

Article: Review

Metabolic crossroads: biochemical nodes integrating energy metabolism and biosynthesis**Encrucijadas del metabolismo: nodos bioquímicos que integran el metabolismo energético y la biosíntesis**¹Mauricio Silverio Mestiza , ²Alfredo Ibarra Sánchez .¹Universidad Insurgentes, Plantel Viaducto-Coruña, Mexico City, 03510, Mexico, Mexico²Department of Pharmacobiology, Center for Research and Advanced Studies, South Unit, Mexico City, 14330, Mexico, Mexico***Corresponding author:** Alfredo Ibarra Sánchez 

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ABSTRACT

Introduction: Metabolic pathways share intermediates that coordinate energy production and biosynthesis. This review analyzes the main biochemical crossroads integrating these functions in the human organism.

Method: A narrative review of biochemistry textbooks, mechanistic reviews and selected experimental studies was undertaken. The initial corpus was supplemented through targeted checks of PubMed records and publisher websites in October 2026, incorporating publications through 2025. The synthesis considered carbon flow, cellular compartments and cofactor function.

Results: Glucose-6-phosphate distributes carbon among glycolysis, glycogen metabolism and the pentose phosphate pathway. Pyruvate connects oxidation, lactate formation and anaplerosis. Acetyl-CoA links nutrient catabolism with oxidation, lipogenesis and ketogenesis. Oxaloacetate and α -ketoglutarate connect the citric acid cycle with gluconeogenesis and nitrogen metabolism. NADPH supports reductive biosynthesis and antioxidant defense, whereas ATP synthesis and consumption couple energy supply to cellular work. Recent experimental evidence highlights the contribution of subcellular localization and interorgan exchange.

Conclusions: Metabolic integration depends on functionally distinct nodes and regulated fluxes. Interpretation requires distinguishing carbon intermediates, redox cofactors and energy nucleotides, considering tissue and compartment differences, and separating biochemical mechanisms from clinical inferences.

Keywords: Energy metabolism; Acetyl coenzyme A; Glycolysis; Citric acid cycle; Pentose phosphate pathway

RESUMEN

Introducción: Las rutas metabólicas comparten intermediarios que coordinan la producción de energía y la biosíntesis en distintos compartimentos y órganos. Objetivo general: Analizar las principales encrucijadas bioquímicas que integran el metabolismo energético y la biosíntesis en el organismo humano.

Metodología: Revisión narrativa de textos de bioquímica, revisiones mecanísticas y estudios experimentales seleccionados. El corpus inicial se complementó mediante consultas dirigidas de registros de PubMed y sitios editoriales en octubre de 2026, incorporando publicaciones hasta 2025. La síntesis consideró el flujo de carbono, la localización subcelular y la función de los cofactores.

Resultados: La glucosa-6-fosfato distribuye carbono entre glucólisis, glucógeno y vía de las pentosas fosfato. El

piruvato conecta oxidación, formación de lactato y anaplerosis; la acetil-CoA vincula catabolismo con oxidación, lipogénesis y cetogénesis. El oxaloacetato y el α -cetoglutarato relacionan el ciclo del ácido cítrico con gluconeogénesis y metabolismo nitrogenado. El NADPH sostiene biosíntesis reductora y defensa antioxidante, mientras que el ATP acopla suministro energético y trabajo celular.

Conclusiones: La integración depende de nodos con funciones diferenciadas y flujos regulados. Su interpretación exige distinguir intermediarios carbonados, cofactores redox y nucleótidos energéticos, considerar tejidos y compartimentos, y separar mecanismos bioquímicos de inferencias clínicas.

Palabras clave: Metabolismo energético; Acetil coenzima A; Glucólisis; Ciclo del ácido cítrico; Vía de la pentosa fosfato

INTRODUCTION

The use of nutrients requires coordinating reactions that take place in different cellular compartments and organs. Carbohydrates, lipids and proteins have different initial transformation pathways, but their products are incorporated into shared intermediates. This organization makes it possible to link the energy supply with the formation of membranes, nucleotides and other molecules essential for cell function [1,2].

The teaching of biochemistry is usually organized by routes, which makes it easier to recognize their enzymes and balances, although it can also make it difficult to identify the connections between them. The concept of metabolic crossroads offers an integrative criterion: the same intermediate can receive substrates from different sources and distribute them to alternative destinations. Acetyl-CoA and the intermediates of the citric acid cycle explain this coordination between oxidation and biosynthesis [3,4].

The existence of chemical connections does not imply that they are all active with the same intensity in any cell. Transport across membranes, enzyme expression, oxygen availability, and hormonal signals condition the direction of flow. In particular, the balance between anaplerotic inputs and cataplerotic outputs is necessary to sustain oxidation when cycle intermediates are used in other pathways [5,6].

