THE USE OF GLYCOMACROPEPTIDE IN NUTRITIONAL MANAGEMENT OF PHENYLKETONURIA PATIENTS

Thesis

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وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
تَعْلَمُ وكَانَ فَضْلُ
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Yassmin Ahmed Ebied Aly

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List of Abbreviations

ACCP ..... American College of Clinical Pharmacy

ALT..... Alanine aminotransferase

ASA..... Amino salicylicylic acid

AST ..... Aspartate aminotransferase

ASUH ..... Ain Shams University Hospitals

BUN ..... Blood urea nitrogen

CCK ..... Cholecystokinin

CH ..... Cyclohydrolase I

DBS ..... Dried blood spot

DHPR..... Dihydropteridine reductase

DTI ..... Diffusion tensor imaging

EEG..... Electroencephalogram

GMP ..... Glycomacropeptide

GTP ..... Guanosine triphosphate

GTPCH ..... Guanosine triphosphate cyclohydrolase

HGB..... Haemoglobin

HPA ..... Hyperphenylalaninemia

IQ ..... Intelligence quotient

IQR..... Interquartile range

LAT1..... L-aminoacid transporter 1

LNAA..... Large neutral amino acids

MARS ..... Moss Attention Rating Scale

MRI..... Magnetic resonance imaging

List of Abbreviations (Cont...)

MRS	Magnetic Resonance Spectroscopy
NIH	National Institutes of Health
PAH	Phenylalanine hydroxylase
PAL	Phenylalanine ammonia lyase
PCD	Carbinolamine dehydratase
Phe	Phenylalanine
PKU	Phenylketonuria
PTPS	Pyrovyl tetrahydropyerin synthase
SLIM	Satiety Labeled Intensity Magnitude
SR	Sepiapterinreductase
Trp	Tryptophan
Tyr	Tyrosine
WCDR	World conference on disaster risk reduction
WPC	Whey protein concentrate

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INTRODUCTION

Phenylketonuria is an inborn error of metabolism characterized by mutations of the phenylalanine hydroxylase (PAH) gene (Blau et al., 2010).

The enzyme phenylalanine hydroxylase (PAH) is responsible for the conversion of phenylalanine to tyrosine. The deficiency results in raised serum phenylalanine concentration and mental retardation if the child does not receive long term treatment with low phenylalanine diet starting within the first weeks of life (Lou, 1985). Untreated phenylketonuria is associated with progressive intellectual impairment, accompanied by a constellation of additional symptoms, which can include eczematous rash, autism, seizures, and motor deficits. Developmental problems, aberrant behavior, and psychiatric symptoms often become apparent as the child grows. (Blau et al., 2010)

Early diagnosis and prompt intervention has undoubtedly allowed most individuals with phenylketonuria to avoid severe mental disability(Blau et al., 2010). Phenotypes can vary from a very mild increase in blood phenylalanine concentrations to a severe classic phenotype with pronounced hyperphenylalaninemia which if untreated, results in profound and irreversible mental disability. (Blau et al., 2010)

Treatment of the PKU patients remains difficult due to progressive decrease in adherence to diet and presence of neurocognitive defects despite therapy. (Blau et al., 2010)

Early diagnosis and prompt intervention has undoubtedly allowed most individuals with phenylketonuria to avoid severe mental disability. (Blau et al., 2010)

I. Phenylketonuria (PKU)

1. Definition:

Classical Phenylketonuria (PKU) can be defined as a rare metabolic disorder caused by a deficiency in the production of the hepatic enzyme phenylalanine hydroxylase (PAH) referred to as "hyperphenylalaninemia" classical PKU is an inherited, autosomal recessive disorder. It is the most common genetic disease involving "amino acid metabolism." PKU is incurable, but early, effective treatment can prevent the development of serious mental incapacity(Michals-Matalon et al., 2002)

2. History of PKU

Although PKU was undoubtedly present in the population before 1934, it was in that year that AsbjørnFølling, a Norwegian biochemist and physician first identified and described this metabolic disorder in two young children (Christ, 2003)

Prior to Følling's discovery, PKU was undetected and individuals with this disorder were not differentiated from the general population of individuals with non-specific neurological and cognitive impairments. (Christ, 2003)

In his first paper on PKU, Følling had theorized that the increased amounts of phenylpyruvic acid observed in the children's urine samples were the result of an inability to metabolize phenylalanine, amino acid (Christ, 2003).

