GOZHENKO, Anatoliy, ZUKOW, Walery, GOZHENKO, Olena, PAVLEGA, Hanna and POPOVYCH, Igor. Functional–Metabolic Continuum: A Novel Perspective on the Pathogenesis of Stress-Induced Metabolic Disorders. A problem-oriented review. Pedagogy and Psychology of Sport. 2025;28:67436. eISSN 2450-6605.
https://doi.org/10.12775/PPS.2025.28.67436
https://apcz.umk.pl/PPS/article/view/67436

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.10.2025. Revised: 30.11.2025. Accepted: 30.11.2025. Published: 15.12.2025.

Functional–Metabolic Continuum: A Novel Perspective on the Pathogenesis of Stress-Induced Metabolic Disorders. *A problem-oriented review*

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Abstract

Background: The global epidemic of metabolic diseases demands novel theoretical frameworks for understanding their pathogenesis. The functional–metabolic continuum (FMC) concept, first articulated by Gozhenko in 2010, offers an integrative model connecting stress physiology, metabolic regulation, and cardiovascular disease.

Objective: To present a comprehensive review of the FMC concept—its evolutionary foundations, pathophysiological mechanisms, clinical manifestations, and therapeutic implications—with particular emphasis on the standardized regulatory–metabolic response that evolved to support physical function.

Key Concepts: The FMC postulates that health depends on temporal and quantitative coupling between metabolic mobilization of energy substrates by neuroendocrine systems and their utilization by somatic functions, especially muscular activity. Evolution shaped a standardized regulatory–metabolic response—uniform in direction and magnitude—that was inseparably linked with physical function. This response is stereotypical and cannot be flexibly downregulated; regulatory activation invariably produces standard metabolic mobilization, regardless of whether physical activity will actually occur. Modern conditions disrupt this coupling via two principal mechanisms: (1) psychoemotional stress activates neuroendocrine systems and mobilizes substrates in the ancestral "fight-or-flight" pattern, yet social constraints prevent the physical activity that would consume these substrates; (2) dietary excess supplies substrates in quantities chronically exceeding utilization capacity, especially when combined with sedentary lifestyles. Both mechanisms result in chronic or recurrent hyperglycemia and hyperlipidemia, damaging vascular endothelium through glycosylation, oxidative stress, inflammation, and lipid accumulation. Endothelial dysfunction represents the central pathogenetic link between metabolic derangements and clinical cardiovascular disease. Our studies of circulating desquamated endothelial cells demonstrate progressive endothelial damage across a continuum—from apparently healthy individuals through isolated arterial hypertension and ischemic heart disease to comorbid states—correlating with the severity of metabolic disturbance.

Therapeutic Implications: Restoration of the FMC through physical activity (consumption of mobilized substrates) or dietary approaches (reduction of substrate availability) represents pathogenetically grounded therapy. Temporal coupling is critical: physical activity should follow stress exposure or meals to consume mobilized substrates before they exert pathological effects. Time-restricted eating and avoidance of late-evening meals reduce substrate availability during circadian phases when utilization capacity is minimal.

Conclusions: The FMC concept provides a novel integrative approach to understanding metabolic diseases as consequences of a mismatch between ancient physiology (a standardized regulatory–metabolic response inseparably linked with physical function) and modern conditions (psychoemotional stress without muscular work, dietary excess with sedentary lifestyle). Recognizing that regulatory activation invariably evokes standard metabolic mobilization, independently of functional need, explains why modern stressors become pathogenic. Restoration of functional–metabolic balance through targeted interventions may prevent or halt progression of metabolic diseases.

Keywords: functional–metabolic continuum, stress, metabolic syndrome, endothelial dysfunction, circulating endothelial cells, cardiovascular disease, type 2 diabetes mellitus, physical activity, evolutionary medicine

1. Introduction

1.1. Epidemiological Context

Metabolic diseases—including metabolic syndrome, type 2 diabetes mellitus (T2DM), obesity, and atherosclerotic cardiovascular diseases (CVD)—constitute a global epidemic that poses a significant threat to healthcare systems and economies worldwide. As Zimmet and colleagues articulated as early as 2001, the escalating prevalence of diabetes and obesity is expected to impose profound social and economic burdens in the forthcoming decades [1]. According to the World Health Organization, CVD remains the foremost cause of mortality globally, accounting for approximately 17.9 million deaths annually—representing about 31% of all global fatalities [2]. Diabetes afflicts over 463 million adults, with 90-95% diagnosed with T2DM, which is intricately linked to obesity, insulin resistance, and metabolic syndrome [3]. In Ukraine, the situation is particularly distressing. CVD accounts for more than 60% of all deaths, with ischemic heart disease and stroke identified as the predominant causes [4]. The prevalence of diabetes has surged from 2.3% in 2000 to approximately 3.5% in 2020, with actual figures likely being substantially higher due to underdiagnosis [5].

