonia, a toxin to the central nervous system. Alpha-keto acids derived from amino acid catabolism fuel the liver [7]. The liver also synthesizes nonessential amino acids and most plasma proteins, including albumin and clotting factors within the coagulation cascade.

The kidney's purpose is to excrete metabolic waste products, which helps maintain the osmolarity of blood. Most substances, especially water and water-soluble constituents, are reabsorbed. A lot of energy is consumed for the process of reabsorption. The kidneys consume 10% of the oxygen used in cellular respiration. Glucose is carried into renal cells via sodium-glucose cotransporter. This transporter is driven by the sodium and potassium gradient powered by Na^+-K^+ ATPase. The kidney is an important site for gluconeogenesis when the body is in a state of starvation [7].

Muscle uses glucose, fatty acids, and ketone bodies as major fuel sources. Muscle has vast storage of glycogen. 75% of glycogen stores are in muscle cells. Muscle lacks glucose-6-phosphatase just like the brain, so glycogen is converted to G-6-P and retains the glucose for fuel. When muscle is contracting, the rate of glycolysis exceeds the rate of the citric acid cycle. The burden of metabolism is shared between muscle and the liver through the Cori cycle. Pyruvate is reduced to lactate, which can flow to the liver to be converted into glucose. Alanine is formed in muscle by the transamination of pyruvate. Muscle can absorb and transaminate branched-chain amino acids but cannot form urea. The nitrogen is released into the blood stream as alanine, and then the liver can remove the nitrogen and dispose it in the form of urea. Pyruvate then is converted into glucose or fatty

acid. Resting muscle acts completely different and uses fatty acid as the main fuel source [7].

Metabolic States at the Organism Level

The body can exist in different states of metabolism. The absorptive state is considered the "fed state." It represents the time when the body is digesting and absorbing nutrients. In this state, anabolism exceeds catabolism. Digestion automatically begins with mastication. Carbohydrate breakdown first starts in the mouth while protein and lipid breakdown begins in the stomach. Exogenous glucose and amino acids are transported from the intestine to the blood. Lipids are packaged into chylomicrons and transported to blood via the lymphatic system. The body is preparing to store for leaner times.

Insulin, one of the most important hormonal regulators of metabolism, is secreted by beta cells of the pancreas. Glucose and the parasympathetic nervous system stimulate the secretion of insulin. Insulin initiates protein kinase pathways stimulating glycogen synthesis in muscle and liver. It also suppresses gluconeogenesis in the liver. Glycolysis in the liver is enhanced increasing the synthesis of fatty acids. The absorptive state promotes glucose entering muscle and adipose tissue. Insulin stimulates the synthesis of glycogen by muscle and the liver. Glucose entering adipose tissue provides glycerol 3-phosphate for the creation of triacylglycerols. Insulin promotes the uptake of branched-chain amino acids by muscle (BCAA). BCAA are valine, leucine, and isoleucine. Insulin favors the building of muscle protein and inhibits degradation of proteins. The absorptive state can take up to 4 hours [7].

The postabsorptive state, also known as the fasting state, occurs after nutrition has been digested, absorbed, and stored. In the postabsorptive state, the body relies on glycogen initially. The fasting state is usually broken up into early and late. The early fasting state is when blood glucose levels begin to decrease. Reflexively, insulin levels decrease, and glucagon levels increase. Glucagon is secreted by alpha cells of the pancreas. Glucagon is the signal for the starvation state. Glycogen storage is mobilized when exogenous glucose is not present. Glucagon triggers glycogen breakdown mainly in the liver. Glycogen is rapidly mobilized. Large amounts of glucose are released from the liver into the blood through the hydrolysis of glucose 6-phosphate. Secondary to demands by peripheral tissues, blood glucose levels are maintained between 70 and 120 mg/dL.

When the body is deprived of nutrition for an extended period, it goes into a "survival mode." This is known as the late fasting stage or preabsorptive stage. Certain organs take priority, such as the brain. Ketones are used as the primary energy source. Fatty acid and triglyceride stores are used to make ketones as starvation continues. Ultimately, during late fasting state, protein from muscle is utilized for glucose synthesis. Low insulin levels trigger the decline of glucose entering muscle and adipose tissue. The overall result from glucagon is the markedly increased release of glucose from the liver's glycogen stores. The muscle and liver use fatty acids as fuel when blood glucose is low. Euglycemia is maintained by the mobilization of glycogen and release of glucose by the liver, the release of fatty acids by adipose tissue, and the shift of the primary fuel source from glucose to fatty acids by muscle and the liver.

