IJBPAS, February, 2026, 15(2): 773-786

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

METABOLIC DISORDERS – A MINI REVIEW

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Received 15th Oct. 2024; Revised 5th Dec. 2024; Accepted 5th Feb. 2025; Available online 1st Feb. 2026

https://doi.org/10.31032/IJBPAS/2026/15.2.9844

ABSTRACT

Metabolic disorders, a diverse group of conditions caused by disruptions in the body's metabolic processes, can significantly impact health and quality of life. These disorders may be inherited or acquired, and they often result from enzyme deficiencies or defects in biochemical pathways. Early detection, typically through newborn screening, is critical for managing many inherited metabolic disorders. Metabolic disorders include an assemblage of diseases whose pathogenesis is varied to say the least. Metabolism comprises all of the chemical reactions that take place in a living system, be it a cell, a tissue, an organ, or an organism. Metabolic reactions are almost all enzyme-catalysed and include transformations of energy and nutrients, syntheses and degradations, and excretions of waste products. Chemical changes concerned with the production, storage, and utilization of metabolic energy for biosynthesis are known as intermediary metabolism. Typically, intermediary metabolism includes all aspects of metabolism (including digestion) except those involved in the transfer of genetic information-replication, transcription, and translation. Metabolic disorders are conditions that affect the body's normal metabolic processes, leading to issues with energy production, storage, or utilization. Examples include diabetes, phenylketonuria (PKU), and lysosomal storage disorders. Treatment often involves lifestyle changes, medications, or specialized diets, depending on the specific disorder

Keywords: Intermediate metabolism, glycogen storage disease, amino acid, nucleotides, digestive fluid, Pompe's disease

INTRODUCTION

Metabolic disorders occur when the breakdown of food to its components becomes disrupted. Disorders in metabolism can be inherited, in which case they are known as inborn errors of metabolism, or they may be acquired during the lifetime. Metabolic disorders can be inherent to severe diseases or conditions, including respiratory or liver failure, chronic obstructive pulmonary disease, cancer, and HIV/AIDS. Occasionally highly complex pathways mediate metabolic disorders. At other times, one base pair of the DNA may be solely responsible. These discoveries have led scientists to develop extraordinary treatments for affected individuals, and the pace of discovery continues to accelerate. The symptoms of metabolic disorders vary among individuals and by the type of the disorder. Some metabolic disorders result in mild symptoms that can be managed with treatment and lifestyle changes, whereas others can cause severe and life-threatening symptoms, such as seizures, breathing problems, and organ failure. Some inherited metabolic disorders can require long-term nutritional supplementation and treatment, however, metabolic disorders that arise as a result of another disease or disorder frequently resolve once the underlying condition is treated **[1, 2]**.

Metabolic disorders are a group of conditions that result from defects in the chemical reactions involved in the body's metabolism. Metabolism refers to the complex series of biochemical processes that convert food and other substances into energy, building blocks for cells, and essential compounds needed for the body to function. In a healthy system, enzymes facilitate these chemical reactions, ensuring the smooth conversion of carbohydrates, proteins, fats, and other nutrients into energy or molecules essential for growth and repair. However, in metabolic disorders, a deficiency or malfunction of enzymes disrupts these processes, leading to an accumulation or deficit of specific compounds, which can have harmful effects on health.

In the last few decades, there has been a significant increase in the incidence of metabolic disorders, including disturbed glucose metabolism, general and abdominal obesity, elevated blood pressure, dyslipidemias, insulin resistance, hyperglycemia, and hyperuricemia that are all risk factors for several serious diseases, such as type 2 Diabetes Mellitus (DM2), cardiovascular disease (CVD), and stroke. Although these risk factors have a genetic component, it is generally accepted that their current elevated incidence in most developed countries is due to a greatly

increased exposure to metabolic insults that has at least two major sources: an obesogenic environment that may facilitate overconsumption, poor nutrition, and sedentarism, i.e., "life-style" (behavioural) factors; and aging populations, wherein the gradual appearance of metabolic disorders can occur due to longer lifespans. Thus, aging can be thought of as a measure of the duration of metabolic insults and lifestyle a measure of their degree **[3, 4]**.

