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Posted Date: 13 April 2026

doi: 10.20944/preprints202604.0801.v1

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*Review*

# Type 2 Diabetes as a Systems-Level Disorder: A Root Driver Model Integrating Metabolic, Nutritional, Hormonal, and Environmental Determinants

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## Abstract

Type 2 diabetes mellitus (T2DM) is conventionally managed as a disorder of hyperglycemia. However, large randomized controlled trials—including ACCORD, ADVANCE, and VADT—demonstrate that intensive glycemic control does not consistently reduce macrovascular complications or all-cause mortality. These findings suggest that hyperglycemia is not the sole driver of diabetic pathology and that additional mechanisms contribute to disease progression. From a systems medicine perspective, T2DM can be understood as a systems-level disorder involving oxidative–reductive imbalance, mitochondrial dysfunction, micronutrient depletion, hormonal dysregulation, and environmental influences. However, a unifying framework integrating these upstream determinants into a coherent systems model remains lacking. One potential mechanism is that hyperglycemia may impair cellular uptake of vitamin C via competitive interactions at glucose transporters, leading to a state of functional intracellular deficiency despite normal plasma levels. This phenomenon may contribute to oxidative stress, endothelial dysfunction, and vascular complications. We propose a three-level model of T2DM management: (1) glucose-centric conventional medicine, (2) metabolic regulation via low-carbohydrate and ketogenic diets, and (3) systems-oriented approaches that integrate nutrient status, redox balance, mitochondrial function, hormonal regulation, and environmental factors. While metabolic therapies represent a major advance, they may not fully restore intracellular and systemic biological function. Systems-level approaches may represent an additional layer for investigation in the management of T2DM.

**Keywords:** type 2 diabetes; systems medicine; insulin resistance; oxidative stress; redox biology; micronutrient deficiency; vitamin C transport; mitochondrial dysfunction; environmental toxins; hormonal regulation

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic diseases worldwide and a leading contributor to cardiovascular morbidity, mortality, and healthcare burden. Despite significant advances in pharmacologic therapies and disease monitoring, the global incidence of T2DM continues to rise, and long-term outcomes remain suboptimal [1,2].

Conventional management of T2DM has been largely centered on the control of blood glucose, with glycated hemoglobin (HbA1c) serving as the primary therapeutic target. This glucose-centric paradigm has led to the development of increasingly effective glucose-lowering agents and strategies. However, accumulating clinical evidence suggests that normalization of glycemic parameters does not consistently translate into proportional reductions in major complications, particularly macrovascular events and all-cause mortality [3–5].

These observations raise important questions regarding the underlying nature of T2DM. Specifically, they suggest that hyperglycemia, while clinically relevant, may not fully capture the

complexity of the disease process. Instead, it may represent one component of a broader network of metabolic and systemic disturbances.

Emerging evidence supports the view that T2DM involves multiple interconnected processes, including oxidative–reductive imbalance, mitochondrial dysfunction, chronic low-grade inflammation, hormonal dysregulation, and alterations in nutrient availability and utilization [6–8]. In addition, environmental factors, including exposure to metabolic disruptors, may contribute to disease development and progression [9]. These processes interact within a dynamic biological system, influencing both the onset and progression of metabolic dysfunction.

Within this context, there is increasing interest in frameworks that move beyond single-parameter models toward a more integrative understanding of disease. Such approaches aim to characterize interactions among metabolic, nutritional, hormonal, and environmental factors, rather than focusing on isolated biomarkers [10].

This perspective is consistent with principles of systems biology, which emphasize network-based regulation and multi-level interactions rather than linear, single-pathway mechanisms [11].

However, a comprehensive framework that integrates these interacting domains into a unified model of T2DM pathophysiology remains incompletely developed.

In this paper, we present a systems-level framework for understanding T2DM, grounded in principles of Integrative Orthomolecular Systems Medicine (IOM). This framework emphasizes the role of upstream determinants—referred to here as root drivers—including nutritional insufficiency, environmental toxic burden, hormonal dysregulation, and metabolic substrate overload. Particular attention is given to intracellular nutrient dynamics, including mechanisms by which hyperglycemia may impair cellular uptake of key micronutrients such as vitamin C.

We further introduce the concept of the Insulin–Cortisol–Vitamin C (ICV) axis as a potential regulatory interface linking metabolic signaling, stress physiology, and intracellular redox balance. Building on these elements, we propose a three-level model of T2DM recognition and management, progressing from glucose control to metabolic regulation and ultimately to systems restoration.

This paper does not seek to replace existing models of T2DM, but rather to extend them by incorporating upstream determinants and system-level interactions. By reframing T2DM within a broader biological context, this approach aims to generate testable hypotheses and to provide a foundation for more comprehensive strategies in both research and clinical care.

2. Evidence from Clinical Trials: Limits of Glycemic Control

Despite decades of emphasis on lowering blood glucose, large randomized controlled trials have demonstrated that intensive glycemic control has limited **and context-dependent impact** on major clinical outcomes [3–5,12].

The ACCORD trial [3], ADVANCE trial [4], and VADT trial [5] consistently showed that while intensive glucose lowering:

- Improves certain microvascular outcomes
- Does not consistently reduce macrovascular events
- Does not significantly reduce all-cause mortality

These findings have been further supported by meta-analyses of randomized trials, which confirm that intensive glycemic control yields modest benefits in microvascular endpoints but does not reliably translate into reductions in macrovascular events or mortality [12].

