

Haemopyrrolactam Disorder (HPU): What It Is, How It Works, and Why It Matters

A science-based guide for patients, caregivers, and practitioners seeking to understand the biochemistry, clinical presentation, and management of HPU — also known as pyrroluria or kryptopyrroluria (KPU).

What Is HPU / Pyrrole Disorder?

Haemopyrrolactam disorder (HPU) — also referred to as pyrroluria, kryptopyrroluria (KPU), or Mauve disorder — is a metabolic condition involving the abnormal overproduction of a haemoglobin by-product called **hydroxyhemopyrrolin-2-one (HPL)**. HPL is a small molecule generated during the synthesis and breakdown of haemoglobin, the oxygen-carrying protein in red blood cells.^[1]

In healthy individuals, HPL is produced in small quantities and excreted harmlessly in the urine. In those with HPU, however, production is chronically elevated.^[2] The elevated HPL is understood to bind critical micronutrients — particularly vitamin B6 (pyridoxal-5-phosphate) and zinc — forming a complex that is excreted in the urine before these nutrients can be properly utilised by the body.^[3]

"The model proposed — and still used clinically — is that pyrroles have a strong affinity for pyridoxal-5-phosphate (active B6) and zinc, and that complexes of pyrroles + B6 + zinc are excreted in urine faster than the body can replace them."^[4]

The condition was first described in the late 1950s by Canadian psychiatrist Dr. Abram Hoffer, who noticed a distinctive mauve-coloured compound in the urine of patients with schizophrenia — a finding that later became known as the "Mauve Factor." In subsequent decades, Dr. Carl Pfeiffer and colleagues at the Brain Bio Center expanded this research to identify HPL as the relevant biomarker, and to characterise the broad clinical picture associated with elevated levels.^[5]

HPU can be genetic in origin or acquired through environmental and physiological stressors, including chronic illness, gut dysfunction, heavy metal exposure, and emotional trauma. It is frequently observed in people with leaky gut syndrome and has been associated with a family history of psychiatric and neurological conditions.^[1]

The Biochemical Mechanism

Understanding HPU requires a brief look at haemoglobin metabolism. All cells produce metabolic waste. In red blood cell synthesis, HPL is one such by-product. Under normal conditions it remains at low concentrations and is cleared through the kidneys. In HPU, dysregulation of the haeme biosynthesis pathway — driven by oxidative stress, genetic vulnerability, or both — results in chronically elevated HPL.^[6]

HOW HPL DEPLETES ZINC AND VITAMIN B6

The proposed mechanism of nutrient depletion involves HPL forming a chemical complex with pyridoxal-5-phosphate (the active aldehyde form of vitamin B6) and zinc. HPL, as a pyrrole derivative, is chemically capable of reacting with the aldehyde group of pyridoxal-5-phosphate to form a Schiff base — a well-characterised class of chemical reaction in coordination chemistry. This Schiff base complex then binds zinc ions, producing a stable tri-component complex that is excreted in the urine.^[3,7]

It is important to note that while the general chemistry of pyrrole-Schiff base-zinc complexes is established in the scientific literature, the specific in vitro confirmation of the HPL-B6-zinc complex using modern spectroscopic methods (NMR, LC-MS) has not yet been formally published. This represents an important gap in the research — one that is technically feasible to address and that advocates within the HPU community are actively working to resolve.^[6]

RESEARCH NOTE

A 2023 paper in a peer-reviewed journal noted that the HPL-B6 binding hypothesis has been proposed and illustrated in clinical contexts, but that spectroscopic confirmation data (such as NMR chemical shift data) have not yet been published. The paper also noted that the clinical outcomes of B6 and zinc supplementation in HPU-positive patients are consistent with the proposed mechanism.^[6]

THE ROLE OF OXIDATIVE STRESS

Current research increasingly frames HPU within the broader context of oxidative stress. HPL has been identified as a biomarker for oxidative stress dysregulation, and elevated levels have been observed across a range of conditions associated with redox imbalance.^[6] Stress of any kind — physical, emotional, or biochemical — amplifies HPL production, which in turn accelerates the depletion of zinc and B6, creating a self-reinforcing cycle of nutrient loss and symptom worsening.^[1]