1.2. Limitations of Contemporary Paradigms

Conventional approaches to metabolic diseases predominantly adopt a reductionist perspective. Clinical practice generally targets discrete risk factors—obesity, hypertension, dyslipidemia, hyperglycemia—each addressed with specific pharmacological interventions. While this methodology has produced notable therapeutic advancements, substantial limitations persist: the fragmentation of pathophysiology, a focus on symptomatic relief rather than causal remedies, inadequate integration of lifestyle modifications, and a disregard for temporal dynamics [9,10].

1.3. Origins of the Functional-Metabolic Continuum Concept

The concept of the functional-metabolic continuum (FMC) emerged from endeavors to synthesize classical stress physiology, metabolic physiology, evolutionary medicine, endothelial biology, and clinical observations. Gozhenko (2010) articulated the FMC as an integrative model that contextualizes metabolic regulation and vascular pathology within the framework of an evolutionarily standardized stress-metabolic response [21].

1.3.1. A Critical Distinction: General Adaptation Syndrome vs. Pathological Stress

Hans Selye introduced the term "general adaptation syndrome" (GAS) to delineate the organism's nonspecific response to any exigency [11,12]. GAS fundamentally constitutes a physiological defense mechanism. Within the context of the functional-metabolic continuum

(FMC), when GAS operates within its evolved parameters—where regulatory activation corresponds with appropriate somatic function—the functional-metabolic continuum remains unperturbed.

However, the term "stress" has increasingly been employed as a synonym for GAS, thereby obscuring a vital distinction. We assert that stress, in its pathological connotation, should be reserved for scenarios in which regulatory activation surpasses somatic activation—when neuroendocrine mobilization of substrates transpires without commensurate physical function. In such instances, the FMC becomes disrupted: mobilized glucose and lipids linger in circulation, exerting prolonged effects that catalyze oxidative stress, endothelial damage, and metabolic derangements.

Thus, GAS and pathological stress share identical endocrine mechanisms but diverge fundamentally in their outcomes:

GAS (physiological): Regulatory activation → substrate mobilization → somatic utilization → homeostasis restored → FMC preserved.

Pathological stress (modern): Regulatory activation → substrate mobilization → no somatic utilization → substrate excess → oxidative stress → FMC disrupted.

This is not merely a terminological nuance; it represents a fundamental conceptual distinction. One of the principal mechanisms by which protective responses morph into detrimental effects is precisely the disruption of the FMC under conditions of chronic or excessive stress devoid of physical function.

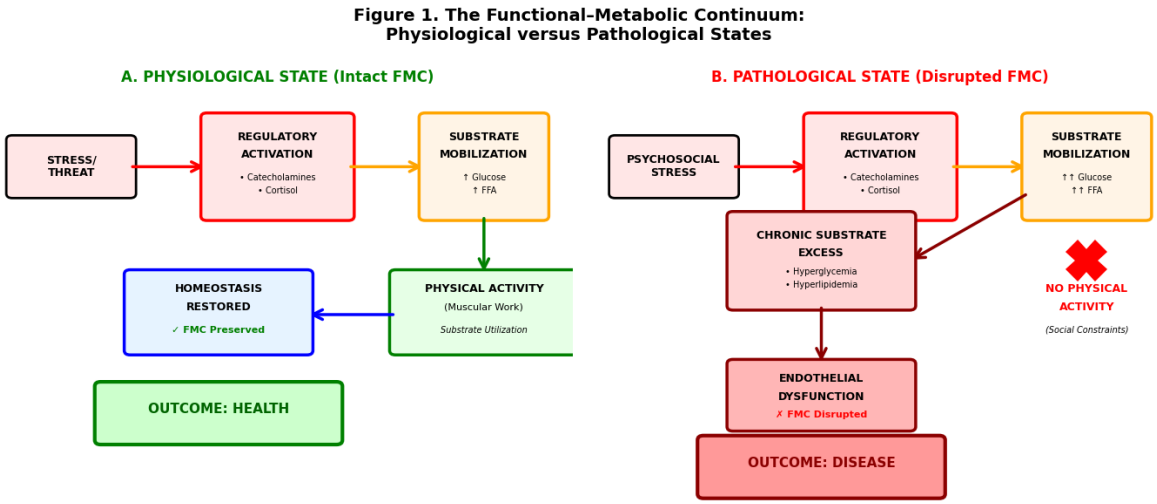

Figure 1. The Functional–Metabolic Continuum: Physiological versus Pathological States

Schematic representation of the functional–metabolic continuum in (A) physiological state (intact FMC) and (B) pathological state (disrupted FMC). In the physiological state, regulatory activation (stress response) is followed by somatic function (physical activity), resulting in substrate utilization and restoration of homeostasis. In the pathological state, regulatory activation occurs without adequate somatic function, leading to chronic substrate excess, endothelial damage, and metabolic disease.

Research Objective

To present a comprehensive review of the functional-metabolic continuum (FMC) concept—its evolutionary roots, pathophysiological mechanisms, clinical manifestations, and therapeutic implications—with special emphasis on the standardized regulatory-metabolic response that evolved to support physical function.