These observations highlight a fundamental limitation in the conventional glucose-centric model of type 2 diabetes management. Contemporary clinical guidelines have also increasingly recognized the importance of factors beyond glycemic control, including cardiovascular risk reduction and metabolic health [13].

A critical question therefore arises:

Why do major complications persist despite improved glycemic control?

One possible interpretation is that hyperglycemia, while clinically important, may represent a downstream manifestation of underlying systemic dysfunction rather than the primary driver of disease.

Accordingly, therapeutic strategies focused exclusively on glucose reduction may be targeting a biological marker without fully addressing the upstream processes responsible for disease progression.

### 3. Type 2 Diabetes as a Systems-Level Disorder

Type 2 diabetes mellitus (T2DM) can be more comprehensively understood as a systems-level disorder involving multiple interconnected biological processes. These include:

- Oxidative–reductive (redox) imbalance
- Mitochondrial dysfunction
- Chronic low-grade inflammation
- Endothelial dysfunction
- Micronutrient depletion
- Hormonal dysregulation
- Environmental toxic burden

Emerging evidence across multiple domains supports the involvement of these processes in the pathophysiology of T2DM and related metabolic disorders [6–8,14,15].

Rather than acting in isolation, these processes interact within a dynamic biological network and converge on a shared biological terrain characterized by disruption of redox balance, impaired mitochondrial function, and altered intracellular nutrient availability. This integrated disturbance contributes to progressive metabolic instability and tissue dysfunction [6–8].

Within this framework, hyperglycemia may be viewed not only as a defining clinical feature, but also as a downstream manifestation of broader systemic dysregulation. As such, therapeutic strategies focused primarily on glucose reduction may not fully address the underlying drivers of disease.

This systems-level perspective provides a conceptual basis for understanding why glucose-centric approaches, while clinically useful, often fail to halt disease progression or prevent long-term complications.

### 4. Metabolic Regulation: Role and Limitations of Low-Carbohydrate and Ketogenic Diets

Dietary carbohydrate restriction, including low-carbohydrate and ketogenic approaches, represents a significant advance beyond conventional glucose-centered management of type 2 diabetes mellitus (T2DM). These strategies directly target one of the primary metabolic drivers of hyperglycemia—excess carbohydrate intake—and have demonstrated substantial clinical benefits [16–18].

#### 4.1. Clinical Benefits

Clinical studies have shown that carbohydrate restriction can:

- Improve glycemic control
- Reduce insulin requirements
- Promote weight loss
- Improve markers of metabolic syndrome
- In some cases, induce partial remission of T2DM

These outcomes support the role of metabolic interventions as an effective strategy for improving short- to medium-term metabolic parameters [16–18].

#### 4.2. Mechanistic Basis

From a physiological perspective, reducing dietary carbohydrate intake decreases postprandial glucose excursions and lowers insulin demand. This shift promotes:

- Improved insulin sensitivity
- Reduced glycemic variability
- Increased reliance on fatty acid oxidation and ketone metabolism

By reducing the primary substrate driving hyperglycemia, these approaches address an important upstream metabolic input into the disease process [17].

#### 4.3. Limitations: A Transitional But Incomplete Layer

While these approaches are mechanistically grounded and clinically effective, their scope is primarily metabolic and may not fully address other dimensions of disease biology.

Despite their clinical effectiveness, metabolic interventions do not fully restore underlying biological function. Even in the presence of improved glycemic control and reduced insulin resistance, several key abnormalities may persist, including:

- Oxidative–reductive (redox) imbalance
- Mitochondrial dysfunction
- Intracellular micronutrient depletion
- Hormonal dysregulation
- Environmental toxic burden

These observations suggest that metabolic regulation, while necessary, may not be sufficient for complete disease resolution [8–10,12,18].

Within a systems framework, low-carbohydrate and ketogenic interventions can therefore be understood as a transitional layer:

- Moving beyond symptom control (glucose lowering)
- Toward improved metabolic regulation
- But not yet achieving full systems restoration

This distinction is important. While metabolic therapies represent a major step forward, they primarily address substrate-level inputs and do not fully resolve upstream drivers such as nutrient insufficiency, toxic exposures, and hormonal imbalance.

#### 4.4. Position Within a Systems Model

Accordingly, metabolic regulation should be viewed as an essential but intermediate stage in the management of T2DM. It provides a necessary foundation upon which more comprehensive, systems-oriented interventions can be built.

This perspective helps explain why some patients experience significant improvement with carbohydrate restriction, while others demonstrate incomplete or variable responses, suggesting the involvement of additional upstream determinants beyond metabolic substrate alone.

## 5. Hyperglycemia and Intracellular Nutrient Dysfunction

#### 5.1. Mechanism of Competitive Transport

Glucose and certain micronutrients—most notably vitamin C in its oxidized form (dehydroascorbic acid)—utilize overlapping transport systems, including facilitative glucose transporters (GLUTs). Under hyperglycemic conditions, elevated extracellular glucose concentrations can competitively inhibit cellular uptake of dehydroascorbic acid via these shared transport pathways [19–21].

As a result, even when plasma levels are sufficient, intracellular delivery may be impaired. This creates a dissociation between circulating nutrient levels and functional cellular availability.



While the magnitude and clinical significance of this mechanism may vary across tissues and physiological conditions, it provides a plausible link between hyperglycemia and intracellular nutrient dysregulation.