This analysis distinguishes three complementary dimensions: the redistribution of carbonate skeletons, the transfer of reducing equivalents, and energy coupling. NADPH is considered a functional node of reducing power, while ATP is involved in energy transfer; neither should be confused with a carbon intermediate such as pyruvate. The aim of this review is to analyze the main biochemical crossroads that integrate energy metabolism and biosynthesis, considering their regulation and their usefulness for interpreting physiological situations [7,8].

LITERATURE REVIEW

2.1 Metabolic convergence of glucose and fructose in glycolysis and its relationship to lipogenesis

The metabolic convergence of glucose and fructose represents a critical point in the integration of human energy metabolism. Both monosaccharides, although structurally similar, follow distinct initial pathways after intestinal absorption; however, they converge on common glycolysis intermediates

that may be directed towards energy production or towards the synthesis of lipids, particularly fatty acids and triglycerides [1,2].

Glucose metabolism and its input into glycolysis

Glucose is a central energy substrate whose utilization varies between tissues and nutritional states. After absorption, it can be phosphorylated to glucose-6-phosphate (G6P) by hexokinases; glucokinase is especially relevant in the liver and pancreatic β cells. G6P is distributed between glycolysis, pentose phosphate pathway, and glycogen metabolism. Phosphofructokinase-1 (PFK-1) is an important glycolytic regulation point, sensitive to energy status and signals such as fructose-2,6-bisphosphate [1]. Pyruvate can be converted to mitochondrial acetyl-CoA by the pyruvate dehydrogenase complex. When conditions favor lipogenesis, citrate exported to the cytosol provides acetyl-CoA by action of ATP-citrate lyase; acetyl-CoA carboxylase and fatty acid synthase are subsequently involved in fatty acid synthesis [2].

Hepatic fructose metabolism and its convergence with glycolysis

Fructose follows a different metabolic pathway, especially in the liver. It is phosphorylated by fructokinase to fructose-1-phosphate, which is cleaved by aldolase B into dihydroxyacetone phosphate (DHAP) and glyceraldehyde. The latter is phosphorylated to glyceraldehyde-3-phosphate (G3P). Both DHAP and G3P are direct intermediates of glycolysis, representing the metabolic convergence point between glucose and fructose [9,10]. A relevant aspect is that fructose metabolism avoids the PFK-1 regulated step, considered the main control point of glycolysis. As a consequence, the flux of fructose-derived carbons into triose phosphate can be faster and less regulated, favoring the formation of pyruvate and, subsequently, acetyl-CoA [9]. This metabolic characteristic has been associated with a higher lipogenic potential under conditions of high fructose intake.

Convergence towards lipogenesis and triglyceride formation

The convergence of glucose and fructose in triose phosphate represents a central metabolic node. When energy input exceeds expenditure, excess acetyl-CoA is channeled into fatty acid synthesis in the liver cytosol. Acetyl-CoA carboxylase converts acetyl-CoA into malonyl-CoA, a limiting step in lipogenesis, and then fatty acid synthase forms palmitate as an initial product [1]. The synthesized fatty acids can be esterified with glycerol-3-phosphate, also derived from glycolytic intermediates such as DHAP, to form triglycerides. These triglycerides are stored in the liver or exported as very low-density lipoproteins (VLDL) to adipose tissue [2]. Thus, both glucose and fructose contribute not only to immediate energy supply, but also to long-term energy storage in the form of fat.

The entry of hepatic fructose below PFK-1 modifies the regulation of triose intake, but does not eliminate controls on their use. The activity of subsequent enzymes, the availability of cofactors, biosynthetic demand, and energy balance condition lipogenesis. Therefore, a biochemical connection between fructose and triglycerides does not, by itself, predict the magnitude of lipid synthesis or a clinical outcome [9,10].

Integration also depends on the availability of fructose to the liver. Jang et al. showed in mice that their intestinal catabolism can reduce the arrival of fructose to the liver and limit hepatic lipogenesis. This result places the intestine as a regulator of substrate supply and requires distinguishing experimental evidence from a direct clinical conclusion [11].

2.2 Metabolic convergence of ribose in nucleic acid synthesis

Ribose occupies a central place in cell metabolism as a structural and functional component of nucleotides, the basic units of nucleic acids. Its role represents a clear example of metabolic convergence, since multiple biochemical pathways converge in the generation of ribose-5-phosphate, an indispensable precursor for the synthesis of purine and pyrimidine nucleotides, as well as fundamental coenzymes such as NAD⁺, FAD and coenzyme A [1,2].

