Weight Management in Phenylketonuria: What Should Be Monitored?

Julio César Rocha[a–c]   Margreet van Rijn[d]   Esther van Dam[d]   Kirsten Ahring[e]
Amaya Bélanger-Quintana[f]   Katharina Dokoupil[g]   Hulya Gokmen Ozel[h]
Anna Maria Lammardo[i]   Martine Robert[j]   Carina Heidenborg[k]
Anita MacDonald[l]

[a]Centro de Genética Médica Doutor Jacinto de Magalhães, CHP EPE, [b]Faculdade de Ciências da Saúde,
Universidade Fernando Pessoa, and [c]Center for Health Technology and Services Research (CINTESIS), Porto,
Portugal; [d]University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Groningen,
The Netherlands; [e]Department of PKU, Kennedy Centre, Copenhagen University Hospital, Glostrup, Denmark;
[f]Unidad de Enfermedades Metabolicas Servicio de Pediatria, Hospital Ramon y Cajal, Madrid, Spain; [g]Department
of Metabolism and Nutrition, Dr. von Hauner Children's Hospital, University of Munich, Munich, Germany;
[h]Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, Ankara, Turkey;
[i]Department of Pediatrics, San Paolo Hospital University of Milan, Milan, Italy; [j]Nutrition and Metabolism Unit,
Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium; [k]Department of Clinical Nutrition and Dietetics,
Karolinska University Hospital, Stockholm, Sweden; [l]The Children's Hospital, Birmingham, UK

Abstract

Background: Severe intellectual disability and growth impairment have been overcome by the success of early and continuous treatment of patients with phenylketonuria (PKU). However, there are some reports of obesity, particularly in women, suggesting that this may be an important comorbidity in PKU. It is becoming evident that in addition to acceptable blood phenylalanine control, metabolic dieticians should regard weight management as part of routine clinical practice. ***Summary:*** It is important for practitioners to differentiate the 3 levels for overweight interpretation: anthropometry, body composition and frequency and severity of associated metabolic comorbidities. The main objectives of this review are to suggest proposals for the minimal standard and gold standard for the assessment of weight management in PKU. While the former aims to underline the importance of nutritional status evaluation in every specialized clinic, the second objective is important in establishing an understanding of the breadth of overweight and obesity in PKU in Europe. ***Key Messages:*** In PKU, the importance of adopting a European nutritional management strategy on weight management is highlighted in order to optimize long-term health outcomes in patients with PKU.

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Introduction

Historically, the main objective of phenylketonuria (PKU) management was to prevent profound and irreversible intellectual disability together with the avoidance of nutritional deficiencies resulting in growth impairment [1]. Traditional low phenylalanine dietary manage-

Júlio C. Rocha
Centro de Genética Médica Doutor Jacinto de Magalhães, CHP, EPE
Praça Pedro Nunes, 88
PT–4099-028 Porto (Portugal)
E-Mail julio.rocha@chporto.min-saude.pt

Table 1. International BMI cut-offs for classifying overweight and obesity according to different definitions

Criteria	Age group	Risk of overweight	Overweight	Obesity
WHO growth charts [8]	<5 years	1 SD	2 SD	3 SD
WHO growth charts [9]	5–19 years	–	1 SD	2 SD
CDC growth charts [12]	2–20 years	–	1 SD	2 SD
IOTF [11]	2–18 years	–	Cut-off corresponding to a BMI of 25 kg/m^2 at 18 years	Cut-off corresponding to a BMI of 30 kg/m^2 at 18 years
WHO adults [6]	Adults	–	25≤ BMI <30 kg/m^2	BMI ≥30 kg/m^2

ment, and more recently with pharmacological treatment, has been very successful in achieving these goals. However, there is concern that obesity may be a common comorbidity. Although in PKU there is still limited evidence, some studies highlight an increased obesity risk particularly in females [2–4]. It is therefore essential that PKU health professionals are able to conduct lifestyle 'risk assessments' to identify potential obesogenic factors, consider trends in nutritional status by systematically monitoring key clinical and biochemical measures, and provide effective nutritional and lifestyle advice in order to avoid obesity. Also, it is important to standardize procedures for data collection in order to monitor trends between centres and countries. This will help clarify if overweight is related to the disorder, the treatment or to a disrupted energy balance.

Therefore, this paper has 3 objectives: (1) to clarify definition and interpretation of measurements for overweight and obesity; (2) to define minimal standards for monitoring overweight and obesity in the PKU clinic; and (3) to propose a 'gold standard' for data collection for assessment of overweight, obesity and lifestyle in PKU.

Defining and Assessing Overweight and Obesity

Adequate assessment depends on age and gender, and careful interpretation is needed particularly in childhood and adolescence, where the correct diagnosis of overweight and obesity is more challenging than in adulthood. Several methods exist for assessing overweight and obesity, all with their pros and cons.

