Mechanisms Underlying Induced Pseudo-Scleroderma among Patients with Phenylketonuria Metabolic Disorder

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Abstract: Pseudo-sclerodermas are neglected dermatological conditions associated with metabolic dysfunction of phenylalanine. Phenylalanine metabolic disorder is an autosomal genetic mutation in phenylalanine hydrolase (PAH). This mutation results in phenylalanine metabolism deficiency and subsequent accumulation of phenylalanine and phenylpyruvic acid in the blood and the cutaneous tissues. The accumulation induces several systemic complications including neurological and dermatological disorders. This report focuses on the mechanisms underlying the induction of the dermatological disorders, current advances in the treatment of phenylketonuria (PKU), and the prospective research areas of interest for the management of dermatological abnormalities in PKU. This metabolic disorder induces chronic bleeding, cellulitis, dermatitis, eczema, psoriasis and parapsoriasis, benign neoplasms of the skin, and melanomas of the skin causing dysregulation of immune cells. The infiltration of CD4+ T-cells and macrophages stimulates IL-4, IL-10, IL-13, and IL-17 leading to the destruction of cutaneous tissues. The insufficiencies of phenylalanine hydroxylase (PAH) and dihydrobiopterin reductase (DHPR) in PKU leads to the accumulation of phenylalanine and phenylpyruvic acid in the corium of the skin. The neurological and psychosocial manifestations of PKU have attracted current advances in therapeutic management targeting the correction of the enzymatic defects in the metabolic pathways or immunoregulation underlying inflammatory conditions to improve the quality of life in PKU patients. However, there is a knowledge gap on the effectiveness of the current therapeutic advance to restore variations in dermatological abnormalities in PKU. Further studies on comorbidities, etiologies, environmental exposures, psychosocial and social effects, and the effects of new therapeutic strategies would provide an insight into the management of pseudo-sclerodermas in PKU disorders.

Keywords: Pseudo-sclerodermas, Phenylalanine metabolic disorder, phenylketonuria (PKU), Dermatological disorders, Phenylalanine hydrolase (PAH), Dihydrobiopterin reductase (DHPR), Current therapeutic advance, Neurological disorder, Melanocytogenesis.

INTRODUCTION

Phenylketonuria (PKU) is a metabolic dysfunction of phenylalanine catabolism caused by a decrease in the activities of phenylalanine hydroxylase or dihydropteridine reductase [1, 2]. This inherited disorder leads to an accumulation of phenylalanine in the bloodstream [3]. The effects of the high blood levels of phenylalanine include muscle rigidity, choreoathetosis, tremors, hyperreflexia, eczema, light complexion, and pseudo-scleroderma [4]. Pseudo-scleroderma (PSC) is the sclerosis of the skin characterized by dry skin, follicular hyperkeratosis, perifollicular skin haemorrhage, and hypertrophic haemorrhagic gingivitis in PKU [5].

PSC also induces other clinical conditions such as eosinophilic fasciitis, dermatomyositis, systemic lupus erythematosus, and porphyria cutanea tarda [6]. The histopathological presentation of PSC is characterized by perivascular inflammation with leucocytes extravasation and dermal hemosiderin deposits [7]. The diagnosis of PSC is challenged by the progressive enlargement of erythematous indurated plaque which shows an ongoing inflammation with lymphocytic infiltration [8, 9]. However, the severity of neurological damage caused by an increased level of phenylalanine and phenylpyruvic acid in the blood has diminished the level of attention given to dermatological abnormalities in PKU individuals [10, 11].

The defects in the central nervous system in PKU can be attributed to phenylalanine and phenylpyruvic acid competitively inhibiting neurotransmitters such as dopamine, epinephrine, norepinephrine, and serotonin in the brain [12, 13]. The inhibition of neurotransmitters and accumulations of phenylalanine and phenylpyruvic cause structural changes in the white matter within the posterior periventricular, frontal, and subcortical areas of the brain [14]. The defect in myelin development increases myelin turnover, decreases synaptogenesis and neuronal digenesis resulting in cognitive-developmental defect and mental retardation [15].

