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The Insulin–Cortisol–Vitamin C Axis: A Missing Regulatory Framework in Metabolic and Hormonal Homeostasis A Narrative Review

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The Insulin–Cortisol–Vitamin C Axis: A Missing Regulatory Framework in Metabolic and Hormonal Homeostasis A Narrative Review

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Abstract

Bioidentical hormone replacement therapy (BHRT) traditionally operates within a triad consisting of sex hormones, thyroid hormones, and adrenal glucocorticoids. Despite widespread adoption, a substantial proportion of patients experience persistent dysglycemia, adrenal instability, fluctuations in symptom control, and inconsistent responses to therapy even when laboratory values appear biochemically normalized. These clinical patterns suggest that an essential regulatory element is missing from the current BHRT conceptual model. This narrative review proposes the **Insulin–Cortisol–Vitamin C (ICV) Axis** as a previously unrecognized hormonal network central to metabolic and endocrine homeostasis. Insulin profoundly influences sex-hormone binding globulin (SHBG), estradiol and testosterone bioavailability, progesterone responsiveness, thyroid hormone conversion, mitochondrial ATP production, and cortisol reactivity—yet insulin is rarely evaluated in BHRT. Cortisol, in turn, directly modulates insulin sensitivity and metabolic function, while vitamin C is required for cortisol synthesis, adrenal recovery, endothelial nitric oxide signaling, mitochondrial redox regulation, and antioxidant defense. Together, disturbances in these three components can generate characteristic clinical presentations frequently encountered in BHRT practice. In parallel, emerging evidence—including metabolic insights from GLP-1 receptor agonist therapy—indicates that vitamin C status and oxidative stress modulation play broader roles in insulin sensitivity and hormonal signaling than previously recognized. Integrating these findings, the ICV Axis provides a **systems-level framework** capable of explaining BHRT treatment failures, variable patient responses, and persistent symptomatology despite standard hormone optimization. The purpose of this review is to synthesize biochemical, endocrine, and nutritional evidence supporting this new axis, and to outline a clinically actionable update to BHRT incorporating insulin dynamics and *vitamin C sufficiency*. Recognition of the ICV Axis represents a conceptual advancement that can improve therapeutic outcomes across metabolic, endocrine, and integrative medical practice.

Keywords: bioidentical hormone replacement therapy (BHRT); cortisol; endocrine regulation; insulin; insulin resistance; metabolic homeostasis; oxidative stress; sex hormones; thyroid hormones; vitamin C

1. Introduction

Insulin resistance (IR) affects over 25% of the global adult population and underlies metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), polycystic ovarian syndrome (PCOS), and accelerated aging. Traditionally, IR is the result of excessive carbohydrate intake, hypercaloric diets, inactivity, and obesity. Dietary interventions—especially low-carbohydrate diets—have proven effective for many individuals. However, clinical

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experience and heterogeneity of treatment outcomes indicate that carbohydrate intake is only one determinant of insulin homeostasis.

Multiple studies demonstrate that insulin sensitivity is influenced by oxidative stress, inflammation, glucocorticoid activity, magnesium insufficiency, micronutrient status, circadian rhythms, mitochondrial function, and chronic psychosocial stress. For example:

- Oxidative stress impairs insulin receptor signaling and contributes to IR in humans and animal models [1,2].
- Psychological stress activates the HPA axis, elevates cortisol, increases fasting insulin, and raises HOMA-IR [3–5].
- Flattened or elevated diurnal cortisol patterns predict development of metabolic syndrome [6–8].
- Low plasma vitamin C is associated with higher prevalence of metabolic syndrome in large observational cohorts [9,10].
- Vitamin C supplementation improves endothelial function and reduces oxidative stress, both central to IR [11–13].
- Vitamin C supplementation helps to significantly resolve hypercortisolemia, which often is the direct biological response to low vitamin C levels in the cells and blood [14–19].

These findings indicate that insulin regulation is embedded in a **broader metabolic-endocrine redox network**, yet current frameworks often treat insulin in isolation.

1.1. A Missing Link: The Role of Vitamin C in [22,23Sensitivity

Vitamin C is an essential redox molecule and enzymatic cofactor involved in:

- scavenging reactive oxygen species [20,21]
- regenerating intracellular glutathione [22,23]
- supporting mitochondrial oxidative metabolism [24–26]
- synthesizing carnitine [24]
- modulating inflammatory cytokines [27–29]
- regulating endothelial nitric oxide [30–32]
- adrenal steroidogenesis and catecholamine synthesis [17,33,34]

Vitamin C insufficiency contributes to and is a direct result of oxidative stress—one of the key drivers of insulin resistance [35]. A 2021 meta-analysis of 28 observational studies found significantly lower vitamin C levels in individuals with metabolic syndrome [10]. A randomized trial demonstrated improved glycemic parameters in type 2 diabetes with vitamin C supplementation [12].

Despite this evidence, vitamin C is seldom considered in insulin resistance frameworks or clinical guidelines [9,36].