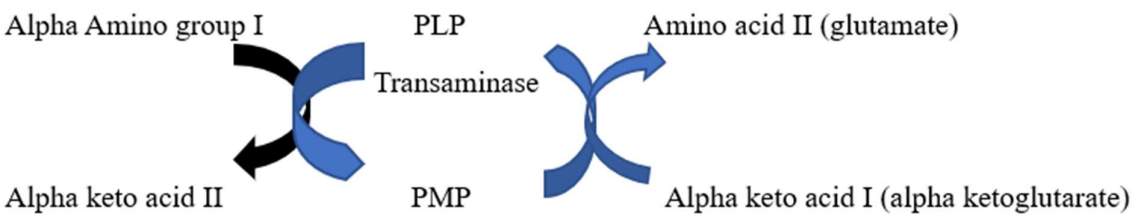
Amino acid metabolism

Amino acids are the building blocks of protein and also found in nitrogenous backbones in neurotransmitters and hormones. Amino acids consist of an amino group ($-NH_2$) and carboxylic group (-COOH) hence the name amino acids. A protein can be defined as long chains or polymers made up of alpha amino acid which is a chiral carbon. These amino acids are linked together by bonds called peptide linkages. About 20 amino acids are responsible for the formation of proteins in humans. These are classified into 'essential amino acids' and 'non-essential amino acids'. non-essential amino acids are synthesised in the body and essential amino acids cannot be synthesised in the body and needed to be taken through diet. 20 amino acids include; alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophane, tyrosine, valine, selenocysteine. In this 9 are essential amino acids. They are; histidine, isoleucine, leucine, lysine, methionine, phenylalanine, thionine, phenylalanine, threonine, tryptophan, valine **[5 ,6]**.

Metabolism

- Transamination
- Deamination
- Decarboxylation

Transamination: Transfer of a of amino groups from amino acid is called Transamination. This takes place in the presence of transaminases, Amino transferases which gets activated in presence of pyridoxal phosphate. This occurs in two steps; i. Transfer of $-NH_2$ in the presence of PLP to form PMP, ii. Amino group of PMP transfers to keto acid to produce new amino acid and PLP.



Deamination: Deamination is the removal of amino group from amino acid in the form of ammonia.

Types of deamination:

i) Oxidative deamination - Removal of ammonia coupled with oxidation is called oxidative deamination. Glutamate dehydrogenase, amino acid oxidase, catalyses this deamination.

ii) Non oxidative deamination - Deamination in the absence of oxygen is called non oxidative deamination. Amino acid dehydrases, amino acid decahydrates, histidine's are the catalyst enzymes involving in this deamination.

Decarboxylation: Amino acid undergo decarboxylation to form their respective amines which are important in biological system. Decarboxylases, histamine, Gamma-Amino butyric acid, catecholamines are involved in decarboxylation. It is dependent on PLP coenzyme **[7, 8]**.

Urea cycle

- Urea is the end product of amino acid metabolism.
- Flans Krebs and Kurt Hensel, it discovered the urea cycle.
- Urea cycle is the 5-step process in which 3 molecules of ATP and 5 different enzymes are involved.