Dr. Følling published his findings and suggested the name 'imbecillitas phenylpyruvica' relating the intellectual impairment to the

excreted substance, thereafter renamed 'phenylketonuria'. (Williams et al., 2008)

Subsequent testing of phenylalanine levels in the blood of PKU patients confirmed Følling's initial theory (Christ, 2003)

Along with this work, Følling and Closs were able to identify increased urinary output of phenylacetic acid and phenylalanine in patients with PKU (Closs & Følling, 1938). Phenylacetic acid was found to be responsible for the characteristic odor. (Christ, 2003)

In the 1950s, Horst Bickel introduced a low-phenylalanine diet to treat phenylketonuria; and in the 1960s, Robert Guthrie introduced a diagnostic test suitable for mass screening for hyperphenylalaninaemia (the Guthrie test)(Blau et al., 2010).By 1965, health policies established PKU screening programs which were in place in 32 American states and in most European countries (Committee for the Study of Inborn Errors of Metabolism, 1975)(Blau et al., 2010).

In the late 1970s, various groups began investigating the molecular basis of PKU. The most notable recent advance in the study of PKU was the establishment, in 1996, of the PAH Mutation Analysis Consortium Database. (Williams et al., 2008)

Nowadays, many countries around the world include a test for hyperphenylalaninaemia in neonatal screening programs which is the Guthrie test or more modern systems based on tandem mass spectrometry(Blau et al., 2010).

The discovery of PKU by Dr. Asbjørn Følling was an important milestone in medicine. The PKU model was used to illustrate how metabolic abnormalities could have neurological effects and how treatment could dramatically affect the clinical manifestations of the disorder. The development of Guthrie's screening test, and dietary treatment, led to the prevention of intellectual impairment in affected children throughout the world. Furthermore, the PKU model has since been used as a template to shed light on over 200 other inborn errors of metabolism. (Williams et al., 2008)

3. Epidemiology of PKU

The prevalence of phenylketonuria varies widely around the world. In Europe the prevalence is about one case per 10,000 live births, but for some areas of Europe it is higher. Persistent hyperphenylalaninaemia is detected in about one in every 4000 births in Turkey because of high consanguinity within the population, and in Northern Ireland. (Blau et al., 2010)

Finland has the lowest prevalence in Europe with one case per 100, 000. In the USA the prevalence is one case per 15, 000.In Latin America it varies from about one case per 50,000 to one per 25, 000 births; prevalence is generally higher in southern Latin America than elsewhere in that region. Estimates of prevalence rates in Asia vary from about one per 15, 000 to one per 100,500 births in regions of China less than one per 200, 000 in Thailand, and about one per 70, 000 in Japan. Africa seems to have a very low prevalence of phenylketonuria and Spain has high prevalence of mild hyperphenylalaninaemia. (Blau et al., 2010)

Table (1**):** Incidence of PKU by population

Region / Country		Incidence of PKU
Asian Populations	China	1 : 17,000
	Japan	1 : 125,000
	Turkey	1 : 2,600
	Yemenite Jews (in Israel)	1 : 5,300
	Scotland	1 : 5,300
	Czechoslovakia	1 : 7,000
	Hungary	1 : 11,000
European Populations	Denmark	1 : 12,000
	France	1 : 13,500
	Norway	1 : 14,500
	United Kingdom	1 : 14,300
	Italy	1 : 17,000
Arabic Populations	Canada	1 : 22,000
Oceania	Finland	1 : 200,000
		Up to 1 : 6,000
	Australia	1: 10,000

Adapted from Scriver and Kaufman (2001).(Williams et al., 2008)

4. Classification and differential diagnosis of PKU

Hyperphenylalaninaemia Guthrie testing has revealed a large pool of infants with moderately elevated serum phenylalanine levels, many of whom do not progress to a classical phenylketonuria pattern. A lot of confusion has arisen from the lack of strict definition of the nomenclature used. Most cases of hyperphenylalaninaemia can be grouped into one of five groups as shown in Table 2.(Yu et al., 1970)