When the liver's glycogen stores become depleted, gluconeogenesis continues, but this only replaces the glucose that has been converted to lactate and alanine to serve as a precursor for gluconeogenesis. With the brain oxidizing glucose into carbon dioxide and water, a source of carbon is in demand. This source shifts to glycerol from adipose tissue undergoing lipolysis and hydrolysis of muscle protein.

The third state is refeeding. When transitioning from pre-absorptive (late starvation) to absorptive state, fat is processed the same as if in normal metabolic state. When refed, the liver does not initially take up glucose. It is left for the peripheral tissues. The liver remains in a gluconeogenic mode. Newly created glucose is used to reform glycogen storage. As blood glucose levels rise, the liver replaces its glycogen storage and then processes excess glucose for fatty acid synthesis.

Energy Requirements

The total energy expenditure (TEE) is composed of resting energy expenditure (REE) or basal energy expenditure (BEE), the thermogenesis, and the energy expenditure from activity. REE represents the number of calories required for a 24-hour period by the body in a non-active state. The patient's basic metabolic rate (BMR) accounts for 60–70% of the total energy expenditure [1]. The BMR measurement is based on body weight, size, composition, gender, age, race, etc. Thermogenesis accounts for heat loss, diet portion, composition, and timing of ingestion. This accounts for approximately 10% of TEE [1]. Activity accounts for the remaining energy expenditure. The energy cost of activity is the most variable and can range anywhere between 5% and 30% of TEE in a healthy individual. In the critically ill patient, the energy of activity is minimal, but multiplication factors are included to account for physiologic stress.

Normal Energy Requirements

Normal metabolism supports all the physiologic processes necessary for an organism's survival – energy for respiration, digestion, cellular repair, normal supply of building blocks, and enzymatic synthesis. It is driven by insulin. In general, most energy comes from carbohydrates, but lipids and proteins also can be consumed as fuel. One also usually thinks of building blocks as protein, but lipids and carbohydrates also form integral components of growth, repair, and respiration. To simplify, the energy required for normal metabolism is approximately 20–25 kcal/kg for ideal body weight. For the individual patient, there are predictive equations with proven validity.

Abnormal Energy Requirements

In the highly metabolically stressed individual (i.e., burns), the energy expenditure can be double that of normal REE, driven by catecholamines and other acute phase hormones and mediators. This then makes REE about 35–40 kcal in these patients. In such patients measuring energy is best.

The Measurement of Energy Requirements

Direct Calorimetry

Direct calorimetry measures the heat exchange between the body and the environment. Heat is the direct by-product of energy utilization. If practical, direct calorimetry would be the gold standard. A direct calorimeter is a chamber or structure that encompasses the subject. The chamber is closed and has a double wall surrounded by ice. By monitoring the ice melting, the amount of heat dissipation could be measured. This methodology is not practical in the clinical environment.

Indirect Calorimetry

Because a direct calorimeter is not practical in the clinical environment, indirect calorimetry is considered more the "gold standard." Indirect calorimetry (IC) is the most accurate method of measuring energy expenditure in the critically ill population. The measurement of IC is performed using a metabolic cart, which can determine a patient's REE. The metabolic cart measures expired gas to determine the volume of air in the lungs. The amounts of oxygen and carbon dioxide are measured (VO_2 and VCO_2) in 1-minute intervals. REE and respiratory quotient (RQ) can be indirectly determined by these measurements. The RQ is the ratio of exhaled carbon dioxide to the amount of consumed oxygen. The abbreviated Weir equation is used to calculate the 24-hour REE (Table 1.1). The RQ helps guide the amount and composition of energy delivery. An RQ <0.8 signifies lipid catabolism which may be an indicator of underfeeding or of inappropriate administrations of fat. Increasing caloric intake, often with increased carbohydrates, should improve the RQ. An RQ >1 indicates high carbon administration from carbohydrate overfeeding. This can affect the respiratory drive due to hypercarbia. Normalizing RQ and avoiding carbohydrate overfeeding can aid in the weaning of ventilation [1].