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These clinical severities of PKU have attracted the attention of researchers and clinicians with little or no emphasis on the dermatological defects of PKU [16].

Dermatological conditions such as cellulitis, rosacea, vitiligo, psoriasis and parapsoriasis, bleeding disorders, benign neoplasms of the skin, non-melanoma skin cancers, melanoma, and dermatitis have been associated with PKU contributing to significant discomfort among affected individuals [17]. The social exclusion and stigmatization associated with odour which emanates from the accumulation of phenylpyruvic acid and subsequent development of dermatological abnormalities contribute to the mental instabilities affecting PKU individuals [18, 19]. Understanding the mechanisms underlying the induction of the dermatological abnormalities in PKU disorders could offer early detection and control measures to reduce adverse dermatological effects caused by increased deposition of phenylalanine and phenylpyruvic acids in the skin tissues. This report focuses on underlying mechanisms and future research areas of interest for dermatological abnormalities in PKU individuals.

Dermatological Disorders Caused by the Deposition of Phenylalanine and Phenylpyruvic Acid on the Skin and their Influence on the Induction of Pseudo-Scleroderma in Phenylketonuria

Several dermatological conditions have been reported in phenylketonuria individuals which imitate scleroderma [16, 19]. To identify dermatological conditions contributing to the risk of inducing pseudo-scleroderma, a short analysis of reported skin disorders was performed using already published data on PKU. The results showed a higher odd ratio for the induction of pseudo-scleroderma for PKU patients with cellulitis (p=0.0092), psoriasis and parapsoriasis (p=0.0147), bleeding disorder (p= 0.0036), benign neoplasms of the skin (p=0.0037), melanoma (p=0.0388), and dermatitis and eczema (p<0.0001). Interestingly, vitiligo which did not seems to influence the induction of pseudo-scleroderma among PKU patients was also identified as a risk factor RR (95% CI) was 0.333 (0.125-0.8885), p= 0.0281 (Table **1**).

The elevated levels of phenylalanine and phenylpyruvic acid in the blood lead to their deposition in the skin tissues [20]. This leads to the stimulation of either systemic or localized inflammation with sclerotic-like lesions on the skin [21]. Again, there is increased permeability of capillaries and proliferation of dermis causing the infiltration of leucocytes and inflammation around the affected sites. CD4+ T-cells mononuclear leucocytes and macrophages predominantly infiltrate the skin and activate DR antigen receptors on MHC class II molecule and IL-2 receptor increasing the secretion of IL-4, IL-10, IL-13 and IL-17 [22, 23]. The observed destruction of cutaneous tissues is due to the underlying conditions induced by PKU [24]. These cause stimulation and production of fibroblast, collagens, proteoglycans, and fibronectin and inhibits the synthesis of matrix metalloproteinases (MMP) by

Table 1: Dermatological Disorders that Influence Induction of Pseudo-Scleroderma in Phenylketonuria

Conditions	OR (95% CI)	z-test	p	RR (95%CI)	z-test	p
Cellulitis	0.6 (0.409-0.881)	2.606	0.0092	0.667 (0.4996-0.8895)	2.755	0.0059
Rosecea	0.571 (0.242-1.352)	1.273	0.2029	0.6429 (0.3396-1.2171)	1.357	0.1745
Vitiligo	0.2 (0.028-1.420)	1.609	0.1076	0.333 (0.125-0.8885)	2.196	0.0281
Psoriasis and Parapsoriasis	0.457 (0.244-0.856	2.439	0.0147	0.5476 (0.3534-0.8485)	2.695	0.007
Bleeding Disorders	0.327 (0.154-0.694)	2.915	0.0036	0.4394 (0.2756-0.7006)	3.455	0.0006
Benign Neoplasms of the Skin	0.633 (0.466-0.862)	2.907	0.0037	0.6944 (0.5493-0.8779)	3.049	0.0023
Non-melanoma Skin Cancers	0.56 (0.272-1.154)	1.572	0.1159	0.633 (0.3717-1.0791)	1.68	0.0929
Melanoma	0.25 (0.067-0.932)	2.066	0.0388	0.375 (0.1805-0.779)	2.63	0.0085
Dermatitis & Eczema	0.7397 (0.664-0.824)	5.498	<0.0001	0.7831 (0.7189-0.8531)	5.597	<0.0001