1.2. Cortisol, Stress, and Insulin Coupling

Cortisol directly raises blood glucose via gluconeogenesis, reduces insulin-mediated glucose uptake, and promotes visceral fat deposition. Excess cortisol—whether due to chronic stress, sleep disruption, exogenous glucocorticoids, or HPA-axis dysregulation—is strongly associated with insulin resistance [34,37–40]. This cortisol–metabolic link has been well described in classic endocrinology literature, such as Rosmond & Björntorp's seminal review on stress-driven metabolic syndrome [41].

Vitamin C is highly concentrated in the adrenal cortex and is required for optimal cortisol synthesis and clearance—a relationship demonstrated in classic adrenal physiology research [34].

1.3. A Unified Model: The Insulin–Cortisol–Vitamin C (ICV) Axis

The cumulative literature suggests a tightly interdependent triad:

- **Cortisol dysregulation → insulin resistance** [34,37,38]

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- **Vitamin C deficiency → cortisol dysregulation + oxidative stress → impaired insulin signaling** [10,12]
- **Insulin dysregulation → oxidative stress → increased vitamin C turnover** [9,35]

Yet no existing metabolic, endocrine, or nutritional framework integrates these three domains into a single explanatory model.

1.4. Purpose of This Review

This narrative review synthesizes evidence to support the conceptual validity of the **ICV Axis**, provides mechanistic insight, evaluates clinical implications, and identifies research gaps necessary to validate this triad as a clinically relevant regulatory system.

2. Physiology of Insulin Regulation

Insulin is an anabolic hormone essential for maintaining glucose homeostasis, promoting nutrient storage, supporting protein synthesis, and regulating lipid metabolism. While commonly framed as a hormone whose secretion depends primarily on dietary carbohydrate intake, insulin regulation is substantially more complex. It integrates signals from the gastrointestinal tract, autonomic nervous system, inflammatory mediators, oxidative stress, mitochondrial function, and the hypothalamic–pituitary–adrenal (HPA) axis.

Understanding insulin physiology requires examining both **baseline secretion mechanisms** and **contextual modulators** that influence insulin sensitivity and metabolic outcomes.

2.1. Glucose-Stimulated Insulin Secretion (GSIS)

Glucose entering pancreatic β-cells via GLUT1/GLUT3 is metabolized through glycolysis and oxidative phosphorylation, increasing intracellular ATP. The resulting rise in ATP/ADP ratio closes ATP-sensitive K+ channels, depolarizing the membrane and opening voltage-gated Ca^{2+} channels. Elevated intracellular Ca^{2+} triggers insulin granule exocytosis.

This canonical pathway has been extensively described and validated in molecular, animal, and clinical studies [42–45].

2.2. Non-Glucose Mediators of Insulin Secretion

Incretins (GLP-1, GIP)

GLP-1 and GIP enhance insulin secretion in a glucose-dependent manner. GLP-1 also reduces glucagon and lower circulating glucose levels, slows gastric emptying, and decreases appetite [46–48].

Amino acids and dietary proteins

Certain amino acids (e.g., leucine, arginine) directly stimulate insulin secretion [49,50].

Free fatty acids (FFAs)

Acute FFA exposure stimulates insulin secretion via G-protein–coupled receptors, but chronic FFA elevation impairs β-cell function [51,52].

2.3. Insulin Sensitivity and Tissue Uptake

Once secreted, insulin facilitates glucose uptake in [53]:

- skeletal muscle
- adipose tissue
- liver (indirectly via suppression of hepatic glucose output)

The primary mechanism is **insulin-stimulated GLUT4 translocation** to the cell membrane in muscle and adipose tissue [53].

Insulin sensitivity is influenced by [53–59]:

- physical activity
- mitochondrial function

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- oxidative stress
- inflammation
- adipokines (adiponectin, leptin)
- magnesium sufficiency
- stress hormones (especially cortisol)

Metabolic flexibility—the capacity to switch between glucose and fat oxidation—also plays a major role in insulin sensitivity [60,61].

2.4. Insulin Resistance: A Multifactorial Process

Insulin resistance arises when insulin receptor signaling is impaired. Multiple cellular and systemic mechanisms converge to disrupt insulin action:

Oxidative stress

Reactive oxygen species (ROS) interfere with insulin receptor substrate (IRS) phosphorylation and downstream signaling, reducing glucose uptake in peripheral tissues [2,62–67].

Inflammation

Proinflammatory cytokines—including TNF-α and IL-6—activate serine kinases that inhibit insulin receptor signaling, impair GLUT4 translocation, and decrease skeletal muscle insulin sensitivity [68–71].

Mitochondrial Dysfunction

Impaired β-oxidation, reduced ATP generation, and elevated mitochondrial ROS contribute to metabolic inflexibility and worsen insulin resistance [72–75].

Lipotoxicity / Ectopic Fat Accumulation

Accumulation of diacylglycerol and ceramides in liver and muscle disrupts insulin signaling via PKC-mediated inhibition of the insulin receptor pathway [76–78].

Circadian Disruption

Circadian misalignment, sleep restriction, and irregular cortisol rhythms rapidly impair insulin sensitivity and raise next-day postprandial glucose responses [79–83].

Chronic Stress & Cortisol Elevation

Sustained or dysregulated cortisol secretion promotes gluconeogenesis, increases hepatic glucose output, reduces peripheral glucose uptake, and induces insulin resistance [37,39,84].

2.5. Insulin Variability and Fluctuations Matter

Emerging evidence suggests that **insulin variability**, not just absolute levels, contributes to metabolic dysfunction.