IC is helpful in patients with chronic respiratory failure, acute respiratory distress syndrome, and obesity because equations that calculate REE

Table 1.1 Equations and formulas

Weir equation	REE = [3.9 (VO_2) + 1.1 (VCO_2)] 1.44 VO_2 = oxygen uptake (ml/min) VCO_2 = carbon dioxide output (ml/min)
Respiratory quotient	RQ = VCO_2/VO_2
Harris-Benedict equations (calories/day)	Male: (66.5 + 13.8 × weight) + (5.0 × height) − (6.8 × age) Female: (665.1 + 9.6 × weight) + (1.8 × height) − (4.7 × age)
WHO	r^2 = 0.53, F = 37.8, P <0.001. Men: REE (kcal/day) = 66.5 + 13.75 (*weight*) + 5.0 (*height*) − 6.76 (age) REE (kJ) = 278 + 57.5 (*weight*) + 7.74 (*height*) − 19.56 (age)
Ireton-Jones (spontaneously breathing)	EE = 629-11 (age) + 25 (actual body weight) − 609 (BMI >27 factor = 1)
Ireton-Jones (ventilated)	EE = 1784-11 (age) + 5(actual body weight) + 244 (factor = 1 for males) + 239 (Diagnosis of trauma = 1) + 804 (BMI >27 factor = 1)
Penn State	REE = Harris-Benedict equation (0.85) + minute ventilation (33) + maximum body temperature within 24-hour period (175)-6433

are not as accurate in these patient populations. IC can help determine whether a patient is being over- or underfed and can also help troubleshoot if inadequate calorie delivery is the cause of delayed wound healing. Several factors can alter the accuracy of indirect calorimeter results. Ventilator settings need to remain constant during the performance of the test, as almost any change made during the testing session will affect results. FiO_2 >60%, positive end-expiratory pressure (PEEP) >12 cm H_2O, thoracostomy tube leaks, any movement, bedside nursing care, and changing nutrition are all examples of factors that can alter results of the REE from indirect calorimetry.

Equations to Calculate REE

There are approximately 200 equations published that calculate REE [1]. Some deal with specific disease states, ages, ethnicities, obesity, etc. One of the most commonly used equations is the Harris-Benedict equation. This equation was developed in 1919 by using indirect calorimetry to estimate REE. It accounts for age, gender, height, and weight. The accuracy of the Harris-Benedict equation has been validated in the healthy, adequately nourished person to be within +14% of REE measured by indirect calorimetry. The Harris-Benedict equation tends to underestimate REE in malnourished, critically ill patients by approximately 22% (Table 1.1). It also underestimates REE in the obese population.

Other equations include the Penn State, Ireton-Jones, World Health Organization (WHO), Owen, Mifflin, and Liu formulas [9]. For overweight and obese patients, all equations underestimate REE by approximately 8%. Even though all equations underestimate when compared to IC, WHO and Harris-Benedict are the most accurate [9, 10]. The Penn State and Ireton-Jones equations tend to be the most commonly used in surgical and critically ill patients. They contain modifiers for severity of illness, stress states, weight, height, temperature, and other factors that might affect REE (Table 1.1).

Sources of Energy

Carbohydrates, proteins, and fats are the building blocks of the body. Glucose is the preferred fuel for metabolism. Fat is stored for times of starvation, and then when blood glucose levels are depleted, fat will be oxidized. Protein is also utilized with glucose is depleted.

Carbohydrates

Glucose is the main source for energy production and primary form of fuel for many cells. Dietary guidelines recommend carbohydrates to make up 50–60% of daily calorie intake.

Carbohydrates are divided into three classifications: monosaccharide, oligosaccharide, and polysaccharide. Monosaccharides cannot be

hydrolyzed any further and are made up of aldoses and ketoses. Aldoses, including glucose, galactose, mannose, and ribose, contain an aldehydic group. Ketoses like fructose contain a ketonic group. Oligosaccharides contain only a few carbohydrate chains linked by a glycosidic bond and include disaccharides and trisaccharides. Polysaccharides, also called glycans, are carbohydrates that contain ten or more monosaccharide chains. Polysaccharides are subclassified into homopolysaccharides (made up of identical monosaccharide chains) and heteropolysaccharide (made up of different monosaccharide chains). Common homopolysaccharides are starch, glycogen, cellulose, and dextran. Common heteropolysaccharides are pectin and mucopolysaccharide.

