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# Living with phenylketonuria in adulthood: The PKU ATTITUDE study

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ABSTRACT

Dietary treatment is the cornerstone of therapy for phenylketonuria (PKU), but adherence to low- phenylalanine diet progressively decreases after adolescence. We designed a survey to characterize the dietary habits of Italian adult PKU patients and to identify psychological factors influencing disease perception and adherence to diet. Participants to the survey ($n = 111$; response rate 94%) were asked to complete a structured questionnaire. Patients appeared to have an altered perception and awareness of the disease. About 40% of them did not consider PKU a disease and, despite declaring regular monitoring of phenylalanine levels (85%), nearly half of them reported a high plasma value over the last 6 months (> 600 µmol/L, 48%) or were unable to specify it (31%). Adherence to PKU diet was unsatisfactory, with increased consumption of natural protein sources and reduced daily use of amino-acid supplements (< 4–5 times/day in 82% patients). In addition to the intrinsic characteristics of AA formula (palatability, ease of use), the most important factor influencing their consumption was the increased social pressure associated with their use (55%). Plasma phenylalanine periodical measurements (61%) and examinations at metabolic centers (49%) were considered relevant for compliance to diet. In Italian adult PKU patients dietary management was found to be inadequate, likely due to inappropriate perception and knowledge of the disease, and lack of awareness of the negative impact of poor metabolic control in adult life. Clinicians should consider implementing more intense and tailored educational measures, as well as structured transitional care processes.

## 1. Introduction

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder that affects about one person every 10,000 births in Europe [1]. PKU is determined by the impairment of phenylalanine hydroxylase (PAH) activity resulting in decreased phenylalanine (PHE) conversion to tyrosine. Deficiency of the hepatic PAH results in a broad spectrum of hyperphenylalaninemia (HPA) ranging from very mild HPA (blood PHE: 120–600 µmol/L), to mild PKU (blood PHE: 600–1200 µmol/L) and classic PKU (blood PHE > 1200 µmol/L) [2]. Accordingly, the alteration leads to high plasma concentrations of phenylalanine (and decreased tyrosine), which accumulates in the tissues and causes damage if left untreated. The most serious consequence is the impaired development of the central nervous system, with intellectual disability frequently being associated with other manifestations, such as motor disturbances, psychiatric symptoms, aberrant behavior, and epilepsy [3]. Low-PHE diet (a personalized dietary plan based on the consumption of normal food sources, low-protein foods and the use PHE-free protein substitutes to cover protein requirements) is the mainstay of treatment of PKU [4]. During childhood adherence to diet is very high, but progressively decreases after adolescence [5–7]. This is likely due to increasing independency of patients from the family as well as to psychological and social burden both in patients and their families [8, 9].

Dietary management in childhood is associated with neurocognitive outcome [10–12]. Individuals with early-treated PKU can achieve normal or near-normal IQ if they maintain good metabolic control through dietary restriction until the age of 12, but even after this age

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there is a correlation between current phenylalanine levels and IQ among individuals aged between 0 and 39 years [13]. PHE levels may still influence the adolescent and adult brain anyway, and patients with elevated PHE levels have been reported to show neuroradiological [14] and neuropsychological deficits, as well as impairment of executive function, speed and attention [15, 16]. In adult PKU patients (age > 32 years) poor cognitive performance, assessed by IQ and information processing, was found to correlate with higher blood PHE levels in adolescence, possibly related to early relaxation of diet at age 10 [15]. Besides, neuroimaging structural alterations in the white matter have been reported in adult PKU patients with insufficient metabolic control, although the lesions do not appear to be associated with clinical symptoms [11, 16, 17]. As there is currently no strong evidence that it is safe to discontinue dietary treatment in adults, lifelong treatment is recommended, even though it is acknowledged that dietary management is associated with significant patient burden [3, 18]. In recent years, the focus has increasingly shifted to the Quality of Life (QoL) of PKU patients previously receiving dietary intervention. Although QoL scores of PKU patients are reported to be generally similar to healthy controls, a chronic disease can engender anxiety and fear of not being able to adequately control the course of the disease [19].

Reviews have recently pointed out that there is a paucity of studies examining the influence of demographic and psychological factors on metabolic control in adult PKU patients [8, 20]. Moreover, no studies have addressed the issue from the point of view of the patient. The aim of this multicenter survey (Analysis of the mosT relevanT and predIctive facTors inflUencing aDherence to PKU diEt [ATTITUDE]) was to collect information on the subjective perceptions of the patients by carrying out in-depth interviews of Italian adult PKU patients.