- Variability in insulin secretion predicts worsening metabolic syndrome markers [85–89].
- Postprandial insulin spikes correlate with endothelial dysfunction [90–94].

2.6. Vitamin C as a Modulator of Insulin Physiology

Although traditionally excluded from mainstream models of insulin regulation, vitamin C participates in multiple biochemical pathways that directly influence insulin sensitivity and metabolic homeostasis. A growing body of evidence demonstrates that vitamin C status affects key regulatory systems involved in glucose uptake, mitochondrial function, endothelial signaling, and inflammatory control. These mechanisms provide a scientifically grounded basis for understanding vitamin C as a physiologically important modulator of insulin action.

Key mechanisms include:

- **Reduction of oxidative stress**, a major contributor to insulin receptor impairment and IRS-1 dysfunction. Vitamin C deficiency is a direct reflection of elevated oxidative load, while supplementation lowers markers of oxidative stress in metabolic syndrome and type 2 diabetes [12,35].

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- **Support of GLUT4 activation and glucose uptake**, partly through antioxidant protection of skeletal muscle and pancreatic β-cells, and through improved mitochondrial redox status [9].
- **Enhancement of mitochondrial function**, including support of electron transport, carnitine-dependent fatty acid oxidation, and the prevention of ROS-mediated inhibition of insulin signaling pathways [26,95–97].
- **Augmentation of endothelial nitric oxide activity**, mediated by preservation of tetrahydrobiopterin and reduction of NO oxidative degradation, which improves insulin-mediated vasodilation and tissue glucose delivery [30].
- **Attenuation of inflammatory pathways**, including reductions in circulating cytokines that inhibit insulin receptor signaling and promote insulin resistance [12,35].

Human studies support the physiological relevance of these mechanisms:

- **Vitamin C levels inversely correlate with metabolic syndrome prevalence**, indicating its potential role in whole-body insulin sensitivity [9,10,98].
- **Vitamin C improves endothelial function**, a key determinant of glucose disposal and vascular insulin responsiveness [32,99,100].
- **Supplementation lowers fasting glucose, triglycerides, LDL cholesterol, HbA1c, and serum insulin in type 2 diabetes**, suggesting improved glycemic control and insulin sensitivity [101].
- **Meta-analyses demonstrate reductions in oxidative stress, improvements in glycemic indices, and reductions in insulin resistance markers** following vitamin C supplementation [12,35].

Collectively, these findings establish vitamin C as a significant modulator of insulin physiology, acting through convergent pathways involving oxidative stress reduction, GLUT4 activation, mitochondrial support, nitric oxide–mediated vascular function, and inflammatory control. These mechanisms form the foundation for Section 3, which examines direct evidence linking vitamin C status to insulin sensitivity and metabolic disease outcomes.

3. Evidence Linking Vitamin C Status and Insulin Sensitivity

A growing body of human, clinical, and mechanistic research demonstrates a significant association between vitamin C status and insulin sensitivity. While vitamin C is traditionally framed as an antioxidant, the evidence outlined below shows that ascorbate participates directly in biological processes central to insulin signaling, glucose uptake, endothelial function, and inflammatory regulation. The totality of this literature supports the hypothesis that vitamin C is an important modulator of insulin homeostasis.

3.1. Observational Evidence: Vitamin C Levels Inversely Correlate With Insulin Resistance and Metabolic Syndrome

Multiple population-based studies report that low circulating vitamin C levels are strongly associated with features of metabolic syndrome—including elevated fasting glucose, central adiposity, hypertension, dyslipidemia, and insulin resistance. A recent NHANES-based analysis confirmed a robust inverse relationship between plasma ascorbate and cardiometabolic risk markers, with individuals in the lowest quartile of vitamin C demonstrating the highest HOMA-IR and metabolic syndrome prevalence [92]. These findings are consistent with prior epidemiologic studies showing that inadequate dietary vitamin C intake predicts higher fasting glucose and impaired insulin sensitivity [93].

3.2. Interventional Trials: Vitamin C Supplementation Improves Glycemic Control and Insulin Biomarkers

Controlled supplementation trials further support a causal role for vitamin C in improving insulin dynamics. Daily oral vitamin C (typically 500–1,000 mg twice per day) has been shown to significantly reduce fasting glucose, HbA1c, triglycerides, LDL cholesterol, and serum insulin levels in individuals with type 2 diabetes, indicating improved insulin sensitivity and glycemic handling [94]. Meta-analytic data reinforce these findings: pooled results from randomized trials reveal that

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vitamin C supplementation lowers oxidative stress markers, improves glycemic control, and reduces HOMA-IR in patients with metabolic syndrome and type 2 diabetes [95].

Although study heterogeneity exists—particularly regarding dose, duration, and population characteristics—the consistency of these results across multiple cohorts provides evidence that vitamin C favorably influences insulin physiology under metabolic stress conditions.