### 5.2. Functional Intracellular Deficiency

This transport-level interference may lead to a state of functional intracellular deficiency, in which cells are unable to access adequate levels of essential micronutrients despite normal or near-normal systemic status.

Such deficiencies are not necessarily due to inadequate intake, but rather to impaired transport and utilization. This distinction has important implications for understanding persistent cellular dysfunction in T2DM.

Although vitamin C provides a well-characterized example, similar mechanisms may apply to other micronutrients influenced by glucose-dependent transport or metabolic competition [21,22].

### 5.3. Pathophysiological Implications

Intracellular micronutrients play essential roles in:

- Antioxidant defense
- Mitochondrial energy production
- Enzymatic reactions in glucose metabolism
- Maintenance of endothelial integrity
- Regulation of inflammatory responses

Impaired intracellular availability of these nutrients contributes to:

- Increased oxidative–reductive (redox) imbalance
- Endothelial dysfunction
- Enhanced glycation and tissue injury
- Impaired cellular repair mechanisms

These processes are central to the development of both microvascular and macrovascular complications [6,14,22,23].

### 5.4. Systems Feedback Loop

The interaction between hyperglycemia and intracellular nutrient dysfunction may form a self-reinforcing cycle:

**Hyperglycemia → impaired nutrient transport → intracellular deficiency → increased oxidative stress → worsening insulin resistance → further hyperglycemia**

This feedback loop provides a mechanistic link between metabolic dysregulation and progressive cellular injury.

Within this framework, hyperglycemia functions not only as a metabolic disturbance, but also as a contributor to intracellular dysfunction, amplifying systemic imbalance.

## 6. The Insulin–Cortisol–Vitamin C (ICV) Axis

### 6.1. Conceptual Framework

The ICV axis is proposed here as a conceptual and hypothesis-generating framework rather than a formally established physiological pathway.

Metabolic regulation in type 2 diabetes mellitus (T2DM) involves complex interactions among hormonal signaling, nutrient availability, and cellular redox balance. While insulin and glucose metabolism have been extensively studied, less attention has been given to how hormonal and metabolic signals interface with intracellular micronutrient dynamics [24–27].

Emerging evidence highlights the close integration of metabolic regulation, stress signaling, and redox biology as interconnected components of systemic homeostasis [28].

We propose the Insulin–Cortisol–Vitamin C (ICV) axis as a **conceptual and hypothesis-generating framework** linking these domains. Within this model, insulin and cortisol represent key hormonal regulators of metabolic and stress responses, while vitamin C reflects a critical component of intracellular antioxidant capacity and redox balance [22].

Rather than functioning as independent pathways, these elements may form an integrated axis through which metabolic state, stress physiology, and cellular nutrient availability are coordinated.

It should therefore be interpreted as an integrative model that synthesizes known relationships among metabolic, hormonal, and redox processes.

### 6.2. Integration of Metabolic, Hormonal, and Redox Regulation

Insulin is the primary anabolic hormone regulating glucose uptake, storage, and utilization. In insulin-sensitive states, it promotes efficient cellular glucose transport and supports metabolic homeostasis. In contrast, insulin resistance impairs glucose uptake and is associated with compensatory hyperinsulinemia and metabolic instability [24].

Cortisol, as a central stress hormone, exerts counter-regulatory effects on insulin by promoting gluconeogenesis, increasing circulating glucose, and modulating inflammatory and immune responses. Chronic elevation of cortisol has been associated with insulin resistance, central adiposity, and metabolic dysregulation [25,26].

Vitamin C plays a central role in maintaining intracellular redox balance, supporting antioxidant defense, endothelial function, and enzymatic processes [22]. As discussed in Section 5, its cellular uptake may be impaired under hyperglycemic conditions due to competition at shared transport pathways [17–19].

Within the ICV framework, these three components are functionally interconnected:

- Insulin influences glucose transport and intracellular metabolic flux
- Cortisol modulates systemic energy balance and stress responses
- Vitamin C supports intracellular redox stability and cellular resilience

Disruption in any one of these domains may influence the others, contributing to a state of integrated metabolic and redox imbalance.

### 6.3. Role in Intracellular Nutrient Availability

A key feature of the ICV axis is its potential role in regulating intracellular nutrient availability, particularly under conditions of metabolic stress.

Hyperglycemia and insulin resistance may impair the cellular uptake of vitamin C and potentially other micronutrients, contributing to functional intracellular deficiency. At the same time, elevated cortisol levels—whether due to chronic stress, inflammation, or metabolic dysregulation—may further exacerbate oxidative stress and alter nutrient utilization [25,26].

Within this context, intracellular vitamin C availability can be viewed as a functional indicator of the balance between metabolic demand and cellular antioxidant capacity. Reduced intracellular levels may contribute to:

- Increased oxidative–reductive (redox) imbalance
- Impaired endothelial and mitochondrial function
- Reduced capacity for cellular repair and adaptation

Thus, the ICV axis provides a conceptual link between hormonal regulation, metabolic state, and intracellular nutrient dynamics.

### 6.4. Implications for Systems-Level Dysregulation

The ICV axis may help explain variability in clinical presentation and treatment response among individuals with T2DM. For example, patients with similar glycemic profiles may exhibit different

degrees of oxidative stress, endothelial dysfunction, or metabolic resilience, potentially reflecting differences in intracellular nutrient status and stress hormone regulation.