Body Mass Index
Body mass index (BMI) has been used in paediatrics since the 1980s [5] and defines the widely used criteria for overweight and obesity in adults (BMI ≥25 kg/m^2

corresponds to overweight and BMI ≥30 kg/m^2 corresponds to obesity) [6]. The preference for its use is from the association with body composition and disease risk factors, as well as being calculated by weight and height measurements only [7]. In paediatrics, comparison with a reference population is required. Several countries have their own nationally representative reference population growth charts [7]. However, the World Health Organization (WHO) growth charts (0–5 years of age) represent a standard of physiological growth, since breastfed children from controlled pregnancies were included [8] and they have also proposed references for children aged 5–19 years [9]. Other international criteria for diagnosing overweight and obesity in paediatrics are available from the International Obesity Task Force (IOTF). Although this can be used for international descriptive and comparative studies, it is not designed for clinical use and so should not replace the national reference data [10]. Nevertheless, IOTF cut-offs expressed as centiles permit comparisons with other international criteria like WHO [11]. Table 1 summarizes internationally available criteria.

Caution is needed when interpreting results from studies using different criteria to classify overweight and obese individuals, for example, IOTF, WHO or other national data, like Centers for Disease Control and Prevention (CDC) [12], since variable results are expected [13]. In addition, more research is needed to better identify universal BMI cut-offs and its association with health outcomes later in life [14].

Body Composition
Although BMI is the most commonly used marker for diagnosing overweight and obesity, it should be highlighted that overweight definition is based on the proportion of body fat to the body weight, which results from increased energy intake, reduced energy expendi-

Table 2. Minimal standards for monitoring overweight and obesity in the PKU clinic

Measure	Justification	Practicalities/check-points
Dietary intake and life-style		
Diet	Diet will modulate the risk of developing overweight and obesity	Total protein, amino acid and natural protein intakes Total energy intakes BH4-treated patients analysed separately Diet practices
Social and life-style	Life-style will modulate the risk of developing overweight and obesity	Daily main occupation: student, employed or no occupation Practice of structured exercise: yes or no
Anthropometry		
BMI	Good epidemiological marker	Weight and height should be measured with the same equipment and at the same moment of the day (morning or afternoon)
Clinical biochemistry		
Glucose and lipid metabolism	Will give a picture about the severity of overweight	Fasting blood glucose and blood lipids: total cholesterol, HDL, LDL, triglycerides

ture or both [15]. According to WHO, the 'real or clinic' overweight is perceived when the adiposity level is sufficiently high to increase morbidity and mortality [15]. Although considered a good screening tool, BMI may not always identify the overfat individuals (increased fat mass percentage), since a stunted linear growth may be responsible for the increased BMI [16]. Even in adults, a rigorous assessment and careful interpretation between BMI and health outcome are needed, since these relationships are not always clear [17]. Considering the wide range of methods available for measuring body composition, it is important to refer that these start with the predictive techniques (skinfold thicknesses and bioelectrical impedance analysis), then reference methods like dual energy X-ray absorptiometry, isotope dilution and air displacement plethysmography, finalizing with the gold standard methods (4-component model for quantifying fat, water, mineral and protein and magnetic resonance imaging for quantifying fat distribution) [18].

Metabolic Comorbidities

The relationship between BMI and disease is mediated by a metabolically abnormal phenotype mainly characterized by dyslipidemia, hypertension, insulin resistance and inflammation, all coexisting with increased abdominal obesity [19, 20]. So, in addition to 'overweight', it is increasingly important to define overfat individuals and particularly those at increased risk of metabolic disturbances. Further, considering that visceral adipose tissue assumes great relevance in terms of the inflamma-

tory impact of the adipose tissue between metabolic syndrome and allied comorbidities [21, 22], understanding the main location of body fat deserves clinical attention. Further study is particularly required to investigate if overweight in PKU is associated with the same abnormal metabolic patterns usually seen in the general population [23].

Assessment of Overweight, Obesity and Lifestyle in Patients with PKU

Published results on overweight and obesity in PKU patients are contradictory; most of them are only representative of single PKU centres and they mainly include children and adolescents [23]. Not all studies demonstrate overweight in patients with PKU [2, 4, 24–27], but a developing trend suggests that overweight in PKU is following the general population [2, 4, 26, 27]. However, this outcome should not be commended, as PKU health care professionals should also focus on general health and prevention of overweight is essential.

Minimal Standards for Monitoring Overweight and Obesity in the PKU Clinic

Minimal standards for monitoring overweight and obesity are proposed in PKU (table 2).

