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Energy requirements of pediatric patients

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To my Grandma Irene

TABLES OF CONTENTS

ABTRACT

Background and aims

Malnutrition is a state in which a deficiency or imbalance of energy, proteins and other nutrients causes measurable adverse effects on functional and clinical outcomes. In particular, the nutritional status of ill children often declines after admission to the hospital and deteriorates during the course of diseases. The reported prevalence of malnutrition in pediatric hospitals ranges from 6 to 30%, however there are currently no recommendations on nutritional evaluation and risk of hospital malnutrition screening.

Ill children are expected to differ in their energy expenditure when compared to healthy counterparts , to the point that growth may cease during the metabolic response to disease or injury, especially if they are in critical conditions.

The most accurate method for determining resting energy expenditure is indirect calorimetry which is based on the measurement of basal metabolism from gas exchanges. However the application of this technique remains still sporadic. Alternatively, in the daily clinical practice, energy expenditure is commonly calculated by the use of predictive equations whose algorithms are based on healthy populations and are not disease-specific. The aim of this research project wasat first to assess the nutritional status of ill children admitted to a tertiary health care of northern Italy by measuring the prevalence of malnutrition and the risk of developing it during hospitalization. In the second step, we investigated energy expenditure in the course of disease in a heterogeneous population of acutely and chronically ill children to evaluate the accuracy of the WHO, Harris-Benedict and Schofield formulae in this population.

Methods

A prospective observational study was at first performed in five pediatric units at the IRCCS Foundation Ca' Granda-Ospedale Maggiore Policlinico in Milan, Italy. In 245 subjects, anthropometric measurements (weight and length) were evaluated within 24 h of admission and repeated the day of discharge in order to assess wasting, stunting, and obesity according to WHO definitions.

A fasting blood sample was collected to analyze nutrition-related haematochemical indexes and to test their role in predicting the length of stay. The nutritional risk was assess using the STRONGkids questionnaire.

Then, a cross-sectional study including 236 infants, children and adolescents, consecutively admitted to the same five Units of this Italian Pediatric Hospital, was performed. Resting energy expenditure was measured by indirect calorimetry and estimated using the WHO, Harris-Benedict and Schofield formulae.

Results

The study population of the first study showed a malnutrition prevalence at admission of 10.2% wasting,and 6.5% stunting, moreover a prevalence of 7% obesity was found. Length of stay was mildly related to the $STRONG_{kids}$ score and was inversely associated with serum albumin. An inverse associations for serum albumin was found also with the questionnaire score. The second analysis showed a mean (standard deviation) bias between the estimated and measured resting energy expenditure of -1 (234), 82 (286), -3 (233) and -2 (214) kcal/die for the WHO, Harris-Benedict, Schofield-weight and Schofield-weight and height formulae, respectively.

Conclusions

To assess nutritional status, nutritional risk and appropriate biochemical indices at admission may help to predict the length of hospital stay and to optimize clinical interventions and follow-up. Furthermore, in ill children standard equations may be inaccurate and feeding strategies based on these equations might result in unintended underfeeding or overfeeding. Cumulative

effects of energy imbalance can negatively impact patient outcomes and must be prevented. Accurate assessment of energy expenditure with the use of indirect calorimetry might optimize when possible energy intake during disease providing adequate feeding strategies

ABSTRACT

Stato dell'arte e obiettivi:
La malnutrizione può essere definita come una condizione in cui uno sbilanciamento in energia o nutrienti, come ad esempio proteine, influisce negativamente sullo stato di salute di un individuo. In particolare, nel bambino con patologia spesso lo stato nutrizionale peggiora dopo il ricovero in ospedale e durante il decorso clinico. La prevalenza di malnutrizione ospedaliera pediatrica varia da un 6 a un 30%, tuttavia ad oggi non esiste un metodo ufficiale per determinare il rischio nutrizionale nei bambini ospedalizzati. È quindi fondamentale eseguire un'adeguata valutazione dello stato nutrizionale al momento del ricovero al fine di prevenire e trattare eventuali condizioni di malnutrizione, soprattutto nel paziente in terapia intensiva.
Il bambino malato può presentare alterazioni del suo dispendio energetico basale rispetto ai suoi coetanei in buono stato di salute e ciò può compromettere il suo adeguato accrescimento, soprattutto nei soggetti con patologie gravi.
La metodica più accurata per la misurazione della spesa energetica a riposo è la calorimetria indiretta, basata sulla determinazione degli scambi gassosi. Tuttavia gli elevati costi, la necessità di personale specializzato e le specifiche condizioni richieste per la sua esecuzione rendono il suo utilizzo nella pratica clinica sporadico. La spesa energetica nel bambino ospedalizzato viene quindi calcolata utilizzando equazioni predittive le quali però sono state elaborate a partite da studi su popolazioni sane. Ciò rende difficile una corretta determinazione dei fabbisogni nel bambino malato e impedisce la somministrazione di una terapia nutrizionale adeguata.
Lo scopo della prima parte di analisi è stato quello di valutare lo stato nutrizionale di bambini ricoverati in un centro di cura terziario di Milano, andando a misurare la prevalenza di malnutrizione e il rischio di svilupparla durante la degenza. Secondariamente, l'obiettivo della ricerca si è focalizzato sulla determinazione del dispendio energetico in bambini affetti da patologia acuta o cronica e sulla valutazione dell'accuratezza di equazioni predittive, quali WHO, Harris-Benedict e Schofield, in questo gruppo di popolazione.
Metodi:
A partire da Luglio 2011 fino a Dicembre 2012 è stato condotto uno studio prospettico osservazionale presso cinque Unità pediatriche della Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano. Su un totale di 245 bambini sono state eseguite misurazioni antropometriche (peso e altezza) entro le 24 ore dal momento del ricovero e ripetute il giorno delle dimissioni al fine di determinare la prevalenza di malnutrizione per difetto acuta (indice di massa corporea < - 2 deviazioni standard), cronica (statura per età < -2 deviazioni standard) e obesità (indice di massa corporea > 2 deviazioni standard). È stato inoltre prelevato un campione di sangue per testare il ruolo di indici ematochimici relativi lo stato nutrizionale nel predire la durata del ricovero. Il rischio di sviluppare malnutrizione è stato valutato per mezzo del questionario STRONGkids.
Tra Settembre 2013 e Marzo 2015 è stato eseguito uno studio trasversale su 236 bambini ricoverati presso la stessa struttura ospedaliera. Il dispendio energetico a riposo è stato misurato per mezzo della calorimetria indiretta e stimato utilizzando le equazioni predittive di WHO, Harris-Benedict e Schofield.
Risultati:
Nella prima parte di analisi, la popolazione studiata ha evidenziato al ricovero una prevalenza di malnutrizione per difetto acuta (10.2%) e cronica (6.5%) inferiori rispetto ad altre indagini eseguite in Italia. La prevalenza di obesità (7%) invece era confrontabile con quella rilevata nelle regioni settentrionali.

La durata del ricovero è risultata debolmente correlata al punteggio calcolato con lo strumento di screening $STRONG_{kids}$ mentre è stata trovata una sua associazione negativa con l'albumina sierica. Tale parametro ematochimico ha presentato un'associazione inversa anche con il valore di rischio calcolato dallo $STRONG_{kids}$.
La seconda parte di analisi ha evidenziato una media (deviazione standard) tra il dispendio energetico a riposo stimato e misurato pari a -1 (234), 82 (286), -3 (233) e -2 (214) kcal/girono per l'equazione di WHO, Harris-Benedict, Schofield-peso e Schofield-peso e altezza, rispettivamente.

Conclusioni:

La valutazione al momento del ricovero dello stato nutrizionale, del rischio di sviluppare malnutrizione e di appropriati indici biochimici può facilitare la predizione della durata della degenza e ottimizzare le cure cliniche e il follow-up.
Inoltre le equazioni predittive per il calcolo del dispendio energetico sono inaccurate nel bambino malato e aumentano quindi il rischio di creare uno sbilanciamento energetico sia per difetto che per eccesso, dannoso per il miglioramento dello stato di salute.
Una corretta misurazione della spesa energetica con la calorimetria indiretta permette di ottimizzare l'apporto calorico in corso di patologia fornendo al bambino una terapia nutrizionale adeguata.

CHAPTER 1

STATE OF THE ART

1. MALNUTRITION IN PEDIATRIC PATIENTS

1.1 Definition of malnutrition

Malnutrition is the cellular imbalance between the supply of nutrients and energy and the body's demand for these to ensure growth, maintenance, and specific functions. It is a continuum that starts with a nutrient intake inadequate to meet physiological requirements, followed by metabolic and functional alterations and in due course by impairment of body composition (1). The term "malnutrition" is commonly used as an alternative to undernutrition but technically it also refers to overnutrition. People are malnourished if their diet does not provide adequate calories and protein for growth and maintenance or they are unable to fully utilize the food they eat due to illness (undernutrition). They are also malnourished if they consume too many calories (overnutrition).

1.2 General causes for malnutrition

In developed countries the main cause of malnutrition is disease. Any disorder, whether chronic or acute, has the potential to result in or aggravate malnutrition in more than one way: response to trauma, infection or inflammation may alter metabolism, appetite, absorption, or assimilation of nutrients. In addition, underlying acute disease (e.g., sepsis, trauma, burn and cancer), chronic illness (e.g., inflammatory bowel disease, congenital heart disease, cystic fibrosis and severe neuromuscular impairment) or medications may increase the imbalance between substrate supply and demands. Mechanical obstructions in the gastrointestinal tract may lead to reduced food intake by causing nausea or vomiting, pain or discomfort induced by the passage of food. The catabolic effects of several mediators such as cytokines (interleukin 1, interleukin 6, and tumour necrosis factor alpha), glucocorticoids, catecholamines, and the lack of insulin growth factor-1 have been extensively studied in recent years, their relevance is however not yet entirely understood (117). Drug-related side effects: (e.g. chemotherapy, morphine derivatives, antibiotics, sedatives, neuroleptics, digoxin, anti histamines, captopril, etc.) can cause anorexia or interfere with the ingestion of food. In geriatric patients further factors such as dementia, immobilisation, anorexia, and poor dentition can further worsen the situation. (81, 90) The reasons for developing malnutrition in sickness are multifactorial, but decreased nutritional intake, increased energy and protein requirements, increased losses together with inflammation probably play the central role.

Apart from diseases, immediate causes of malnutrition are associated with environmental, economic, and sociopolitical factors, considered underlying and basic causes. Underlying causes are those that take place at the household level and can be categorized into three main factors: food insecurity; defective maternal and child caring practices; and unsafe water, poor

sanitation, and inadequate health services. The first factor leads to inadequate dietary intake, the last cluster to disease, whereas the intermediate factor may contribute to both immediate causes. Underlying causes are directly influenced by basic causes such as limited education, poverty, and marginalization. The status of women in particular (education, income) tends to influence infant and child feeding. Food security is related to a complex interaction of factors that include agricultural and food production policies, regulation of food marketing and advertisement, and food subsidies.
Additionally, sociocultural elements such as religious beliefs and traditions can affect food preferences and net energy intake.

1.3 Malnutrition in infancy and childhood

Children have a high energy need per unit of body mass compared with adults and have limited energy reserves. Furthermore, children have a need for growth, which puts them at a particularly high risk of malnutrition because of these higher demands. Growth depends on a permanent increase in fat and lean body mass, which requires positive energy and nitrogen balance, therefore, any increase in nutritional demands competes with the specific needs of growth, especially during infancy and adolescence. Consequently, sustained nutritional imbalance induces growth retardation, with a decrease in longitudinal growth (height gain over time) and height-for-age ratio (height divided by the expected height for age, taken as 50th centile for height). The most obvious and earliest sign of malnutrition in such situations is the absence of normal weight gain, followed by weight loss with visible decrease in fat and muscle mass. Children with acute malnutrition present with decreased weight for height but may present with normal height for age.
Each form of malnutrition depends on what nutrients are missing in the diet, for how long and at what age. The most basic kind is called protein energy malnutrition (PEM), a condition in which the most salient elements are a depletion of body energy stores and of tissue proteins, observed over a range of combinations and severity, and usually accompanied by micronutrient deficiencies. Prolonged protein-energy malnutrition remains a major cause of infant and childhood morbidity and mortality in underdeveloped parts of the world.
In the first stages of PEM, a decrease in energy intake is followed by an adaptive reduction in energy expenditure (EE). When the decrease in EE cannot compensate for the insufficient intake, energy is mobilized from fat depots, thus leading to loss of body weight (119). Mobilization of energy from lean body mass also occurs as skeletal muscle protein catabolism contributes energy via conversion of glucogenic amino acids, such as alanine. In children, an additional critical adaptive response is reduction in or cessation of longitudinal growth, which results in chronic undernutrition (stunting). These changes are usually associated with multiple micronutrient deficiencies of variable severity.
As protein and energy deficits progress, the initial adaptation evolves into accommodation, a term coined by Waterlow to describe a response in which normal functions are present but operating at a reduced level (adaptation); survival is achieved at the cost of suppressing or severely reducing certain key physiologic functions (accommodation). For example, protein catabolism is an adaptive mechanism to provide glucose during periods of fasting, such as nighttime sleep. Similarly, prolongation of the half-life of plasma albumin is an adaptive mechanism to reduce protein synthesis. However, if protein synthesis is further curtailed, plasma albumin concentration will fall to abnormal concentrations, thus resulting in clinical

edema (118, 126). In children with Severe Protein-Energy Malnutrition (SPEM) immunity defense responses are diminished because many immune proteins (e.g., immunoglobulins, complement components, acute phase proteins) are reduced or depleted. Similarly, lymph nodes, adenoids, and the thymus may be reduced in size (20, 123). Phagocytosis, chemotaxis, and intracellular functions are also impaired. As a consequence, the usual clinical signs of infection (inflammation, fever) may not be present in the child with SPEM suffering an acute infectious episode. Instead, signs of the failure of homeostasis, such as hypoglycaemia or hypothermia, may appear. Reduction in hemoglobin concentration and red cell mass almost always accompanies PEM, as a result of bone marrow suppression and reduced oxygen needs, the latter related to depleted skeletal muscle mass. These adaptive responses are reversed when and if nutritional rehabilitation is successful. Administration of hematinics to a SPEM patient will not induce a hematopoietic response until dietary treatment produces an increase in lean body mass. Giving iron early in treatment can increase free iron, with promotion of free radicals and their damaging effects, and can also make some infections worse. Total body potassium decreases in SPEM because of the reduction in muscle proteins and increased urinary and fecal losses. At least one third of the cell's energy expenditure results from the sodium/potassium-adenosine triphosphatase (Na /K ATPase) pump. In patients with SPEM, this pump slows down because of the diminished energy substrates (ATP). This leads to potassium loss and increased intracellular sodium. Water accompanies the sodium influx, and intracellular overhydration may occur. These alterations in cell electrolytes and energy sources may explain, at least in part, the increased fatigability and reduced strength of skeletal muscle, which can even affect respiratory muscles.