This framework also suggests that metabolic interventions alone—such as carbohydrate restriction—may not fully restore intracellular redox balance if underlying hormonal dysregulation or nutrient transport impairment persists.

Accordingly, the ICV axis supports a systems-level view in which effective management of T2DM may require coordinated consideration of:

- Metabolic control (insulin and glucose dynamics)
- Stress physiology (cortisol regulation)
- Intracellular nutrient availability (e.g., vitamin C and related micronutrients)

Further investigation is needed to clarify the quantitative relationships among these components and to determine their potential role in guiding therapeutic strategies.

## 7. A Root Driver–Based Systems Model of Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) may be more comprehensively understood as a systems-level disorder arising from the interaction of multiple upstream determinants, rather than as a condition defined solely by dysregulated glucose metabolism. Building on the preceding sections, we propose a root driver–based systems model in which metabolic dysfunction emerges from the convergence of several primary domains.

### 7.1. Nutritional Insufficiency

Adequate availability of essential micronutrients is fundamental to cellular metabolism, mitochondrial function, and maintenance of oxidative–reductive (redox) balance [6,7,29]. In T2DM, deficiencies in key nutrients—including vitamin C, thiamine, magnesium, and others—are commonly observed [30–33].

Importantly, such deficiencies may not be solely attributable to inadequate intake. As discussed in Section 5, hyperglycemia can impair intracellular transport of certain micronutrients, leading to functional deficiencies at the cellular level despite normal or near-normal plasma concentrations.

These disturbances compromise enzymatic processes involved in glucose metabolism, reduce mitochondrial efficiency, and increase susceptibility to oxidative stress, thereby contributing to progressive metabolic dysfunction.

### 7.2. Environmental Toxic Burden

Environmental exposures represent an important but often underappreciated contributor to metabolic disease. Persistent organic pollutants, heavy metals, and other environmental toxicants have been associated with insulin resistance, mitochondrial impairment, and disruption of endocrine signaling pathways [15,34–36].

These agents can increase oxidative stress, interfere with cellular energy production, and alter metabolic regulation. In addition, certain toxic exposures may act as endocrine disruptors, further contributing to hormonal imbalance.

Within a systems framework, environmental toxic burden can be viewed as an upstream stressor that amplifies metabolic and cellular dysfunction.

### 7.3. Hormonal Dysregulation

Hormonal systems—including insulin, cortisol, thyroid hormones, and sex steroids—play central roles in maintaining metabolic homeostasis. Dysregulation of these systems contributes to insulin resistance, altered energy partitioning, and chronic low-grade inflammation [24–26].

The Insulin–Cortisol–Vitamin C (ICV) axis [37], introduced in Section 6, provides a conceptual model linking metabolic signaling, stress physiology, and intracellular redox balance. Disruption of



this axis may contribute to impaired metabolic flexibility and reduced cellular resilience under conditions of chronic metabolic stress.

Hormonal dysregulation therefore represents both a driver and a mediator of systemic dysfunction in T2DM.

7.4. *Metabolic Substrate Overload*

Chronic exposure to excess metabolic substrates—particularly high glycemic load and sustained carbohydrate intake—constitutes a primary input into the development of hyperglycemia and hyperinsulinemia.

This metabolic overload promotes:

- Increased oxidative stress
- Formation of advanced glycation end products
- Progressive insulin resistance
- Dysregulation of lipid metabolism

These mechanisms are well-established in the pathophysiology of diabetes and its complications [23]. While dietary interventions such as carbohydrate restriction can mitigate this driver, long-standing exposure may result in persistent downstream effects that are not fully reversible by metabolic correction alone.

7.5. *Chronic Inflammation and Immune Dysregulation*

Chronic low-grade inflammation is a hallmark of T2DM and plays a central role in the development of insulin resistance and vascular complications [8,27]. Inflammatory signaling pathways interact closely with metabolic and hormonal systems, contributing to endothelial dysfunction, tissue injury, and impaired repair mechanisms.

Immune dysregulation may arise from multiple upstream influences, including nutrient deficiencies, toxic exposures, metabolic stress, and alterations in gut barrier function. Once established, inflammation further amplifies metabolic dysfunction, creating a bidirectional relationship between immune activation and metabolic instability.

7.6. *Systems Integration and Feedback Loops*

These root drivers do not act independently; rather, they interact within a dynamic and interconnected system. Their combined effects converge on a shared biological terrain characterized by disruption of redox balance, mitochondrial dysfunction, and impaired intracellular nutrient utilization [6–8].

Within this integrated system:

- Hyperglycemia functions both as a marker and a propagator of dysfunction
- Intracellular nutrient depletion amplifies oxidative stress
- Redox imbalance further exacerbates insulin resistance and metabolic instability

These interactions give rise to self-reinforcing feedback loops. A representative pathway can be conceptualized as:

**Metabolic substrate overload → intracellular nutrient dysfunction → redox imbalance → insulin resistance → worsening hyperglycemia**

In this model, mitochondrial dysfunction is positioned primarily as a downstream amplifier of upstream disturbances rather than as an initiating cause.

Summary of the Model

The root driver–based systems model provides a unifying framework that integrates metabolic, nutritional, hormonal, and environmental dimensions of T2DM. It helps explain:

- The persistence of complications despite glycemic control

- Variability in patient response to metabolic interventions
- The need for multi-dimensional therapeutic strategies

By shifting the focus from isolated biomarkers to interacting upstream determinants, this model offers a foundation for a more comprehensive understanding of disease mechanisms and for the development of systems-oriented approaches to prevention and treatment.