Delaying diagnosis and treatment of overweight will reduce the chances of a successful intervention. The concept of diet for life adopted in PKU management [31]

Table 3. Proposed 'gold standard' assessment for data collection in PKU

Measure	Justification	Practicalities/check-points
Dietary intake and life-style		
Diet	Diet will modulate the risk of developing overweight and obesity	Total protein, amino acid and natural protein intakes Total energy intakes and % of calories from fat and carbohydrate Carbohydrate intakes, mainly amounts of mono and disaccharide ingestion BH4-treated patients analysed separately BH4-treated patients diet patterns detailed Low protein food intake: types, categories and % of the total daily energy intake
Social and life-style	Life-style will modulate the risk of developing overweight and obesity	Daily main occupation: student, employed or no occupation Frequency, duration and intensity of physical activity and exercise activities Eating patterns behaviour; frequency of snacks Patient/caregiver knowledge about healthy foods in PKU
Anthropometry and body composition		
BMI	Good epidemiological marker	Need to use standard methods and calibrated equipment's Weight and height should be measured with the same equipment and at the same moment of the day (morning or afternoon)
Waist circumference	Good association with abdominal adiposity	Need to use standard technique Need to have trained heath care professionals
Body composition	To differentiate overweight from overfat and to help nutritional status interpretation	To select an available method in each clinic To follow standardized procedure in every measurements in order to obtain at least body fat %
Clinical biochemistry		
Glucose metabolism	Insulin resistance is on the basis of metabolic syndrome	To measure fasting blood glucose Add A1C haemoglobin and insulin, especially when insulin resistance is suspected to occur (presence of visceral obesity)
Lipid metabolism	Dislipidemia is an important feature of metabolic syndrome being linked with insulin resistance	To measure blood total cholesterol, HDL, LDL, triglycerides Need to control the fasting time period in order to have reliable markers Apolipoproteins measurement would be recommended
Inflammation	Inflammatory markers are associated with abdominal obesity	To measure c-reactive protein, especially high-sensitivity c-reactive protein When possible, cytokines could be monitored, especially in the presence of visceral obesity
Other clinical data		
Blood pressure	It is a metabolic syndrome component well associated with the global cardiovascular risk	Use standard techniques and procedures The presence of the 'white coat effect' should be recognized Careful interpretation is needed in paediatrics

should guide health care professionals into caring for all aspects of health and not solely focused on phenylalanine levels.

Proposed 'Gold Standard' Assessment for Data Collection in PKU

In PKU, in order to understand the European prevalence of overweight and obesity, it is important to assess and collect data in a standardized manner. Table 3 describes a proposed 'gold standard assessment' tool. From the beginning, it is important to differentiate between cross-sectional and longitudinal data. Cross-sectional data will give an indication of the population under immediate follow-up; longitudinal data will demonstrate the evolution of overweight and obesity and a careful interpretation of data will allow the identification of critical periods, helping to clarify if specific PKU treatment strategies have an obesogenic effect. Some studies have already identified adolescence, especially in females [2, 4, 28], and early infancy [29], as critical periods, thereby requiring particular attention. Preventing an early BMI rebound [29] and an understanding of

Table 4. Patients', families' and other longitudinal data to be collected in patients with PKU

Measure	Justification	Practicalities/check-points
Patient-related data		
Disorder	Disorder severity may affect metabolism, dietary restrictions, adherence and metabolic control	Classification in terms of HPA, mild PKU or classical PKU Late treated patients should be analysed separately
Early health and nutrition	Early health and nutrition are important determinants of overweight development later in life	Birth weight Breastfeeding length Amount of total protein intake in the first 1–2 years of life Degree of prematurity Weight gain pattern in the first years of life Age at BMI rebound Age at menarche Other disorders/comorbidities and/or exposure to chronic anti-biotherapy in the first years of life
Family-related data		
Nutritional status	Family overweight is positively associated with patients tendency	Identify the presence of overweight or obesity in both parents Are there other siblings with overweight or obesity? Examine dietary pattern of the family Document parental BMI and waist circumference

feeding and lifestyle behaviour during adolescence should be beneficial [30] (see table 4 for patient and family data collection).

Importance of Data Collection in Clinical Setting

Adopting standard procedures to monitor dietary intake, weight gain, body composition and clinical biochemistry within the clinical setting not only enables systematic monitoring of nutritional status. It will also enable the application of early preventative action to avoid the development of overweight and obesity. This should help in the provision of appropriate dietary counselling on the use of special low-protein foods; type of phenylalanine-free L-amino acid supplement; choice of natural protein sources particularly in sapropterin responsive patients who may have a higher natural protein tolerance; and also any requirement for additional exercise programmes.

Conclusion

In PKU, nutritional status, particularly being overweight, deserves our attention as it influences long-term health status. Until now, the limited evidence within the field of overweight in PKU does not clarify if this is a serious issue in this special group of individuals. There is an urgent need to have a systematic and standardized overweight-related data collection in European representative cohorts of PKU patients, so that different treatment interventions and approaches can be compared.

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