3.3. Mechanistic Studies Demonstrating Improvements in Insulin Signaling

Vitamin C exerts several mechanistic effects directly relevant to insulin action:

- **Reduction of Oxidative Stress:** Vitamin C decreases reactive oxygen species that otherwise impair insulin receptor substrate (IRS) phosphorylation and downstream signaling, thereby maintaining insulin responsiveness [98].
- **Support of GLUT4-Mediated Glucose Uptake:** Ascorbate appears to enhance GLUT4 translocation and skeletal muscle glucose uptake, supporting peripheral insulin sensitivity [9,12,99,102,103].
- **Mitochondrial Protection:** Vitamin C contributes to mitochondrial function through antioxidant roles and carnitine synthesis pathways, both of which support metabolic flexibility and glucose utilization [9,103,104].

These mechanistic pathways align with clinical observations showing improved insulin sensitivity following vitamin C replenishment.

3.4. Endothelial Function: Vitamin C Enhances NO Bioavailability and Insulin-Mediated Vasodilation

Insulin's ability to stimulate glucose uptake in skeletal muscle partly depends on endothelial nitric oxide (NO) availability, which regulates the vasodilation required for glucose and insulin delivery to peripheral tissues. Vitamin C sustains endothelial NO synthase (eNOS) activity by maintaining tetrahydrobiopterin (BH4) and reducing oxidative inactivation of NO [99]. Interventional trials in humans show that vitamin C supplementation improves endothelial-dependent vasodilation, a process strongly linked to improved insulin-mediated glucose disposal and overall metabolic health [101].

3.5. Anti-Inflammatory Effects: Vitamin C Reduces Cytokines That Impair Insulin Signaling

Chronic low-grade inflammation is a major driver of insulin resistance. Vitamin C supplementation has been shown to reduce proinflammatory cytokines—such as TNF-α, IL-1β, and CRP—that impair insulin receptor kinase activity and GLUT4 signaling pathways [10]. By lowering inflammatory burden, vitamin C indirectly improves insulin sensitivity and helps restore metabolic homeostasis, particularly in individuals with metabolic syndrome, obesity, or chronic stress.

3.6. Summary of Evidence

Consistent observational, interventional, and mechanistic findings support the conclusion that vitamin C is a significant modulator of insulin physiology. The effects are mediated through:

- reduction of oxidative stress
- enhancement of GLUT4 activation and glucose uptake
- mitochondrial support and metabolic flexibility
- improvement of endothelial NO-dependent vasodilation
- suppression of inflammatory pathways that impair insulin receptor activity

Taken together, these findings establish vitamin C as a biologically plausible and clinically relevant component of insulin regulation and provide the scientific rationale for examining vitamin C as a central element within the proposed Insulin–Cortisol–Vitamin C (ICV) Axis.

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4. The Insulin–Cortisol–Vitamin C (ICV) Axis: A Unified Regulatory Framework

Insulin homeostasis is commonly assessed in isolation—primarily as a function of dietary carbohydrate intake, pancreatic β-cell output, and peripheral insulin receptor sensitivity. However, evidence reviewed in Sections 2 and 3 indicates that insulin dynamics cannot be fully understood without integrating (1) cortisol regulation and (2) vitamin C status. Both are key determinants of oxidative stress, inflammation, glucose disposal, mitochondrial function, and vascular signaling—each of which directly modulates insulin action.

The **ICV Axis** proposes that insulin, cortisol, and vitamin C form a *tightly interdependent* regulatory triad. Disturbances in any one component propagate through the other two, creating self-reinforcing cycles of metabolic dysfunction. This section outlines the physiological basis for this coupling, describes known interactions between these pathways, and highlights their combined relevance to metabolic and endocrine homeostasis.

4.1. Bidirectional Coupling Between Insulin and Cortisol

Cortisol is a potent counter-regulatory hormone whose primary role is to increase glucose availability during stress and upregulate vitamin C uptake into the cells [15,105,106]. Cortisol directly antagonizes insulin by:

- stimulating hepatic gluconeogenesis [107–111]
- inhibiting peripheral glucose uptake [37,39,56,112–115]
- promoting muscle proteolysis and lipolysis [116–120]
- favoring visceral adiposity [39,121–123]

Elevated or dysregulated cortisol patterns—whether due to chronic psychosocial stress, sleep disruption, systemic inflammation, or HPA-axis dysfunction—consistently correlate with impaired insulin sensitivity and higher fasting insulin levels [37,41,108,109,121,124,125]. Numerous observational and clinical studies demonstrate:

- psychological stress elevates cortisol and increases HOMA-IR [125–128].
- disrupted diurnal cortisol rhythms predict incident metabolic syndrome [7,129–131].
- exogenous glucocorticoid exposure produces profound insulin resistance [39,113,132–134].

Conversely, hyperinsulinemia may affect the HPA axis through central feedback mechanisms, promoting additional cortisol release. Thus, **cortisol and insulin form a bidirectional loop**, where abnormalities in one reinforce abnormalities in the other.