## 8. The Nutrient Demand Principle and Its Clinical Implications

### 8.1. The Nutrient Demand Principle Hypothesis

The Nutrient Demand Principle proposes that as metabolic disease severity increases, physiological demand for key micronutrients correspondingly rises. Under conditions of chronic metabolic stress—such as hyperglycemia, oxidative–reductive (redox) imbalance, inflammation, and increased metabolic turnover—cellular requirements for essential nutrients may exceed levels achievable through standard dietary intake alone [6,30,38–40].

In this context, restoration of intracellular function may require not only adequate intake, but also sufficient delivery, transport, and utilization of micronutrients at the cellular level. Consequently, conventional nutritional recommendations may be insufficient to meet the increased demands associated with metabolic disease states, particularly in the presence of impaired transport mechanisms and altered metabolic flux [21,38].

This hypothesis provides a potential explanation for the persistence of metabolic and vascular dysfunction despite apparent adequacy of dietary intake and standard clinical management.

This concept is consistent with evidence that oxidative stress and inflammation increase turnover, utilization, and depletion of key micronutrients, thereby increasing physiological requirements under conditions of chronic disease.

### 8.2. Clinical and Research Implications

The Nutrient Demand Principle has several implications for both clinical practice and future research:

- Glycemic control alone may be insufficient as a sole therapeutic endpoint, as it does not directly address intracellular nutrient availability or redox balance
- Intracellular micronutrient status represents a critical but under-measured dimension of metabolic health, with potential relevance to disease progression and treatment response [6,21]
- Environmental and hormonal factors should be incorporated into metabolic research, given their influence on nutrient demand, transport, and utilization
- Systems-level interventions may be required to achieve durable clinical outcomes, integrating metabolic, nutritional, hormonal, and environmental domains

### 8.3. Position Within a Systems Framework

Within the broader systems model proposed in this paper, the Nutrient Demand Principle serves as a functional bridge between upstream drivers and downstream cellular dysfunction. It links metabolic stress, impaired nutrient availability, and redox imbalance into a unified conceptual framework.

Further investigation is warranted to quantify nutrient demand under varying metabolic conditions and to determine how targeted nutritional strategies may contribute to restoring intracellular and systemic function.

## 9. Key Nutrients in Systems Dysfunction

### 9.1. Vitamin C Status in Type 2 Diabetes: Clinical Evidence

Patients with type 2 diabetes mellitus (T2DM) frequently exhibit reduced circulating levels of vitamin C, as well as evidence of impaired intracellular availability [30,39,41].

This reduction has been associated with poor glycemic control, increased oxidative stress, and higher prevalence of vascular complications.

Meta-analyses of randomized controlled trials suggest that vitamin C supplementation may:

- Reduce fasting plasma glucose [38,42]
- Lower glycated hemoglobin (HbA1c) [38,42]
- Improve markers of oxidative stress and antioxidant capacity [43,44]

These findings support a potential role for vitamin C in modulating metabolic and redox processes in T2DM. As discussed in Section 5, impaired cellular uptake under hyperglycemic conditions may further contribute to functional intracellular deficiency, highlighting the importance of considering both systemic levels and intracellular availability.

While vitamin C serves as a representative example, similar principles may apply to other micronutrients involved in cellular metabolism and redox regulation.

### 9.2. Thiamine (Vitamin B1) and Glucose Metabolism

Thiamine is a critical cofactor in carbohydrate metabolism and mitochondrial energy production. It plays a central role in enzymatic pathways that regulate glucose oxidation and cellular energy balance [45–47].

In T2DM, several abnormalities related to thiamine have been reported, including:

- Increased renal clearance leading to reduced plasma levels
- High prevalence of functional deficiency
- Impairment of mitochondrial and endothelial function

Clinical studies suggest that thiamine or its derivatives (e.g., benfotiamine) may improve endothelial function and reduce markers of microvascular dysfunction. These effects are consistent with its role in mitigating metabolic stress and supporting mitochondrial function.

### 9.3. Magnesium and Insulin Resistance

Magnesium is an essential cofactor in numerous enzymatic reactions, including those involved in insulin signaling, glucose transport, and ATP metabolism [48–50].

Low magnesium status has been consistently associated with:

- Increased insulin resistance [51–53]
- Poor glycemic control [53,54]
- Elevated risk of cardiovascular risk [55]

Magnesium deficiency may impair insulin receptor activity, reduce cellular glucose uptake, and contribute to systemic inflammation and endothelial dysfunction. Given its central role in metabolic regulation, adequate magnesium status is an important component of maintaining insulin sensitivity and metabolic stability.

### 9.4. Integration Within a Systems Framework

These nutrients—vitamin C, thiamine, and magnesium—illustrate how micronutrient status intersects with metabolic, mitochondrial, and redox processes in T2DM. Their deficiencies may arise from a combination of inadequate intake, increased physiological demand, impaired transport, and altered utilization.

Within the systems model proposed in this paper, micronutrient insufficiency is not an isolated phenomenon, but part of a broader network of interacting disturbances. Addressing these

deficiencies may therefore represent an important component of strategies aimed at restoring intracellular function and improving overall metabolic resilience.