Cardiac output, heart rate, and blood pressure decrease; and central circulation takes precedence over peripheral circulation. Cardiovascular reflexes are altered, leading to postural hypotension and diminished venous return. These circulatory changes also impair heat generation and loss. Peripheral circulatory failure comparable to hypovolemic shock may occur. The reduced kidney filtration capacity may result in volume overload and heart failure under relatively moderate water loads. Impaired intestinal absorption of lipids and carbohydrates and decreased glucose absorption are relatively frequent, but they can be partially compensated for by higher intake, to permit nutritional recovery (105).

However, reduced intestinal motility and intestinal bacterial overgrowth may predispose patients to diarrhea. The adaptive response of energy homeostasis involves several endocrine changes (123). Insulin secretion is reduced and glucagon and epinephrine release are increased in response to reduced plasma glucose and free amino acid concentrations. These changes lead to decreases in muscle protein synthesis, lipogenesis, and growth and increases in lipolysis and glycogenolysis. Insulin resistance at the periphery increases, probably from the increase in plasma free fatty acids. Secretion of human growth hormone is stimulated, and insulinlike growth factor activity is reduced, as a response to low plasma concentration of amino acids. These changes also decrease muscle protein synthesis and glucose uptake by tissues and growth as well as increase lipolysis and visceral protein synthesis. The stress induced by persistent starvation, further amplified by infections, stimulates epinephrine and cortisol secretion. These changes also increase lipolysis, glycogenolysis, muscle protein catabolism, and visceral protein turnover. SPEM early in life may result in impaired brain growth, nerve myelination, neurotransmitter production, and nerve conduction velocity.

The metabolic factors leading to edematous SPEM (kwashiorkor) are not yet fully understood, but severe protein deficiency is an important causal factor. Lack of vitamins and minerals present in protein foods of animal origin is also important. Other factors that may contribute to kwashiorkor, with its characteristic edema, hypoalbuminemia, and enlarged fatty liver, are as follows: overloading of a severely malnourished person with carbohydrates; metabolic stress induced by infections; lower adrenocortical response that reduces the efficiency to preserve

visceral proteins; and effects of free radicals, which are increased by infections, toxins, sunlight, trauma, and catalysts such as iron (105).
Furthermore, in infancy malnutrition is associated with reduced or delayed mental and psychomotor development (70, 79). Longitudinal studies have revealed that malnutrition during infancy is associated with increased behavior problems during childhood, including attention deficit and aggressive behaviour (37, 38, 39). Early childhood malnutrition has also been related to externalizing behavior in both childhood and adolescence (76, 77).
Increasing evidence suggests that many common adult diseases have their origins in fetal and early life, as described in the "fetal origins hypothesis" by David J. Barker, a British physician and epidemiologist. It is suggested that inadequate nutrition in utero "programs" the fetus to have metabolic characteristics that can lead to future disease. Barker argued that individuals starved during fetal life and early infancy are more likely to become overweight as adults, and that they are more likely to suffer from diseases associated with obesity (5). Intrauterine malnutrition may also result in type II diabetes (6) or a induce a higher risk for cardiovascular disease as described in the Dutch famine studies (103, 104). This famine was precipitated by the Nazi occupation of the Netherlands, in which many Dutch were reduced to eating tulip bulbs in a desperate attempt to forestall starvation. Nutrition in the Netherlands had been adequate up to October 1944; however, the Nazis had occupied the country and cut off food shipments after that date. By November 1944, official rations had fallen below 1000 dietary calories per day, and by April 1945, they were down to 500 calories per day. The famine was known to have affected fertility, weight gain during pregnancy, maternal blood pressure, and infant birth weight. Stein et al. (113) examined the relationship between prenatal exposure to famine and the conscription records of over 400000 18 year-old men. Famine exposure was defined using birth date and place of birth. No effects were found on IQ scores, but the obesity rate was doubled among those who had been exposed in the first trimester (101).
The mechanisms underlying this hypothesis are related to epigenetics, which refers to the ways in which the developmental environment can influence the mature phenotype (122).
Epigenetic processes, such as DNA methylation and histone modification, are induced by cues from the developmental environment, thus modulating gene expression (developmental plasticity). Maternal and early postnatal undernutrition can induce a series of thrifty phenotypes as a defensive response of the developing fetus or infant against an immediate challenge. For example, maternal undernutrition reduces the number of nephrons in the child, and this may be related to low mRNA expression resulting from a mutation of the paired box gene 2 (PAX2) during kidney development (100). Fewer nephrons have been related to hypertension later in life (132). Proteinrestricted diets have been associated with reduced promoter methylation and increased expression in the liver of the transcription factor peroxisome proliferator-activated receptor-α (PPAR-α), which causes an increase in circulating concentrations of the ketone β-hydroxybutyrate and glucose (73, 74). Even mild undernutrition can cause phenotypic modifications that affect physiology to aspects of the predicted adult environment (e.g., sparse environment) more precisely (42). If the adaptive change is not appropriate for the subsequent environment (e.g., energyrich environment), the risk of disease increases.

1.4 Diagnostic criteria of malnutrition in children

The diagnostic criteria of malnutrition are based on its severity (mild, moderate, severe) and time course (acute, chronic) and are determined primarily by anthropometry. Growth is the best

indicator of nutritional status and using growth curves remains the simplest way for assessing nutritional status in children (65).
Other clinical and biochemical findings become evident later in the progression of the disease. The WHO developed child growth reference standards that can be used across different countries to estimate growth adequacy or to diagnose underweight (130).
In children less than 5 years of age, weight for height (WH) is an index of current nutritional status, and lower values indicate recent depletion of body mass (wasting). In older children and adolescents, the body mass index (BMI)-for-age is used instead of WH. Height for age (HA) indicates long-term growth retardation (stunting), but often with adequate weight relative to height (125). Weight for age (WA) indicates growth delay, but it cannot discriminate recent body mass depletion from low stature resulting from chronic undernutrition. The cutoff points to assess severity and duration of PEM are shown in **Table 1**:

Table 1. Classification of PEM: cutoff for severity and duration

CLASSIFICATION OF SEVERITY OF CURRENT (WASTING) AND PAST OR CHRONIC (STUNTING) PROTEIN-ENERGY MALNUTRITION				
	WASTING		STUNTING	
	0-5 y	5-18 y	Adults	0-18 y
	WH[a]	BMI FOR AGE[b]	BMI[c]	HA[d]
Mild	-1.1 - -2.0 Z	-1.1 - -2.0 Z	17.0-18.4	-1.1 - -2.0 Z
Moderate	-2.1 - -3.0 Z	-2.1 - -3.0 Z	16.0-16.9	-2.1 - -3.0 Z
Severe	< -3.0 Z	< -3.0 Z	< 16.0	< -3.0 Z

BMI, body mass index; HA, height for age; WH, weight for height.

a. Based on the 2006 World Health Organization (WHO) child growth standards for 0 to 5 years.
b. Based on the 2007 WHO growth reference data for 5 to 19 years.
c. Based on the classification proposed by James et al (59).
a. Based on the 2006 WHO child growth standards for 0 to 5 years and the 2007 WHO growth reference data for 5 to 19 years.

The unit measure used in children is the Z-score, which defines standard deviations from the reference median value. The diagnostic criteria for SPEM in children aged 6 to 60 months may include two additional indicators: midupper arm circumference (MUAC) inferior to 115 mm and the presence of bilateral edema.
Edematous malnutrition (kwashiorkor) is characterized by soft, pitting, painless edema, usually in the feet and legs, but sometimes extending to the perineum, upper extremities, and face. Most patients have skin lesions, often confused with pellagra, in the areas of edema. The epidermis peels off in large scales, exposing underlying tissues that are easily infected. Weight deficit, after accounting for the weight of edema, is usually not as severe as in marasmus.

1.5 Hospital malnutrition

The health status is intimately connected with the nutritional status; the maintenance of health status corresponds to the maintenance of the structural and functional body entirety (body composition and body function, respectively) through energy (energy balance) and substance exchange (energy and non-energy nutrients) with the environment. Any alteration of this fragile balance generates malnutrition, a term which encompasses undernutrition, overnutrition, or the copresence of both the conditions (26).

Malnutrition is common in the hospitalized paediatric population. The nutritional status of children often declined after admission to the hospital and a poor nutritional status relates to worse clinical outcomes such as prolonged recovery times, greater requirements for high dependency or intensive care, increased complication rates, increased nosocomial infections and, at worst, death (71, 108, 109). Due to the longer length of stay in hospital and more intensive treatment of malnourished patients, malnutrition has undeniably also become an economical issue. There is a further negative impact on growth and development with prolonged undernutrition (96).

The prevalence of disease associated malnutrition in hospitalised children in Europe has been reported to range from 6% to 30% (48).

The reported prevalence of acute malnutrition over the previous 10 years in hospitalized children in Germany, France, UK, and USA has varied from 6% to 14%, whereas in Turkey a prevalence of malnutrition of up to 40% has been reported. Very recently, a national survey in 41 hospitals in the Netherlands showed that 19% of children had acute and/or chronic malnutrition at admission (65).

Malnutrition has been reported to be highly prevalent in children with an underlying disease. Compared with data from 20 to 30 years ago, the prevalence rate of malnutrition has been reported to be lower, especially in children with cystic fibrosis and malignancies, but in children with chronic inflammatory diseases such as chronic kidney disease, acute and chronic malnutrition remain very prevalent (64).

In the pediatric intensive care unit (PICU), children with malnutrition have been demonstrated to have increased duration of mechanical ventilation, length of stay (LOS) and mortality (24, 98). Furthermore, malnutrition is common among critically ill children with rates reported to be as high as 53% (24). Critically ill children often have lower nutrition stores compared to critically ill adults, and are thus likely to be at higher risk of malnutrition.

The situation can be further aggravated in hospital due to adverse hospital routines that lead to insufficient nutrient intake (27).

On the other hand, there has been a global epidemic of childhood obesity over recent years (4): in community-based settings, up to 23% of Australian children were classified as obese and overweight (9, 94). In some countries, the prevalence of obesity has been reported to be even higher in hospitalized children than in children seen in outpatient or community settings (80,93). There is also evidence that the parents of these children may not be fully aware of the problem or its implications, and they may not receive nutritional counselling during their hospital stay (86).

1.6 Pediatric nutrition screening tools

Children admitted to hospital are at risk of developing malnutrition, even when nutritional status is normal at the time of admission (1). To prevent malnutrition, and especially hospital-acquired malnutrition along with its complications, early identification of nutritional depletion is essential, ideally on admission to the hospital, so that appropriate nutritional intervention can be initiated at an early stage.

In adult clinical practice, there are several widely used nutritional risk-screening tools, such as such as the Subjective Global Assessment (SGA), the Mini Nutritional Assessment (MNA) or the Nutritional Risk Score (NRS) (66).

Instead, in children, who may be considered even more vulnerable, no nutritional risk tool has yet been developed and accepted across Europe. The clinical implications of diseases are different for children, the underlying cause and pathology differ in some instances, and the impact of disease on growth and subsequent development is an additional important complicating factor. In order to improve nutritional care in pediatric hospitals, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (www. ESPGHAN.org) Committee on Nutrition has recommended the establishment of nutrition support teams whose tasks should include among others 'identification of patients at risk of malnutrition, provision of adequate nutritional management, education and training of hospital staff and audit of practice'. However, these recommendations have not been widely introduced into routine clinical practice (1).

Currently, there is no consensus on the ideal method to determine which children on admission are at risk to develop malnutrition during a hospital stay. Such an approach provides the physician with the opportunity to apply appropriate nutritional interventions, in the hope of preventing complications.

A nutritional risk screening tool is basically different from measuring actual nutritional status with anthropometric, dietary, biochemical, and immunologic measures. In this way it is possible to identify only patients who are already undernourished and not those at risk of malnutrition (102, 129).

Nutrition screening identifies individuals who may benefit from more extensive nutrition evaluation and intervention (67). The main objective of screening is the early detection of a condition at a point when treatment is more effective, less expensive, or both. In general, screening processes compare specific individual characteristics to factors associated with risk of an unfavorable consequence (131). An effective nutrition screening must be accomplished quickly with readily available information and must be applicable to the population being screened. Reliability and validity are essential components of any nutrition screening process (63).

Decisions for acceptable levels of sensitivity and specificity involve weighing the consequences of leaving cases undetected (false-negatives) against incorrectly classifying healthy persons as having the condition (false-positives) (51). During the last few years, impressive efforts have been made to create simple and useful nutrition screening tools in hospitalized children (41, 53, 83).

Secker and Jeejeebhoy (2007) (108) and Sermet- Gaudelus et al. (2000) (109) developed the Pediatric Nutritional Risk Score and the Subjective Global Nutritional Assessment, respectively. These identify children at risk of malnutrition during hospitalization. Sermet-Gaudelus et al. developed and tested a screening tool based on prospective nutritional assessment and a weight loss greater than 2% from admission weight as the cut-off for nutrition risk. Nutritional risk was assessed prospectively in 296 children by evaluating various factors within 48 h of admission. Multivariate analysis indicated that food intake less than 50%, pain,

and grade 2 and 3 pathologic conditions (P=0.0001 for all) were associated with weight losses of greater than 2%. The Pediatric Nutritional Risk Score (PNRS) ranged from 0 to 5 and was calculated by adding the values for the significant risk factors as follows: 1 for food intake less than 50%, 1 for pain, 1 for grade 2 pathologic condition and 3 for grade 3 pathologic condition. A score of 1 or 2 is supposed to indicate moderate risk and a score of at least 3 to indicate high risk of malnutrition. Although this tool appears to be quick and simple to use, the study does not detail on the conditions required for implementation (e.g. staff training and resources) or the reliability and the reproducibility of the tool in practice. Secker and Jeejeebhoy developed and tested a Subjective Global Nutritional Assessment (SGNA) score for children having major thoracic or abdominal surgery evaluated prospectively. The SGNA consisted of a nutrition-oriented physical examination and information on the child's recent and current height and weight, parental heights, dietary intake, frequency and duration of gastrointestinal symptoms, current functional capacity and recent changes. The SGNA was tested on a population of children undergoing surgery, and the occurrence of nutrition- associated complications was documented at 30 days after surgery. SGNA divided children into three groups: well nourished, moderately malnourished and severely malnourished. The children categorized as malnourished had a higher rate of infectious complications and a longer postoperative length of stay than the well nourished children. However, the tools of Sermet-Gaudelus et al. and Secker and Jeejeebhoy are considered too complicated and time-consuming to use in daily clinical practice. A simpler tool was developed by McCarthy et al. [32], the Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP). It is a 5-step tool that was tested in comparison to a full nutritional assessment in a group of 89 children aged 2–17 years admitted for surgery (83). STAMP consists of three elements: clinical diagnosis (classified by the possible nutritional implications), nutritional intake and anthropometric measurements (weight). Each element is scored and nutritional risk is translated into the need for a referral for full assessment. No outcomes were evaluated with the STAMP tool.