## 2. Materials and methods

Over a 12 month period (from August 2016 to August 2017) 116 adult patients were recruited for the study. Patient inclusion criteria for enrollment were: confirmed diagnosis of PKU by neonatal screening, age ≥ 16 years, treatment with a PHE-restricted diet from birth and/or tetrahydrobiopterin (BH4) and IQ > 70.

A total of 116 eligible patients were contacted: 111 (97%) were selected to participate in the study, considering gender, disease severity and age criteria; reasons of exclusion were: refusal to participate ($n$ = 4), and recent childbirth ($n$ = 1).

In our sample, 88 patients were affected by the classical form and 23 were affected by the mild form. A total of 92 patients were on PHE restricted diet only; 19 patients over the last 4 years were found to be BH4 responsive and therefore therapy was switched from dietary treatment alone to BH4 treatment.

The study was carried out at five different Italian centers (listed among authors' affiliations) distributed throughout the country (North = 2; Centre = 2; South = 1). Except for one center (Division of Inherited metabolic diseases of Padova) all other patients were followed by pediatricians or pediatric neurologists. These centers continue to care for PKU patients even after they become adults. Transition program is available in very few centers in Italy. Furthermore, these centers were chosen because their clinical team included a dedicated psychologist.-.

The survey was developed based on a survey that was already used for other chronic diseases, such as diabetes, and modified for PKU. It has been already used in a single-center (Padua) pilot study. Responders were asked to complete a two-section survey. The first part of the survey addressed socio-demographic (family, school or work environment, leisure time) and general clinical data, as well as disease-related symptoms. Then, patients prescribed a low-PHE nutritional plan only were asked to complete the second part of the survey, which investigated dietary habits and psychological factors influencing adherence to diet more in depth. Standard operating methodology was achieved before data collection by organizing a training session with all involved healthcare professionals. At each center, all patients were evaluated by the same medical doctor and psychologist. Specifically, the former was responsible for survey explanation, written informed consent and clinical examination, while the latter administered the survey.

The study was performed in compliance with local regulatory requirements and written informed consent was obtained from all subjects or their legally authorized representatives.

### 2.1. Statistical analysis

Descriptive statistical analyses were carried out. Categorical variables were presented as counts and percentages, while continuous variables were reported as mean and standard deviation (normal distribution) or median and inter-quartile range (IQR; non-normal distribution). Categorical variables were compared using Fisher's exact test. All statistical analyses were performed using SAS® software (SAS Institute Inc., Cary, NC, USA).

## 3. Results

A total of 111 patients answered the survey across the 5 metabolic centers (Bari: 35, Padua: 34, Fano: 18, Rome: 16 and Piacenza: 8). Regarding demographic features of the study population, these were similar across recruiting centers: overall, 61 females (55%) and 50 males (45%); age range 19–30 years, mean 24 years old.

The first part of the survey was completed by all patients ($n$ = 111), while results regarding dietary habits and psychological factors influencing adherence to diet refer to patients not taking BH4 and following a dietary prescription only ($n$ = 92).

Information on family, school or work environment, and leisure time is reported in Table 1. Data appeared to be mainly in agreement with those of the general Italian population [22]. Seven patients out of 111 (6.3%) claimed to study and work at the same time, while 17

**Table 1**
Information on family, school or work environment, and leisure time ($N$ = 111).

| Question | N (%) |
|---|---|
| Category B driving license (YES) | 83 (84.6)* |
| Who are you living with? | |
| - *Alone* | 14 (12.6) |
| - *With my family* | 97 (87.4) |
| Are you married or do you have a partner? (YES) | 54 (48.6) (55.1)* |
| Please indicate your father's highest qualification in terms of education: | 63 (56.8) |
| - *primary or junior high school leaving certificate (8 years of education)* | 37 (33.3) |
| - *high school leaving certificate (13 years of education)* | 11 (9.9) |
| - *University Bachelor's degree or postgraduate diploma (≥16 years of education)* | |
| Please indicate your mother's highest qualification in terms of education: | 74 (66.7) |
| - *primary or junior high school leaving certificate (8 years of education)* | 30 (27.0) |
| - *high school leaving certificate (13 years of education)* | 7 (6.3) |
| - *University Bachelor's degree or postgraduate diploma (≥16 years of education)* | |
| Are you attending school? (YES) | 39 (35.1) |
| - *high school (13 years of education)* | 24 |
| - *University (≥16 years of education)* | 14 |
| - *Not specified* | 1 |
| Are you currently working? (YES) | 62 (55.9) |
| Does your work involve travelling? (YES) | 12 (10.8) |
| Do you practice sports? (YES) | 58 (52.3) |

* Calculated on those aged ≥18 years ($n$ = 98).