## 10. Environmental and Toxicological Contributions

Environmental exposures represent an important but often underrecognized contributor to metabolic dysfunction in type 2 diabetes mellitus (T2DM). A growing body of evidence implicates persistent organic pollutants (POPs), heavy metals, and other environmental toxicants in the development of insulin resistance and metabolic disease [15,56–58].

These exposures may influence metabolic regulation through several interconnected mechanisms:

- **Increased oxidative–reductive (redox) imbalance**, contributing to cellular stress and tissue injury
- **Impairment of mitochondrial function**, reducing energy efficiency and metabolic flexibility
- **Disruption of endocrine signaling**, including interference with insulin action and hormonal regulation. These factors represent an often overlooked upstream driver of metabolic disease.

Emerging evidence also supports a role for endocrine-disrupting chemicals in modulating metabolic pathways relevant to insulin resistance and energy homeostasis.

In addition, certain environmental toxicants act as endocrine disruptors, altering hormonal pathways that are critical to glucose metabolism, energy homeostasis, and inflammatory regulation.

Within the systems framework proposed in this paper, environmental toxic burden can be viewed as an upstream driver that interacts with nutritional status, hormonal regulation, and metabolic inputs. These interactions may amplify systemic dysfunction and contribute to variability in disease progression and treatment response.

Recognition of environmental and toxicological factors expands the understanding of T2DM beyond traditional metabolic paradigms and highlights the importance of incorporating environmental context into both research and clinical strategies.

## 11. Testable Hypotheses and Research Implications

The root driver–based systems model proposed in this paper generates a set of testable hypotheses that may help explain the observed gap between glycemic control and clinical outcomes in type 2 diabetes mellitus (T2DM). These hypotheses are intended to be falsifiable and to guide future experimental and clinical investigation.

### 11.1. Intracellular Nutrient Discrepancy Hypothesis

Individuals with similar glycemic markers (e.g., HbA1c) will exhibit significant variability in intracellular micronutrient status—particularly vitamin C—reflecting differences in cellular transport and utilization rather than intake alone.

This hypothesis may be evaluated through direct or surrogate measures of intracellular nutrient levels and correlated with clinical outcomes independent of plasma concentrations.

### 11.2. Functional Vitamin C Deficiency Hypothesis

Correction of intracellular vitamin C deficiency will improve markers of endothelial function, oxidative stress, and possibly insulin sensitivity, independent of changes in blood glucose levels.

This hypothesis can be tested through controlled supplementation studies with endpoints that extend beyond glycemic measures.

### 11.3. Toxic Burden–Insulin Resistance Hypothesis

Markers of environmental toxic exposure will correlate with insulin resistance and metabolic dysfunction, independent of traditional risk factors such as body mass index, caloric intake, or glycemic control.

This relationship may be explored through epidemiological studies and mechanistic investigations assessing toxin burden alongside metabolic parameters.

### 11.4. ICV Axis Dysregulation Hypothesis

Disruption of the Insulin–Cortisol–Vitamin C (ICV) axis will be associated with impaired metabolic flexibility and variability in response to dietary interventions, including low-carbohydrate and ketogenic therapies.

This hypothesis may be evaluated by assessing hormonal profiles, intracellular nutrient status, and treatment response in stratified patient populations.

### 11.5. Nutrient Demand Principle Hypothesis

As metabolic disease severity increases, physiological demand for key micronutrients will rise, such that standard dietary intake becomes insufficient to restore intracellular function without targeted supplementation.

This hypothesis may be tested by correlating disease severity with nutrient requirements and by evaluating clinical outcomes following targeted nutritional interventions.

### 11.6. Implications for Research Design

These hypotheses suggest that future research in T2DM may benefit from incorporating:

- Measures of **intracellular micronutrient status**, in addition to circulating levels
- Assessment of **environmental exposures and toxic burden**
- Integration of **hormonal and stress-related variables**, including cortisol dynamics
- Evaluation of **redox balance and mitochondrial function** as intermediate endpoints

Such approaches may help identify subgroups of patients with distinct underlying drivers and may improve the precision of therapeutic strategies.

### 11.7. Summary

Collectively, these hypotheses extend the current understanding of T2DM beyond a glucose-centered model and provide a framework for investigating upstream determinants of metabolic dysfunction. By emphasizing testability and integration across biological systems, this approach aims to facilitate the development of more comprehensive and effective strategies for both research and clinical care.

## 12. Toward a Systems-Based Therapeutic Model of Type 2 Diabetes

The following model is presented as a conceptual framework for systems-oriented intervention rather than as prescriptive clinical guidelines.

Effective management of type 2 diabetes mellitus (T2DM) requires a transition from isolated biomarker control to coordinated restoration of systemic biological function. Within the framework of Integrative Orthomolecular Systems Medicine (IOM), therapeutic strategy is directed at upstream drivers and the underlying biological terrain, rather than solely at downstream glycemic indices.

A systems-based therapeutic model integrates the following core domains:

### 12.1. Dietary Strategy: Reduction of Metabolic Substrate Overload

Dietary intervention forms the foundational layer of metabolic regulation. Reduction of dietary glycemic load—particularly through low-carbohydrate or ketogenic approaches—directly addresses



hyperglycemia and hyperinsulinemia, which serve as primary metabolic inputs driving oxidative stress and insulin resistance.

While effective for improving glycemic markers and reducing pharmacologic dependence, dietary strategies alone do not fully restore intracellular metabolic integrity.