Gerasimidis et al. (41) developed the Paediatric Yorkhill Malnutrition Score (PYMS), which is a four-stage evaluation based on four questions considering the BMI value, recent weight loss, decreased intake the previous week, and expected affected nutrition by the admission/condition for the next week. Each step bears a score of up to 2, and the total score reflects the degree of the nutrition risk of the patient. The validity of this tool was assessed by comparison with a full dietetic assessment as a golden standard for nutritional assessment (dietary history, anthropometric measurements, nutrition-associated physical examination, ability to maintain age appropriate energy levels, and review of medical notes). Children were classified as having low, medium, or high malnutrition risk. Of the 247 children studied (1e16 y old), the nurse-rated Pediatric Yorkhill Malnutrition Score identified 59% of those rated at high risk by full dietetic assessment. Of those rated at high risk by the nursing Pediatric Yorkhill Malnutrition Score, 47% were confirmed as having high risk on full assessment.

Hulst et al. (53) developed a simple tool of assessing nutritional risk. This tool, Screening Tool Risk on Nutritional status and Growth ($STRONG_{kids}$), has been developed and tested in a multicenter study that included 424 children aged 3.5 years (range 31 days to 17.7 years) admitted to seven academic and 37 general hospitals in the Netherlands. It consists of four elements: subjective clinical assessment, high-risk disease, nutritional intake and weight loss or poor weight gain. Measurements of weight and length were also performed. SD scores of 2 or less for weight-for-height and height-for- age were considered to indicate acute and chronic malnutrition, respectively. The four questions in this tool can be completed just after admission and are not time-consuming. With this tool, the risk can immediately be calculated. The survey in the Netherlands showed that in 98% of the 424 children included, the tool was successfully applied. Using this tool, a significant relation was found between having a ''high-risk'' score, a negative SD score in WFH, and a prolonged hospital stay.

However, the $STRONG_{kids}$ has two weak points: the subjective clinical assessment item 'was carried out by skilled pediatricians', whereas one would ideally wish for a screening tool that can be applied by all healthcare workers; the 4th item 'weight loss or poor weight gain' or anthropometric indices calculation require either previous knowledge of the child weight/ length (rarely available beside infancy) or time-consuming assessment and interpretation of these indexes.

For people with cystic fibrosis (CF) a specific nutrition screening tool was derived from standards for BMI, weight gain, and height velocity according to the recommendations of the CFF Clinical Practice Guidelines Subcommittee on Growth and Nutrition (112).

2. ENERGY REQUIREMENTS OF ILL CHILDREN

2.1 Introduction

Human beings need energy to perform and regulate all biochemical processes that maintain the structural and biochemical integrity of the body; to perform internal work of circulation, respiration, and muscle contraction; and to perform external work (13, 68, 69). All energy used for body maintenance, activity and growth is derived from chemical free energy of food provided by carbohydrates, fats, protein and alcohol. Our ability to use the chemical free energy of diet results from the development of the biochemical, structural, and physiologic apparatus that permits the transformation of chemical free energy into other energy forms essential for life. Part of the energy from food, on the order of 5%, is thermodynamically obligated for conversion to heat because the entropy of the metabolic end products is greater than the initial substances. Conversion of food energy into high-energy biochemical compounds is an inefficient process, with approximately 50% lost as heat. Through biochemical transformations, approximately 45% of the energy of food is available to the body, primarily as adenosine triphosphate (ATP). Eventually, all the energy of food is lost from the body in the form of heat or external work. The energy in foods is expressed as a unit of heat, the calorie. A calorie is defined as the amount of heat required to raise the temperature of 1 g of water by 1°C from 15°C to 16°C. The scientific international unit of energy is the joule (J), defined as the energy expended when 1 kg is moved 1 m by a force of 1 newton. In 1956, an international committee standardized the equivalency of these units as 1 cal = 4.1868 J, but the figure of 4.184 is more commonly used in nutrition studies. For practicality, a kilocalorie (kcal), which is 1000 times the energy of a calorie (cal), is commonly used in nutrition. The potential energy contribution of food is determined experimentally by measuring the heat evolved in a bomb calorimeter when foodstuffs are completely combusted to carbon dioxide (CO_2) and water (8). The actual amount of heat evolved per gram of foodstuff varies according to its chemical composition. Average values are 4.1 kcal/g of carbohydrate, 9.3 kcal/g of fat, and 5.4 kcal/g of protein. The body cannot oxidize nitrogen, and therefore energy resulting from the oxidation of the nitrogenous component of protein is unavailable to the body. Consequently, only 4.2 kcal/g protein is potentially available to the body. The physiologic fuel value is compromised further by the apparent digestibility of various foodstuffs that vary among food sources. These factors result in physiologic fuel values of 4 kcal/g for carbohydrate, 9 kcal/g for fat, and 4 kcal/g for protein, also known as the Atwater factors. The physiologic fuel value for alcohol is 7 kcal/g. Protein oxidation is largely determined by protein intake, whereas the relative contributions of glucose or free fatty acids (FFAs) to the fuel mix are more variable. Glucose oxidation is adjusted to carbohydrate intake to maintain stable glycogen stores. Fat intake, in contrast, does not promote its own oxidation, and under conditions of positive energy balance, some fat will be deposited. Most cells can use the metabolic intermediates of carbohydrates, fats, and proteins interchangeably to regenerate ATP, with a few exceptions. The brain preferentially uses glucose and is able to use ketone bodies after adaptation to starvation, but it does not use FFAs. Red blood cells also depend on glucose. At rest, the brain (20%), internal organs (25% to 30%), and skeletal muscle (20%) account for the majority of energy turnover. During vigorous activity, skeletal muscle overwhelms the utilization of other tissues. In the postabsorptive state, FFAs are mainly oxidized by muscle, whereas during exertion, muscle's own glycogen reserve is used, with a subsequent shift toward use of FFAs mobilized from muscle fat stores and adipose tissue. When alcohol is consumed, it promptly appears in the circulation and is oxidized at a rate determined largely by its concentration and by the activity of liver alcohol dehydrogenase. Oxidation of alcohol rapidly reduces the oxidation of the other substrates used for ATP

regeneration. Ethanol oxidation proceeds in large part through conversion to acetate and oxidative phosphorylation. Approximately 80% of the energy liberated by ethanol oxidation is used to drive ATP regeneration, and approximately 20% is released as heat.

2.2 Components of total energy expenditure

Total energy expenditure (TEE) expended over 24 hours is the sum of basal energy expenditure (BEE), the energy expenditure of physical activity (EEPA), the thermic effect of food (TEF) and in less frequent situations cold-induced thermogenesis.

2.2.1 Basal energy expenditure

Basal energy expenditure (BEE) is the energy needed to maintain all vital body functions:
- at the cellular level: the pumping of ions across membranes to maintain normal chemical gradients, the turnover of proteins and other cellular constituents;
- at the organ level: e.g. the contraction of cardiac and respiratory muscles.

BEE is defined as the energy used to maintain the basic physiological functions of the body at rest under strictly defined conditions: after an overnight fast corresponding to 12-14 hours of food deprivation, awake, supine, resting comfortably, motionless, no strenuous exercise in the preceding day (or eight hours of physical rest), being in a state of "mental relaxation" and in a thermoneutral environment. BEE is the main component (45-70 %) of TEE (32).

Factors that influence basal metabolic rate in individual humans:

- Body surface and body mass are positively correlated with basal metabolic rate but negatively correlated to basal metabolic rate per m2 body surface or kg body mass.
- Lean body mass: muscular tissue and especially organs expend more energy compared to fat tissue. Fat free mass (FFM) contains the metabolically active compartments of the body and therefore is the major predictor of basal metabolism. FFM was the single best predictor of REE, and it accounted for 73% of its variability; FM accounted for only an additional 2%.
  Together, the brain, liver, heart, and kidneys account for approximately 60% to 70% of RMR in adults, but they represent less than 6% of body weight. Skeletal muscle accounts for only 20% to 30% of RMR and comprises 40% to 50% of body weight.
  The lower body fat percentage in males is one reason why men generally have a 10-15% higher basal metabolic rate than women.
- Age: after the age of 20 years basal metabolic rate declines at a rate of approximately 1% to 2% per decade in weight-constant persons. This decline is attributable to loss of FFM and gain of less metabolically active fat associated with aging.
- Diet: starvation can reduce basal metabolic rate by 30%.
- Body temperature: for each centigrade raise in body temperature , basal metabolic rate increases by approximately 10%.
- Ethnicity: the BEE, expressed per kilogram of body weight or per kilogram of FFM, is on the order of 5% to 10% lower in African-Americans compared with whites. Differences in relative contributions of organs and tissues to FFM may explain the differences in BEE among ethnic groups. Lower RMR in African-American women

compared with white women is attributed to the greater proportion of low-metabolic-rate skeletal muscle and bone in African-Americans (62).

- Thyroid, adrenal and sympatic activity influence basal metabolic rate.

2.2.2 Resting energy expenditure

By definition, resting energy expenditure (REE) is the energy expended when the body is at rest, which is when no extra energy is used for muscular effort. In many studies, for practical reasons since conditions for measuring BEE are more stringent, REE instead of BEE is measured. Changes in REE are used to measure the expenditure of many processes such as thermoregulation, eating and excess post-exercise oxygen consumption. Practically, REE is measured in conditions less stringent than the ones that prevail for measurement of BEE (i.e. 3- to 4-hour fasting period is required and the time of day and prior physical activity are not controlled), so that REE is usually slightly higher than BEE (approximately up to 10%-20%).

2.2.3 Sleeping energy expenditure

Sleeping energy expenditure can be measured instead of BEE or REE to estimate daily energy requirements. It is approximately 5% to 10% lower than the BEE (40). Sleeping energy expenditure can be considered as a practical means to approach BEE particularly in infants for whom the criteria related to measurements of BEE would be impractical.

2.2.4 Thermogenesis

Thermogenesis augments basal metabolism in response to stimuli unassociated with muscular activity. Stimuli include food ingestion and cold and heat exposure. Thermogenesis has two components: obligatory and facultative thermogenesis (60, 61). Obligatory thermogenesis depends on the energy cost of digesting, absorbing, and processing or storing nutrients. The magnitude of this component is determined by the metabolic fate of the ingested substrate. Obligatory thermogenesis also may be potentiated by exercise, a frequent meal pattern, and increased meal size. Facultative or regulatory thermogenesis represents the additional energy expenditure not accounted for by the known energy costs of obligatory thermogenesis. The sympathetic nervous system plays a role in modulating facultative thermogenesis.
When the ingestion of a meal is the stimulus, the process can be referred to as postprandial thermogenesis, thermic effect of a meal or heat increment. When the chronic effect of a diet is the stimulus, the overall response can be referred to as dietary induced thermogenesis. This component is associated with the digestion, absorption, transport, interconversion and, where appropriate, deposition/storage of nutrients. These metabolic processes increase REE, and their energy expenditure is known as the thermic effect of food (TEF). The increments in EE above BMR, divided by the energy content of the food consumed, vary from 5% to 10% for

carbohydrate, 0% to 5% for fat, and 20% to 30% for protein. A mixed meal elicits an increase in EE equivalent to approximately 10% of the calories consumed.
A change in environmental temperature (cold temperature) induces the production of heat in response to temperatures below thermoneutrality. Cold-induced thermogenesis can be divided into two types: shivering thermogenesis and non-shivering thermogenesis. The thermoneutral zone (or the critical temperature) is the environmental temperature at which oxygen consumption and metabolic rate are lowest (56). The relative contribution of cold-induced thermogenesis to TEE has decreased in recent decades due to the increase in time spent in enclosed and heated environments.

2.2.5 Physical activity

EE for physical activity represents the most variable component of TEE, both within and between subjects, ranging from 15 % of TEE in very sedentary individuals to 50 % or more of TEE in highly active individuals. Physical activity level (PAL) is defined as the ratio of daily TEE to basal energy expenditure (BEE) (TEE/BEE) and is commonly used to describe typical activity levels. In whole room calorimeter studies, the TEE/BEE ratio averaged 1.32 in groups with no exercise, 1.42 in those who did 30 to 75 minutes/day of exercise, and 1.60 in those who did 100 to 180 minutes/day (124). The value of 1.4 multiplied by BEE represents maintenance energy requirement and covers BEE, TEF, and minimal activity.
In more active groups, the PAL ranges from 1.4 to 1.7, and it ranges from 2.0 to 2.8 in very active groups. Moderate levels of exercise do not appear to increase subsequent EE markedly. Substrate utilization during exercise depends mainly on relative intensity. Fat is the main energy source in muscle and at the whole body level during rest and mild exercise (11). As exercise intensity increases, a shift from the predominant use of fat to carbohydrate occurs. Other factors such as exercise duration, gender, training status, and dietary history play secondary roles (12). The peak rate of fat oxidation is achieved at approximately 45% of VO_2max, and for exercises at greater than 50% of VO_2max, the oxidation of FFAs declines in muscle, both as a percentage of total energy and on an absolute basis. The main carbohydrate energy source is muscle glycogen, supplemented by blood glucose and lactate. If exercise persists beyond 60 to 90 minutes, fat oxidation will rise as carbohydrate fuel sources become depleted. In this case, the intensity of exercise must drop because of depletion of muscle glycogen, decreased blood glucose, and fatigue (95).

2.2.6 Growth

The increase in EE induced by growth results from the expenditure for protein and lipid synthesis and their deposition in newly-formed tissue. The energy requirement for growth relative to maintenance is low except for the first months of life. As a percentage of total energy requirements, the energy cost of growth decreases from 35% at 1 month to 3% at 12 months of age, and it remains low until puberty, at which time it increases to 4% (17). During childhood, girls grow slightly more slowly than boys, and girls have slightly more body fat. During adolescence, the gender differences in body composition are accentuated (28, 35, 115). Adolescence in boys is characterized by rapid acquisition of FFM, a modest increase in FM in

early puberty, followed by a decline. Adolescence in girls is characterized by a modest increase in FFM and continual FM accumulation.