the increased secretion of IL-4 and TGF-β. IL-17 overexpression in the skin of the affected individuals enhances the stimulation of IL-1 and TNF-α from macrophages [25, 26]. These cytokines stimulate collagen production and induce IL-6, PDGF, ICAM-1, VCAM-1, and connective tissue growth factor (CTGF) [27, 28]. The skin disorders induced by the increased deposition of phenylalanine and phenylpyruvic acid are responsible for the alterations observed in the T-lymphocytes and cytokines which induce the dermatological changes of PKU [29].

Mechanism of Regulation of Melanocytes Production and the Role of Phenylalanine

Phenylalanine from protein dietary source plays a significant role in the melanogenesis of the skin and its deficiency results in a range of dermatological complications [30]. In the case of Phenylketonuria, induction of pseudo-scleroderma is a common presentation of dermatological abnormalities observed in metabolic deficient individuals [17, 19]. However, skin pigmentation and its regulation are not fully understood [31, 32]. This section briefly focuses on melanocytogenesis and the role of dietary phenylalanine. The mechanism underlying the melanocytogenesis is initiated with catabolism of phenylalanine which is control by a series of critical enzymes [33, 34]. In the skin, L- phenylalanine is hydrolyzed to L-tyrosine by phenylalanine hydroxylase (PAH) and the cofactor (6R) -L-erythro-5,6,7,8-tetrahydrobiopterin (6BH4) keeping its 7-isomer (7BH4) in a reduced form by dihydrobiopterin reductase for the production L-tyrosine. The active form of tyrosinase convert L-tyrosine into melanocytes and some of the L-tyrosine is converted to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase isoform I (THI) in the melanosomal cytosol [35, 36]. In low pH, L-DOPA is catalyzed to p-protein by active met-tyrosinase [37]. L-DOPA is then converted to L-tyrosine in the presence of 6BH4 /7BH4, melanocyte-stimulating hormone (α-MSH and β-MSH) and inactive tyrosinase to mature pigmented melanocytes [38] (Figure **1**).

Consequences of Enzyme Deficiencies in the Melanocytogenesis Caused by Phenylketonuria Metabolic Disorder

The autosomal genetic deficiency which causes metabolic disorder in phenylalanine induces several dermatological conditions called pseudo-scleroderma [39, 40]. These skin abnormalities are linked with enzyme deficiencies along the pathway of the