The pentose phosphate pathway as the central axis

The main metabolic source of ribose-5-phosphate is the pentose phosphate (PPV) pathway, also known as the phosphogluconate pathway. This pathway derives from glucose-6-phosphate, a key intermediate of glucose metabolism, and serves two essential functions: the generation of NADPH and the production of five-carbon sugars [2]. In its oxidative phase, VPP converts glucose-6-phosphate to ribulose-5-phosphate, producing NADPH in the process. Subsequently, in the non-oxidative phase, ribulose-5-phosphate can be isomerized to ribose-5-phosphate by the action of phosphopentose isomerase. This ribose-5-phosphate constitutes the point of convergence between carbohydrate metabolism and nucleotide biosynthesis [1]. In addition, the non-oxidative phase allows a dynamic interconversion between three-, four-, five-, six-, and seven-carbon sugars using enzymes such as transketolase and transaldolase. This implies that glycolytic intermediates such as fructose-6-phosphate and glyceraldehyde-3-phosphate can be transformed into ribose-5-phosphate according to cellular needs, demonstrating the metabolic flexibility of the system [12].

Ribose activation and nucleotide formation

Ribose-5-phosphate is activated to form 5-phosphoribosyl-1-pyrophosphate (PRPP) by PRPP synthetase. PRPP is involved in the de novo synthesis of purines and pyrimidines and in the rescue of puric bases. In humans, pyrimidine rescue depends primarily on nucleoside phosphorylation, so PRPP should not be attributed an equivalent involvement in all rescue pathways [1].

In purine synthesis, the ring is progressively built on activated ribose. In pyrimidine synthesis, the ring is formed before binding to PRPP. The resulting ribonucleotides originate RNA precursors and are involved in energetic, regulatory, and coenzymatic functions. Deoxyribonucleotides are required for DNA synthesis; their formation involves the reduction of ribonucleotides by ribonucleotide reductase and other transformations, including thymidylate synthesis [2,12].

Metabolic Integration and Regulation

The choice between ribose-5-phosphate and NADPH production depends on different needs. When the cell demands nucleotides, the non-oxidative phase of the pentose phosphate pathway can provide ribose from glycolytic intermediates without requiring equivalent production of NADPH. On

the other hand, lipid biosynthesis and antioxidant defense favor the flow that provides reducing power. Regulation is therefore functional and does not mean that both products are always generated in a fixed proportion [8,12].

2.3 Metabolic convergence of proteins in energy and biosynthetic metabolism

Proteins represent not only fundamental structural and functional components of the cell, but also a relevant source of metabolic intermediates. The metabolic convergence of proteins occurs mainly through the catabolism of amino acids, whose carbon skeletons are integrated into central pathways such as glycolysis, the citric acid cycle, and gluconeogenesis. In this way, protein metabolism is closely connected to carbohydrate and lipid metabolism, constituting a highly integrated system [1,2].

Protein degradation and nitrogen fate

The hydrolysis of dietary or cellular proteins releases amino acids that can be incorporated into new proteins, give rise to nitrogenous compounds, or participate in energy metabolism. In many cases, transaminases transfer the amino group to α -ketoglutarate and generate glutamate. Glutamate dehydrogenase can release ammonium by oxidative deamination; however, not all amino acids follow an identical nitrogen removal sequence [1]. In humans, hepatic ureagenesis is a major route of nitrogen removal, with contributions of ammonium and aspartate. Glutamine and alanine also contribute to nitrogen transport between tissues [13].

Convergence of the carbon skeletons

Once the amino group is removed, the carbon skeletons of amino acids are transformed into common metabolic intermediates. Depending on their structure, they can be converted into pyruvate, acetyl-CoA, acetoacetyl-CoA, or citric acid cycle intermediates such as oxaloacetate, fumarate, succinyl-CoA, or α -ketoglutarate [2]. This diversity results in the classification of amino acids as glucogenic, ketogenic, or mixed. Glucogenic amino acids generate precursors for gluconeogenesis, allowing glucose synthesis under conditions of prolonged fasting. Ketogenic amino acids, on the other hand, produce acetyl-CoA or acetoacetate, which can be involved in the synthesis of ketone bodies or fatty acids [1]. The most important point of convergence is the citric acid cycle, where multiple carbon skeletons are integrated for complete oxidation to CO_2 , generating reducing equivalents (NADH and FADH_2) that feed the respiratory chain for ATP production. In this way, proteins can contribute significantly to the energy balance, especially in carbohydrate restriction states.