2.2.7 Pregnancy

The additional energy requirements of pregnancy include increased basal metabolism and energy cost of physical activity and energy deposition in maternal and fetal tissues. The BEE increases as a result of the metabolic contribution of the uterus and fetus and the increased internal work of the heart and lungs (55). In late pregnancy, the fetus accounts for approximately 50% of the increment in BEE. The energy cost of weight-bearing activities was increased by 19% after 25 weeks of gestation . The gross energy cost of non-weight-bearing activities increased on the order of 10% and the net cost on the order of 6% in late pregnancy (99). The energy cost of tissue deposition can be calculated from the amount of protein and fat deposited in the fetus, placenta, amniotic fluid, uterus, breasts, blood, extracellular fluid, and adipose tissue. Hytten and Chamberlain (55) estimated that 925 g protein and 3.8 kg fat, equivalent to 41,500 kcal, were associated with a weight gain of 12.5 kg and a birth weight of 3.4 kg.

2.2.8 Lactation

Consistent with the additional energy cost of milk synthesis, basal metabolism of lactating women increased on the order of 4% to 5% (15, 106, 111). Although TEE may be slightly lower in the first months postpartum, TEE does not appear to differ from nonpregnant, nonlactating values thereafter *(*18, 36, 43, 78). Energy cost of lactation is estimated from milk production rates and the energy density of human milk. Milk production rates averaged 0.78 L/day from 0 to 6 months postpartum (2, 16, 49) and 0.6 L/day from 6 to 12 months postpartum (25). Energy density measured by bomb calorimetry or proximate macronutrient analysis averaged at 0.67 (range, 0.64 to 0.74) kcal/g (91). Energy mobilized from maternal tissue stores can subsidize the energy cost of lactation. Gradual weight loss averaging -0.8 kg/month in the first 6 months postpartum is typical in well-nourished lactating women (18).

2.3 The measurement of energy expenditure

Methods used to measure EE in humans include direct calorimetry, indirect calorimetry, and noncalorimetric methods (61).

Direct calorimetry is the measurement of the heat emitted from the body over a given period. A direct calorimeter chamber measures heat loss by radiation, convection, conduction, and latent heat arising from vaporization of water. Heat sink calorimeters capture the heat produced by liquid-cooled heat exchangers. Gradient layer calorimeters measure heat loss by a network of thermocouples in series surrounding the insulated chamber.

Indirect calorimetry estimates heat production indirectly by measuring oxygen consumption (VO2), CO2 production (VCO2), and the respiratory quotient (RQ), which is equal to the ratio

of the VCO2 to VO2. The principles of indirect calorimetry will be better explained in the following paragraph.
Another approach to measure TEE is the doubly labelled water technique (DLW). This method was developed about 50 years ago. DLW is based on the differences in turnover rates of $^{2}H_2O$ and H_2 ^{18}O in body water. After equilibration both ^{2}H and ^{18}O are lost as water whereas only ^{18}O is lost by respiration as carbon dioxide. The difference in the rate of turnover of the two isotopes can be used to calculate the carbon dioxide-production rate, VCO_2. Assuming a mean respiratory quotient (i.e. VCO_2/VO_2) of 0.85, the oxygen consumption rate (VO_2) and thus EE can then be calculated from VO_2 and VCO_2. The DLW technique is validated against indirect calorimetry and is now considered to be a gold standard for measurements of TEE under free-living conditions. The advantage of this technique is the noninvasive, nonintrusive manner in which it measures TEE. In weight-stable individuals, the DLW method may be used to assess energy requirements. The disadvantages of the method are the high cost of ^{18}O and expensive, sophisticated mass spectrometric equipment and the expertise required to measure ^{18}O and ^{2}H.
Twenty-four hour heart rate and activity monitors have been widely used to assess physical activity and TEE. Calculations of TEE from 24-h heart rate and activity monitors are based on intraindividual calibrations of VO_2 against heart rate using open circuit indirect calorimetry and ergometry. Heart rate monitors are robust and function well under field conditions. They save 24-h heart rate data. Free-living energy expenditure is derived from the minute-by-minute recordings of heart rate using the individual regression line for VO_2 versus heart rate. The individual nature of the heart rate versus VO_2 relationship makes it necessary to establish a regression equation for each participant at several levels and intensities of activity. One has to keep in mind that factors other than VO_2 (e.g. emotions, body position, ambient temperature, individual muscle groups exercised) also have an impact on heart rate. The method has been validated against DLW and indirect calorimetry. The major shortcoming of the 24-h heart rate method is its inaccuracy at low levels of physical activity. Variations at the lower end of the calibration curve may result in large errors in predicted TEE. The prediction error may reach about 15%.
Movement counters have also been widely applied in physical activity research. The most frequently used is the pedometer: a mechanical step counter, which records movement in one direction. A pedometer does not record non-step activities, such as during bicycling. It also cannot measure EE at different speeds of walking or running. Accelerometry techniques (e.g. triaxial accelerometry) have been developed to assess body acceleration in two or three planes of space. When compared with measurements of TEE or activity energy expenditure (AEE) accelerometers provide direct measurements of physical activity. However, physical activity is not equivalent to the energy cost of activity. Therefore activity monitors have limitations in quantifying TEE.

2.4 Indirect calorimetry

2.4.1 Introduction

The measurement of EE is the most accurate method to assess energy needs. Indirect calorimetry is based on noninvasive measurement of carbon dioxide production (VCO_2) and

oxygen consumption (VO_2). This technique arose from the observations of Lavoisier and Laplace that heat production of animals as measured by calorimetry was equal to that released when organic substances are burned, and that the same quantities of oxygen were consumed by the two processes.
The ultimate goal of nutrient metabolism is to produce energy. The most common way of extracting the chemical energy of a substrate is to completely oxidize it to carbon dioxide and water. The final common pathway of all cellular fuels, ie, carbohydrates, fats, and proteins, therefore is oxidation. The heat generated by biologic combustions is utilized to maintain body temperature. Because of its isothermia, however, the body cannot use heat to perform work. The chemical energy of oxidizable substrates is therefore transferred on to some all-purpose carriers, which bring the free energy to where it is needed. Chemical (biosyntheses), osmotic (active transports), and mechanical (muscular contraction) work is thus made possible.
Total average daily energy expenditure in kcal can be calculated by measuring the amount of oxygen used, and carbon dioxide released, by the body and the principle to calculate it from gas exchange was described by Weir (127):

The Weir' equation:
Energy Expenditure (Kcal/d) = 3.941 x VO2 (L/min) + 1.106 x VCO2 (L/min) - 2.17 x UrN (g/d)

Weir demonstrated that the error in neglecting the effect of protein metabolism on the caloric equivalent of oxygen is 1% for each 12.3% of the total calories that arise from protein. Therefore, the foregoing equation can be reduced to the following:
Energy Expenditure (Kcal/d) = 3.9 x VO2 (L/min) + 1.1 x VCO2 (L/min).

2.4.2 The respiratory quotient

Respiratory quotient (RQ) is defined as the ratio between VCO2 and VO2 (ie, VCO2/VO2) and reflects substrate utilization. The complete oxidation of glucose results in an RQ equal to 1.0. The complete oxidation of fat and protein results in an RQ averaging about 0.71 and 0.84, respectively, depending on the chemical structure of the foodstuff. Based on several physiologic studies, a very specific well-documented physiologic range for the overall RQ exists between 0.67 to 1.3 (10). With these limits of physiologic capability, values for RQ measured at the time of IC that are outside this range may be interpreted as nonphysiologic and presumably generated by some error in calibration, leak in the system, or artifactual influence. In this manner, the overall RQ is a clinically useful parameter to help substantiate test validity for IC measurements (85).
The measured RQ of a subject on a typical Western diet or mixed fuel nutritional regimen should theoretically fall in a range between 0.85 and 0.90. If the subject is overfed and lipogenesis occurs, the RQ may be displaced upward above 1.0. Alternatively, if the patient is underfed and begins to use endogenous fat stores to meet caloric requirements, the measured RQ may be displaced downwards below 0.85. Used in this manner, the RQ in theory becomes a valuable tool for nutrition assessment, identifying the metabolic consequences of over- and underfeeding. (82). This principle has been supported in the past by studies that suggested that high carbohydrate feedings, especially when given in excess of caloric requirements, lead to net lipogenesis, increased VCO2, and a resultant rise in RQ (3, 22, 45, 75).

Unfortunately, many factors exist (e.g. underlying chronic disease, acid/base disturbances, hyper or hypoventilation, the metabolism of a pharmacological agent, the stress response caused by acute disease process) that may displace the measured RQ in a manner that is difficult to identify clinically. These results suggest that while IC provides sufficient accuracy in estimating total 24-hour energy expenditure from the short-term measured REE, considerable uncertainty exists in using this method to assess carbohydrate and fat use. Therefore, one of the major clinical benefits of the measured RQ is to validate an IC study confirming that the measured values for RQ fall in the physiologic range (85).

2.4.3 Practical conditions of execution

The metabolic cart must be calibrated using standard gas mixtures (4% CO2, 16% O2, Balance Nitrogen) immediately before each examination. The methodology of measurement is standardized. It is necessary to ascertain whether the subject is in the postabsorptive state: after an overnight fast an individual is expected to oxidize mainly lipids and to display an RQ close to 0.8, whereas after feeding he is expected to oxidize mainly carbohydrates and to show an RQ close to 1. If the patient is mechanically ventilated, the conditions of exam execution are more complex. Nonetheless in this condition indirect calorimetry proves to be very useful (7).
Furthermore, subjects had to stay in a supine position, awake, motionless and breathe into mask connected to metabolic cart.
In the past, the Douglas bag method has been used for many measurements of basal and resting metabolism. In this method, all expired air is collected into a nonpermeable bag with a capacity up to 150 L. After a known period, the volume of expired air at standard temperature and pressure dried, and the concentrations of O2 and CO2 are measured from which $\dot{V}O_2$ and VCO2 and RQ are calculated. Commercial metabolic carts in laboratory and clinical settings have largely replaced the Douglas bag method.
Throughout a 24-hour period, EE may range from 10% below to 23% above a single measured "snap-shot" REE (128).
Because of the variability in REE, any measurement over a shortterm period of time (≤60 minutes), which is then extrapolated to represent the 24-hour total energy expenditure (TEE), may introduce significant error (110). To improve the degree to which a "snapshot" shortterm (20 to 60 minutes) IC study accurately reflects TEE in a 24-hour period, the concept of steady state (SS) was introduced into the methodology of IC testing. Designated as the end-point of IC testing, the steady-state interval cuold been defined by change in VO2 and VCO2 of <10% over a period of 5 consecutive minutes. The steady-state interval purportedly represents the baseline physiologic state in which measurements should reflect substrate use and the true REE. Achieving SS during IC testing is recommended to assure validity and reduce error from artifactual influences. Failure to achieve steady state does not necessarily invalidate the study but does signify the introduction of greater error and less accuracy in representing or extrapolating the short-term REE to the 24-hour TEE (84).

2.5 The prediction of energy expenditure

Indirect calorimetry allows accurate assessment of REE but it requires specialized equipment and trained personnel, factors that limit its availability. In multicenter studies, IC was reportedly used in only a minority of centers worldwide (87, 120).

The methods available to determine energy requirements instead IC are predictive methods. Equations for predicting REE are historically based on easily measurable parameters such as body mass, height, sex, age and also ethnicity. These equations are derived by regression analysis of the data from a group of subjects whose REE is measured by direct or indirect calorimetry.

The first set of equations was proposed as early as 1919 by Harris and Benedict, and has been one of the most used set of equations (46). Metabolic parameters were determined by indirect calorimetry on 136 men and 103 women. From these measurements they derived regression formulae which estimated REE from height, weight, age, and sex.

In 1985 Schofield (107) Schofield reviewed previously published studies reporting on the BEE of healthy children and adults. He synthesized the results of 114 different studies, including the study that had introduced the Harris-Benedict equation at the beginning of the 20th century. Schofield data included a total of 7173 BEE measurements. These data were subsequently used for the development of the FAO/WHO/UNU equations, as well as the Schofield equations (called Schofield [weight] and Schofield [weight and height]).

In 1985, the two most frequently used equations were the Harris-Benedict and the Schofield equations, but they are suspected to overestimate REE. The Harris-Benedict database included a relatively small number of subjects, with no children or adolescents below the age of 15 years, and a significant number of measurements were obtained by the use of closed-circuit indirect calorimetry, whilst the Schofield database included a large number (~40 %) of physically very active (Italian) subjects.

The FAO/WHO/UNU equation was developed based on a large number of measurements (greater than 7500) from children and adolescents 3–18 years of age from both underdeveloped and developed countries (30). Additional predictive equations commonly used in practice include the Ireton-Jones equation as published in 1992 (57), the Mifflin- St Jeor equations(89), and the Ireton-Jones equation for obese individuals (58). Equations used specifically to predict REE in critically ill patients include both the Swinamer (114) and the Penn State (33) formulas. The Mifflin-St Jeor equation was derived in a group of 498 healthy subjects, 47% of whom were defined as obese. The Ireton-Jones 1992, Swinamer, and Penn State equations were developed from hospitalized patient data sets.

Henry in 2005 (50) also developed a new database including 10,552 basal metabolic rate values collected from 166 previous investigations(the Oxford database) from a wide range of researchers. These algorithms excluded the Italian subjects from the Schofield/ FAO/WHO/UNU database, as it was believed that these subjects may have been responsible for the overestimation of predicted REE when using those equations, and also included a larger number of people from tropical areas. Hence, the Oxford equations may be more representative of healthy populations in contemporary society.

Presently, clinicians primarily use the FAO/ WHO/UNU, Schofield, and Oxford equations in their practice (19).

2.6 Nutritional requirement in ill infant and children

2.6.1 Introduction

Human energy requirements are estimated from measures of EE plus the additional energy needs for growth, pregnancy and lactation. Recommendations for dietary energy intake from food must satisfy these requirements for the attainment and maintenance of optimal health, physiological function and well-being. Energy balance is achieved when input (i.e. dietary energy intake) is equal to output (i.e. total energy expenditure), plus the energy cost of growth in childhood and pregnancy, or the energy cost to produce milk during lactation. When energy balance is maintained over a prolonged period, an individual is considered to be in a steady state. This can include short periods during which the day-to-day balance between intake and expenditure does not occur. An optimal steady state is achieved when energy intake compensates for total energy expenditure and allows for adequate growth in children, and pregnancy and lactation in women, without imposing metabolic, physiological or behavioural restrictions that limit the full expression of a person's biological, social and economic potential (31).