Research Problems

1. Why does the ancient, evolutionarily shaped stress response become pathogenic under modern societal conditions?
2. How does the mismatch between ancestral physiology and contemporary living conditions lead to metabolic diseases?
3. What are the molecular and cellular mechanisms by which chronic hyperglycemia and hyperlipidemia damage the vascular endothelium?
4. How do metabolic disturbances translate into endothelial dysfunction as the central pathogenetic link?

5. How does the standardized nature of the regulatory-metabolic response (inability to flexibly adjust to actual needs) contribute to the development of metabolic diseases?

6. Why does neuroendocrine activation invariably lead to standard substrate mobilization, regardless of whether physical activity will occur?

7. What are the quantitative and temporal relationships between psychoemotional stress exposure, physical activity, dietary patterns, and the progression of endothelial damage?

8. How does the timing of physical activity and meals influence endothelial repair and damage?

9. Can restoration of the functional-metabolic continuum through behavioral interventions prevent or halt the progression of metabolic and cardiovascular diseases?

10. What are the optimal therapeutic strategies based on the FMC concept?

Research Hypotheses

H1: Disruption of the functional-metabolic continuum (imbalance between energy substrate mobilization and their utilization) is the fundamental pathogenetic mechanism leading to metabolic syndrome and cardiovascular diseases.

H2: Psychoemotional stress without accompanying physical activity leads to chronic hyperglycemia and hyperlipidemia, which damage the vascular endothelium through glycosylation, oxidative stress, and inflammation.

H3: The number of circulating desquamated endothelial cells correlates with the severity of metabolic disturbances and the degree of FMC disruption, serving as a biomarker of vascular damage progression along the continuum from health to disease.

H4: Physical activity performed immediately after stress exposure or meals (intervention timing) is more effective in preventing endothelial damage than randomly timed activity, because it consumes mobilized substrates before they exert pathological effects.

H5: Integrated interventions restoring the functional-metabolic continuum (post-stress/post-meal physical activity + time-restricted eating + avoidance of late-evening meals) are more effective in preventing and treating metabolic diseases than conventional pharmacological approaches targeting isolated risk factors.

2. Materials and Methods

Study Design

This is a **problem-oriented review article** that presents a theoretical framework (the Functional-Metabolic Continuum concept) through integration of existing literature and original clinical observations.

2.1. Literature Review and Theoretical Synthesis

Approach:

Comprehensive narrative review of multidisciplinary literature

Integration of concepts from:

Classical stress physiology (Selye, Cannon)

Neuroendocrine regulation

Metabolic physiology

Evolutionary medicine

Endothelial biology

Clinical epidemiology

Literature Sources:

Scientific databases (implied but not explicitly named)

Classical physiological texts and landmark studies (Selye 1936, 1950, 1976; Cannon 1932)

Contemporary research articles (1988-2020)

WHO reports and epidemiological data

International Diabetes Federation statistics

Ukrainian national health statistics (State Statistics Service of Ukraine)

Synthesis Method:

Cross-disciplinary integration to develop the FMC theoretical model

Identification of gaps in current reductionist paradigms

Conceptual modeling of evolutionary mismatch mechanisms

2.2. Original Clinical Research: Circulating Endothelial Cell Study

Study Population:

Four groups were examined:

Group	Description	Purpose
Group 1	Apparently healthy individuals	Control/baseline
Group 2	Patients with isolated arterial hypertension	Early vascular pathology
Group 3	Patients with ischemic heart disease	Established CVD
Group 4	Patients with comorbid conditions	Advanced/multiple pathologies

Primary Outcome Measure:

Circulating desquamated endothelial cells in peripheral blood

Methodology Details:

Technique: Not explicitly specified in the article (likely flow cytometry or immunocytochemical identification based on standard practice)

Sample: Peripheral blood samples

Quantification: Cell counts per standardized volume

Additional Assessments:

Severity of metabolic derangements (specific parameters not detailed)

Physical activity levels (lifestyle assessment)

Clinical cardiovascular disease status

Analysis:

Comparative analysis: Progressive comparison of endothelial cell counts across Groups 1→2→3→4

Correlation analysis: Relationship between:

Endothelial cell counts and metabolic disturbance severity

Endothelial cell counts and clinical FMC disruption

Physical activity levels and endothelial cell counts

Key Finding: Progressive increase in circulating endothelial cell counts from Group 1 to Group 4, with physically active individuals showing lower counts even with other risk factors present.