#### *12.2. Nutritional Optimization: Correction of Intracellular Deficiency*

Restoration of intracellular micronutrient status is central to IOM Systems Medicine. Key nutrients—including vitamin C, thiamine, magnesium, and others—support mitochondrial function, enzymatic activity, and redox balance.

Importantly, in the context of hyperglycemia, functional intracellular deficiencies may persist despite adequate intake, necessitating targeted and, in some cases, higher-than-standard supplementation. This approach is consistent with the Nutrient Demand Principle, which posits that physiological requirements increase in states of chronic disease.

#### *12.3. Redox Restoration: Rebalancing the Oxidative–Reductive System*

Disruption of the oxidative–reductive (redox) system represents a central convergence point of metabolic, nutritional, and environmental stressors. Therapeutic strategies aimed at restoring redox balance—including optimization of antioxidant systems and support of endogenous defense pathways—are essential for reducing oxidative stress, improving endothelial function, and stabilizing metabolic control.

#### *12.4. Hormonal Regulation: Reestablishing Endocrine Homeostasis*

Hormonal systems—including insulin, cortisol, thyroid hormones, and sex steroids—play critical roles in energy metabolism, mitochondrial function, and inflammatory regulation. Dysregulation of these systems contributes to insulin resistance and metabolic instability.

Within the IOM framework, particular attention is given to the Insulin–Cortisol–Vitamin C (ICV) axis as a key interface linking metabolic control, stress physiology, and intracellular nutrient dynamics. Restoration of hormonal balance is therefore an integral component of systems-level intervention.

#### *12.5. Reduction of Toxic Burden: Addressing Environmental Drivers*

Environmental exposures, including persistent organic pollutants and heavy metals, represent upstream contributors to oxidative stress, mitochondrial dysfunction, and endocrine disruption.

A comprehensive therapeutic model includes identification and mitigation of these exposures, alongside support for endogenous detoxification pathways. Addressing toxic burden reduces ongoing biological stress and facilitates recovery of metabolic and cellular function.

Further validation through controlled clinical studies will be required to determine the efficacy and generalizability of this approach.

### **Systems Integration**

These therapeutic domains are not independent interventions but components of an integrated systems strategy. Their coordinated application targets the core pathological loop underlying T2DM: metabolic overload → intracellular nutrient dysfunction → redox imbalance → hormonal disruption → insulin resistance

Intervention at multiple nodes within this system is required to achieve durable clinical improvement.

### **Clinical Implication**

A systems-based therapeutic model reframes T2DM management from glucose-centered control to restoration of biological function. While pharmacologic and metabolic interventions remain

important, long-term resolution of disease progression requires addressing upstream drivers and reestablishing systemic balance.

### 13. A Three-Level Model of T2DM Recognition and Management

The management of type 2 diabetes mellitus (T2DM) can be conceptualized as a progression across three hierarchical levels, reflecting increasing depth of pathophysiological understanding and therapeutic scope.

#### *Level 1: Conventional Medicine — Glucose Control*

- **Primary focus:** Blood glucose
- **Strategy:** Pharmacologic lowering of glycemia
- **Limitation:** Targets a downstream marker rather than upstream drivers

Conventional management has been highly effective in reducing acute metabolic complications and remains essential in many clinical contexts, particularly for short-term risk control and stabilization.

However, its primary limitation lies in its focus on hyperglycemia as the central therapeutic target, without fully addressing the underlying systemic disturbances that drive disease progression.

#### *Level 2: Metabolic Medicine — Carbohydrate Restriction and Ketogenic Therapy*

- **Primary focus:** Insulin resistance and metabolic regulation
- **Strategy:** Reduction of dietary carbohydrate load, including low-carbohydrate and ketogenic approaches
- **Strength:** Mechanistically grounded and clinically effective in improving glycemic control and reducing insulin demand
- **Limitation:** Does not fully restore intracellular and systemic biological function

By directly reducing the primary metabolic input—excess glucose—this level represents a significant advance beyond glucose-centric management.

However, despite improvements in metabolic markers, underlying abnormalities may persist, including oxidative–reductive imbalance, intracellular micronutrient deficiency, hormonal dysregulation, and environmental toxic burden.

#### *Level 3: IOM Systems Medicine — Systems Restoration*

- **Primary focus:** Restoration of whole-system biological function
- **Scope includes:**
  - Nutritional optimization (intracellular micronutrient status)
  - Redox balance
  - Mitochondrial function
  - Hormonal regulation
  - Environmental and toxicological factors

At this level, T2DM is addressed as a systems-level disorder involving interconnected biological networks.

Therapeutic strategy is directed toward upstream drivers and the underlying biological terrain, rather than isolated metabolic parameters.

#### *Key Insight*

Hyperglycemia should be understood not only as a clinical marker, but also as an active participant in disease propagation.

Through mechanisms such as impaired intracellular nutrient transport—particularly of vitamin C—it contributes to oxidative stress, metabolic instability, and progressive insulin resistance.

### *Conceptual Implication*

This three-level model reframes T2DM management as a continuum:

**glucose control → metabolic regulation → systems restoration**

Each level provides incremental benefit, while the third level is designed to address the full complexity. Optimal care requires integration across all three levels, with progression toward systems-level intervention as the ultimate therapeutic objective.