The energy requirements of infants and young children should balance EE at PALs conducive to normal development and should allow for deposition of tissues at rates consistent with health. Because of the dominant contribution of the brain (60% to 70%), basal metabolism is highest during the first years of life (52). The BEE and TEE are influenced by age (older greater than younger), gender (males greater than females), and feeding mode (breast-fed less than formula-fed infants) (17). The dietary references intakes (DRI) for infants and young children are based on a single equation using weight alone to predict TEE, plus an allowance for growth. Energy requirements of older children and adolescents are defined to promote normal growth and maturation and to support a desirable PAL consistent with health. Energy requirements of children and adolescents are highly variable as a result of differences in growth rate and physical activity.

Moreover, the prediction of energy requirement during illness is further challenging. Ill children are expected to differ in their energy expenditure when compared to healthy children up to the point that growth may cease during the metabolic response to disease or injury, especially if they are in critical conditions. The energy burden is variable and may be dependent on the type, severity, and stage of illness. Failure to accurately estimate EE leads to erroneous energy prescription and results in unintended energy imbalance. Energy imbalance is associated with poor outcomes and may be particularly relevant to infants and children with existing malnutrition or obesity.

Any state of disease, whether critical or not, may directly or indirectly alter components of EE and subsequently have marked effects on nutritional status (23).

Disorders afflicting critically ill children are known to alter EE. For instance, elevated EE is found in children with burns, neonatal septicaemia, congenital heart disease and head injury. Drugs used for sedation and muscle paralysis during mechanical ventilation decrease EE (121).

Previous studies using indirect calorimetry have shown that energy requirements are higher in critically ill pediatric patients and that REE is higher than that expected by a factor of 1.2–1.5 (44, 97, 116). Presumably, this is secondary to the metabolic response of the body to injury, sepsis, or surgical stress. In normal persons, the work of breathing represents 3–5% of the total metabolic rate. However, Bursztein et al. (14) reported a 24% reduction in the metabolic rate after mechanical ventilation was instituted in critically ill patients. Critically ill patients with

sepsis, trauma, or in a postsurgical state have an increased catabolic response, and this response has been shown to be proportional to the degree of metabolic insult (21).

2.6.2 The metabolic response to injury

The human response to the stress of injury, illness, or surgery is stereotypical and involves a series of metabolic changes. This metabolic response is driven by a complex neuroendocrine system and may be correlated to the nature and severity of the insult. In its original description, the response was characterized as biphasic, with brief ebb phase followed by a hypermetabolic flow phase . This hypermetabolic phase is catabolic and it is driven initially by a cytokine surge and increased counter regulatory hormones with insulin and growth hormone resistance. The result is breakdown of endogenous body stores, in particular muscle mass, to provide free amino acids that are used for the inflammatory response, tissue repair, and wound healing (88).
Recent accounts of measured energy expenditure have shown a muted hypermetabolic response after major illness, injury, or surgery. One exception is burn injury, which is characterized by a profound hypermetabolic response that may be sustained for several weeks. By contrast, metabolic measurements in most other illnesses reveal a muted and brief hypermetabolic response, compared with past descriptions. Other factors that impact the nature of the stress response include nutritional status, endogenous metabolic reserve, and interventions in the postinjury period. In the chronically ill child or one with protracted acute illness, the hypermetabolic response is expected to abate, and energy expenditure returns to baseline. Furthermore, the energy expenditure incurred by the stress response may be variable throughout the course of chronic illnesses, especially in illnesses that are characterized by episodic flares, worsening, or intercurrent complications. Therefore the metabolic response to stress cannot be accurately predicted and the metabolic alterations may change during the course of disease. Although nutrition support therapy cannot reverse or prevent this response, failure to provide optimal nutrients during this stage will result in exaggeration of existing nutrient deficiencies and in malnutrition, which may affect clinical outcomes.
Both underestimation and overestimation of energy needs during protracted illness may impact the ability to match the requirements with intake and result in energy imbalance.
Unintended underfeeding could be potentially harmful in ill children, particularly in those with preexisting malnutrition. Cumulative energy deficits are associated with loss of muscle mass, poor wound healing, increased risk of infections, increased morbidity, and a higher risk of mortality in critically ill adults (29). Both energy and protein deficits are undesirable. Protein deficits have been associated with nutritional deterioration in critically ill infants and children (54).
In recent years, there has been an increase in awareness of overfeeding, in which energy delivery is much higher than the requirements. This is due to the overestimation of energy needs, either due to inaccuracy of the common equations used for this purpose or due to the use of stress factors based on presumed hypermetabolism. Occult overfeeding is probably prevalent in children with chronic illnesses. Excess of energy from carbohydrate sources increases carbon dioxide production (VCO2) which results in increased respiratory rate and ventilator work. This condition may worsen respiratory insufficiency in patients with chronic pulmonary illness because their inability to adequately eliminate increased carbon dioxide that is produced when excessive nutrients are metabolized.
The harmful effects of overfeeding may result also in hepatic dysfunction due to steatosis and incipient intrahepatic cholestasis within 5 days of excessive parenteral nutrition. After 21 days,

biopsy results showed bile duct proliferation, canicular bile plugs and centrilobular cholestasis with bile pigment in hepatocytes and periportal inflammation (72).
Energy requirements are commonly determined using predictive equations of EE, derived from data of healthy subjects, but may not be accurate in pediatric patients. Therefore, accurate assessment of total EE is an essential tool for nutritional support in ill children.

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CHAPTER 2

AIM OF THE STUDY

The principal aim of this project research was to assess the nutritional status of children admitted to a tertiary health care center in order to improve nutritional support during hospitalization. Knowledge of metabolism, energy expenditure and nutrient requirements in ill children may provide information concerning nutritional needs and support both in the medium and long term.

Despite this knowledge, malnutrition still exists in hospitals and is often unrecognized.

The firth work, presented in topic 1, describes a prospective observational study performed within five pediatric clinical units at the IRCCS Foundation Ca' Granda-Ospedale Maggiore Policlinico in Milan, Italy. This project was undertaken to determine the prevalence of malnutrition in hospitalized children and to ascertain nutritional risk by application of the $STRONG_{kids}$ in order to identify subjects who will require nutritional evaluation or support during their inpatient stay.

Identification of children at high risk for malnutrition could facilitate the introduction of early and timely nutritional support and prevent the short or long-term impacts of malnutrition upon growth and development.

An additional aim was to characterize the distribution of risk across a number of variables, including biochemical indices, length of hospital stay and presence of underlying diagnosis.

Subsequently this first step of the study, the research project was carried out to better investigate the energy expenditure in hospitalized children, focusing on its variations in relationship to different diseases, stress or injury factors.

In this second part of the analysis, described in topic 2, the principal aims were to assess the basal energy expenditure depending on specific disease with the use of indirect calorimetry and to evaluate the accuracy of the WHO, Harris-Benedict and Schofield formulae in a large series of acutely and chronically ill children followed at the Pediatric Hospital.

An accurate evaluation of energy requirements allows to get directions about the appropriate feeding regimen administered together with the pharmacological therapy and, therefore, to prevent potentially negative impact on the evolution of the disease itself (eg. conditions of ketosis, protein catabolism, essential fatty acids utilization, hyperglycemia and / or impaired blood sugar levels).

In the medium and long-term individualized dietary plan, optimized in both caloric content and macronutrients composition, may be applied in order to avoid relapses of acute disease and to influence positively conditions such as overweight and obesity leading to the development of respiratory and gastrointestinal diseases.

CHAPTER 3

Topic 1

SHORT COMMUNICATION

Nutritional assessment and risk of malnutrition in hospitalized children in northern Italy

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Hospital malnutrition is a state in which a deficiency or imbalance of energy, proteins and other nutrients causes measurable adverse effects on functional and clinical outcomes. The nutritional status of children often declines after admission to the hospital, possibly slowing recovery time and increasing susceptibility to infection.
The reported prevalence of malnutrition in pediatric hospitals ranges from 6% to 30% (6) and may also depend on the operational definition of malnutrition and the study population (2). There are currently no recommendations on nutritional evaluation and risk of hospital malnutrition screening.
The aim of this study was to assess the nutritional status of hospitalized children, as measured by the prevalence of malnutrition, the risk of developing malnutrition and the role of biochemical indices in predicting the length of hospitalization.
This cohort study was performed between 1 July 2011 and 31 December 2012 in five clinical units at the IRCCS Foundation C a Granda-Ospedale Maggiore Policlinico in Milan, Italy. We calculated that 300 subjects were needed to estimate a 20% prevalence of malnutrition on admission with a precision of 5% (exact 95% CI, 25% to 35%). Accordingly, 300 (88%) of 340 consecutive patients agreed to participate in the study and were recruited from the pediatric (n=111), short observation and emergency (n=70), nephrology (n=53), intensive care (n=50) and cystic fibrosis (n=16) units. Children admitted to the study showed the following disorders: lung and heart (n=62), kidney (n=52), rheumatologic (n=47), neurologic (n=28), blood (n=30), gastrointestinal (n=14), liver (n=6) and endocrine (n=6). Patients were included if they were aged between 1 month and 17-year-old and were admitted to the hospital during the study period for more than 24 h and their parents provided informed consent. Infants who were born before 37 weeks of gestation and were under 1-year-old were excluded, as were patients who were hospitalized for more than 60 days. The study was approved by the institutional ethics committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Anthropometric parameters included weight, height/length and body mass index (BMI). Weight was measured in all children using calibrated standard equipment on admission and discharge. Supine length was measured in children aged 2 years or less and standing height in children over the age of 2 years. Wasting was defined as BMI of less than – 2 standard deviation scores (SDS). Stunting was defined as length or stature of less than – 2 SDS for the child's age. Obesity was defined as BMI > 2 SDS. Nutritional risk was assessed using the $STRONG_{kids}$ questionnaire (7). At admission and discharge, a fasting blood sample was collected to analyse nutrition-related haematochemical indexes inclusive of insulin-like growth factor 1 (IGF-1), prealbumin, transferrin, albumin, insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides. For the statistical analysis, continuous data were reported as median and interquartile range (IQR) because of skewed distributions. Somers' D was used to evaluate the association between length of stay and selected anthropometric and biochemical indices. Statistical significance was assigned to a value of $p < 0.05$.
Of the 300 patients, 245 (82%) could be analyzed. They had a median (IQR) age of 6 (10), and 117 (44.5%) of them were females. The median (IQR) length of stay was 6 (5) days. Wasting was detected in 25 (10.2%) of the patients at admission and in 19 (8.1%) at discharge. At admission, stunting was present in 16 (6.5%) patients. Nutritional care and support was provided for wasting children. The prevalence of obesity was 7.0% at admission and 6.9% at discharge. When it came to the biochemical indices, length of stay was inversely associated with serum albumin (-10% probability of longer stay, 95% CI -19 to -1%, $p = 0.02$ for every 1 g/dL increase of albumin). Length of stay was not associated with BMI ($p = 0.347$) and the STRONGkids questionnaire score ($p = 0.08$). The questionnaire score was inversely associated with serum albumin (-20% probability of higher SK score, 95% CI -29 to -7%, $p = 0.001$, for every 1 g/dL increase of albumin). Albumin levels ranged from 1.2 to 5.3 g/dL, median 4.1

g/dL in the whole population. Other negative association trends ($0.10 > p > 0.05$) were found between serum HDL levels and high questionnaire score values.
Children already malnourished on admission may be at risk of further nutritional and clinical deterioration. Our study population showed a lower malnutrition prevalence at admission than another Italian survey (3), while the prevalence of obesity was comparable to that found in northern Italian children (9).
Length of stay was mildly related to the questionnaire score and in agreement with its potential predictive value. The inverse associations found for serum albumin with either length of stay and the questionnaire score suggest that chronic malnutrition may not just relate to, but also be predictive of, the length of hospital stay. Indeed, albumin is the indicator of nitrogen anabolism with the longest half-life – of around 20 days – while other anabolic indicators, such as insulin-like growth factor-1, prealbumin, transferrin, whose half-life ranges from one to 7 days, did not show any type of relationship.
Associations involving serum albumin have already been described in hospitalized adults (5), but there have been few reports in children so far (8). The decrease in serum albumin concentrations only seems to develop late in the course of malnutrition, and as a consequence, it may take place in the most severe cases.
A negative trend between serum HDL-C and LDL-C and clinical risk has been described in adults (7,4) and also in pediatric patients (1). Nevertheless, the biological bases connecting lower serum albumin and HDL cholesterol with gravity of disease deserve further investigation, because malnutrition may be just a part of the whole picture. In conclusion, assessing nutritional status, nutritional risk and appropriate biochemical indices at admission may help to predict the length of hospital stay and to optimize clinical interventions and follow-up.

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CONFLICT OF INTEREST
The authors disclose no conflict of interests.

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CHAPTER 4

Topic 2

ACCURACY OF PREDICTION FORMULAE FOR THE ASSESSMENT OF RESTING ENERGY EXPENDITURE IN HOSPITALIZED CHILDREN

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Short title: Estimation of REE in hospitalized children

Submitted.

ABSTRACT

Background and aim: Resting energy expenditure (REE) is commonly estimated from prediction formulae but it is largely unknown how these formulae perform in the pediatric hospital setting.

Methods: We performed a cross-sectional study of 236 infants, children and adolescents consecutively admitted to the Intermediate Care, Emergency, Nephrology, Intensive Care, and Cystic Fibrosis Units of an Italian Pediatric Hospital. REE was measured by indirect calorimetry and estimated using the WHO, Harris-Benedict and Schofield formulae.

Results: The mean (standard deviation) difference between the estimated and measured REE was -1 (234), 82 (286), -3 (233) and -2 (214) kcal/die for the WHO, Harris-Benedict, Schofield-weight and Schofield-weight and height formulae, respectively. Even though the WHO and Schofield formulae gave accurate estimates of REE at the population level, all the formulae were not accurate enough to be employed at the individual level.

Conclusions: Commonly used prediction formulae should not be used to estimate REE in hospitalized children.

1. INTRODUCTION

1.1 State of the art

Malnutrition is common in hospitalized children and is associated with increased length of stay and complications (6,1). An adequate assessment of nutritional status is central to the prevention and treatment of hospital malnutrition in children, especially in intensive care units (19).

The estimation of total energy expenditure, the first step of tailoring nutritional support, usually starts from the measurement or the estimation of basal or resting energy expenditure (REE) (3,13,17). REE can be measured using indirect calorimetry (IC) but is more commonly estimated using prediction formulae (10). As pointed out by recent reviews, these formulae have not undergone an extensive evaluation in heterogeneous clinical populations (3,17).

Most clinical validation studies of REE formulae have been performed in mechanically ventilated children (14). Even if the measurement of REE in such children may be especially reliable (18), the findings obtained in mechanically ventilated children cannot be generalized to spontaneously breathing children (17). The four most commonly employed REE prediction formulae are the WHO equation, the Harris-Benedict equation, the Schofield equation based on weight, and the Schofield equation based on weight and height (10). Although these formulae have been validated with variable results in healthy children, their accuracy in ill children is mostly unknown (3,17).