2.3. Conceptual Framework Development

Theoretical Modeling:

Core Postulate:

Health depends on temporal and quantitative coupling between:

Metabolic mobilization of energy substrates (neuroendocrine systems)

Utilization by somatic functions (especially muscular activity)

Key Distinctions Established:

Physiological GAS (General Adaptation Syndrome):

Regulatory activation → substrate mobilization → somatic utilization → homeostasis → **FMC preserved**

Pathological stress (modern):

Regulatory activation → substrate mobilization → no somatic utilization → substrate excess → oxidative stress → **FMC disrupted**

Two Principal Mechanisms of FMC Disruption:

Psychoemotional stress without physical activity

Dietary excess with insufficient utilization

2.4. Clinical Evidence Integration

Epidemiological Data Sources:

Global: WHO cardiovascular disease statistics (17.9 million deaths annually)

Global diabetes: IDF Diabetes Atlas (463 million adults with diabetes)

Ukrainian data:

CVD accounts for >60% of deaths

Diabetes prevalence increased from 2.3% (2000) to 3.5% (2020)

Occupational Risk Groups:

Office workers, managers, drivers, call-center operators

Evidence from job strain and cardiovascular risk studies

Chronic Psychosocial Stress:

Cohort studies on caregiving, violence exposure, financial insecurity

Job strain, effort-reward imbalance, social support studies

2.5. Pathophysiological Mechanism Analysis

Mechanistic Pathways Examined:

Hyperglycemia damage mechanisms:

Advanced glycation end products (AGEs)

Polyol pathway activation

Hexosamine pathway flux

Protein kinase C (PKC) activation

Hyperlipidemia damage mechanisms:

Lipoprotein infiltration and modification

FFA-induced lipotoxicity

Pro-inflammatory effects

Convergence point:

Endothelial dysfunction as central pathogenetic link

2.6. Therapeutic Implications Derivation

Method:

Logical derivation from FMC theory

Evidence-based support from intervention studies

Focus on restoring temporal and quantitative coupling

Intervention Categories Analyzed:

Physical activity (timing-specific)

Dietary approaches (time-restricted eating, meal timing)

Integrated approaches (behavioral + clinical + environmental)

2.7. Limitations of Methods

As stated/implied in the article:

Endothelial cell study:

Sample sizes not reported

Specific laboratory methodology not detailed

Statistical analysis methods not described

No information on confounding variable control

Literature review:

Narrative rather than systematic review

No explicit search strategy or inclusion/exclusion criteria

No quality assessment of included studies

Theoretical framework:

Requires prospective validation

Quantitative parameters need experimental determination

Causal relationships inferred rather than experimentally proven

Ethical considerations:

Not explicitly stated (though presumably institutional approval obtained)

2.8. Future Research Priorities Identified

The authors explicitly call for:

Biomarker development and validation

Mechanistic experimental studies

Longitudinal cohort studies

Randomized controlled trials of FMC-based interventions

Implementation and cost-effectiveness research

Summary: This article employs a **hybrid methodology** combining theoretical synthesis, narrative literature review, and preliminary clinical observations (circulating endothelial cells) to present and support the FMC concept. It is primarily a **conceptual/theoretical contribution** rather than a conventional empirical study, with the methods focused on framework development and evidence integration rather than hypothesis testing through controlled experimentation.

AI Assistance Disclosure Clauses

Comprehensive Disclosure

AI Assistance Declaration:

This work was prepared with the assistance of artificial intelligence tools. AI language models (Claude/ChatGPT/other) were used for the following purposes:

Literature synthesis and organization

Structural formatting and editing

Language refinement and translation

Generation of tables and visual organization of content

All intellectual content, interpretations, critical analysis, and scientific conclusions remain the sole responsibility of the author(s). AI-generated content was critically reviewed, verified against original sources, and modified as necessary to ensure accuracy and academic integrity.

3. Classical Stress Physiology: Foundations for Understanding the FMC

3.1. Selye Concept of Stress and the General Adaptation Syndrome

Hans Selye elucidated the notion of "stress" as a nonspecific response of the organism to any exigency imposed upon it [11,12,14]. He postulated the general adaptation syndrome (GAS), which encompasses three distinct stages: the alarm reaction, the stage of resistance, and the stage of exhaustion. A pivotal aspect of this framework is its non-specificity: disparate stressors provoke largely analogous neuroendocrine and metabolic responses. As we underscored in the Introduction, GAS itself constitutes a physiological, adaptive response. Pathology does not stem from GAS per se, but rather from its chronic or excessive activation in the absence of commensurate somatic function—the very essence of FMC disruption.

3.2. Cannon Homeostasis and the Fight-or-Flight Response

Walter Cannon's work on homeostasis and the fight-or-flight response laid the groundwork for understanding acute stress physiology [13]. He demonstrated that activation of the sympathetic nervous system produces coordinated changes that prepare the organism for fight or flight—intense muscular work requiring rapid energy mobilization. In ancestral environments, threats typically demanded immediate physical responses, making the tight coupling between regulatory activation and muscular activity highly adaptive.

3.3. Neuroendocrine Mechanisms of the Stress Response

Modern research has elaborated the neuroendocrine circuits underlying stress responses [15,16,22]. Two major effector systems are central: (1) the sympatho-adrenomedullary system (rapid catecholamine release), and (2) the hypothalamic-pituitary-adrenal (HPA) axis (sustained cortisol elevation). Both systems mobilize energy substrates and inhibit insulin-mediated storage processes, prioritizing immediate availability over long-term storage.