Proteins

Proteins are complex formations of amino acids. Daily protein requirements are dependent on the rate of protein catabolism [11]. In any hypermetabolic state, the rate of protein catabolism is significantly increased [12]. Therefore, normal protein requirements of 0.8–1 g/kg are increased in critically ill individuals to a minimum of 1.2–1.5 g/kg [13]. These increased protein requirements are in part due to the production of acute phase reactants in the critically ill, increased wound healing, and mobilization of peripheral protein stores for gluconeogenesis. Starvation and decreased mobility also increase protein turnover [14]. This can lead to acute decrease in lean muscle mass in the critically ill.

Certain amino acids are needed in a higher quantity in stressed states compared to normal conditions. For example, acute phase proteins contain high amounts of tryptophan, tyrosine, and phenylalanine, so in the stressed state there is increased need for these amino acids. Increased muscle breakdown can occur to provide these amino acid components. Loss of lean body mass in ICU patients is linked to increased complication rates including pneumonia, impaired wound healing, and even increased mortality [15].

In critically ill patients, protein losses, including those secondary to ongoing chest or abdominal drainage, severe burns or breakdown of the skin, proteinuria, or intestinal secretions, should be fully replaced. As stress resolves, the individual's protein needs decrease. According to ASPEN and ESPEN guidelines, patients with severe trauma (ISS >18) or multiple complications with moderate trauma may require increased protein intake with immune-enhancing diets that include protein of 2.2–2.5 g/kg daily. There is thought that these diets are associated with less infections, lower incidence of multi-system organ failure, and shorter hospital and ICU lengths of stay. These diets should only be continued, however, for 7–10 days, and then patients can be transitioned back to more standard nutritional repletion [13, 16]. Of note, protein requirements may be even higher than this in patients with burns or severe sepsis, with requirements of even up to 2.5–3 g/kg.

The calculation of a nitrogen balance can help determine the effectiveness of protein intake. A negative energy balance is noted to correlate with increased morbidity and mortality in the critically ill patient [17]. Nitrogen balance is calculated as nitrogen intake minus the output. Protein is 16% nitrogen, so the nitrogen intake is calculated by taking daily protein intake in grams and dividing by 6.25. The output calculating requires a 24-hour urine measurement to obtain a urine urea nitrogen. Urea excretion in the stool is estimated as 4–6 g/d and can be added to the total. It is therefore important to note that in states of diarrhea, the nitrogen output calculation may be inaccurate. Aiming for a positive nitrogen balance of 4–6 g/d is recommended [17].

Protein overfeeding has significant disadvantages, including azotemia and potentially even renal failure. Recent studies in the critically ill population demonstrate that provision of protein is linked to positive outcomes when compared to provision of total energy.

Lipids

Fatty acid oxidation is a mitochondrial aerobic process that breaks down a fatty acid into acetyl CoA units. Acetyl CoA is a common intermediate between metabolic pathways. Fatty acids can

be converted to ketone bodies which are used as fuel for extrahepatic tissues. Cholesterol, steroids, arachidonic acid, and eicosanoids are all derived from fatty acids. Excess fatty acids are stored as triglycerides in adipose tissue.

The maximum lipid delivery is 1–1.2 g/kg/d. An anti-inflammatory lipid profile, which includes omega-3, borage oil, and antioxidants, has not improved outcomes in patients with ARDS or sepsis. Omega-6 fatty acid increases inflammation. Current ASPEN guidelines recommend holding soy-based parenteral fat emulsions for the first week in critically ill patients as these products contain high levels of omega-6 fatty acids, known to be pro-inflammatory. Guidelines recommend a maximum dose of 100 g/wk if there is a concern for essential fatty acid deficiency. Alternatives to soy-based lipid emulsions are now available in the United States. SMOF (soybean oil, medium-chain triglycerides, olive oil, and fish oil) emulsion can be considered in the critically ill patient [13].

Alternate Sources of Energy

There are some new developments that suggest lactate is used by mitochondria as a fuel source and the "buildup" of lactate is not secondary to a lack of oxygen but more of an issue with the mitochondria inability to process the lactate. New research shows the brain can switch to lactate as a fuel source during higher levels of activity using the by-product of muscles as a secondary fuel [18].

Normal Metabolic Processes

The major metabolic pathways include glycolysis, gluconeogenesis, glycogen metabolism, fatty acid metabolism, citric acid cycle, oxidative phosphorylation, and amino acid metabolism.