4.2. The Central Role of Vitamin C in Adrenal Physiology and Cortisol Regulation

Vitamin C concentrates in the adrenal cortex at the highest levels found in any human organ, reflecting its essential role in adrenal steroidogenesis. Ascorbate is required for:

- optimal activity of 11β-hydroxylase and other cortisol-synthesizing enzymes [135–137]
- neutralization of reactive oxygen species generated during steroid synthesis [17,33,138–140]
- catecholamine biosynthesis, particularly norepinephrine [141–143]

Under stress, vitamin C is rapidly consumed, and adrenal ascorbate stores decline significantly [15,17,137]. Vitamin C insufficiency impairs both cortisol synthesis and cortisol clearance, resulting in:

- prolonged cortisol elevations [14,15,144]
- diminished HPA axis resilience [14,15,135,137]
- exaggerated glucose responses to stress [14,137]
- downstream worsening of insulin sensitivity [9,10,15]

4.3. Vitamin C as a Regulator of Insulin Sensitivity

Section 3 establishes that vitamin C influences multiple pathways essential for insulin action, including:

- oxidative stress reduction

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- preservation of insulin receptor function
- enhancement of GLUT4-mediated glucose uptake
- mitochondrial redox support
- maintenance of endothelial nitric oxide bioavailability
- suppression of pro-inflammatory cytokines

Together, these effects position vitamin C as a **direct modulator of insulin sensitivity**, and not merely a general antioxidant. Vitamin C deficiency or suboptimal status—common in individuals with chronic illness, metabolic syndrome, or elevated oxidative stress—can therefore contribute directly to impaired insulin signaling [10,35,36,145–147].

4.4. Integration of Insulin, Cortisol, and Vitamin C: A Systems Physiology Model

The combined evidence supports a unified model wherein insulin, cortisol, and vitamin C act as a **coupled metabolic–endocrine axis**:

4.4.1. Core Relationships

- **Cortisol → Insulin:** cortisol elevation increases glucose output and insulin secretion.
- **Insulin → Cortisol:** hyperinsulinemia amplifies central HPA-axis activation and promotes visceral adiposity, further elevating cortisol.
- **Cortisol → Vitamin C**: cortisol directly increases intracellular vitamin C levels by stimulating the synthesis of vitamin C transporters and resulting in an anti-inflammatory impact in cells and tissues.
- **Vitamin C → Cortisol:** vitamin C regulates cortisol synthesis and shutdown; deficiency prolongs cortisol elevation.
- **Vitamin C → Insulin:** vitamin C improves insulin sensitivity via oxidative stress reduction, GLUT4 facilitation, mitochondrial support, and endothelial function.
- **Insulin → Vitamin C:** hyperglycemia and oxidative load increase vitamin C turnover, depleting tissue reserves.

Importantly, recent commentary on modern metabolic therapies aligns with the ICV-axis concept. As illustrated in *GLP-1 Receptor Agonists and Vitamin C: A Powerful Anti-Aging Combination*, chronic use of GLP-1RAs may exert many of their beneficial metabolic and anti-aging effects via enhanced intracellular vitamin C uptake, redox normalization, improved mitochondrial function, and optimized insulin sensitivity — effectively functioning as proof-of-concept that vitamin C status can modulate the same pathways described in the ICV model [148].

4.4.2. The Dysregulation Cycle

A disturbance in any one component—cortisol excess, vitamin C deficiency, or insulin resistance—propagates through the other two, forming a self-amplifying cycle:

1. **Stress → cortisol ↑**
2. **Cortisol ↑ → glucose ↑ → insulin ↑**
3. **Insulin ↑ → oxidative stress ↑ → vitamin C depletion**
4. **Vitamin C ↓ → impaired cortisol regulation + reduced insulin sensitivity**
5. **Cycle repeats**, leading to entrenched metabolic dysfunction.

This cycle helps explain:

- persistently high insulin despite low-carbohydrate diets
- stress-related metabolic deterioration
- mitochondrial dysfunction
- endothelial dysfunction
- BHRT instability (via SHBG alterations, thyroid conversion issues, and altered adrenal output)
- heterogeneity in response to GLP-1 receptor agonists

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- metabolic syndrome and fatigue syndromes refractory to standard treatment

4.5. Clinical Relevance of the ICV Axis

The ICV Axis provides a mechanistic explanation for numerous clinical observations:

Low-carb nonresponders

Individuals who do not improve insulin sensitivity despite dietary carbohydrate restriction often show:

- elevated cortisol
- low vitamin C status
- increased oxidative stress
- inflammation or sleep disruption

The ICV model explains persistent insulin resistance in this subgroup.

BHRT instability

Insulin sensitivity influences:

- SHBG levels
- free estrogen/testosterone
- progesterone sensitivity
- thyroid conversion

Cortisol and vitamin C both modulate these pathways, suggesting an integrated framework for hormone therapy optimization.

Metabolic syndrome & cardiometabolic risk

ICV dysregulation aligns with hallmark features of metabolic syndrome, including:

- hyperinsulinemia
- central adiposity
- endothelial dysfunction
- hypertension
- dyslipidemia

GLP-1 agonist variability

Variations in vitamin C status and HPA-axis function may partially explain heterogeneous responses to GLP-1 therapies.

4.6. Implications for Research and Clinical Practice

The ICV Axis suggests new directions for:

- biomarker development (vitamin C status, cortisol rhythms, oxidative stress indices)
- clinical trials (vitamin C repletion + stress modulation + metabolic therapy)
- personalized medicine approaches integrating diet, micronutrition, and endocrine regulation

Despite strong mechanistic and associative evidence, causal validation of the ICV Axis requires prospective interventional studies.

