Phenylketonuria (PKU; MIM 261600) is an inborn error of amino acid metabolism caused by reduced phenylalanine hydroxylase (PAH; EC 1.14.16.1) activity (Blau et al. 2010). After the discovery by Dr. Asbjørn Følling (Folling 1994), the first treatment approach was proposed by Dr. Horst Bickel in 1950s (Bickel et al. 1953). Despite new therapies have recently emerged [large neutral amino acids (LNAA), Glycomacropeptide (GMP) and Sapropterin (BH₄)] (Ney et al. 2014), the proposed dietary phenylalanine (Phe) restriction is still the mainstay of treatment for patients with PKU. This is achieved through a natural protein restricted diet giving simultaneously a Phe-free amino acid mixture (protein substitute), nowadays enriched with vitamins and minerals (Giovannini et al. 2012). In order to satisfy patient’s energy needs and to improve dietary compliance, special low protein foods are currently available for inclusion in the diet. The nutritional composition of these foods reveals a significant richness in carbohydrates and fat, while protein and Phe content are almost negligible (Rocha et al. 2007).

When diet is implemented in the first weeks of age and treatment is adequately continued, mental retardation is avoided which constitutes an important conquest comparing to the picture usually seen before newborn screening programs implementation (Blau et al. 2011). The tremendous success of this dietary treatment opened new horizons and a careful nutritional status management is nowadays recommended for these patients. An adequate growth promotion was naturally considered one of the major objectives, although its interpretation may not be straightforward in diseases like PKU (MacDonald et al. 2011). In fact, the major protein ingestion of patients with PKU is derived from the chemically manufactured protein substitutes. The efficacy and bioavailability of these protein substitutes seems to be lower than of intact protein which probably justifies the extra nitrogen intake.
suggested for these patients (MacDonald et al 2011). Classical forms of the disease, under reduced natural protein intakes, seem to have a less favorable growth outcome (Rocha et al 2013). However, BH₄-treated patients may also manifest growth impairment, despite their increased natural protein tolerance, sometimes may allow a normal diet (Aldamiz-Echevarria et al 2013). Again, since growth is a complex physiologic phenomenon not only dependent on protein intake (Lifshitz 2009), further studies are desirable in PKU (Dokoupil et al 2012).

Considering the food pattern characteristics, particularly the high energy intake to promote anabolism (Dobbelaere et al 2003; Huemer et al 2007), the interest on the energetic balance and on the concomitant consequences in terms of obesity development has been increasing (Giovannini et al 2012). Early studies in the USA reported a tendency to overweight in PKU (Holm et al 1979; White et al 1982; McBurnie et al 1991). The same tendency was also underlined one decade later by the study from Acosta and co-workers (Acosta et al 2003). In Europe, the prevalence of overweight within Italian patients with HPA and PKU was 25% at the age of 8 years (Scaglioni et al 2004). More recently, this issue was underlined again at least during adolescence (Belanger-Quintana and Martinez-Pardo 2011), particularly in females (Burrage et al 2012) and specially when dietary compliance was poor (Doulgeraki et al 2014). Although a tendency for a higher prevalence of overweight was found in UK female adults (Robertson et al 2013), global prevalence of overweight and obesity does not seem to differ from the general population (Rocha et al 2012; Robertson et al 2013).

Finding similar overweight prevalence in PKU and general population should not be viewed linearly as a positive result. In fact, patients with PKU are constantly under nutritional advice, and health care professionals should make all the efforts to prevent overweight development. Overweight and obesity are usually associated with several cardiometabolic markers that increase the risk of cardiovascular disease and type 2 diabetes (Despres and Lemieux 2006; Van Gaal et al 2006). Reaven (Reaven 1988) proposed the metabolic syndrome (MetSyn) concept where insulin resistance would be on the basis of the aggregation of other abnormalities related with blood pressure, high density lipoprotein-cholesterol (HDL-c), triglycerides (TG) and glucose. Several other definitions have been developed by different organisms like World Health Organization (WHO) (Alberti and Zimmet 1998), the National Cholesterol Education Program Adult Treatment Panel III (Grundy et al 2004), the European Group for the Study of Insulin Resistance (Balkau and Charles 1999) and more recently the
International Diabetes Federation (Alberti et al 2005). Although the physiopathology of MetSyn has not been clarified yet, insulin resistance and central obesity (Despres and Lemieux 2006) are considered major factors. In addition, the presence of atherogenic dyslipidemia, characterized by increased TG and reduced HDL-c, is also relevant (Alberti et al 2006).