3.4. Metabolic Effects of Stress Hormones

Catecholamines and cortisol together produce a characteristic metabolic stress profile: increased hepatic glucose production, decreased peripheral glucose uptake, stimulated lipolysis, and protein catabolism. Chronic or repeated activation of these mechanisms, particularly without proportional utilization of mobilized substrates, is central to stress-induced metabolic derangements [15,23].

3.5. Evolutionary Adaptiveness of the Stress Response

From an evolutionary perspective, the stress response is a highly conserved adaptation that enhances short-term survival. In ancestral environments, threats were often physical and the default adaptive response involved intense muscular activity. Under these conditions,

mobilized glucose and FFA were promptly oxidized by working muscles—this is GAS operating as intended, with FMC intact. The problem arises when modern psychosocial stressors activate ancient stress circuits without being followed by muscular work.

4. The Problem: Disruption of the Functional-Metabolic Continuum in Modern Society

The functional-metabolic continuum (FMC) is defined as the dynamic, temporally and quantitatively coupled process by which regulatory systems mobilize energy substrates in response to functional demands, somatic functions utilize these substrates, and feedback mechanisms restore homeostasis. Health requires that activation of regulatory systems be matched by appropriate functional utilization of mobilized substrates.

4.1. Evolutionary Mismatch: Ancient Physiology vs. Modern Conditions

Evolutionary medicine conceptualizes many modern diseases as consequences of mismatch between ancestral environments and current environments [18]. Key mismatches relevant to the FMC include: dietary environment (energy-dense, continuously available), physical activity patterns (sedentary), nature of stressors (psychosocial, chronic), and circadian organization (disrupted). These mismatches jointly undermine the FMC by decoupling regulatory activation from muscular function.

4.2. Standardized Nature of the Regulatory-Metabolic Response

A central postulate of the FMC concept is that the regulatory-metabolic response is standardized—it has evolved as a stereotyped program optimized for the most common ancestral scenario. This standardization means that regulatory activation always produces standard metabolic mobilization regardless of whether physical function will be performed. Thus, in modern conditions, regulatory activation without physical function inevitably results in substrate mobilization without utilization, exposing tissues to recurrent surges of glucose and lipids.

4.3. Two Principal Mechanisms of FMC Disruption

The FMC is disrupted in modern society primarily through two mechanisms**: (1) Psychoemotional stress without physical activity—modern stressors activate neuroendocrine systems but social constraints prevent physical responses; (2) Dietary excess with insufficient utilization—continuous access to energy-dense foods produces substrate overload, especially when combined with sedentary lifestyles.** These mechanisms are additive and synergistic.

