Phenylketonuria (PKU) is an established inherited amino acid disorder with a very traditional dietary therapy, but there is still more to learn and verify about its nutritional composition, application and overall effectiveness. Although in the 1950s, the first patient successfully treated with diet therapy patently established the role of a low phenylalanine protein substitute, in present times, it is still necessary to characterise the most effective source of artificial protein; defining its optimal amino acid profile; and identifying nutrient modulation that will improve the functionality of protein substitutes. It is also important to understand the impact of a life-long synthetic diet on gut microbiota, metabolomics and inflammatory status.

In early-treated patients with PKU, it is unclear if co-morbidities such as overweight, obesity, hypertension and diabetes are higher than in the general population and if these are associated with increased cardiovascular risk. It is also uncertain if overweight and obesity in PKU is related to early dietary practices, the nutritional composition of protein substitutes and special low-protein foods, impact of the dietary treatment on satiety, disordered eating patterns, non-adherence with the low phenylalanine diet and poor metabolic control, or if this is even a consequence of the disorder. In a generation of ageing patients, the impact of intermittent and suboptimal dietary adherence on nutritional status deserves systematic study.
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