## **14. Discussion**

### *14.1. Persistence of the Glucose-Centric Paradigm*

Despite accumulating evidence that intensive glycemic control does not consistently reduce macrovascular outcomes or mortality, the glucose-centric model of T2DM management remains dominant in clinical practice. Several factors contribute to its persistence.

First, blood glucose is easily measurable, quantifiable, and directly linked to diagnostic criteria, making it a convenient clinical target. Second, pharmacologic interventions that lower glucose produce rapid and observable effects, reinforcing their perceived efficacy. Third, the structure of clinical trials, regulatory pathways, and reimbursement systems has historically prioritized glycemic endpoints, further entrenching this paradigm.

However, this model primarily targets a downstream marker rather than the upstream drivers of disease, which may explain the persistent gap between glycemic control and long-term clinical outcomes.

### *14.2. Integration with Existing Medical Practice*

The IOM Systems Medicine framework is not intended to replace conventional or metabolic approaches, but to extend and integrate them within a broader systems-level understanding.

Conventional pharmacologic therapies remain essential for acute risk management and stabilization. Metabolic strategies, including low-carbohydrate and ketogenic diets, represent a critical advancement by directly addressing insulin resistance and substrate overload.

Within this context, IOM Systems Medicine functions as a higher-order framework that incorporates these approaches while addressing additional dimensions of disease, including intracellular nutrient status, redox balance, hormonal regulation, and environmental influences.

Thus, the model is inherently integrative, positioning existing therapies within a more comprehensive and biologically coherent structure.

### *14.3. Clinical Implications*

Adopting a systems-based perspective has several important clinical implications.

First, it shifts therapeutic focus from exclusive reliance on glycemic targets to broader markers of biological function, including nutrient status, oxidative stress, and hormonal balance.

Second, it supports the use of targeted nutritional and orthomolecular interventions to correct intracellular deficiencies that may not be apparent through conventional laboratory assessment.

Third, it highlights the importance of environmental and lifestyle factors as modifiable drivers of disease progression.

Importantly, this approach may help explain inter-individual variability in treatment response, even among patients with similar glycemic profiles, and supports a more personalized and adaptive model of care.

### *14.4. Limitations of the Current Model*

Several limitations should be acknowledged.

The IOM Systems Medicine framework is, at present, a conceptual and integrative model that synthesizes evidence from multiple domains, including nutrition, metabolism, endocrinology, and

environmental health. While individual components of the model are supported by existing literature, the full systems-level integration has not yet been validated through large-scale, prospective clinical trials.

Measurement of key variables—such as intracellular micronutrient status, redox balance, and toxic burden—remains technically challenging and is not routinely available in standard clinical settings.

The complexity of systems-level interventions may also present practical challenges in implementation, including issues related to patient adherence, cost, and the need for clinician training in integrative approaches.

Furthermore, causal relationships between specific upstream drivers and clinical outcomes remain to be established through prospective and interventional studies.

Finally, heterogeneity among patient populations may influence the relative contribution of different upstream drivers, highlighting the need for stratified and individualized approaches in future research.

14.5. Future Research Directions

The proposed framework generates multiple avenues for future investigation.

Prospective studies are needed to evaluate whether correction of intracellular nutrient deficiencies—particularly vitamin C—can improve clinical outcomes independent of glycemic control.

Further research should explore the role of environmental toxic burden in insulin resistance and metabolic dysfunction, including its interaction with nutritional and hormonal factors.

The Insulin–Cortisol–Vitamin C (ICV) axis warrants additional investigation as a potential regulatory interface linking metabolic and stress-related pathways.

In addition, the development of clinically accessible biomarkers for intracellular nutrient status and redox balance would significantly enhance the ability to operationalize this model in practice.

Ultimately, validation of a systems-based therapeutic approach will require integrated clinical trials that move beyond single-variable interventions toward multi-domain strategies.

15. Conclusion

Type 2 diabetes mellitus (T2DM) is not solely a disorder of elevated blood glucose, but a systems-level condition characterized by impaired intracellular nutrient availability, disruption of the oxidative–reductive (redox) system, and progressive metabolic dysfunction.

While low-carbohydrate and ketogenic approaches represent a significant advance by addressing key metabolic drivers, they do not fully restore the underlying biological terrain.

Integrative Orthomolecular Systems Medicine (IOM) provides a unifying framework that integrates nutrient status, redox balance, mitochondrial function, hormonal regulation, and environmental influences into a coherent model of disease pathophysiology and intervention.

Optimal management of T2DM may therefore benefit from progression across three hierarchical levels:

**glucose control → metabolic regulation → systems restoration**

This progression reflects a shift from targeting downstream biomarkers to addressing upstream drivers and restoring systemic biological function.

**Competing Interests:** Richard Z. Cheng, M.D., Ph.D., is a Board Director of the Riordan Clinic, an institution that conducts research and clinical services related to intravenous vitamin C. The present manuscript is a conceptual and literature-based analysis and does not report proprietary data, commercial products, or patient-level outcomes. No financial compensation was received for the preparation of this manuscript.

**Funding:** This work received no external funding.

**Ethics Approval and Consent to Participate:** Not applicable. This manuscript is a conceptual synthesis of published literature and does not involve new human or animal subject research.

**Consent for Publication:** Not applicable.

**Data Availability:** No new datasets were generated or analyzed. All information presented is derived from published and publicly available sources cited in the manuscript.

**Author Contributions:** R.Z.C. conceived the conceptual framework, performed the literature synthesis, and wrote the manuscript.

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