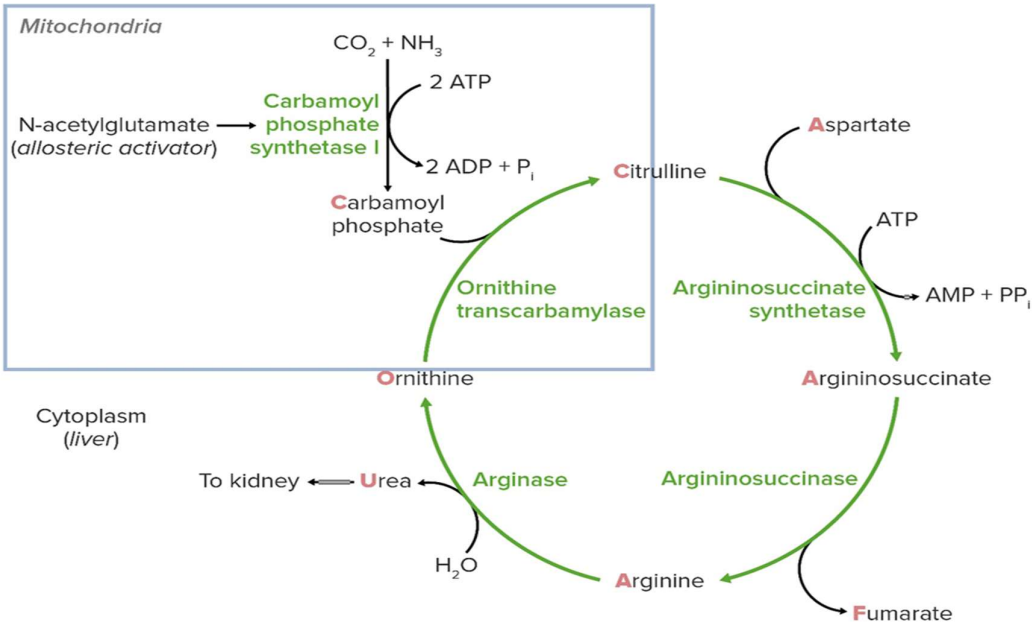


Figure 1: Urea cycle

Metabolic disorders of urea cycle:

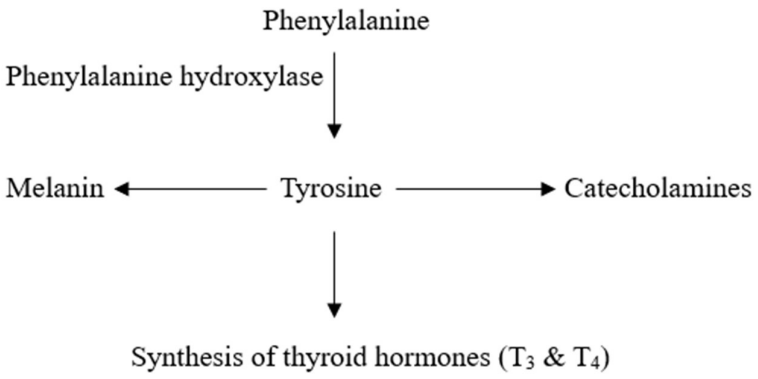
Biochemical Defect	Disorder
Carbamoyl phosphate synthetase-I	Hyperammonaemia I
Ornithine Transcarbamylase	Hyperammonaemia II
Arginino succinate synthetase	Citrullinemia
Arginosuccinase	Arginosuccinic aciduria

Metabolic disorders of amino acids [5, 9, 10]

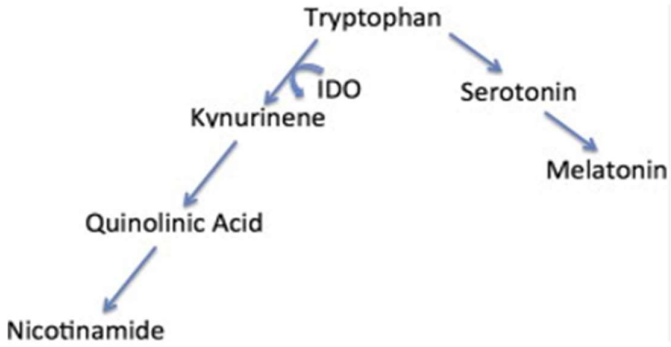
Glycine:

Disorder	Biochemical Defect	Clinical Manifestation
Glycinuria	Defective renal reabsorption	Causes formation of oxalate renal stones
Primary hyperoxaluria	Glycine transaminases	Oxalosis
Glycine encephalopathy	Defect in glycine cleavage system	High levels of glycine in cerebrospinal fluid

Phenylalanine & tyrosine:

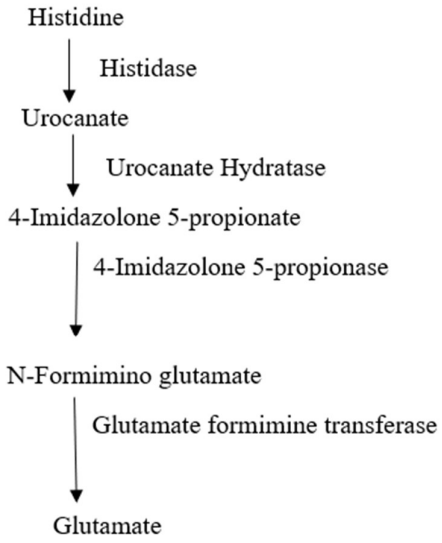


Tryptophan:



Disorder	Biochemical Defect	Clinical Manifestation
Phenyl ketonuria	Phenylalanine hydroxylase enzyme	Effect on CNS, low pigmentation, hypothyroidism
Tyrosinemia type I	Fumary/acetoacetate hydrolase	Liver failure, rickets, renal tubular dysfunction
Tyrosinemia type II	Tyrosine trans aminase enzyme	Skin and eye lesions
Alkaptonuria /black urine disease	Homogentisate oxidase	Ochronosis Arthritis
Albinism	Tyrosinase enzyme	Susceptibility to cancer Photophobia
Hypopigmentation	Decreased synthesis of melanin	Vitiligo Leukoderma
GTP cyclohydrolase I deficiency	GTP cyclohydrolase enzyme	Neurological dysfunction, tremors, abnormal moments
Hyperphenylalaninemia	6-Pyruvoyl tetrahydropterin synthase deficiency	Deficiency of dopamine, serotonin

Histidine:



Disease	Biochemical Defect	Clinical Manifestation
Histidinemia	Histidase	Mental retardation, defect in speech
Urocanase deficiency	Urocanase	Liver dysfunction
Formimino transferase deficiency	Formimino transferase	Liver damage

Proline:

Disease	Biochemical defect	Clinical manifestation
Hyperprolinemia type I	Proline oxidase	Seizures neurological defects

Sulphur containing amino acids (cystine, cysteine, methionine):

Disease	Biochemical Defect	Clinical Manifestation
Cystinuria	Defective carrier system for cysteine ornithine arginine and lysine	Cystine stones in kidneys and urinary tract
Cystinosis	Defective lysosomal function	Cystine crystals deposited in liver spleen kidney bone marrow, Amino aciduria, Renal failure
Homocystinuria type I	Cystathionine synthetase	Thrombosis, Osteoporosis, Mental Retardation
Homocystinuria type II	N^5-N^{10}-Methylene the reductase enzyme	No symptoms
Homocystinuria type III	N^5-N^{10}-Methyl the homocysteine methyl transferase	No symptoms
Homocystinuria type IV	N^5-Methyl the homocysteine methyl transferase	No symptoms

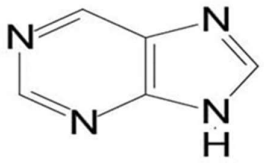
Branched amino acids (valine, leucine, isoleucine):

Disease	Biochemical Defect	Clinical Manifestation
Maple syrup urine disease	Alpha ketoacid dehydrogenase	Acidosis, lethargy, convulsions, Mental Retardation, coma, death within one year
Intermittent branched chair ketonuria	Impairment of alpha ketoacid dehydrogenase	Symptoms are not severe like MSUD
Hypervalinaemia	Increased concentration of valine in plasma	No symptoms

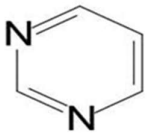
Metabolism of nucleotides

Nucleotides forms the chains encoding the information content in RNA and DNA. Nucleotides are the basic building blocks of nucleic acids (RNA and DNA). A Nucleotide consists of a sugar molecule either ribose in RNA and deoxyribose in DNA attached to a phosphate group and a nitrogen containing base. The bases used in DNA are adenine (A) cytosine (C), guanine (G) and thymine (T). In RNA the base uracil (U) takes place of thymine. DNA and RNA molecules are polymers made up of long chains of nucleotides.

Nitrogenous base: Nitrogenous bases are also called Nucleobases, are the biological compounds that forms nucleosides and in turn nucleotides. The function of these nitrogenous bases is to form base pairs leading to formation of long chain helical structures. There are five types of nucleobases which are adenine (A), cytosine (C), guanine (G), thymine (T), uracil (U) divided into purines and pyrimidines. adenine and guanine are derived from purines and cytosine, thymine, uracil are derived from pyrimidines. Thymine and uracil can be differentiated by the presence or absence of a methyl group on fifth carbon **[3, 11]**.