4.7. Summary of Section 4

The **Insulin–Cortisol–Vitamin C Axis** offers a new conceptual framework for understanding metabolic and hormonal homeostasis. Evidence from endocrinology, nutrition science, stress physiology, and redox biology supports a tightly interdependent triad, where disturbances in one element propagate through the others and contribute to chronic metabolic disease. Integrating this model into clinical practice may improve treatment outcomes for insulin resistance, metabolic syndrome, BHRT, and cardiometabolic disease.

5. Integrating the ICV Axis Into Existing BHRT Frameworks

Bioidentical hormone replacement therapy (BHRT) is widely used to address age-related declines in sex hormones, mitigate menopausal and andropausal symptoms, support metabolic

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health, and improve quality of life. Traditional BHRT models focus on the gonadal axis (estrogen, progesterone, testosterone), thyroid optimization, and—less consistently—the adrenal pathway. However, **insulin is not typically conceptualized as a formal hormonal axis within BHRT**, despite its central regulatory role in metabolism, inflammation, vascular function, body composition, and endocrine crosstalk.

The Insulin–Cortisol–Vitamin C (ICV) Axis offers a **new integrative framework** that bridges metabolic endocrinology with micronutrient biochemistry and stress physiology, providing a more comprehensive foundation for BHRT clinical decision-making. Incorporating the ICV Axis into BHRT represents an advancement in root-cause physiology and may improve therapeutic consistency, resilience, and long-term outcomes.

5.1. Why Insulin Should Be Considered a Hormonal Axis in BHRT

Insulin is an anabolic hormone with broad effects on receptor expression, steroidogenesis, hepatic sex-hormone binding globulin (SHBG) synthesis, thyroid conversion, adrenal signaling, and mitochondrial function [149–151]. Dysregulated insulin—whether chronically elevated, suppressed, or highly variable—can significantly alter the clinical response to BHRT [152,153]. The insulin–SHBG relationship was demonstrated as early as 1988 in Plymate's foundational study showing hyperinsulinemia suppresses hepatic SHBG production [154].

Key reasons insulin belongs in BHRT frameworks:

- **Insulin modulates SHBG**, directly altering free vs. total estrogen and testosterone levels [154–157].
- **Hyperinsulinemia drives androgen excess** in women and disrupts progesterone balance [158–160].
- **Hypoinsulinemia reduces IGF-1 and DHEA**, impairing anabolic signaling and resilience [161,162].
- **Insulin variability amplifies adrenal stress**, increasing cortisol fluctuations and undermining BHRT stability [107,109].
- **Insulin sensitivity affects thyroid hormone conversion** and metabolic rate—core BHRT targets [163–165].

Yet BHRT practice rarely measures fasting insulin, postprandial insulin, or insulin variability, and almost never addresses insulin as a therapeutic target.

5.2. How Cortisol Links Insulin and Sex Hormone Physiology

The adrenal cortex produces cortisol in response to physiologic and psychologic stress. Cortisol directly elevates glucose and induces insulin secretion. Conversely, insulin fluctuations affect circadian cortisol patterns and HPA-axis reactivity [166–168].

In BHRT:

- **High cortisol → impaired thyroid function → altered sex hormone utilization** [169–171]
- **High insulin → augmented cortisol response → sleep disturbance, mood changes, abdominal fat gain** [172,173]
- **Low vitamin C → impaired cortisol recovery → prolonged stress response** [14,15,144]

This triad becomes especially relevant in peri- and post-menopausal physiology, where adrenal compensation is already taxed.

5.3. A Critical Missing Component: Vitamin C in BHRT Physiology

Vitamin C has not historically been included in BHRT, yet it is essential for:

- adrenal steroidogenesis [34,142]
- catecholamine biosynthesis [142,174]
- nitric-oxide mediated vascular responses [30,142]
- mitochondrial ATP production [13,26,142]

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- glutathione regeneration [175–177]
- redox balance in ovarian and testicular tissues [178–180]
- neutralization of cortisol-induced oxidative damage [14,15,144]

Vitamin C insufficiency amplifies BHRT side effects such as emotional lability, sleep disruption, hot flashes, fatigue, poor stress tolerance, and suboptimal metabolic response [181,182].

By introducing vitamin C into the BHRT conceptual model, the ICV Axis provides the **first micronutrient-integrated BHRT physiology framework**.

5.4. Why Existing BHRT Models Fail Without Insulin–Cortisol–Vitamin C Integration

- Even well-designed BHRT programs sometimes exhibit [153,183–190]:
- inconsistent symptom improvement
- persistent fatigue
- continued weight gain
- elevated inflammatory markers
- fluctuating hot flashes or night sweats
- unstable mood
- reduced libido
- plateaued metabolic progress

Many of these clinical patterns correlate more closely with **insulin, cortisol, redox status, and vitamin C levels** than with sex hormone dosing.

Without addressing the ICV Axis, clinicians may mistakenly escalate estrogen, progesterone, or testosterone dosing when the root cause is metabolic-endocrine imbalance—not sex hormone deficiency.