Interrelationship with carbohydrates and lipids

Glycogenic amino acids provide precursors for glucose synthesis, while ketogenic amino acids generate acetyl-CoA or acetoacetate. Leucine and lysine are exclusively ketogenic; other amino acids can provide products of both classes. During fasting, alanine released by muscle participates in the glucose-alanine cycle, and glutamine contributes to nitrogen metabolism and gluconeogenesis, with special renal relevance under certain conditions [2,13]. The replacement of cycle intermediates by amino acid carbon skeletons has an anaplerotic function, while the input of acetyl-CoA, by itself, does not produce a net gain of cycle intermediates [5].

2.4 Integration of lipids with central metabolism

Triacylglyceride lipolysis releases fatty acids and glycerol. Fatty acids are activated to acyl-CoA; long-chain fatty acids require the carnitine system to access mitochondrial oxidation. β -oxidation produces acetyl-CoA and reducing equivalents. Glycerol can be transformed into glycerol-3-phosphate and then dihydroxyacetone phosphate, linking fat mobilization with glycolysis or gluconeogenesis depending on tissue and nutritional status [1,13].

Acetyl-CoA derived from pair-chain fatty acids does not allow for a net production of glucose in humans: the pyruvate dehydrogenase complex reaction is irreversible and the cycle does not generate a net gain of oxaloacetate from those acetyl groups. Odd-chain fatty acids provide propionyl-CoA, which can be converted to succinyl-CoA and contribute to anaplerosis. This distinction avoids generalizing that all lipid components have the same glycogenic potential [1,6].

In the liver, oxaloacetate availability and hormonal regulation condition the distribution of acetyl-CoA between oxidation and ketogenesis. Exported ketone bodies can be used in extrahepatic tissues. On the other hand, when fatty acid synthesis is favored, malonyl-CoA provides units for elongation and inhibits carnitine palmitoyltransferase 1 (CPT1), limiting the entry of long-chain fatty acids into the mitochondria [13].

Deja et al. studied the connection between these functions through genetic and pharmacological interventions on hepatic acetyl-CoA carboxylases. Their experiments linked decreased malonyl-CoA synthesis to increased fat oxidation, pyruvate carboxylation, and gluconeogenesis. The study shows that a lipogenic intermediate can simultaneously modify the contribution of carbon to the cycle and the production of glucose; its therapeutic interpretation requires considering the model and conditions of the intervention [14].

2.5 Regulation, compartmentalization and tissue specificity of nodes

Metabolic crossroads are not defined solely by the number of pathways that share a compound. Their contribution depends on the activity of regulatory enzymes, access to subcellular reservoirs, and tissue specialization. Glucose-6-phosphate, pyruvate, acetyl-CoA, oxaloacetate, and α -ketoglutarate are carbon distribution points; NADPH is primarily involved in reducing transfers. Therefore, the proximity of two reactions in a biochemical map does not guarantee that there is a relevant flow between them in a given physiological condition [1,6,13].

Enzymatic control of carbon distribution

The proportion of glucose-6-phosphate directed to glycolysis, glycogen or pentose phosphate responds to energy and biosynthetic needs. The activity of PFK-1 contributes to regulate the flow of glucose to triose phosphate; glycogen synthase and glycogen phosphorylase condition storage and mobilization, and glucose-6-phosphate dehydrogenase guides the supply of NADPH. Hepatic intake of fructose by fructose-1-phosphate avoids PFK-1, but remains subject to substrate availability and subsequent regulation. Thus, two sugars can share intermediates without experiencing identical regulatory restrictions [1,8–10].

Competition between oxidation, replenishment and biosynthetic output

The functional decision of pyruvate is expressed in the competition between pyruvate dehydrogenase, pyruvate carboxylase and lactate dehydrogenase. The first favors the entry of acetyl groups in oxidation; the second replenishes oxaloacetate to sustain the cycle and, in suitable tissues, gluconeogenesis; the third allows pyruvate and lactate to be interconverted according to the NADH/NAD⁺ balance. Acetyl-CoA allosterically activates pyruvate carboxylase and, together with the energy state, contributes to orienting this partition. An increase in pyruvate intake does not allow us to anticipate the fate of carbon without considering enzymatic activity and demand [5,6,13,16].

The exit of oxaloacetate or α -ketoglutarate into gluconeogenesis, aspartate, or glutamate requires that the cycle maintain sufficient intermediates. Anaplerosis, including pyruvate carboxylation and the contribution of some amino acids, compensates for cataplerosis; otherwise, an increase in acetyl-CoA does not ensure sustained oxidation. Transaminations between α -ketoglutarate and glutamate integrate carbon metabolism with nitrogen transport, but the outcome depends on cofactors, substrates, and the physiological role of tissue. This view explains cycle continuity as a dynamic balance, not as a closed sequence [5,6,13,19].