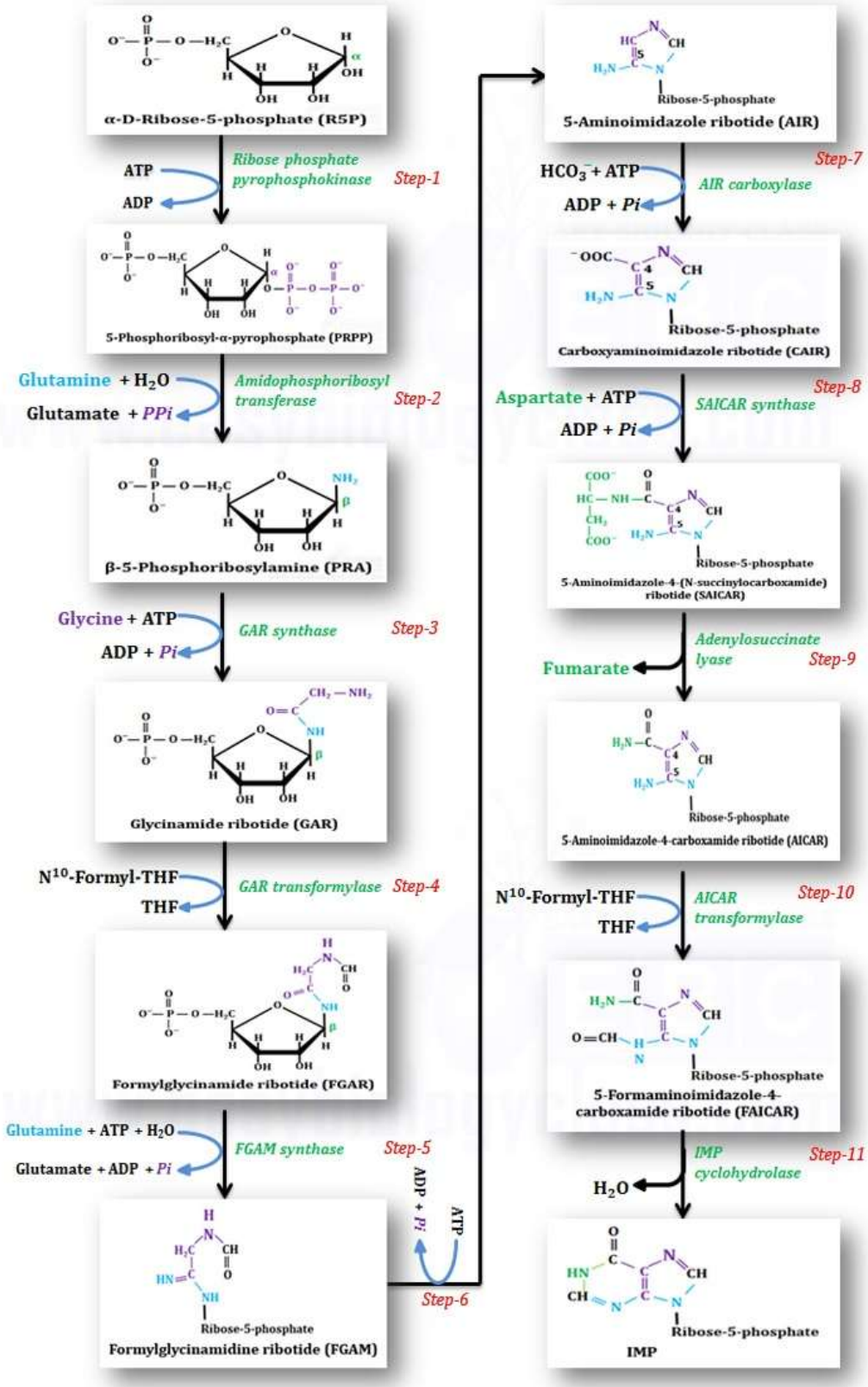
Purine



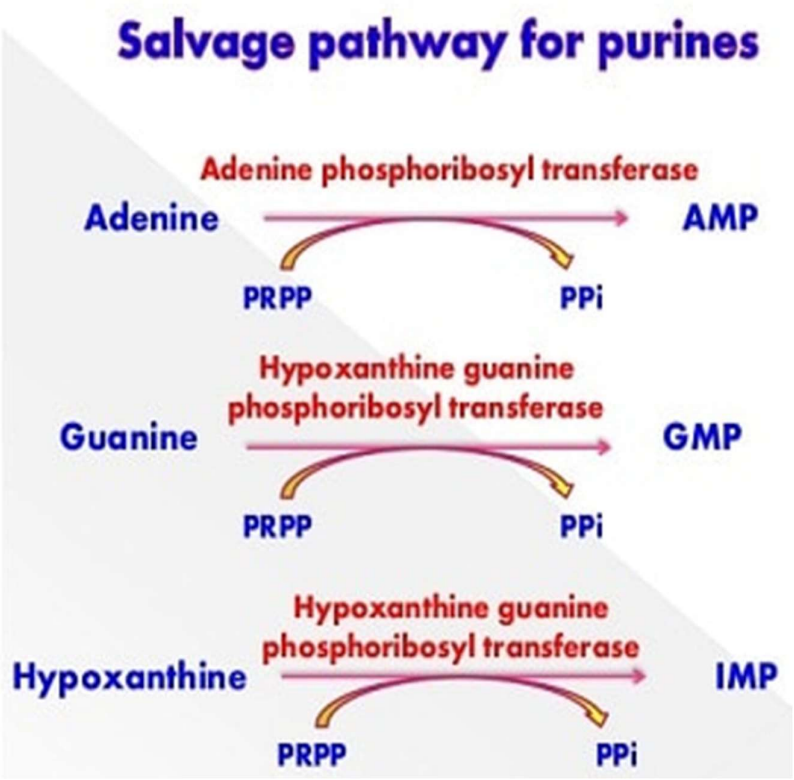
Pyrimidine

Biosynthesis of purine ribonucleotides

The purines are not synthesised directly but are synthesised as ribonucleotides. Organs like liver can synthesis purine nucleotides and erythrocytes, polymorphonuclear leukocytes and brain cannot synthesis purines. Purines are necessary for many essential biochemical processes **[12-14]**.