1.2 Aim of the study

The aim of the present study was to evaluate the accuracy of the WHO, Harris-Benedict and Schofield formulae in a large series of acutely and chronically ill children followed at an Italian Pediatric Hospital.

2. PATIENTS AND METHODS

2.1 Study design

We performed a cross-sectional study of 236 infants, children and adolescents consecutively admitted to the Intermediate Care, Emergency, Nephrology, Intensive Care, and Cystic Fibrosis Units of the De Marchi Pediatric Hospital (Milan, Italy) between September 2013 and March 2015. Patients from all Units were excluded from the study in the presence of: 1) respiratory quotient < 0.67 or > 1.3 (10); 2) need of supplemental oxygen; 3) inability to maintain the fasting state for at least 4 hours. Patients from the Nephrology Unit were excluded from the study in the presence of: 1) nephrotic syndrome; 2) treatment with intravenous methylprednisolone; 3) kidney transplantation with circulating anti-donor antibodies; 4)

hemodialysis or peritoneal dialysis with acute disease, e.g. influenza. Patients from the Emergency Unit were excluded from the study in the presence of: 1) gas leaks > 10%; 2) inspiratory oxygen fraction > 40%. The study was approved by the Ethical Committee of the De Marchi Pediatric Hospital and the parents of the children gave their written informed consent.

2.2 Anthropometry

Weight, length (< 2 years) or height (≥ 2 years), arm circumference and triceps skinfold were measured following international guidelines (11). BMI was calculated as weight (kg) / length or height $(m)^2$. Standard deviation scores (SDS) of weight, length, height, weight-for-length, weight-for-height, BMI, arm circumference and triceps skinfold were calculated using the WHO reference data (21,22) .

2.3 Measurement of REE

REE was measured in thermoneutral conditions using an open-circuit indirect calorimeter (Vmax 29, Sensor Medics, Yorba Linda, CA, USA). An 8-hour fasting period was recommended, but a fasting period of at least 4 hours was acceptable for patients age ≤ 2 years. In spontaneously breathing patients, a canopy was positioned around the patient's head and the expired air was drawn from the hood at a fixed rate (7). In patients requiring mechanical ventilation, the calorimeter was connected to the ventilator (Dräger Babylog VN500, Dräger, Andover, MA, USA). No changes in the ventilator settings were done for at least 1 hour prior to the REE measurement. The patients were measured in the supine position for at least 30 min, including a 5-min acclimation period (7). REE was calculated from oxygen uptake and carbon dioxide output using Weir's equation (20).

2.4 Estimation of REE

REE was estimated using the four most commonly employed formulae (10): 1) the WHO formula, 2) the Harris-Benedict formula, 3) the Schofield formula based on weight and, 4) the Schofield formula based on weight and height. The formulae were calculated as reported by current guidelines and illustrated in **Table 1**(10).

Table 1 – Algorithms of the four prediction equations for REE used in the study .

Resting Energy Expenditure Prediction Equation		
Harris-Benedict	Men	REE: 66.47+13.75*wt+5.0*ht-6.76*age
	Women	REE: 655.1+9.56*wt+1.85*ht-4.68*age
FAO/WHO/UNU	Males (0-3 y)	REE: 60.9*wt-54
	Females (0-3 y)	REE: 61.0*wt-51
	Males (3-10 y)	REE: 22.7*wt+495
	Females (3-10 y)	REE: 22.4*wt+499
	Males (10-18 y)	REE: 17.5*wt+651
	Females (10-18 y)	REE: 12.2*wt+746
Schofield (weight and height)	Males (0-3 y)	REE: 0.167*wt + 1517.4*ht - 617.6
	Females (0-3 y)	REE: 16.25*wt + 1023.2*ht - 413.5
	Males (3-10 y)	REE: 19.60*wt + 130.3*ht + 414.9
	Females (3-10 y)	REE: 16.97*wt + 161.8*ht + 371.2
	Males (10-18 y)	REE: 16.25*wt + 137.2*ht + 515.5
	Females (10-18 y)	REE: 8.365*wt + 465*ht + 200
Schofield (weight)	Males (0-3 y)	REE: 50.48*wt-30.33
	Females (0-3 y)	REE: 58.29*wt-31.05
	Males (3-10 y)	REE: 22.7*wt+505
	Females (3-10 y)	REE: 20.3*wt+486
	Males (10-18 y)	REE: 17.7*wt+659
	Females (10-18 y)	REE: 13.4*wt+693

All equations are in kcal; wt = weight (kilograms); ht = height (centimeters for Harris–Benedict, and meters for Schofield formula based on weight and height); age is in years.

2.5 Statistical analysis

Most variables were not Gaussian-distributed and all are reported as percentiles. Bland-Altman plots of the bias (estimated REE - measured BEE) vs. the average [(estimated REE + measured REE) / 2] and of the percent bias [estimated REE - measured REE) / measured REE] vs. the average were used to evaluate the presence of proportional bias (2,4). Proportional bias was detected in all cases so that the Bland-Altman limits of agreement (LOA) could not be calculated. The absolute bias but not the percent bias was Gaussian-distributed as determined by using kernel density plots and the Shapiro-Wilk test. The comparison of the measured and estimated values of REE was performed using Student's t-test for paired data. We evaluated the association of the percent bias of the Schofield-weight equation with sex, age, weight and respiratory insufficiency (RI) using multivariable median regression (9). The response variable was percent bias (continuous, %) and the predictors were sex (discrete, 0 = female; 1 = male), age (continuous, years), weight (continuous, kg) and RI (discrete, 0 = no; 1 = yes). All the relationship of the outcome with the continuous predictors were linear, as detected also by using multivariable fractional polynomials (16). Statistical analysis was performed using Stata 14.1 (Stata Corporation, College Station, TX, USA).

3. RESULTS

3.1 Clinical and anthropometric features of the patients

A number 236 consecutive patients (200 Caucasians, 85% and 123 boys, 52%) aged 0.04 to 17.7 years were studied. Among them, 210 (89%) were spontaneously breathing.

The reasons for hospitalization were (in order of frequency): 1) RI (n = 81); 2) kidney disease (n = 51); 3) rheumatic disease (n = 32); 4) cystic fibrosis (n = 18); 5) blood disease (n = 17); 6) gastrointestinal disease (n = 16); 7) neurological disease (n = 12); 8) infectious disease (n = 6); 9) slow growth (n = 3).

The anthropometric and metabolic measurements of the patients are given in **Table 2**. The median SDS of weight-for-age, length-for-age, height-for-age, weight-for-length, weight-for-height and BMI-for-age were negative, signaling values always under the 50th percentile. The median BMI-for-age was -0.33 SDS, corresponding to the 37th percentile and 28 children (12%) had a BMI-for-age < 2 SDS. The median (interquartile range) BEE was 895 (419 to 1315) kcal/day.

Table 2 – Anthropometric and metabolic measurements of the study children

	n	P_{50}	P_{25}	P_{75}
Age (years)	236	6.6	0.8	11.4
Weight (kg)	236	19.7	7.9	36.7
Weight-for-age (SDS WHO)	152	-0.74	-1.67	0.16
Length (cm)	79	62.00	57.00	72.00
Length-for-age (SDS WHO)	79	-0.55	-1.70	0.41
Height (cm)	157	135.0	116.0	152.0
Height-for-age (SDS WHO)	157	-0.72	-1.49	0.12
Weight-for-length (SDS WHO)	79	-0.43	-1.56	0.80
Weight-for-height (SDS WHO)	49	-0.16	-1.06	0.34
Body mass index (kg/m^2)	236	15.9	14.7	18.5
Body mass index-for-age (SDS WHO)	236	-0.33	-1.20	0.69
Arm circumference (cm)	223	17.0	14.0	21.0
Arm circumference-for-age (SDS WHO)	72	-0.34	-1.62	0.68
Triceps skinfold (mm)	219	9.6	7.7	12.7
Triceps skinfold-for-age (SDS WHO)	71	-0.01	-0.42	1.19
Resting energy expenditure (kcal/day)	236	895.0	419.5	1315.0
Resting energy expenditure (kcal/kg weight)	236	40	32	53

Abbreviations: P_x = X^{th} percentile; SDS = standard deviations scores; WHO = World Health Organization.

WHO SDS were calculated as follows: weight-for-age from 0 to 10 years; length-for-age for age < 2 years; height-for-age for age ≥ 2 years; weight-for-length for length from 45 to 110 cm; weight-for-height for height from 65 to 120 cm; arm circumference-for-age from 0.25 to 5 years; triceps skinfold-for-age from 0.25 to 5 years.

3.2 Accuracy of prediction formulae

The bias of the prediction formulae is given in **Table 3**. Both the absolute and the percent bias decreased for increasing value of the average (data not shown) so that the calculation of LOA was unwarranted. However, because IC is a reference method, the estimates reported in **Table 3** quantify the error of the formulae and its inter-individual variability.

Using the WHO formula, the percent bias was ≤ 20% in 39 (16%) and ≥ 20% (28%). This offers a rough but clinically useful measure of how many children would go underfed or overfed using such equation (13). The corresponding numbers were 24 (10%) and 96 (40%) for the Harris-Benedict formula; 37 (16%) and 67 (28%) for the Schofield-weight formula and; 34 (14%) and 61 (26%) for the Schofield-weight and stature formula.

Table 3 – Absolute and percent bias associated with the estimation of resting energy expenditure.

	n	mean	SD	P_{50}	P_{25}	P_{75}
Bias - WHO (kcal)	236	-1	234	-11	-134	117
Bias - WHO (%)	236	—[†]	—[†]	-2	-16	25
Bias - Harris-Benedict (kcal)	236	82[*]	286	76	-103	270
Bias - Harris-Benedict (%)	236	—[†]	89 —[†]	8	-9	65
Bias - Schofield Weight (kcal)	236	-3	233	-14	-140	122
Bias - Schofield Weight (%)	236	—[†]	—[†]	-2	-15	27
Bias - Schofield Weight & Height (kcal)	236	-2	214	-18	-134	120
Bias - Schofield Weight & Height (%)	236	—[†]	—[†]	-2	-14	22

[†] Not given because not Gaussian-distributed

[*] $p < 0.001$ (Student's *t*-test for paired data).

Abbreviations: SD = standard deviation; $P_x = X^{th}$ percentile.

Bias is calculated as (estimated resting energy expenditure – measured resting energy expenditure); percent bias is calculated [(estimated resting energy expenditure – measured resting energy expenditure) / measured energy expenditure)].

Figure 1 plots the joint contribution of sex, age, weight and RI to the percent bias of the Schofield formula (multivariable median regression). The median percent bias was lower in males than in females (-11%, 95%CI -20% to -2%, p = 0.021), was not associated with age (p = 0.411) or weight (p = 0.793) and was higher (35%, 95%CI 23 to 46%) in children with RI (p < 0.001).

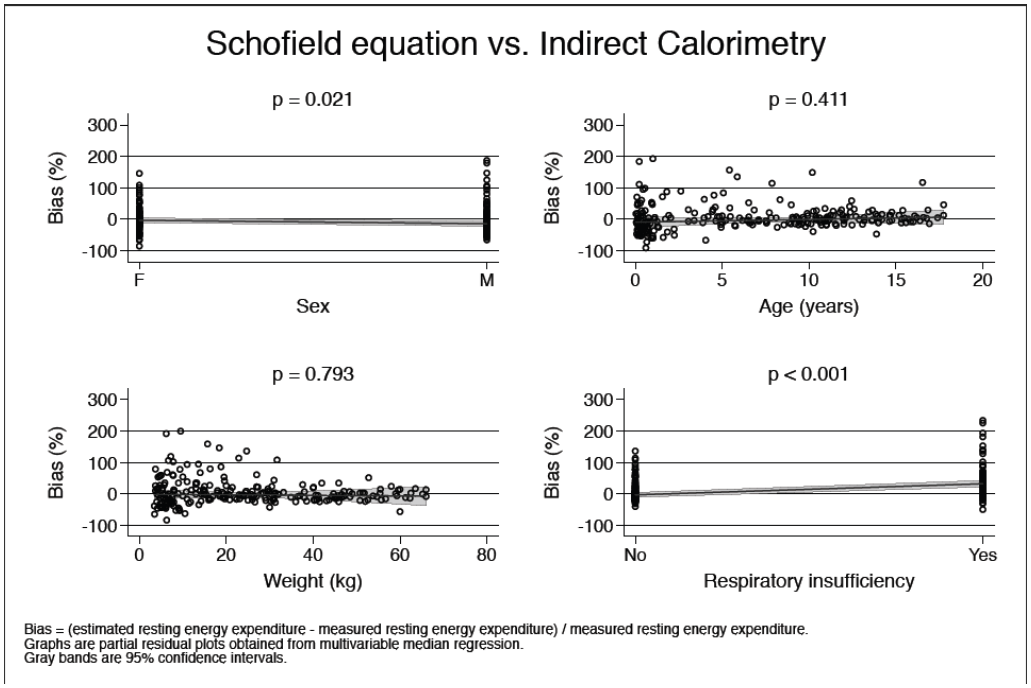

Figure 1. Contribution of sex, age, weight and RI to the percent bias of the Schofield formula (multivariable median regression).

4. DISCUSSION

Most of the available clinical validation studies of REE formulae have been performed in mechanically ventilated children (3,17). In the present study, we evaluated the accuracy of the most commonly employed REE prediction formulae in a large sample of hospitalized children. We found that, even though the Schofield formulae offered accurate estimates of REE at the population level (small mean bias), all the formulae were not accurate enough to be safely employed at the individual level (large SD of the bias). This finding has important implications for the treatment and prevention of hospital malnutrition (1). Our results highlight the risk of underfeeding or overfeeding in hospitalized children in whom the energy prescription is based on REE estimated from prediction equations.

In order to evaluate how REE formulae perform in the pediatric hospital setting, we chose to study an heterogeneous population of hospitalized children. An obvious limitation of this approach is that, for most of the diseases that we have studied, we do not reach a sufficient number of children to test whether purposely developed population-specific formulae perform better than traditional formulae. Further studies should be performed to test whether population-specific formulae can improve the accuracy of REE estimation in the pediatric hospital setting.

The mean bias of the WHO (-1 kcal/day), Schofield-weight (-3 kcal/day) and Schofield-weight and height (-2 kcal/day) formulae was much lower than the mean bias of the Harris-Benedict (82 kcal/day) formula. However, if one considers the large SD of the bias observed for all

formulae, it is very clear that none of these formulae can be applied satisfactorily at the individual level. (It should be noted that the calculation of LOA in our study was not possible because of the presence of negative proportional bias for all formulae, independently from the fact that the bias was expressed as absolute or percentage values).