Cofactors and Enzymes

Enzymes are the workhorse of metabolic pathways. They catalyze the innumerable biochemical processes that are vital for the living cell and organism. Their proper function is dependent on multiple elements including temperature, pH, availability of substrates, and presence of cofactors. The physiologically stressed patient has derangements in virtually all these variables that can lead to enzyme dysfunction, such as fever, acidosis, or severe malnutrition. Additionally, malabsorption secondary to GI tract dysfunction or disease states amplifies the issue for already nutritionally deficient individual by further decreasing substrates and cofactor availability. Provisions must be made for the patient with enzyme deficiencies, such as those who are lactose intolerant, as most western diets contain dairy products. This can lead to added substrate and cofactor perturbations as well as enzyme dysfunction.

Most commercially available formulas provide daily recommended intake (DRI) for vitamins and trace elements (see Table 1.2) [20]. Patients with severe malnutrition, high losses as with enteric fistulae, bypass procedures, and/or malabsorption may require additional supplementation. Many vitamins act as cofactors for various metabolic processes, including a vital role in the production of ATP. Deficiencies lead to detrimental physiologic conditions.

Vitamin B6 deficiency is associated with hyperhomocysteinemia and hyperglycemic states in surgical intensive care unit patients [20, 21]. Supplementation increases the immune response of critically ill patients [22]. Signs and symptoms or vitamin B1 deficiency are nonspecific and include paresthesias, ascending paralysis of motor neurons, memory loss, high-output cardiac failure, edema, and lactic acidosis. Appropriate supplementation can prevent negative consequences [23]. Vitamin B2 (riboflavin) is a key factor for flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), two important components of oxidative reduction. A large proportion of critically ill individuals have suboptimal vitamin B2 status, which can be significantly improved with supplementation. However, this improvement is transient and deteriorates with discontinuation of the intake [24, 25].

Table 1.2 Recommended daily allowance of vitamins and trace minerals

	M/F	Males	Females		
Fat-soluble vitamins			Typical	Pregnant	Lactating
A (mcg)		900	700	770	1300
D (mcg)	15–20				
E (mg)	15				19
K (mcg)		120	90		
Water-soluble vitamins					
B_1 (mg)		1.2	1.1	1.4	1.4
B_2 (mg)		1.3	1.1	1.4	1.6
B_5 (mg)	5			6	7
B_6 (mg)		1.3–1.7	1.5	1.9	2
B_{12} (mcg)	2.4			2.6	2.8
C (mg)		90	75	85	120
Folate (mcg)	400			600	500
Biotin (mcg)	30				35
Other nutrients					
Choline (mg)		550	425	450	550
Trace elements					
Copper (mcg)	900			1000	1300
Chromium (mcg)		30–35	20–25	30	45
Fluoride (mg)		4	3		
Iodine (mcg)	150			220	290
Iron (mcg)		8	18	27	9
Manganese (mg)		2.3	1.8	2	2.6
Molybdenum (mcg)	45			50	50
Selenium (mcg)	55			60	70
Zinc (mg)		11	8	11	12

Adapted from Ref. [19]

Therapeutic Interventions

Outcome specific data is lacking regarding certain vitamin deficiencies in critical illness; therefore provision of adequate supplementation should be the goal, to provide adequate substrate and cofactors necessary to support the metabolic demands of the stressed patient.

Normal Metabolism

In a homeostatic state, the human body will utilize the equivalent of the kilocalories that are consumed. The substrate that the body preferentially metabolizes is glucose, which undergoes aerobic metabolism in the mitochondria to produce ATP. Complex carbohydrates, fats, and proteins can all be metabolized to provide glucose for aerobic respiration and other substrates that can be utilized to produce ATP necessary for cellular division, growth, and maintenance of homeostasis. When disease processes affect the consumption of nutrients, metabolism of those nutrients, or lead to an increased need for nutrients, this alters the metabolism of the patient.

When nutritional metabolism is marginally changed, the patient's body will reach a new or different steady state without loss of function, which is defined as adaptation. One example of this is an overall decrease in the resting energy expenditure during early starvation to preserve available resources for essential functions. Over time, adaptation allows the body to continually change its composition without a detrimental effect to the patient's overall health. However, once the disturbances become more severe, then the homeostatic capacity may be overcome. This can lead to accommodation, which is defined as