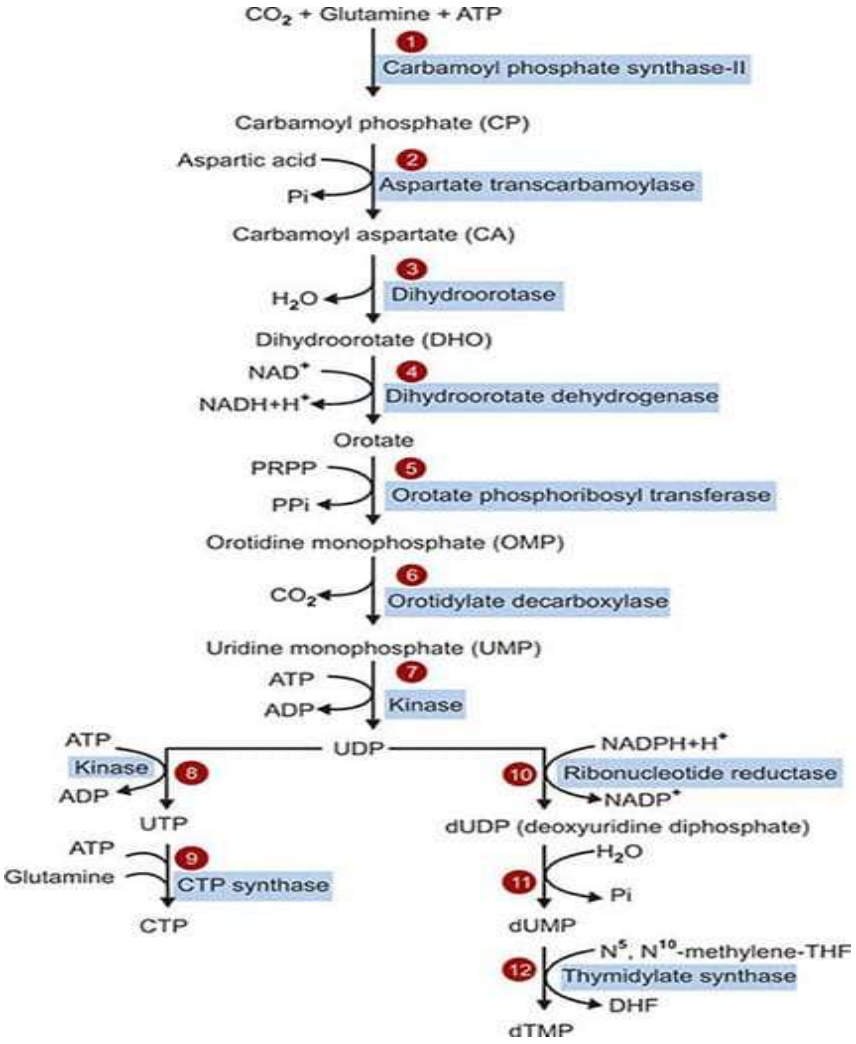
Inosine Monophosphate (IMP) Synthesis



Disorders

Disorder	Biochemical defect	Clinical manifestation
Hyperuricemia	Increase concentration of uric acid in serum	Gout, hypertension, rapid renal insufficient renal stones and failure
Uricosuria	Increased uric acid secretion	
Gout	Over production of uric acid	
Gouty arthritis	Deposition of sodium urate crystals in joints	Inflammation of joints
PRPP synthetase deficiency	Variant form of PRPP synthase not under feedback regulation	Gouty arthritis, nerve deafness
Lesch-Nyhan syndrome	HGPRT deficiency	Mental retardation, aggressive behaviour, learning disabilities
Secondary hyperuricemia	Increased degradation of nucleic acids	Cancer, psoriasis
Pseudogout	Deposition of calcium pyrophosphate crystals	
SCID	Adenosine deaminase deficiency	Muscle cramps, myalgia, muscle weakness
Impairment of t-cell function	Purine nucleotide phosphorylase deficiency	Mental retardation, ataxia, hypertonia
Hypouricemia	Decreased uric acid defect in xanthine oxidase	Xanthine stones in urinary tract
Xanthinuria 2	Aldehyde oxidase deficiency	UTI, nephrolithiasis, acute renal failure
Xanthinuria 1	Xanthine dehydrogenase deficiency	Xanthine lithiasis, UTI, acute renal failure

Biosynthesis of pyrimidine ribonucleotides



Disorders

Disorder	Clinical Manifestation
Ortic aciduria	Anaemia, retarded growth
Reyes syndrome	Ornithine Transcarbamylase defect
OA Type 1 (orotate phosphoribosyl transferase deficiency)	Megaloblastic anaemia
Ureidopropionase deficiency	Hypotonia, seizures, optic atrophy