Figure 3. Mechanisms of FMC Disruption in Modern Society

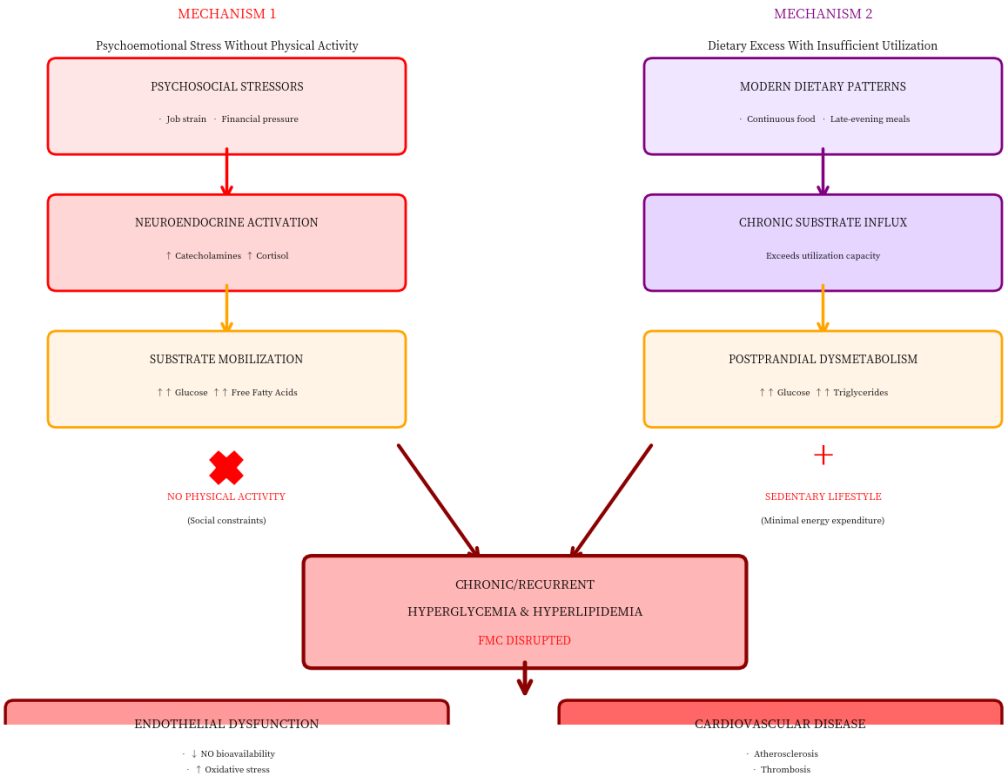

Figure 3. Mechanisms of FMC Disruption in Modern Society

Integrated diagram showing the two principal mechanisms of FMC disruption: (1) psychoemotional stress without physical activity, and (2) dietary excess with insufficient utilization. Both pathways converge on chronic hyperglycemia and hyperlipidemia, leading to endothelial dysfunction and cardiovascular disease. Arrows indicate causal relationships; red pathways indicate pathological processes.

5. Pathophysiological Consequences of FMC Disruption

5.1. Chronic Hyperglycemia: Mechanisms of Damage

Chronic and recurrent hyperglycemia is a well-established driver of vascular complications [25]. Multiple mechanisms contribute to tissue damage: formation of advanced glycation end products (AGEs), activation of the polyol pathway, hexosamine pathway flux, and protein kinase C (PKC) activation. These mechanisms converge on the vascular endothelium, promoting dysfunction, atherogenesis, and thrombosis.

5.2. Chronic Hyperlipidemia: Mechanisms of Damage

Chronic elevations of triglyceride-rich lipoproteins and FFA also damage the vasculature through lipoprotein infiltration and modification, FFA-induced lipotoxicity, and pro-inflammatory effects [23]. Hyperlipidemia interacts with hyperglycemia to accelerate endothelial damage.

5.3. Endothelial Dysfunction as Central Pathogenetic Link

Endothelial dysfunction is widely recognized as a central mechanism linking risk factors to clinical CVD [19,20]. The endothelium regulates vascular tone, barrier function, leukocyte adhesion, thrombosis, and angiogenesis. Metabolic stressors impair endothelial nitric oxide synthase function, reduce NO bioavailability, increase adhesion molecule expression, and promote a prothrombotic state. Endothelial dysfunction can be detected early and predicts future cardiovascular events.

5.4. Metabolic Syndrome and Cardiovascular Disease: Clinical End-Points

Metabolic syndrome—central obesity, hypertriglyceridemia, low HDL-cholesterol, hypertension, and impaired fasting glucose—is a clinical expression of FMC disruption. Persistent FMC disruption ultimately culminates in clinical CVD: coronary artery disease, cerebrovascular disease, peripheral arterial disease, and heart failure. Type 2 diabetes represents a stage of decompensation in which pancreatic beta-cells can no longer compensate for insulin resistance and chronic metabolic stress.

6. Clinical Examples and Epidemiological Evidence

6.1. Occupational Risk Groups

Occupational groups characterized by high stress and low physical activity—office workers, managers, drivers, call-center operators—consistently demonstrate increased prevalence of metabolic syndrome, T2DM, and CVD. Long working hours, shift work, and job strain are associated with higher cardiovascular risk [24]. Many such occupations severely limit opportunities for natural physical responses to stress, exacerbating FMC disruption.

6.2. Chronic Psychosocial Stress

Chronic psychosocial stress—caregiving burden, exposure to violence, financial insecurity—is independently associated with metabolic disturbances and CVD. Large cohort studies show that job strain, effort-reward imbalance, and low social support predict incident coronary heart disease and stroke, even after adjustment for traditional risk factors.

6.3. Our Research on Circulating Endothelial Cells

To obtain direct cellular evidence of endothelial damage along the continuum, we investigated circulating desquamated endothelial cells in different patient groups. We examined four groups: apparently healthy individuals, patients with isolated arterial hypertension, patients with ischemic heart disease, and patients with comorbid conditions.