5.5. Practical Integration: Updating BHRT to the ICV Model

Incorporating the ICV Axis into BHRT practice includes (Figure 1):

- **Adding insulin evaluation** (fasting, postprandial, HOMA-IR, insulin variability) before and during BHRT [152,153,191,192]
- **Assessing cortisol patterns**, including morning peak, diurnal slope, and stress load [193–195]
- **Evaluating vitamin C status**, oxidative stress markers, and inflammation [36,196]
- **Supporting adrenal and redox capacity** through vitamin C, sleep repair, stress reduction, and mitochondrial nutrition [15,17,135]
- **Titrating sex hormone doses** based on metabolic–endocrine balance rather than isolated hormone levels [183,197,198]
- **Considering metabolic flexibility** and the patient's insulin response to diet, fasting, exercise, and stress [199–201]

This integrated approach is more physiologic, more personalized, and more aligned with systems biology.

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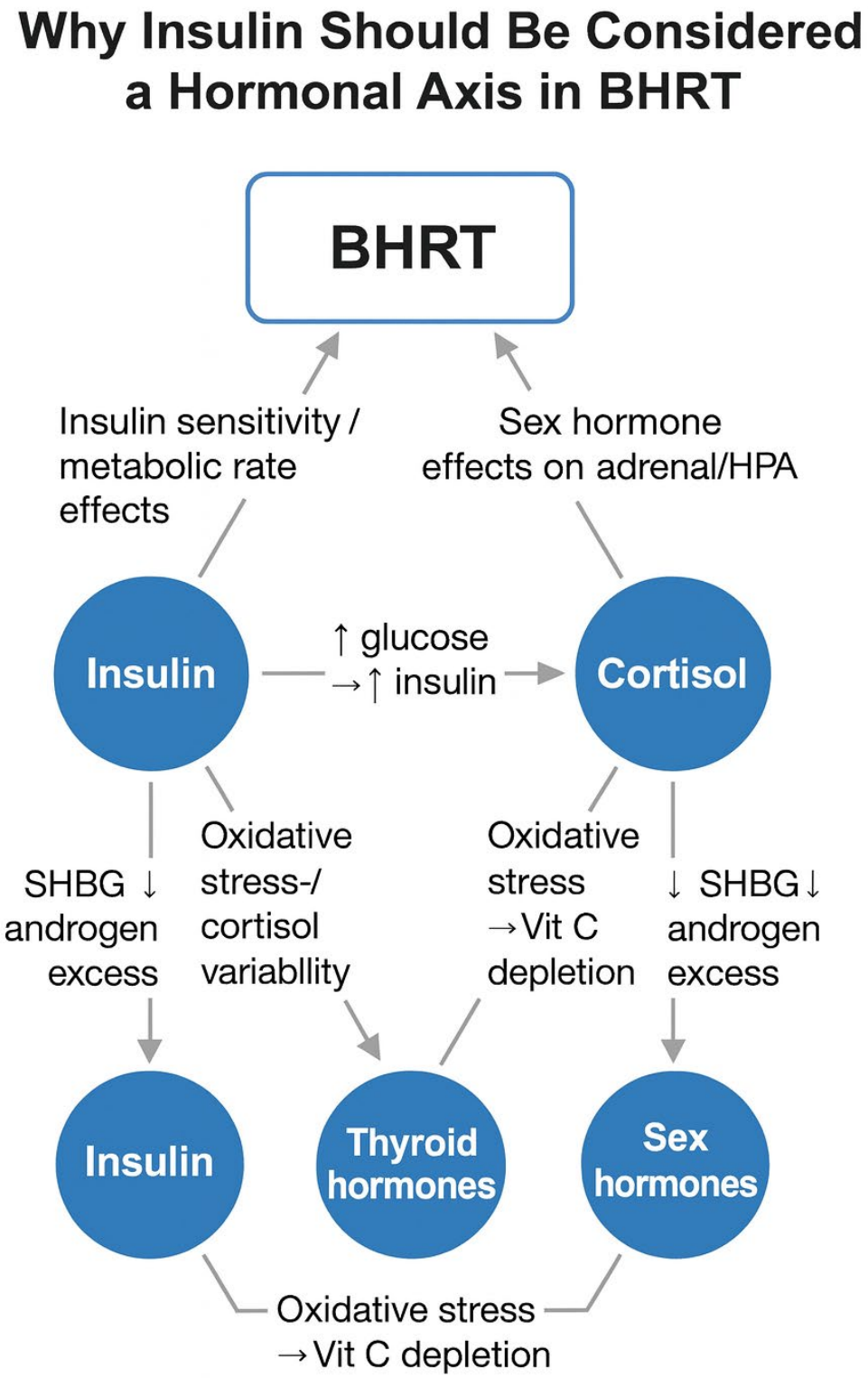

Figure 1. The ICV Axis as a regulatory hub in BHRT.

Legend:

- **Blue circles** = key hormonal/metabolic nodes
- **Blue rounded rectangle** = BHRT regulatory inputs
- **Gray arrows** = primary directional influences

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• **Dashed arrows** (if present) = feedback effects

• **Labels** = dominant mechanistic pathways (e.g., ↑ glucose → ↑ insulin; oxidative stress → vitamin C depletion; SHBG ↓ → androgen excess).

The ICV Axis (insulin–cortisol–vitamin C) interacts directly with thyroid and sex hormone physiology, influencing SHBG, androgen balance, adrenal load, oxidative stress, thyroid conversion, and metabolic rate. These relationships help explain variable or unstable BHRT outcomes when insulin and cortisol dynamics or vitamin C status are not addressed.