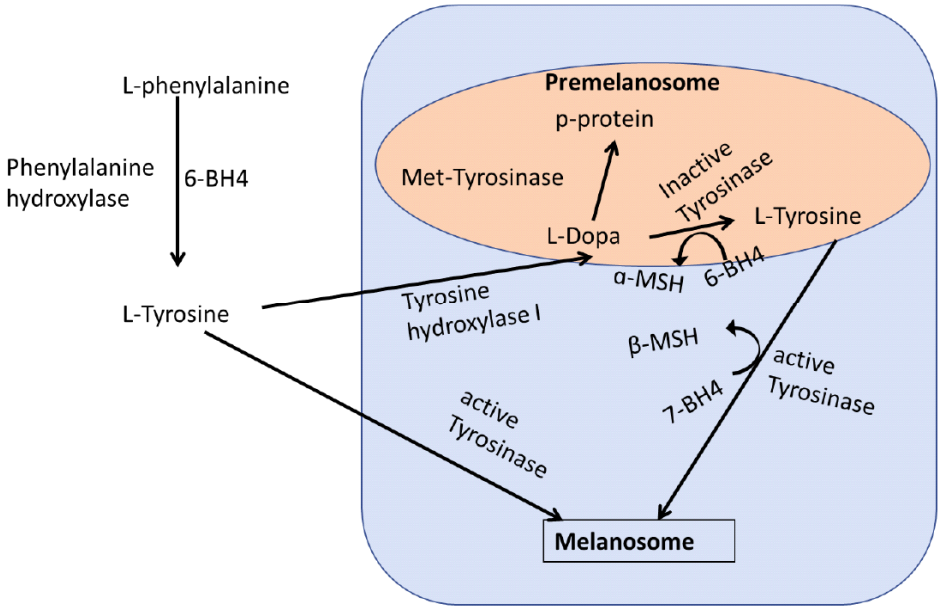

Figure 1: Mechanism underlying melanocytogenesis

L-phenylalanine from dietary source is hydrolysed to L-tyrosine by the enzyme phenylalanine hydroxylase (PAH) in the presence of cofactor L-erythro-5,6,7,8-tetrahydrobiopterin (6BH4). L-tyrosine and 6BH4 are actively diffused into the melanosome to form melanin. L-tyrosine is converted to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase isoform I (THI). The L-DOPA binds to met-tyrosinase to form p-protein at a lower pH. The L-DOPA in the presence of met-tyrosinase, 6BH4 & alpha-melanocyte stimulating hormone activates (α-MSH), the inactive tyrosinase. The activated tyrosinase then catalyse 7-isomer (7BH4), beta-melanocyte stimulating hormone (β-MSH) and L-DOPA to melanin in the melanosome.

melanocytogenesis [41]. Two major enzymes which are associated with phenylketonuria are phenylalanine hydroxylase (PAH) and dihydrobiopterin reductase (DHPR) act on the initial step of the catabolic pathway of phenylalanine [42, 43]. The 6BH4 dependent PAH converts phenylalanine to tyrosine which is converted to phenylpyruvic acid by tyrosinase aminotransferase (TAT) [44]. The insufficiencies of PAH and DHPR cause accumulation of phenylalanine and phenylpyruvic acid in the corium of the skin (Figure **2**). Several neurological and dermatological and social factors are associated with the defect in the metabolism of phenylalanine in PKU [45, 46]. The chronic bleeding into the skin and dysregulation of immune cells induces cellulitis, dermatitis, eczema, psoriasis and parapsoriasis, benign neoplasms of the skin and melanomas of the skin [47-49]. The analysis of dermatological factors in PKU contributing to pseudo-scleroderma showed that vitiligo is not a pseudo-scleroderma. However, it remains a risk factor for the induction of pseudo-scleroderma (Table **1**). Vitiligo is caused by a deficiency in tyrosinase which converts L-tyrosine into melanocytes [50]. This occurs at a later stage in the phenylalanine metabolism and it separated from the initial steps involved in pseudo-scleroderma [51]. This finding showed that there is insufficiency in tyrosinase to convert the limited L-tyrosine into melanocytes leading to uneven distribution of melanin across the skin which characterize the presentation of Vitiligo among PKU individuals.

Current Emerging Therapies for the Management of Complications Associated with Phenylketonuria Metabolic Disorder

There is no absolute treatment for phenylketonuria metabolic disorder [52]. Therefore, restriction of phenylalanine containing foods is the ideal measure for controlling the complications associated with this genetic disease [53]. There are also several emerging therapeutic agents which target specific phenylalanine metabolic pathways to partially control the complications in PKU. However, long-term usage of these therapies may be associated with poor prognosis [54]. The correction of somatic gene mutation of phenylalanine hydroxylase by specific genome integration could be the future therapeutic measure to offer complete remedy for PKU disorder [55]. Although gene therapy is still at its infancy, the successful