UMP synthase deficiency	Hereditary orotic aciduria megaloblastic anaemia immune deficiency
OMP decarboxylase deficiency	Neurological abnormalities
Dihydro pyrimidine dehydrogenase deficiency	Development delay, seizures, spasticity, microcephaly
Pyrimidine 5-nucleotide deficiency	Haemolytic anaemia

Carbohydrate metabolism

The major source of energy for living cells is the carbohydrates. Carbohydrates are synthesised by green plants during photosynthesis by the use of CO_2, Light and H_2O. The central molecule of carbohydrate metabolism is glucose **[15-19]**.

Glycolysis disorders

Disease	Enzyme Defect	Clinical Manifestation
Haemolytic anaemia	Glucose-6-phosphate dehydrogenase (inherited sex-linked trait)	Haemolytic jaundice, haemolysis
Wernicke Korsakoff syndrome	Transketolase	Mental disorder, loss of memory, partial paralysis. The symptoms are manifested in vitamin deficiency alcoholism
Essential pentosuria	Xylitol dehydrogenase	Excretes large amounts of l xylulose in urine. essential pentosuria is a symptomatic and the individuals suffer from no ill effects
Galactosemia	Galactose-1 phosphate uridyltransferase	Galactosemia, Galactosuria, cataract, hypoglycaemia, loss of weight, hepato splenomegaly, jaundice, mental retardation.
Essential fructosuria	Fructokinase	This is an asymptomatic condition with excretion of fructose in urine
Hereditary fructose intolerance	Absence of enzyme aldolase b	Intracellular accumulation of fructose-1-phosphate, severe hypoglycaemia, vomiting, hepatic failure
Lactose intolerance	lactase	Flatulence