5.6. Summary: Why This Is a Landmark Advancement in BHRT

Introducing insulin as a hormonal axis within BHRT—and connecting it mechanistically to cortisol and vitamin C—represents a **paradigm shift**. BHRT has long operated within a tripartite model (sex hormones, thyroid, adrenal), but the ICV Axis reveals an overlooked regulatory dimension essential for metabolic stability and hormone responsiveness.

This framework positions BHRT within a broader systems-medicine context and lays the groundwork for:

- more effective interventions
- fewer treatment failures
- better metabolic outcomes
- improved patient resilience
- a unified model connecting nutrition, hormones, stress physiology, and redox biology

The ICV Axis therefore provides a **novel, scientifically grounded, and clinically actionable expansion** to the existing BHRT paradigm.

6. Implications for Research and Clinical Practice

The proposed Insulin–Cortisol–Vitamin C (ICV) Axis expands existing models of metabolic regulation by integrating endocrine physiology, redox biology, and micronutrient status into a unified framework. While traditional approaches to insulin resistance and metabolic syndrome emphasize carbohydrate reduction, pharmacologic therapies, or isolated hormonal modulation, the ICV model underscores the importance of **systems-level interactions** often overlooked in clinical practice.

6.1. Implications for Endocrinology and BHRT Practice

Current BHRT paradigms focus primarily on sex hormones (estradiol, progesterone, testosterone), thyroid hormones, and occasionally DHEA. Insulin is rarely conceptualized as a hormone requiring balanced homeostasis within the same framework, despite its broad downstream effects on SHBG, free hormone fractions, adipokines, and metabolic signaling. Incorporating insulin dynamics and micronutrient status—particularly vitamin C sufficiency—may improve BHRT outcomes, reduce dose variability, and help explain clinical scenarios where hormone replacement appears biochemically adequate but symptomatically insufficient.

6.2. Implications for Metabolic and Nutritional Medicine

The ICV Axis suggests that insulin resistance cannot be fully corrected by diet alone. Individuals adhering to low-carbohydrate or ketogenic interventions may exhibit persistent dysglycemia due to unaddressed oxidative stress, chronic cortisol elevation, micronutrient depletion, or endothelial dysfunction. Integrating vitamin C assessment and adrenal–stress evaluation may help identify resistant phenotypes and guide more comprehensive treatment strategies.

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6.3. Implications for Cardiometabolic and Chronic Disease Care

Because insulin resistance, oxidative stress, and cortisol dysregulation contribute to cardiovascular disease, NAFLD, and accelerated biological aging, the ICV Axis may provide a framework for identifying individuals at high risk even when traditional parameters appear normal. Addressing vitamin C insufficiency and cortisol disruption may improve metabolic flexibility, endothelial function, and mitochondrial resilience across diverse patient populations.

6.4. Implications for Lifestyle, Stress, and Circadian Medicine

The ICV model reinforces the need for stress-modulating interventions—sleep optimization, circadian alignment, physical activity, and psychosocial resilience—alongside nutritional support. This broader approach aligns with real-world clinical experience that metabolic therapies often fail when chronic stress or micronutrient depletion remains untreated.

6.5. A New Conceptual Lens for Integrative Orthomolecular Medicine (IOM)

The ICV Axis is consistent with IOM principles emphasizing biochemical individuality, redox balance, mitochondrial function, and structural nutrient sufficiency. By framing insulin dysregulation within a broader network of micronutrients and hormonal physiology, the ICV model provides a conceptual bridge between orthomolecular medicine, metabolic therapy, and modern endocrinology.

7. Conclusions

Insulin homeostasis is traditionally viewed as a function of dietary carbohydrate load, adiposity, and lifestyle behavior. However, substantial evidence indicates that insulin dynamics are deeply intertwined with cortisol physiology, oxidative stress, mitochondrial function, endothelial nitric oxide signaling, and micronutrient availability—particularly vitamin C.

This narrative review synthesizes these domains and proposes the **Insulin–Cortisol–Vitamin C (ICV) Axis**, a novel conceptual framework that unifies metabolic, endocrine, and redox physiology. The model suggests that disturbances in any component of the axis may propagate through the system, contributing to insulin resistance, metabolic syndrome, BHRT instability, dysglycemia, and impaired responses to lifestyle or pharmacologic interventions.

Although the ICV Axis remains a theoretical construct, it is grounded in established endocrine physiology, vitamin C biochemistry, oxidative stress research, and clinical observations in metabolic and chronic disease practice. Future mechanistic studies, interventional trials, and clinical evaluations are needed to validate the ICV model, assess its predictive utility, and explore therapeutic strategies targeting this triad.

The ICV Axis represents a **paradigm shift** in the understanding and treatment of insulin resistance and related chronic diseases—expanding the scope of metabolic and hormonal medicine to include redox biology and micronutrient sufficiency as central determinants of metabolic health.

Additional detail establishing the important impact of this ICV model is available [148].

Declarations

Author Contributions:

- *Conceptualization:* T.E.L., R.H., R.Z.C.
- *Writing – original draft:* R.Z.C.
- *Writing – review & editing:* All authors
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The authors declare no conflicts of interest.

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