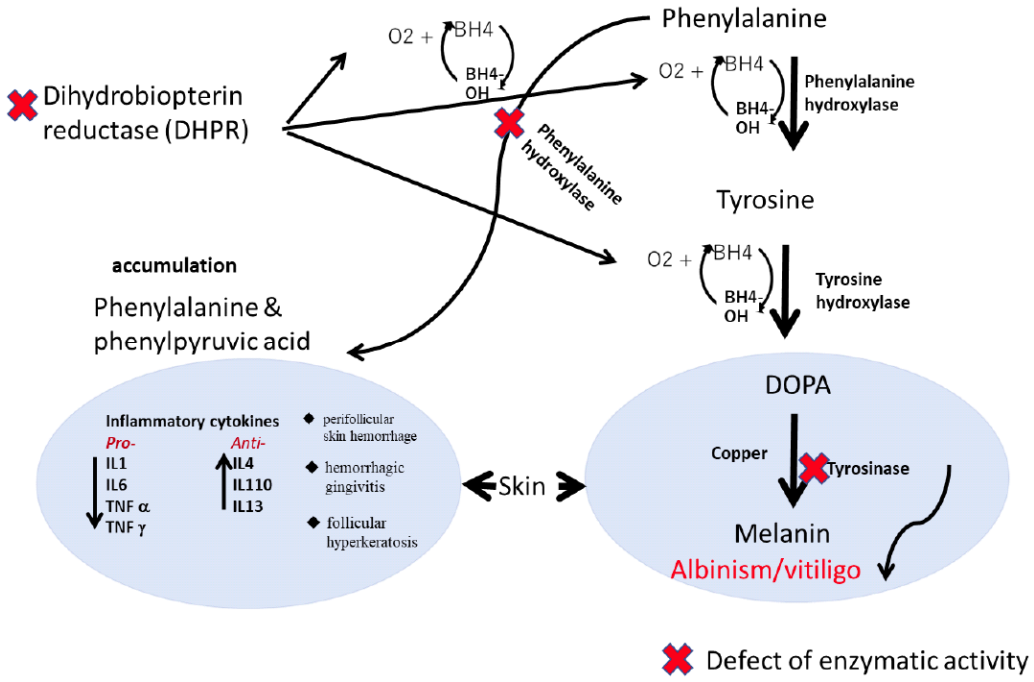

Figure 2: Enzymatic defects associated with the induction of pseudo-scleroderma in phenylketonuria

An autosomal mutation in phenylalanine hydroxylase (PAH) and dihydrobiopterin reductase (DHPR) which catalyzes the initial stage of phenylalanine metabolism by insufficiently converting phenylalanine to tyrosine leading to accumulation of phenylalanine in the blood and tissues. This induces a range of dermatological abnormalities broadly called pseudo-scleroderma. The limited tyrosine is further catalyzed by tyrosine aminotransferase (TAT) to glutamate and phenylpyruvic acid. These accumulations induce neuronal digenesis, cognitive-developmental defects and mental retardation aside the dermatological abnormalities. The limited DOPA in the tissues is not sufficiently converted to melanin by tyrosinase leading to skin decolouration conditions such as albinism and vitiligo which are frequently observed in phenylketonuria patients.

Table 2: Some of the Current Therapeutic Regiments for the Management of Phenylketonuria

Drug	Target
Dasatinib	Tyrosine Kinase Inhibitor
Sapropterin-dihydrochloride	Modified Cofactor BH4
Phenylalanine ammonia lyase	Degradation of Serum Phenylalanine
Mycophenolate	Inosine Monophosphate Dehydrogenase Inhibitor
Alefacept	Inhibits T Lymphocyte Activation
Azathioprine	Inhibits Lymphocyte Proliferation
Rituximab	Inhibits Monoclonal Antibody
Sirolimus	mTOR inhibitor

treatment of hyperphenylalaninaemia in *Pahenu2* mouse model by site-specific genome integration of *Pah* cDNA provides a promising result [56, 57]. When well-developed, it could be used for human treatment of PKU. Other therapeutic products which target a modified cofactor BH4 which can be used by mutant PAH to convert phenylalanine to tyrosine such as Sapropterin dihydrochloride have shown to be safe and effective in some selected PKU individuals [58]. Enzyme replacement therapy have proved to reduce the complications associated with PKU by rapidly catabolizing phenylalanine and reducing the serum levels [59]. An enzyme such as phenylalanine ammonia-lyase (eg. PhenylaseTM) which reduces the half-life of phenylalanine in the serum and its subsequent degradation has also been explored [60].