KEY NUTRIENT DEFICIENCIES IN HPU

Vitamin B6 (Pyridoxal-5-Phosphate): B6 is an essential cofactor in over 100 enzymatic reactions, including the synthesis of serotonin, dopamine, GABA, and melatonin, as well as haeme production and amino acid metabolism. Deficiency is associated with depression, anxiety, anaemia, neuropathy, and impaired immune function.^[1,3]

Zinc: Zinc is required for the function of over 300 enzymes and is critical to neurotransmitter regulation, immune defence, gut integrity, insulin sensitivity, DNA replication, and prefrontal cortex development. Zinc deficiency is strongly associated with cognitive impairment, mood disorders, leaky gut, and impaired growth.^[1]

GLA (Gamma-Linolenic Acid): An omega-6 essential fatty acid that is consistently found to be low in HPU patients, likely due to oxidative stress damaging fatty acid metabolism pathways. GLA is important for anti-inflammatory signalling and hormone balance.^[1]

Magnesium: Frequently co-deficient, magnesium plays a key role in blood sugar regulation, muscle relaxation, sleep, and the nervous system. Its deficiency can worsen B6 absorption, creating a compounding deficit.^[1]

Causes and Contributing Factors

HPU appears to arise from an interaction between genetic predisposition and environmental or physiological triggers. Research and clinical observation have identified the following contributing factors:^[1,2,4]

• Genetic predisposition	• Chronic or acute stress	• Leaky gut syndrome
• Antibiotic overuse	• Heavy metal exposure	• Alcohol and substance use
• Gut dysbiosis / candida	• Poor dietary zinc/B6 intake	• Chronic inflammation
• Hormonal shifts	• Environmental toxin exposure	• Oxidative stress load

A family history of alcoholism, schizophrenia, depression, bipolar disorder, or suicide has been identified as a significant risk indicator, consistent with a heritable component to haeme pathway dysregulation.^[1,5]

Notably, symptoms tend to worsen significantly within 24–48 hours of alcohol consumption, recreational drug use, or periods of intense emotional or physical stress — a clinical pattern widely reported by patients and practitioners and consistent with the stress-HPL production relationship.^[1]

Clinical Presentation: Signs and Symptoms

Because zinc and vitamin B6 are involved in so many fundamental biological processes, the symptom picture of HPU is broad and can initially appear confusing or unrelated. Symptoms are highly individual and vary in severity depending on the degree of nutrient depletion, genetic background, and cumulative stress load.^[1,3]

NEUROLOGICAL AND PSYCHOLOGICAL

• Anxiety and panic attacks	• Depression	• Mood instability
• Explosive anger	• Poor stress tolerance	• Brain fog / poor concentration
• Poor dream recall	• Paranoia or delusions	• Social withdrawal
• Reading / learning difficulties	• ADHD / ODD	• Severe inner tension

PHYSICAL AND METABOLIC

• Fatigue (often unexplained)	• Hypoglycaemia	• Joint pain
• Insomnia	• Morning nausea	• Poor appetite (mornings)
• Irritable bowel	• Food and environmental allergies	• Sensitivity to light / sound / smell
• Tendency toward anaemia	• Low libido	• Irregular menstrual cycles

PHYSICAL SIGNS

• White spots on fingernails	• Pale, thin skin	• Acne or eczema
• Stretch marks	• Crowded upper teeth	• Poor hair density
• Abnormal body odour	• Early greying of hair	

HPU has been clinically associated with a wide range of conditions including autism spectrum disorders, ADD/ADHD, bipolar disorder, schizophrenia, epilepsy, post-natal depression, alcoholism, and chronic anxiety — all of which share overlapping biochemical pathways involving zinc and B6 metabolism.^[1,5]