Subcellular Barriers and Equivalent Transport

Mitochondrial acetyl-CoA is used in oxidation and, in the liver, can fuel ketogenesis; cytosolic lipid synthesis requires acetyl units outside the mitochondria. Its passage does not occur by free diffusion of acetyl-CoA through the inner membrane: the exported citrate can be cleaved by ATP-citrate lyase to form cytosolic acetyl-CoA. Similarly, oxaloacetate does not directly cross that membrane and its functional exchange is related to malate, aspartate, and transporters. The connection drawn between compartments is therefore a mediated relationship, not a direct transfer of all the molecules represented [3,4,18].

Compartmentalization also separates cofactor functions. Reducing equivalents of cytosolic NADH can be transferred via shuttles; cytosolic NADPH serves biosynthesis and antioxidant protection, while the mitochondrial compartment has its own regeneration and consumption systems. Experimental data on mitochondrial CoA import and acyl-CoA profiles reinforce that a value measured in the whole cell does not necessarily reflect local availability for each reaction. Consequently, integrated interpretation requires distinguishing metabolite transport, chemical group transfer, and electron movement [7,18].

Tissue specialization and coordination between organs

The same node takes on different meanings depending on the tissue. The liver expresses glucose-6-phosphatase and can release glucose, while muscle uses its glucose-6-phosphate primarily for its own demands. Adipose tissue incorporates carbon into triacylglycerides; during the mobilization of reserves, its fatty acids and glycerol follow different fates in other organs. Muscle can export lactate and alanine, and liver and kidney participate differently in gluconeogenesis. Consequently, integration does not consist of a uniform network within each cell, but of specialized and connected flows at the organic scale [1,2,13].

Redox cofactors and cell work capacity

NADPH and ATP allow us to recognize forms of convergence other than carbon exchange. NADPH provides reducing equivalents for glutathione biosynthesis and regeneration, while ATP transfers free energy to transport, contraction, and synthesis. Its availability depends on production, consumption, and regulation reactions in specific compartments. The function of these cofactors cannot be equated to that of acetyl-CoA or oxaloacetate: the former couple chemical transformations and work; the latter provide carbon units for alternative pathways. This difference guides the classification in Table 1 and the reading of Figure 1 [2,7,8,13].

2.6 Energy coupling, nutritional status and cell work

ATP synthesis and its hydrolysis couple energy-releasing reactions with labor-intensive ones. This does not make ATP a carbon destination: the products of oxidation feed the electron transport, while carbon can be oxidized or diverted into biosynthesis. ATPase activity, active transport, and synthesis demands vary between organs and physiological states. Therefore, energy integration should be examined alongside carbon and reducing power requirements, rather than reducing metabolic physiology to a single common end-pathway [1,2].

Demand, oxidative capacity and choice of fuels

The distribution of fuels changes with diet, fasting and muscle activity. The liver coordinates storage, glucose release and production of ketone bodies; the muscle modifies the use of glucose and fatty acids according to its needs; the brain and other organs consume fuels according to availability and their enzymatic equipment. The supply of acetyl-CoA must be accompanied by oxidative capacity and sufficient intermediates in the citric acid cycle. Hormonal control and transport between organs are therefore determinants of flow, although the basic reactions represented are chemically possible in different tissues [1,6,13].

Mitochondrial respiration and ATP provision

Mitochondrial electron transport uses electrons contributed by NADH and flavoproteins via inputs that are not identical. Cytosolic NADH equivalents reach respiration via shuttles; electron transport drives a proton gradient that ATP synthase uses to generate ATP. Respiratory capacity is dependent on oxygen, ADP, mitochondrial integrity, and substrate availability, and can be partially decoupled from the carbon supply. In addition, substrate-level phosphorylation produces ATP during glycolysis and other nucleotide triphosphate in the cycle; therefore, energy yield should not be reduced to a single arrow to ATP synthase [1,2,13].

ATP, ADP, and AMP relationships as regulatory signals

The ratios between ATP, ADP, and AMP reflect the relationship between energy supply and expenditure. The energy load, defined as $([ATP] + 0.5[ADP])/([ATP] + [ADP] + [AMP])$, allows this state to be expressed without confusing it with an isolated concentration. AMPK-mediated signaling favors responses compatible with lower energy availability; other enzymes and circuits respond to reaction products, hormones, or redox changes. Skeletal muscle, for example, uses phosphocreatine to

transiently dampen its demand. These signals modify the flow of connected pathways, but they do not establish a universal and identical direction in all cells [2,13].