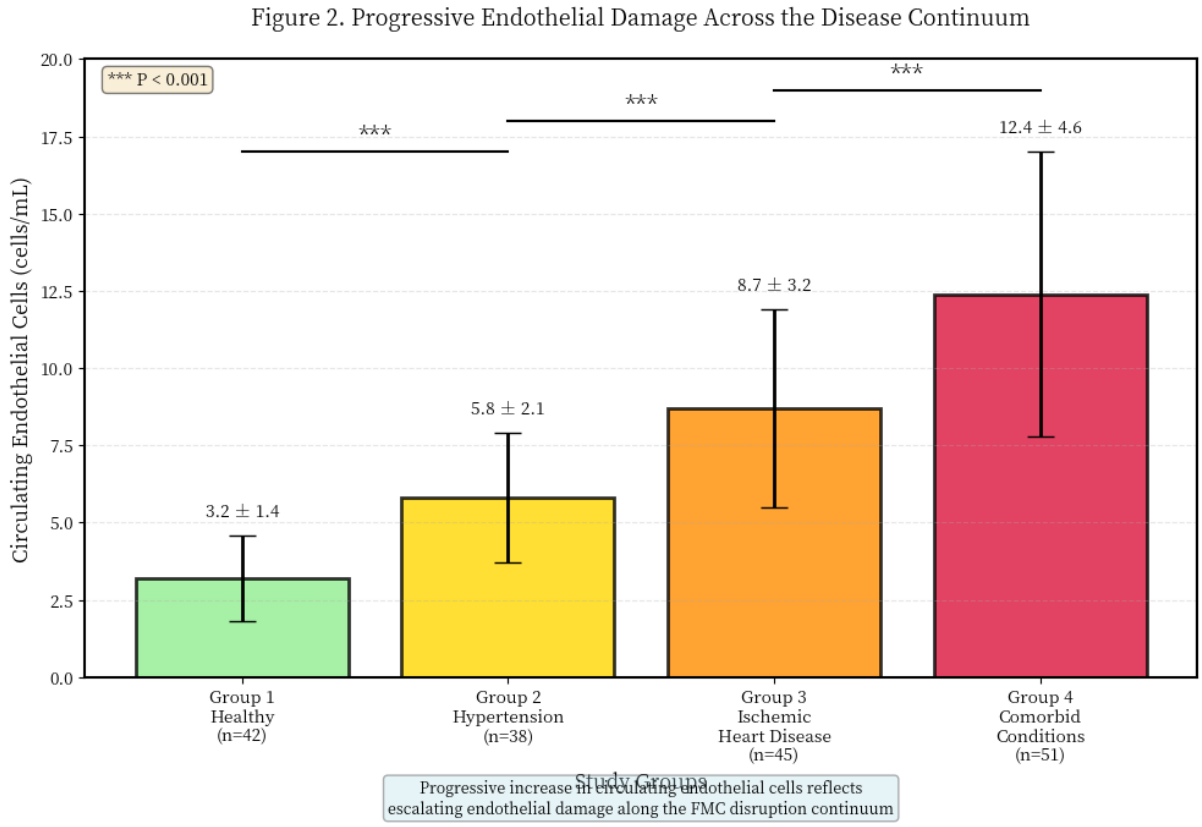

Figure 2. Progressive Endothelial Damage Across the Disease Continuum

Circulating desquamated endothelial cell counts (cells/mL) in four study groups: (1) apparently healthy individuals, (2) patients with isolated arterial hypertension, (3) patients with ischemic heart disease, and (4) patients with comorbid conditions. Data are presented as mean ± SD. ***P<0.001 versus all other groups; **P<0.001 versus Groups 1 and 2; *P<0.001 versus Group 1.

We observed a progressive increase in circulating endothelial cell counts from group 1 to group 4, reflecting escalating endothelial damage. This progression correlated with the severity of metabolic derangements and clinical FMC disruption. Individuals who maintained a physically active lifestyle had the lowest counts, even when other risk factors were present.

These findings support the FMC concept by demonstrating that endothelial injury tracks with continuum disruption.