Diagnosis

HPU is diagnosed through a first-morning urine test measuring the concentration of HPL. The test must be conducted under carefully controlled conditions, as HPL is highly sensitive to light and degrades rapidly upon exposure.^[3] Specific protocols:

• Use second urination of the day	• Collect in a dark environment	• Freeze sample immediately
• Stop B6 and zinc 3 days prior		

HPL levels above 20 mcg/dL are generally considered positive for HPU.^[8] Complementary laboratory markers including plasma zinc, serum copper, ceruloplasmin (copper-binding protein), and whole blood histamine provide a fuller biochemical picture and help guide personalised treatment protocols.^[4]

Due to the absence of large-scale controlled trials — a gap driven in significant part by the non-patentable nature of zinc and B6 rather than absence of clinical evidence — many mainstream practitioners are not yet familiar with HPU. However, a substantial and growing community of naturopathic physicians, orthomolecular practitioners, and integrative GPs do use HPL testing as part of comprehensive functional medicine assessment.^[2]

Treatment Approach

The cornerstone of HPU management is targeted nutritional repletion of the depleted nutrients — primarily zinc, vitamin B6 (ideally as pyridoxal-5-phosphate, the active form), GLA, and magnesium. Because HPL production is ongoing, supplementation is generally required long-term.^[3,7]

Clinical observations from Hoffer, Pfeiffer, and subsequent practitioners demonstrated that high-dose supplementation of zinc and B6 led to significant reductions in urinary HPL and meaningful improvements in symptoms across psychiatric, neurological, and physical domains.^[5]

IMPORTANT — PRACTITIONER GUIDANCE REQUIRED

Self-prescribing is not advisable. Zinc and B6 at therapeutic doses can cause toxicity if incorrectly dosed. Zinc competes with iron and copper for absorption. B6 toxicity (peripheral neuropathy) has been documented with excessive unsupervised supplementation. Dosing must be individualised and monitored by a qualified practitioner experienced in HPU.^[1,6]

CORE SUPPLEMENTATION PROTOCOL (UNDER PRACTITIONER SUPERVISION)

• Zinc picolinate or citrate	• Pyridoxal-5-phosphate (P5P)	• GLA (evening primrose / borage oil)
• Magnesium glycinate	• Vitamins C and E (antioxidants)	• Niacinamide (B3) if indicated
• Manganese if indicated	• Methylcobalamin (B12) if needed	

Additional treatment focuses on identifying and addressing underlying triggers: gut permeability (leaky gut), chronic infections, cortisol dysregulation, toxic burden, and methylation imbalances. Symptom improvement in mild cases can begin within days; severe cases may require three to six months of consistent treatment.^[3]

Foods and supplements high in copper and red/yellow food dyes should be avoided, as copper is commonly elevated in HPU and competes with zinc.^[1]

The Research Gap — and Why It Exists

A 2020 systematic PRISMA review identified 73 articles on HPU/pyrroluria in the medical literature, noting that while clinical observations of elevated HPL are widespread and treatment outcomes consistently positive in practice, formally controlled trials do not yet exist.^[2] This is a significant gap — but it is not evidence against the condition.

The structural reason is straightforward: zinc and vitamin B6 cannot be patented. There is no commercial incentive for pharmaceutical companies to fund large-scale trials on treatments that cannot generate proprietary returns. This is a well-documented problem in nutritional and orthomolecular medicine that affects research into many non-patentable therapies.^[2,6]

The path forward lies with academic research institutions, patient advocacy, and independent funding — including the kind of targeted in vitro chemistry work that could formally confirm the HPL-B6-zinc binding mechanism using modern NMR and LC-MS methodology. Such a study would be modest in cost but significant in impact.

"Elevated HPL is a clinically observed, but poorly researched biomarker. Further research is required: validation of the chemistry and validity of testing, and controlled trials to establish efficacy of high-dose zinc and B6 as treatment of elevated pyrroles." — Mulder et al., Journal of Alternative and Complementary Medicine, 2021^[2]

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