Integration during fasting and feeding

During feeding, hormonal conditions predominate that can favor nutrient utilization and storage; in fasting, the mobilization of reserves, hepatic production of glucose and, depending on the duration, ketogenesis, increase. The same intermediary can participate in different processes because the supply of substrates, the expression and regulation of enzymes, and the exchange between organs change. The functional reading of a metabolic crossroads must therefore specify three questions: in which compartment does the compound exist, what reaction controls its fate, and what tissue contributes or uses the product. With these criteria, the route map ceases to be a list of possibilities and becomes an explanation of physiological regulation [1,13].

METHOD

A conceptual narrative review was conducted on the integration of energy metabolism and biosynthesis in the human organism. Sources were identified from biochemistry manuals used to establish reactions and localization, mechanistic reviews to examine regulation, and experimental studies to contrast specific connections. Topics were identified as glycolysis and pentose phosphate, the fate of pyruvate, acetyl-CoA reservoirs, anaplerosis and cataplerosis, nitrogen metabolism, and the functions of NADPH and ATP. The selection was based on its ability to support the relevant nodes and physiological conditions, not on a predetermined quota of publications.

The complementary search was carried out through directed queries in PubMed and scientific journal sites during October 2026, considering publications until 2025. Combinations of the terms fructose metabolism, pentose phosphate pathway, pyruvate metabolism, acetyl-CoA compartmentalization, anaplerosis, cataplerosis, lactate homeostasis and metabolic regulation were used, with reading of titles, abstracts and relevant texts. Priority was given to research that explained enzymatic mechanisms, compartment differences, tissue specialization or metabolic flow variations. Experimental articles in cells or animals were distinguished from texts oriented to human physiology and previous references were maintained when they constituted relevant mechanistic antecedents.

The selected sources were organized by the categories of analysis announced in the introduction: (a) origin and destination of the substrate; (b) regulatory reaction or enzyme; (c) cytosolic, mitochondrial or interorganic location; (d) tissue function; and (e) type of evidence that supports the connection. For each node, the existence of a reaction was contrasted with the conditions necessary for it to contribute to physiological flow. Coincidences and precisions were integrated between manuals, reviews and experimental works, avoiding equating particular experiments with general clinical conclusions. For its explanatory purpose, a narrative thematic synthesis was used, without applying procedures typical of a systematic review or statistical measures of effect.

RESULTS

The analysis identified five carbon nodes of interconversion or distribution (glucose-6-phosphate, pyruvate, acetyl-CoA, oxaloacetate, and α -ketoglutarate), a reducing cofactor (NADPH), and an energy-coupled nucleotide (ATP). Table 1 does not present them as equivalent centers: it summarizes distinct connections, compartment barriers, regulation, and tissue functions. The presence of a pathway in the network indicates biochemical possibility, but does not guarantee predominant flow. This depends on the local concentration of substrates, enzyme activity, hormonal signals, and cellular demand [1,6–8,13].

Differentiated controls were identified in the distribution of carbon. In the liver, glucose-6-phosphate can be distributed between glycolysis, glycogen, pentose phosphate, and glucose release, according to expressed enzymes and signals of nutritional status. Fructose provides triose phosphate by a sequence that avoids PFK-1; this modifies the entry point, without canceling out any subsequent regulation. For pyruvate, the competition between dehydrogenase, carboxylase, and lactate dehydrogenase relates oxidation, anaplerosis, and lactate exchange. The availability of oxaloacetate and α -ketoglutarate in turn conditions the continuity of the cycle and the outputs towards nitrogen synthesis or transport [5,6,8–10,13].

Subcellular localization was a second decisive condition: mitochondrial acetyl-CoA does not circulate freely to the cytosol, so lipid production uses acetyl unit transfer mechanisms; oxaloacetate is related to transport pathways through interconvertible metabolites. Energy and reducing power do not form a single reservoir either: cytosolic NADH equivalents are transferred by shuttles, while NADPH functions depend on specific generation and use systems. Thus, the connections identified are relevant only when there is transport equipment and enzyme activity compatible with the compartment [3,7,18].

Tissue specialization constitutes the third dimension. The liver integrates glucose production, storage, lipid synthesis and ketogenesis; muscle adapts fuel use to its demand and can export lactate and alanine; adipose tissue mobilizes fatty acids and glycerol, which do not share the same degradative pathway. The glycolytic pathway of glycerol passes through glycerol-3-phosphate and dihydroxyacetone phosphate, while fatty acids are incorporated into β -oxidation. Table 1 summarizes these requirements together with the differentiated contribution of NADPH to biosynthesis and antioxidant defense and ATP to cell work [1,2,13].

Table 1.