In PKU it is unknown if obesity etiology is a result of the underlying condition, a treatment consequence, or an outcome of inadequate metabolic control. Birth weight and parental weight are well known contributing factors, justifying a careful interpretation of these data. Also, an early body mass index rebound in infancy is also a determinant factor for later obesity development and should also be prevented in PKU (Scaglioni et al 2004). Regarding disease severity, there are conflicting data in the literature and, at this moment, it is not possible to clarify whether classical forms of the disease would be more susceptible for overweight development (Rocha et al 2013). Another aspect that should be analyzed in each cohort of patients is the existence of growth impairment. Some studies have been reporting this and its consequences in terms of overweight development later in life should be taking into account. Beyond this factor, the modifiable dietary factors should also be analyzed, in order to prevent weight rise, but also metabolic comorbidities, particularly central obesity and dyslipidemia (Rocha et al 2012; Kanufre et al 2015). Overweight has a primary origin in a disturbed energetic balance (Deheeger et al 1996) and in PKU increased energy intake is usually recommend in order to prevent catabolism (Illsinger et al 2005), that would have deleterious effects on metabolic control (MacDonald et al 2006). From the available studies, energy intakes in PKU seems to match the recommendations while carbohydrate ingestion is usually above 50% of the total energy intake (Rocha et al 2013). A healthy diet usually promotes the consumption of food sources rich in complex, fiber-rich carbohydrate sources. In PKU, there are not yet enough studies documenting in detail food patterns. Anyway, it seems that carbohydrate sources used in PKU may have sometimes excessive sugar content and may be low in fiber (Rocha et al 2013). Another crucial component of the typical diet in patients with PKU is special low protein foods. These may have a contribution to the total energy intake of around 50% in classical forms of the disease. So, it seems prudent to know in detail all the nutritional composition of these foods, since their contribution will have a great influence in nutritional status. It is important to know how different is their fat, sugar and energy contents compared with general foods. Also, fiber, sodium and other micronutrients should be checked. Nutritional status management in PKU is no longer just controlling Phe levels. We should aim for optimizing global nutritional status since it will influence long-term outcome at several levels. On the
other hand, fruits and vegetables are usually referred on the exchanges tables used in several treatment centers. However, some studies already documented that free ingestion of fruits and vegetables may not affect metabolic control in PKU (MacDonald et al 2003; Rohde et al 2012; Zimmermann et al 2012). This information should be used and translated into the clinical practice because it can result in a good strategy for health promotion, considering the benefits of fruit and vegetable ingestion (Koletzko et al 2013). Regarding protein, excessive ingestion in the first years of life should be prevented, taking into account the known effects in terms of overweight development later in life (Socha et al 2011). Considering the reduced protein content in human milk (Gillman 2008), breastfeeding should be recommended in PKU (Motzfeldt et al 1999). The other component of the protein intake in PKU is the protein substitutes, mainly composed by Phe-free amino acid mixtures. The number of these has been increasing dramatically with different presentation forms, nutritional composition and target ages. A careful analysis of their individual nutritional composition is needed in order to better match them with individual patient’s needs.

Finally, but not less important, physical activity has a great influence on body weight and body composition. However, there are no studies describing the physical activity behavior in patients with PKU. The concept of diet for life, should also be adapted to the concept of treatment for life, since nowadays other treatments are available for PKU patients. In that way, physical activity together with a ‘balanced’ diet should be recommended in parallel with any other of the treatment strategies proposed. Health care professionals have now the challenge to better define nutritional needs of each patient in order to optimize both metabolic control but also long-term health outcome.

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