Despite the highly variable age and weight of our children, we found that they were not associated with the percent bias of the Schofield-weight formula. However, being male was associated with lower bias and having RI with greater bias.
Our findings about the accuracy of the Schofield formulae agree with those of other researchers who studied mechanically ventilated children or children recovered in Intensive Care Units (5,14). Our conclusion that REE formulae should not be used in hospitalized children, be they under mechanical ventilation or not, is the same offered by most studies of mechanically ventilated children (14,15,18). It is also worth noting that, in a clinical population made mostly of children with failure to thrive (8), the Schofield-weight formula proved slightly better than the Harris-Benedict formula.

In conclusion, commonly used prediction formulae should not be used to estimate REE in hospitalized children. Further studies are needed to test whether population-specific formulae can improve the accuracy of REE estimation in the hospital setting.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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CHAPTER 5

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In children nutritional status may deteriorate over the course of a hospital admission, especially in patients with an underlying disease. Thus, the attention for nutrition during infancy and childhood should be e a priority in order to ensure a normal growth and an improved state of health together with the pharmacological therapy.

This thesis work studied two principal topics: in a first stage of analysis the aim was to assess the nutritional status of children admitted to a tertiary care center by evaluating the prevalence of malnutrition, both under and overnutriotion, and the risk to develop it during the hospital stay. The second stage of the analysis consisted of a cross-sectional study conducted in patients admitted to different pediatric settings at the same hospital, "De Marchi" Clinic in Milan, in order to better investigate the metabolic response to illness and the changes in basal energy expenditure in children.

In **Topic 1** it was found that the prevalence of wasting and stunting are lower than another Italian survey, in particular acute malnutrition improves thanks to nutritional care and support provided to children. Instead, the prevalence of obesity is comparable to data collected in the northern Italy (2), confirming the general shift of the nutritional concerns in children from under-nutrition to over- nutrition especially in developed countries.

Over 30 years to early in the current century the prevalence of overweight amongst school age children and teens in the United States tripled from 5 to more than 16% (5). Similar data from the United Kingdom and other countries also illustrate rising rates of obesity (13,1).

Although studies continue to highlight the high incidence of undernutrition in patients, the increasing incidence of obesity in the general population suggests that an ever increasing number of obese subjects will be admitted to hospital. Nutritional problems are often misdiagnosed, and especially the co-presence of under and overnutrition is not usually recognized (3).

Another aspect investigated in this research project was the assessment of the prognostic power on clinical outcome of a nutritional risk screening tool, i.e. the $STRONG_{kids}$. This method is easy-to-use and rapid, with a median completion time of only 3 min. However, the length of stay (LOS), the principal index which describes hospitalization and possible complications associated with it, was mildly related to the questionnaire score.

In any case, further analysis are necessary to find the best screening tool aimed to identifying the clinical conditions of malnutrition, even when under and overnutrition coexist, in order to optimize clinical interventions and follow-up.

Lastly, in this first part of the study, serum biomarkers have been used to evaluate the adequacy of nutritional status during hospital admissions. In fact, serum biomarkers, measured as part of routine blood tests, are objective and relatively convenient to use. In critically ill adults, albumin, pre-albumin, transferrin and retinol binding protein have been used to assess nutritional status. In particular, in this population group, prealbumin and retinol binding protein are nutritional biomarkers with the best prognostic value (4,9).

In contrast, we found that in ill children, especially those with chronic disease, albumin had the most consistent prognostic value (showing significant inverse correlations with hospital LOS and $STONG_{kids}$ score). Instead, prealbumin, commonly thought to be the most sensitive indicator of nutrition status due to its shortest half-life (2 days), did not show any significant association with clinical outcomes in this cohort. Nevertheless, care must be taken not to solely

consider nutrition status as the only factor that modulates the levels of these proteins in the setting of illness. For example, low albumin levels can also be reflective of severity of disease in patients with cardiac disease and liver failure (6). Moreover, albumin, prealbumin and transferring are negative acute phase reactants, so they are down-regulated during periods of stress and inflammation (8). Studies have shown that feeding, no matter how adequate, may not be able to correct visceral protein concentrations (12,10). Instead of improvements of nutritional state, changes in visceral protein concentrations may be more indicative of an overall improvement in medical status of patients.

In **Topic 2** the principal purpose was to better investigate the energy expenditure in hospitalized children, focusing the research on its variations in relationship to different diseases. In particular the aim was to describe the metabolic state based on measured energy expenditure and the agreement between measured and estimated REE by the most common employed standard equations.

In fact, in clinical practice, in the absence of direct data from indirect calorimetry, a variety of algorithms have been developed and employed as a surrogate method to estimate energy expenditure. According to an European survey by van der Kuip et al (2004) (11) , in the majority of European PICUs energy requirements are estimated by means of weight and age or by using predictive formulae, mainly those published by Schofield. These equations are based on demographic and anthropometric variables such as age, sex, weight, and height. Most equations used to estimate REE were derived from healthy population data, hence, they have a high likelihood of inaccuracy in determining accurate REE in sick patients. There have been several reports of inaccuracy of these equations in children with chronic illnesses. General predictive equations (eg, the FAO/WHO/UNU and Harris-Benedict equations) are inefficient in predicting REE in most cases because they are not disease specific and are based on the assumption that weight may truly reflect body composition, which does not always hold true.

The study population included in the present analysis was composed of 236 consecutive patients admitted to different wards of a large Italian Pediatric Hospital. The sample was large and heterogeneous with regard to demographics, anthropometry and conditions.

We have found that all the equations considered are not accurate enough to be safely employed at the individual level for planning feeding strategies, both in chronically ill children than in patients with less severe clinical conditions , because of the large standard deviation of the bias (about more than 200 kcal/day). Their use is restricted to a population level.

Larger and multicentric studies are needed in order to obtain a wide set of data able to suggest possible corrections to available equations or to test whether population-specific formulae can improve the accuracy of REE estimation in the clinical setting reducing the error in establishing caloric losses and then dietary requirements. These aims may have a strong influence on the health conditions of pediatric populations, particularly if affected by chronic inflammatory disorders, since any type of energy imbalance may accumulate over time, with deterioration of nutritional status and negative impact on patient outcomes.

Recently, Mehta et al. (2015) (*7*) described a VCO_2-based equation, which is able to predict the measured REE and metabolic state of critically ill children undergoing mechanical ventilation in the PICU. This simplified equation may be a superior alternative to standard equations because predicts REE with higher accuracy. In fact, stand-alone VCO_2 monitors are routinely available in most PICUs but future studies are needed to validate this new formula.

In conclusion, the equations used to predict energy expenditure may actually lead to a high probability of unintended underfeeding or overfeeding of ill children and then to a higher risk of malnutrition.

Indirect calorimetry remains the most accurate indicator of REE for planning feeding strategies and the standard against which matching the calculated values of energy expenditure to improve their predictivity.

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CHAPTER 6

Appendix 1. PAPERS PUBLISHED

Paper n. 1

Luca Valenti , Patrizia Riso, Alessandra Mazzocchi, Marisa Porrini, Silvia Fargion, Carlo Agostoni. **Dietary Anthocyanins as Nutritional Therapy for Nonalcoholic Fatty Liver Disease.** Oxidative Medicine and Cellular Longevity Volume 2013, Article ID 145421, 8 pages http://dx.doi.org/10.1155/2013/145421

Abstract:

Nonalcoholic fatty liver disease (NAFLD), defined by excessive lipid accumulation in the liver, is the hepatic manifestation of insulin resistance and the metabolic syndrome. Due to the epidemics of obesity, NAFLD is rapidly becoming the leading cause of altered liver enzymes in Western countries. NAFLD encompasses a wide spectrum of liver disease ranging from simple uncomplicated steatosis, to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Dietmay affect the development of NAFLD either by increasing risk or by providing protective factors. Therefore, it is important to investigate the role of foods and/or food bioactives on the metabolic processes involved in steatohepatitis for preventive strategies. It has been reported that anthocyanins (ACNs) decrease hepatic lipid accumulation and may counteract oxidative stress and hepatic inflammation, but their impact on NAFLD has yet to be fully determined. ACNs are water-soluble bioactive compounds of the polyphenol class present in many vegetable products. Here, we summarize the evidence evaluating the mechanisms of action of ACNs on hepatic lipid metabolism in different experimental setting: in vitro, in vivo, and in human trials. Finally, a working model depicting the possible mechanisms underpinning the beneficial effects of ACNs in NAFLD is proposed, based on the available literature.

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Review Article

Dietary Anthocyanins as Nutritional Therapy for Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD), defined by excessive lipid accumulation in the liver, is the hepatic manifestation of insulin resistance and the metabolic syndrome. Due to the epidemics of obesity, NAFLD is rapidly becoming the leading cause of altered liver enzymes in Western countries. NAFLD encompasses a wide spectrum of liver disease ranging from simple uncomplicated steatosis, to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Diet may affect the development of NAFLD either by increasing risk or by providing protective factors. Therefore, it is important to investigate the role of foods and/or food bioactives on the metabolic processes involved in steatohepatitis for preventive strategies. It has been reported that anthocyanins (ACNs) decrease hepatic lipid accumulation and may counteract oxidative stress and hepatic inflammation, but their impact on NAFLD has yet to be fully determined. ACNs are water-soluble bioactive compounds of the polyphenol class present in many vegetable products. Here, we summarize the evidence evaluating the mechanisms of action of ACNs on hepatic lipid metabolism in different experimental setting: *in vitro*, *in vivo*, and in human trials. Finally, a working model depicting the possible mechanisms underpinning the beneficial effects of ACNs in NAFLD is proposed, based on the available literature.

1. Introduction

In the last decades, the pandemic of overweight and obesity related to sedentary lifestyle and excess intake of refined foods has led to a dramatic rise in the prevalence of the metabolic syndrome and associated conditions, such as type 2 diabetes and dyslipidemia, leading to accelerated atherosclerosis [1], but also to nonalcoholic fatty liver disease (NAFLD) [2, 3].

Lifestyle and dietary habits represent both major risk and protective factors in the development and progression of degenerative diseases [4].

Diets rich in fruits and vegetables are among the recommended lifestyle modifications to decrease the risk of degenerative diseases, such as cardiovascular disease but also to reduce the complications associated with metabolic disorders and advanced atherosclerosis. Diet is in fact affordable and available and usually does not include the side effects and the metabolic and physiologic burden that medications impose on body systems [5].

In this regard, many different dietary components are under study for their possible pharmacologic activity in several pathophysiological conditions at different levels (e.g., vascular, immune, hepatic, etc.).

Most bioactive compounds have been documented in fruits and vegetables [6] and their mechanisms of action investigated both in *in vitro* and in *in vivo* models. In particular, great interest has been devoted to several classes of polyphenols and especially to a specific subset of molecules called anthocyanins (ACNs).

Paper n. 2

Carlo Agostoni, Emilio Fossali, Edoardo Calderini, Alberto Edefonti, Carla Colombo, Alberto Battezzati, Simona Bertoli, Antonio Pio Mastrangelo, Cinzia Montani, Arianna Bisogno, Valentina De Cosmi, Alessandra Mazzocchi, Claudia Maffoni, Michela Perrone, Giorgio Bedogni. **Nutritional assessment and risk of malnutrition in hospitalised children in northern Italy.** Acta Paediatr. 2014 Sep;103(9):e416-7.

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SHORT COMMUNICATION

Nutritional assessment and risk of malnutrition in hospitalised children in northern Italy

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Hospital malnutrition is a state in which a deficiency or imbalance of energy, proteins and other nutrients causes measurable adverse effects on functional and clinical outcomes. The nutritional status of children often declines after admission to the hospital, possibly slowing recovery time and increasing susceptibility to infection.

The reported prevalence of malnutrition in paediatric hospitals ranges from 6% to 30% (1) and may also depend on the operational definition of malnutrition and the study population (2). There are currently no recommendations on nutritional evaluation and risk of hospital malnutrition screening.

The aim of this study was to assess the nutritional status of hospitalised children, as measured by the prevalence of malnutrition, the risk of developing malnutrition and the role of biochemical indices in predicting the length of hospitalisation.

This cohort study was performed between 1 July 2011 and 31 December 2012 in five clinical units at the IRCCS Foundation Cà Granda-Ospedale Maggiore Policlinico in Milan, Italy. We calculated that 300 subjects were needed to estimate a 20% prevalence of malnutrition on admission with a precision of 5% (exact 95% CI, 25% to 35%). Accordingly, 300 (88%) of 340 consecutive patients agreed to participate in the study and were recruited from the paediatric (n = 111), short observation and emergency (n = 70), nephrology (n = 53), intensive care (n = 50) and cystic fibrosis (n = 16) units. Children admitted to the study showed the following disorders: lung and heart (n = 62), kidney (n = 52), rheumatologic (n = 47), neurologic (n = 28), blood (n = 30), gastrointestinal (n = 14), liver (n = 6) and endocrine (n = 6). Patients were included if they were aged between 1 month and 17-year-old and were admitted to the hospital during the study period for more than 24 h and their parents provided informed consent. Infants who were born before 37 weeks of gestation and were under 1-year-old were excluded, as were patients who were hospitalised for more than 60 days. The study was approved by the institutional ethics committee of the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy.