Nodes that connect energy metabolism and biosynthesis

Node and Type	Selective connection	Regulation and localization	Functional expression by tissues
G6P · Carbon	Glycolysis, glycogen and pentose phosphate	PFK-1 and G6PD; cytosolic pathways	Liver: glucose export; muscle: own use
Pyruvate · Carbon	Acetyl-CoA, lactate, alanine and oxaloacetate	mitochondrial PDH and pyruvate carboxylase; LDH	Muscle: lactate/alanine; liver: oxidation/gluconeogenesis

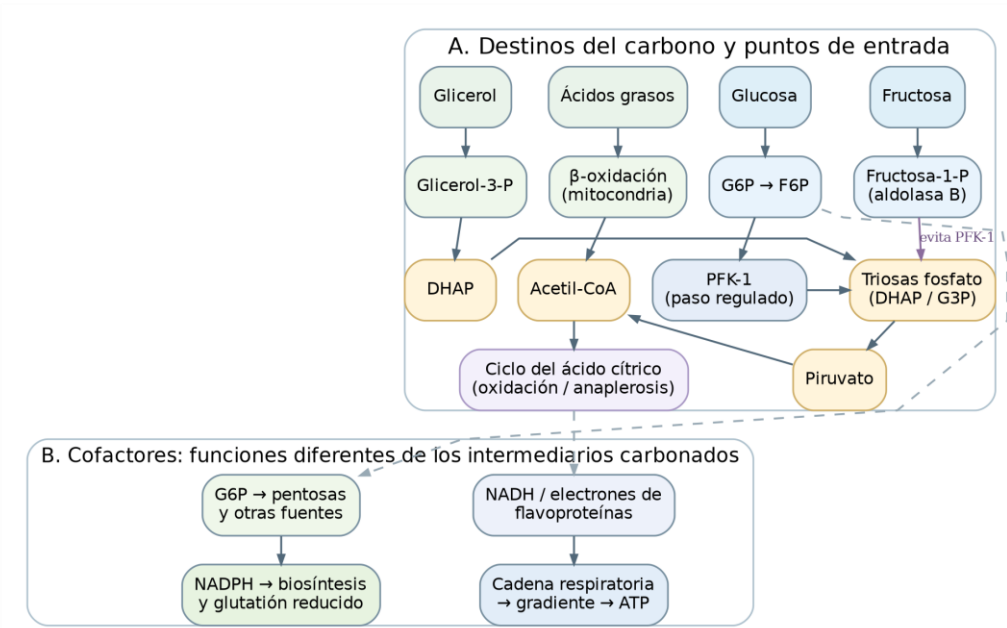
Node and Type	Selective connection	Regulation and localization	Functional expression by tissues
Acetyl-CoA · Carbon	Citrus Cycle, Lipogenesis, and Ketogenesis	Mitochondrial and cytosolic reservoirs; citrate output	Liver: ketogenesis and lipids; other tissues: oxidation
Oxaloacetate · Carbon	Citrus cycle, aspartate and gluconeogenesis	Anaplerosis and cataplerosis; malate/aspartate exchange	Liver and kidney: glycogenic precursor; others: cycle
α-ketoglutarate · carbon	Citrus, glutamate, and nitrogen cycle	Transaminases and mitochondrial/cytosolic availability	Liver: nitrogen fate; others: transport and synthesis
NADPH · cofactor redox	Reducing synthesis and regeneration of GSH	Pentose phosphate and compartment-generating enzymes	Lipogenesis and antioxidant defense with variable demand
ATP · energy nucleotide	Transport, contraction and biosynthesis	Oxidative and substrate-level phosphorylation; ATP/ADP/AMP	Differentiated demand in muscle, liver and other tissues

Note. The carbonate nodes, the NADPH and the ATP fulfill different functions. Own synthesis from [1,6–8,13,18].

Figure 1 separately represents the catabolism of fatty acids by β-oxidation and the incorporation of glycerol as triose phosphate through glycerol-3-phosphate and DHAP. It also distinguishes the sequence of PFK-1-regulated glucose from the hepatic entry of fructose by fructose-1-phosphate and aldolase B. Its purpose is to show relevant connections and controls, not to quantify reaction rates or propose simultaneous flows for all tissues. NADPH generation and ATP synthesis are listed as differentiated functions of carbon distribution [1,7–10,13].

Figure 1.

Central Connections of Metabolism and Cofactor Functions



Note. G6P: glucose-6-phosphate; PFK-1: phosphofructokinase-1; DHAP: dihydroxyacetone phosphate; G3P: glyceraldehyde-3-phosphate. Prepared by the authors from [1,7–10,13].

DISCUSSION

Synthesis makes it possible to distinguish biochemical connections from functional flows. Carbon nodes distribute matter between oxidation and biosynthesis; NADPH and ATP, on the other hand, couple electron and energy transfer to other reactions. The decisive difference is that these processes are regulated and compartmentalized. An arrow between substrate and product identifies a possible route, but its participation depends on enzymes, transporters, and tissue needs. Thus, the integrative framework does not presuppose that all the fates of an intermediate are activated simultaneously or that all nutrients converge in a single physiological response [1,6,7,13].