Glycogen storage diseases

Disorder	Enzyme Defect	Clinical Manifestation
TYPE I Von Gierke's	Glucose-6-phosphatase	Fasting Hypoglycaemia Lactic acidaemia Hyperlipidaemia Ketosis Gouty arthritis
Type II Pompe's disease	Lysosomal alpha 1, 4- glucosidase	Glycogens accumulation in lysosome
Type III Cori's disease	Amylo alpha-1,6-glucosidase	Similar to type 1 but mild
Type IV Andersons disease	Glucosyl 4,6 transferase	Cirrhosis
Type V Mc Ardle's disease	Muscle glycogen phosphorylase	Muscle cramps
Type VI Her's disease	Liver glycogen phosphorylase	Liver enlargement Hypoglycaemia Ketosis
Type VII Tarui's disease	Phosphofructokinase	Muscle cramps Haemolysis
Type VIII Glycogen synthase deficiency	Glycogen synthase	Hypoglycaemia Hepatomegaly Growth retardation
Type IX phosphorylase kinase deficiency	Liver phosphorylase b kinase	Hypoglycaemia Hepatomegaly Growth retardation
Type XI Fanconi-Bickel syndrome	Glucose utilization disorder GLUT 2 mutation (glucose galactose transporter defect)	Hepatomegaly Tubulopathy Rickets
Type 9 A1	Alpha 2 phosphorylase kinase	Hepatomegaly Growth retardation Hypercholesterolemia Hypertriglyceridemia Hyperketosis
Type 9B	Beta muscle phosphorylase kinase	Short stature Hepatomegaly Diarrhoea Hypotonia
Type 9C	Hepatic phosphorylase kinase	Growth retardation Hepatomegaly Hypotonia Cognitive delay
Type 9D	Alpha muscle phosphorylase kinase	Muscle weakness Muscle atrophy
Type 10	Muscle phosphoglycerate mutase	Cramps

		Rhabdomyolysis **Myoglobinuria** **Gout** **Arteriosclerosis**
Type 12 aldolase	**Fructose 1,6 biphosphate aldolase**	**Myopathy** **Mental retardation** **Delay puberty** **Anaemia** **Dysmorphic faces** **Hepatosplenomegaly**
Type 13 enolase 3 deficiency	**Beta enolase**	**Exercise intolerance myalgia** **Rhabdomyolysis**
Type 14	**Phosphoglucomutase**	**Cleft palate** **Bifid uvula** **Pierre robin sequence** **Hepatopathy** **Cardiomyopathy**
Type 15	**Glycogenin**	**Cardiac arrhythmia** **Muscle weakness**

CONCLUSION

A metabolic disorder is a disorder that negatively alters the body's processing and distribution of macronutrients such as proteins, fats, and carbohydrates. Metabolic disorders can happen when abnormal chemical reactions in the body alter the normal metabolic process. It can also be defined as an inherited single gene anomaly, most of which are autosomal recessive. Some of the symptoms that can occur with metabolic disorders are lethargy, weight loss, jaundice, and seizures. The symptoms expressed would vary with the type of metabolic disorder. Metabolic disorders can then be classified according to their dependence/independence on educational level and/or age taken as measures of degree and duration of metabolic insult exposure.

The distinct risk profiles potentially indicate different aetiologies for the different disorders and this is also indicated by their quite different prevalence as a function of age. Moreover, we conclude that the distinct profiles indicate that both clinical and public health interventions for a given metabolic disorder need to be tailored to age and education (lifestyle) specific groups. The fact that educational level correlates with better health in many, but not all, of the metabolic variables and, in particular, in the components of MS, requires much more study to determine those characteristics that differentiate the lifestyle decisions of one educational group vs. another.

Over the past few decades, advancements in enzyme replacement therapy, gene therapy, and dietary management have greatly improved the prognosis for those affected. Looking to the future, precision medicine, gene editing, and personalized treatments offer hope for better outcomes and, potentially, long-term cures for many metabolic conditions. As research

continues to advance, a deeper understanding of these disorders and more sophisticated treatments will likely improve the lives of those affected, moving beyond symptom management toward addressing the root causes of these conditions. With continued innovation in diagnostics, therapeutics, and healthcare technology, the future of managing metabolic disorders appears promising, paving the way for more effective interventions and enhanced quality of life for individuals worldwide.

Source of support

Nil

Conflict of interest

None

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