Apart from the therapeutic designs which target the phenylalanine metabolic pathway, there are also immunomodulating therapies which regulate T-cell activation and reduce inflammatory mediators such as the suppression of lymphocytes proliferation, macrophage activation and inhibition of B-cell function and antibody production (Table **2**) [61, 62].

DISCUSSION

The skin is one of the primary tissues affected by phenylketonuria even though little attention has been giving to dysfunctional groups of skin conditions called pseudo-scleroderma [63]. The neurocognitive and psychiatric conditions in phenylketonuria have gained the attention of researchers contributing to substantial knowledge in neurological dysfunction [64]. The contribution of dermatological abnormalities to severe mental retardation, neurological abnormalities, physical, emotional and social life of PKU patients should as well be of interest to researchers and clinicians [65]. Phenylalanine metabolism and tyrosine byproducts play an essential role in the synthesis of melanocyte, thus any defect in the phenylalanine metabolic pathway would significantly affect the skin and compromise the quality of life [66]. This report focuses on the underlying factors for the induction of pseudo-scleroderma among PKU patients.

Cellulitis, psoriasis and parapsoriasis, bleeding disorder, benign neoplasms of the skin, melanoma and dermatitis and eczema are presented as major conditions of pseudo-scleroderma in PKU patients [67]. Vitiligo, a defect in the skin colouration, although frequently observed in the PKU was not identified as one of the pseudo-sclerodermal conditions [38, 51]. However, vitiligo was identified as a risk factor for pseudo-scleroderma in PKU patients. An inflammatory process characterizes the presentation of these benign diseases of the subcutaneous tissues [68]. The infiltration of inflammatory cells such as lymphocytes and macrophages lead to leucocyte-mediated endothelial damage, necrosis, erythema, eosinophilic and defect in the skin pigmentation [69]. The impact of these dermatological diseases has multidimensional effects on the quality of life, interpersonal relationships, education and professional career of PKU patients [70].

The pathophysiology of pseudo-scleroderma is induced by mutations in the phenylalanine hydroxylase gene or dihydrobiopterin reductase gene which act on the upstream of melanocyte biogenesis [71]. These enzymatic defects impair the metabolism of phenylalanine to tyrosine required for the pigmentation of the skin [56]. This defect causes high blood levels of phenylalanine and phenylpyruvic acid and its ultimate deposition in the skin tissues [20]. The accumulation of the phenylalanine and phenylpyruvic acid in the skin induces a wide range of dermatological manifestations of clinical importance [59]. The current therapeutic

advances target the correction of the enzymatic defects in the metabolic pathways or immunoregulation underlying inflammatory conditions to improve the quality of life in PKU patients [60]. Although these therapeutic regiments have a high potential to improve the general clinical condition of PKU patients, it remains a limited knowledge for its effective role in the restoration of the numerous skin abnormalities [61].

In conclusion, the dermatological diseases associated with PKU patients are largely neglected. Thus, there is a knowledge gap in terms of the mechanisms involved in the wide variations dermatological abnormalities induced by increased serum phenylalanine and phenylpyruvic acid. The understanding of the pathophysiology of pseudo-sclerodermas in PKU would improve its clinical management. Future studies should focus on elucidation of the effects of comorbidity between pseudo-sclerodermas and neurological disorders to understand the contribution of dermatological abnormalities to neuropsychiatric manifestations in PKU. Additional studies on etiologies, effects of new therapeutic strategies, contribution of environmental exposures, psychosocial and social effects on the management of dermatological abnormalities in PKU patients would provide an insight to the management of pseudo-sclerodermas in PKU disorders.

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