The relationship between glucose and fructose illustrates why the existence of a convergence point does not in itself determine a pathophysiological outcome. Both provide phosphate triose, but the flow depends on the input, the participating organs, and the regulation. The experimental evidence of Jang et al. on the gut expands the explanation focused exclusively on the liver [11]. In 2025, Jung et al. showed in male mice that an inulin-adapted microbiota could catabolize fructose and attenuate or reverse hepatic metabolic alterations. These results point to a level of regulation dependent on diet and microbiota, without demonstrating by themselves an equivalent therapeutic benefit in humans [21].

In the citric acid cycle, the availability of intermediates is as relevant as the input of acetyl groups. The use of oxaloacetate for gluconeogenesis or other intermediates for biosynthesis requires replacement. The distinction between anaplerosis and cataplerosis explains why a greater supply of acetyl-CoA does not guarantee greater oxidation when other components limit the flow [5,6]. The results of Deja et al. provide an experimental example of this interdependence: modifying the production of malonyl-CoA altered connections between fat oxidation and hepatic glucose production [14].

Compartmentalization adds a limitation to the general diagrams. A connection may be chemically possible and still depend on different transporters, shuttles, or reservoirs. Liu et al.'s experiments on mitochondrial supply of CoA show that concentrations measured in the whole cell do not necessarily describe the availability of cofactors within each compartment [18]. Therefore, didactic representations should identify what is transported: the substrate, carbon units, or reducing equivalents.

Lactate introduces a similar precision into the energetic interpretation. Its formation allows NAD⁺ to be regenerated and should not be attributed exclusively to the absence of oxygen. The results on the co-regulation of glycolysis and lipolysis show that their homeostasis participates in the exchange of fuels, rather than being only a terminal indicator of glycolysis [17]. The concentration of a metabolite is also not directly equivalent to its rate of production or utilization; this difference must be considered when relating route diagrams with experimental measurements.

The conceptual usefulness of this organization lies in relating each node to verifiable questions: what carbon enters or exits, which enzyme regulates the passage, which subcellular barrier must be overcome and which organ can execute the transformation. Table 1 and Figure 1 integrate these conditions without confusing β -oxidation with the use of glycerol or the entry of fructose with that of glucose. It is a biochemical synthesis based on the literature and not an evaluation of educational or therapeutic results; the eventual efficacy of didactic or clinical applications requires studies specifically designed to measure it.

The main limitations stem from the narrative nature and targeted selection of sources. Clinical effect size was not estimated and risk of bias was not formally assessed. In addition, some of the update comes from cultured cells and animal models, the results of which should not be automatically translated into nutritional or therapeutic decisions. The scheme simplifies pathways, isoforms, and differences between organs to maintain readability; future research can contrast these connections using flow measurements and compartment analysis.

CONCLUSIONS

The main nutrients are integrated through shared intermediates that connect oxidation, storage and biosynthesis. Glucose-6-phosphate, pyruvate, acetyl-CoA, oxaloacetate and α -ketoglutarate allow the organization of the carbon flow, while NADPH supports reducing processes and ATP participates in energy coupling.

The function of each node depends on the cell compartment, enzymatic regulation, the balance between anaplerosis and cataplerosis and communication between organs. Therefore, convergence does not imply that all pathways operate simultaneously or that the same nutrient has an invariable destination.

The representation of these connections offers an integrative framework for studying biochemistry and understanding responses to fasting, diet, and changes in energy demand. Its clinical application requires additional specific evidence to distinguish plausible mechanisms, experimental results, and demonstrated effects in humans.

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ETHICAL CONSIDERATIONS

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The study was developed through a literature review based exclusively on previously published documentary sources. It did not involve the direct participation of human or animal beings, the performance of interventions, the use of biological samples, or access to personally identifiable data. Consequently, it did not require approval from an ethics committee or the obtaining of informed consent. During the research process, the principles of scientific integrity, adequate attribution of authorship, rigorous citation, and responsible use of the sources consulted were observed.

ARTIFICIAL INTELLIGENCE (AI) USAGE STATEMENT

The authors state that the AI tool was used exclusively to support the organization of the article and the translation of the text. Its use did not determine the scientific content, study design, selection of sources, data analysis, interpretation of results, or conclusions. Full responsibility for the content remains with the authors.

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The authors declare that they have no conflicts of interest related to this study and that all the procedures followed comply with the ethical standards established by the journal. They also confirm that this work is unpublished and has not been published, either partially or totally, in any other publication.

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