Anthropometric parameters included weight, height/length and body mass index (BMI). Weight was measured in all children using calibrated standard equipment on admission and discharge. Supine length was measured in children aged 2 years or less and standing height in children over the age of 2 years. Wasting was defined as BMI of less than – 2 standard deviation scores (SDS). Stunting was defined as length or stature of less than – 2 SDS for the child's age. Obesity was defined as BMI > 2 SDS. Nutritional risk was assessed using the STRONGkids questionnaire (3). At admission and discharge, a fasting blood sample was collected to analyse nutrition-related haematochemical indexes inclusive of insulin-like growth factor 1 (IGF-1), prealbumin, transferrin, albumin, insulin,

Paper n. 3

Lotte Lauritzen, Paolo Brambilla, Alessandra Mazzocchi, Laurine B. S. Harsløf, Valentina Ciappolino and Carlo Agostoni. **DHA Effects in Brain Development and Function.** Nutrients 2016, 8(1), 6; doi:10.3390/nu8010006

Abstract:

Docosahexaenoic acid (DHA) is a structural constituent of membranes specifically in the central nervous system. Its accumulation in the fetal brain takes place mainly during the last trimester of pregnancy and continues at very high rates up to the end of the second year of life. Since the endogenous formation of DHA seems to be relatively low, DHA intake may contribute to optimal conditions for brain development. We performed a narrative review on research on the associations between DHA levels and brain development and function throughout the lifespan. Data from cell and animal studies justify the indication of DHA in relation to brain function for neuronal cell growth and differentiation as well as in relation to neuronal signaling. Most data from human studies concern the contribution of DHA to optimal visual acuity development. Accumulating data indicate that DHA may have effects on the brain in infancy, and recent studies indicate that the effect of DHA may depend on gender and genotype of genes involved in the endogenous synthesis of DHA. While DHA levels may affect early development, potential effects are also increasingly recognized during childhood and adult life, suggesting a role of DHA in cognitive decline and in relation to major psychiatric disorders.

nutrients

MDPI

Review

DHA Effects in Brain Development and Function

Lotte Lauritzen [1,*], Paolo Brambilla [2,3], Alessandra Mazzocchi [4], Laurine B. S. Harslof [1], Valentina Ciappolino [2] and Carlo Agostoni [4]

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Abstract: Docosahexaenoic acid (DHA) is a structural constituent of membranes specifically in the central nervous system. Its accumulation in the fetal brain takes place mainly during the last trimester of pregnancy and continues at very high rates up to the end of the second year of life. Since the endogenous formation of DHA seems to be relatively low, DHA intake may contribute to optimal conditions for brain development. We performed a narrative review on research on the associations between DHA levels and brain development and function throughout the lifespan. Data from cell and animal studies justify the indication of DHA in relation to brain function for neuronal cell growth and differentiation as well as in relation to neuronal signaling. Most data from human studies concern the contribution of DHA to optimal visual acuity development. Accumulating data indicate that DHA may have effects on the brain in infancy, and recent studies indicate that the effect of DHA may depend on gender and genotype of genes involved in the endogenous synthesis of DHA. While DHA levels may affect early development, potential effects are also increasingly recognized during childhood and adult life, suggesting a role of DHA in cognitive decline and in relation to major psychiatric disorders.

Keywords: docosahexaenoic acid; brain development; desaturases; psychiatric disorders

1. Introduction

Long chain polyunsaturated fatty acid (LC-PUFA), including docosahexaenoic acid (DHA) and arachidonic acid (AA), are incorporated into membrane phospholipids and, apart from their structural role in these membranes, they also act as precursors of autocoid signaling molecules (e.g., docosanoids) and as potent activators of a number of gene transcription factors (e.g., peroxisome proliferator activated receptors). The essentiality of n-3 LC-PUFA is generally mainly contributed to the incorporation of DHA in uniquely high levels in the central nervous system—although DHA is incorporated in most other tissues where it may also have important functional effects.

Overall, membrane PUFA composition (the principal components of which are linoleic acid (LA), AA and DHA) seems to be more responsive to DHA in the diet than to intake of LA and AA [1]. Animal studies have demonstrated that an increase in dietary α-linolenic acid (ALA) is almost completely reflected in membrane n-3/n-6 PUFA-ratios at LA/ALA intakes of <10, whereas the dietary balance between ALA and LA has little influence at higher ALA intakes, and a similar

Appendix 2. PAPERS UNDER SUBMISSION

Paper n.1

Valentina Rosato, Valeria Edefonti, Maria Parpinel, Gregorio Paolo Milani, Alessandra Mazzocchi, Adriano Decarli, Carlo Agostoni, Monica Ferraroni. **Breakfast energy contribution, breakfast nutrient composition, and overweight in free-living individuals: a systematic review.**

Abstract:

Previous systematic reviews on the relation between overweight or obesity and breakfast focused on frequency of consumption and only partially accounted for breakfast nutritional profiles. Given the central role of these aspects, we conducted a systematic review of the literature on this putative relation with a specific focus on breakfast energy intake and/or breakfast composition. Among the 814 articles identified from the literature search in PubMed, 19 met the inclusion criteria (i.e., studies providing a quantitative estimate of the relation between any measure of weight, overweight, and obesity and breakfast energy intake or breakfast macronutrient composition; we excluded studies based on subjects with acquired metabolic disorders, such as diabetes or impaired glucose tolerance). Of the 16 studies evaluating the amount of energy intake at breakfast, 4 found that a lower energy intake at breakfast is significantly associated to obesity in children, adolescents, and adults, while 2 partially overlapping studies found that a higher energy intake is significantly associated with a higher body mass index in children. Of the 8 studies investigating breakfast composition, 3 suggested that a breakfast characterized by a higher amount of carbohydrates and a lower amount of fats is significantly related to a normal weight among adults, whereas the others reported mixed results. In conclusion, there is some evidence that a lower energy intake at breakfast is related to obesity, although the studies are still scanty and heterogeneous; studies on nutrient composition of breakfast showed inconsistent results. Most of this evidence is based on cross-sectional studies.

Paper n.2

Carlo Agostoni, Alberto Edefonti, Edoardo Calderini, Emilio Fossali, Carla Colombo, Alberto Battezzati, Simona Bertoli, Gregorio Milani, Arianna Bisogno, Michela Perrone, Silvia Bettocchi, Valentina De Cosmi, Alessandra Mazzocchi, Giorgio Bedogni. **Accuracy of prediction formulae for the assessment of resting energy expenditure in hospitalized children**.

Abstract:

Background and aim: Resting energy expenditure (REE) is commonly estimated from prediction formulae but it is largely unknown how these formulae perform in the pediatric hospital setting.

Methods: We performed a cross-sectional study of 236 infants, children and adolescents consecutively admitted to the Intermediate Care, Emergency, Nephrology, Intensive Care, and Cystic Fibrosis Units of an Italian Pediatric Hospital. REE was measured by indirect calorimetry and estimated using the WHO, Harris-Benedict and Schofield formulae.

Results: The mean (standard deviation) difference between the estimated and measured REE was -1 (234), 82 (286), -3 (233) and -2 (214) kcal/die for the WHO, Harris-Benedict, Schofield-weight and Schofield-weight and height formulae, respectively. Even though the WHO and Schofield formulae gave accurate estimates of REE at the population level, all the formulae were not accurate enough to be employed at the individual level.

Conclusions: Commonly used prediction formulae should not be used to estimate REE in hospitalized children.

Appendix 3. ABSTRACT AND POSTERS

Abstract n.1

CONGRESSO NAZIONALE SINU
Bologna, 22-23 Ottobre 2012

Proteine: come integrare qualità e quantità proteica: Variabilità dei valori di riferimento in età pediatrica.

C Agostoni, A Mazzocchi, M Perrone. Clinica Pediatrica, IRCCS Ospedale Maggiore – Policlinico, Dipartimento di Scienze Cliniche e di Comunità, Università di Milano.

La questione della variabilità dei valori di riferimento in età pediatrica è centrata in primo luogo sul rilevante gap tra raccomandazioni e consumo, in particolare nei primi 2-3 anni di vita, quando l'assunzione arriva a quasi 3 volte i limiti raccomandati, senza apparenti problematiche sullo stato di salute. Al di là delle raccomandazioni, che si basano ancora su calcoli e derivazioni che tengono conto di valori derivati (assuntivi o presunti) di spesa energetica, la domande a cui dobbiamo rispondere sono: 1 da dove deriva questo eccesso di proteine? 2 quali conseguenze può avere sull'assetto metabolico e sulla salute a medio e lungo termine dell'individuo?

L'eccesso principale di proteine è rappresentato dalle proteine di origine animale, e tra queste dalle proteine del latte vaccino, a partire già da prima del dodicesimo mese di vita, per una introduzione più precoce effettuata in molti bambini a dispetto delle raccomandazioni delle principali Istituzioni ed Organismi Scientifici pediatrici di non introdurre il latte vaccino prima del compimento del dodicesimo mese di vita.

Dopo avere dato la risposta alla prima domanda, rimane la considerazione sui possibili effetti metabolici e sullo stato di salute. Il latte vaccino contiene circa 3.5 grammi di proteine per 100 ml, di elevato valore biologico. Studiando formule derivate da latte vaccino nei più piccoli, ed effetti di somministrazione diretta di latte vaccino nei bambini più grandi, è stata osservata una associazione diretta tra quota proteica assunta col latte vaccino e livelli circolanti di IGF-1. Nel caso delle formule ad elevato contenuto proteico è stata anche osservata l'associazione con un maggiore incremento di massa corporea nei primi due anni , con un possibile aumento del rischio di obesità nell'età successive. Tra le proteine del latte vaccino, caseina e siero-proteine si associano ad aumentata secrezione di molecole pro-anabolizzanti, ovvero IGF-1 e insulina, rispettivamente.

La precoce introduzione di latte vaccino, ed il suo contenuto proteico, sembrerebbe quindi poter influire negativamente sullo sviluppo dei determinanti più precoci della sindrome metabolica (sovrappeso ed obesità). Più dubbio rimane il ruolo delle proteine derivate da altre fonti alimentari, anche animali. Inoltre non va ignorato il valore delle altre componenti nutrizionali naturalmente associate agli alimenti. Il latte vaccino rimane un alimento di elevato valore biologico ed indubbio significato nutrizionale. Tuttavia, mentre è possibile che possa avere un effetto positivo sulla crescita in condizioni di limitata disponibilità di altri alimenti di elevato valore biologico, il suo ruolo in una società dove l'accesso agli alimenti ad elevata densità calorica è più ampio e facilitato va probabilmente riconsiderato per ottimizzarne gli effetti positivi e ridurne il possibile impatto negativo. Per questo motivi sembra ragionevole consigliare di ritardare l'introduzione del latte vaccino nella dieta almeno dopo l'anno di vita,

continuando a utilizzare il latte materno o, in alternativa, formule a basso apporto proteico. Dopo l'anno di vita, rimane da studiare il significato funzionale di introdurre subito il latte vaccino o proseguire con formule modificate in modo da equilibrare l'assunzione sia di macro che di micronutrienti. La questione dell'eccesso globale di proteine nella dieta delle prime epoche di vita e delle altre fonti alimentari rimane scarsamente studiato.

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Abstract n.2

MILANO PEDIATRIA 2014. Nutrizione Genetica Ambiente per l'educazione alla salute.
20-23 Novembre 2014

La sicurezza degli alimenti: l'impegno dell'Europa. Carlo Agostoni, Alessandra Mazzocchi. Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano

Verso la fine degli anni 90 la ricerca sui cosiddetti nutrienti funzionali è andata incontro ad una grande sviluppo, e sono stati fatti numerosi interventi di inserimento di questi composti negli alimenti. Nell'ambito della nutrizione pediatrica, ed in particolare per gli alimenti per il primo anno di vita, è stato proposto l'utilizzo di diversi nutrienti con effetti, potenziali o postulati, sullo sviluppo neuro comportamentale, sulle difese immunitarie, la prevenzione delle allergie, l'ambiente e la funzione intestinale. Conseguentemente, ed in particolare per accertare la sicurezza di queste aggiunte, questi nuovi e rapidi cambiamenti hanno richiesto urgentemente una legislazione per la loro regolamentazione. Nel 2002, il Parlamento Europeo ha adottato una regolamentazione (EC 178 / 2002) che normava i principi generali e le richieste relative alle leggi sugli alimenti e le procedure in materia di sicurezza alimentare. All'interno di queste normative si situa la creazione della Autorità Europea della Sicurezza Alimentare (EFSA) , col compito precipuo di dare indicazioni tecniche e scientifiche in relazione agli alimenti ed alla sicurezza alimentare ed all'utilizzo in nutrizione umana attraverso procedure indipendenti e trasparenti, e di comunicare tali provvedimenti al pubblico.

Poster n.1

YIM meeting. 8th- 9th June 2015 – Rome

P78

NUTRITIONAL STATUS AND ENERGY EXPENDITURE IN JIA PATIENTS WITH DIFFERENT DISEASE ACTIVITY

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Background and Aim

Juvenile idiopathic arthritis (JIA) is the most frequent chronic inflammatory rheumatic disease in childhood, encompassing all forms of arthritis beginning before the age of 16 (1). Several studies have demonstrated that the nutritional status in JIA patients is often impaired (2); protein–energy malnutrition is very prevalent among children with JIA, with rates that vary between 20 and 40%. The aim of our study was to evaluate the nutritional status and calculate the energy expenditure in JIA patients, classified per JIA category and level of disease activity.

Subjects and Methods

Resting energy expenditure (REE) was assessed by indirect calorimetry in unselected JIA patients hospitalized in our Centre. The measurements was normalized to fat free mass (FFM). Anthropometric measurements (weight, height and body mass index), body circumferences and skinfold thickness were recorded to estimate body composition; a 24-hour recall was performed for the nutritional assessment. The nutritional status was evaluated according to WHO reference data. The results were calculated in different JIA categories, and divided considering the high disease activity cut off as by recent definition in JADAS (3).

Results

The nutritional status and the energy expenditure in our study population are shown in Table 1.

Table 1. REE and nutritional status in different JIA categories. Data are expressed as median (range).

	Resting Energy Expenditure (Kcal/die)	Nutritional status (BMI SDS)
Oligoarthritis (N 9)	837 (400 – 1360)	- 0.17 (-1.37 – 1.40) (normal weight)
JADAS 10 < 4.2	937	0.22 (normal weight)
JADAS 10 ≧ 4.2	912	- 1.37 (mild malnutrition)
Polyarthritis (N 11)	1022 (471 – 1254)	- 0.35 (-2.30 – 1.28) (normal weight)
JADAS 10 < 10.5	1022	1.28 (overweight)
JADAS 10 ≧ 10.5	1254	- 0.38 (normal weight)
Systemic (N 1)	1564	1.35 (overweight)
Psoriatic arthritis (N 1)	476	1.41 (overweight)

The energy expenditure was assessed in 22 unselected JIA patients, 9 with oligoarthritis, 11 with rheumatoid factor-negative polyarthritis, 1 with systemic arthritis, 1 with psoriasis arthritis; aged between 2.5 and 12.5 years. The median (range) of JADAS 10 was 13 (4.5-26.3).

Conclusions

Concerning nutritional status, JIA patients with oligoarthritis are normal weight, except the subject with a JADAS 10 ≥ 4.2 who shows a mild malnutrition. Children with polyarthritis are normal weighing while the two patients with systemic arthritis and with psoriatic arthritis, are overweight. The protocol study is still in progress and will consider the influence of different disease activity degree. Furthermore, it will provide a comparison with the REE measured in controls of the same gender and age.

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A very important thanks goes to my family!! Without you all this would never have happened.
A special thought to my Grandma Irene! You always encourage me in my studies! I am sure you will do it also this time!
And last but not least… Thanks to all my awesome friends Arianna (thank you for all our coffee breaks!I love them!!!best part of my job), Chiara, Merve, Marialuigia, Patrizia end Elisa!Thank you for always being there for me!!