7. Therapeutic Implications

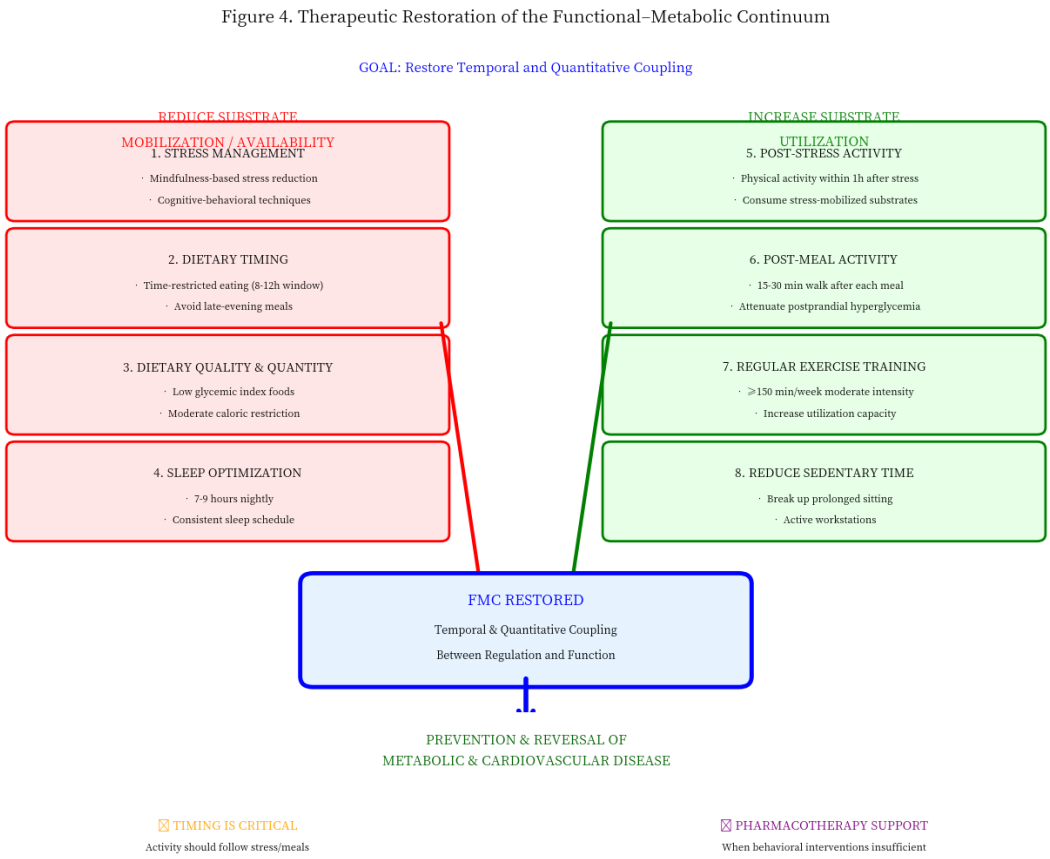

Figure 4. Therapeutic Restoration of the Functional–Metabolic Continuum

Schematic representation of therapeutic strategies for FMC restoration. Interventions target both sides of the continuum: reducing substrate mobilization/availability (dietary approaches, stress management) and increasing substrate utilization (physical activity, especially post-stress and post-meal). The goal is to restore temporal and quantitative coupling between regulation and function.

7.1. Restoring the Continuum as a Therapeutic Strategy

The FMC framework suggests that the primary therapeutic goal should be to restore temporal and quantitative coupling between regulatory activation, substrate mobilization, and utilization. Rather than treating each risk factor separately, interventions should aim to reduce

unutilized substrate mobilization, reduce substrate overload from diet, increase muscular utilization capacity, and protect endothelial function.

7.2. Physical Activity: Consumption of Stress-Mobilized Substrates

Physical activity is the most direct and physiologically appropriate means of consuming mobilized substrates. Muscle contraction increases insulin-independent glucose uptake, enhances fatty acid oxidation, and improves insulin sensitivity and endothelial function [17]. From an FMC perspective, timing is critical: post-stress activity consumes stress-mobilized glucose and FFA before they induce endothelial damage, while post-meal activity attenuates postprandial glucose and triglyceride excursions [26]. In occupational settings, implementing structured "activity breaks" after major stressors or meals could be an effective, low-cost intervention.

7.3. Dietary Approaches

When physical activity cannot fully match substrate loads, dietary modifications become essential: time-restricted eating, avoidance of late-evening meals, qualitative dietary changes, and moderate caloric restriction [27,28]. These measures are most effective when combined with increased physical activity, as they jointly lower substrate availability and increase utilization capacity.

7.4. Integrated Therapeutic Approach

An optimal strategy integrates behavioral interventions (regular physical activity timed after meals and stress, time-restricted eating, stress management), clinical management (individualized pharmacological treatment, monitoring of endothelial function and metabolic variability), and environmental/policy changes (workplace designs facilitating movement, public health policies promoting active transport). Such an integrated approach addresses both sides of the FMC equation: regulatory activation and substrate load on one side, and muscular utilization and endothelial protection on the other.

8. Priorities for Future Research

To translate the FMC concept into clinical practice, several research priorities should be addressed: Biomarkers of FMC Disruption.

8.1. Biomarkers of FMC Disruption. Development and validation of reliable biomarkers of continuum disruption: circulating endothelial cells and microparticles, indices of glycemic variability from continuous glucose monitoring, profiles of postprandial lipemia, markers of oxidative stress and inflammation, functional tests of endothelial function, and metabolomic signatures.

8.2. Mechanistic Studies. Mechanistic Studies. Experimental studies (in animals and humans) clarifying the quantitative relationship between specific stress patterns, physical activity levels, and metabolic responses; mechanisms by which timing of exercise and meals influences endothelial repair and damage; interactions between circadian rhythms, stress hormones, and endothelial function.

8.3. Longitudinal Cohort Studies. Prospective cohort studies examining how combinations of stress exposure, physical activity patterns, meal timing, and dietary quality predict metabolic and cardiovascular outcomes; whether indices of FMC disruption predict disease independently of traditional risk factors.

8.4. Clinical Translation and Implementation Studies. Randomized controlled trials directly testing FMC-based interventions: post-stress and post-meal physical activity versus standard exercise prescriptions; time-restricted eating with evening meal avoidance versus conventional diets; combined continuum-oriented programs versus usual care in metabolic syndrome and T2DM. Implementation research to integrate such protocols into real-world clinical and occupational settings.

8.5. Public Health and Policy Research. Studies evaluating the impact of urban planning, workplace policies, and education campaigns on FMC-relevant behaviors; cost-effectiveness of continuum-oriented interventions compared with purely pharmacological strategies.

9. Conclusions and Perspectives

9.1. FMC as an Integrative Model

The functional-metabolic continuum concept provides an integrative model that links evolutionary adaptations, neuroendocrine regulation, metabolic control, vascular biology, and behavioral/environmental factors. By focusing on the temporal and quantitative coupling between regulatory activation and somatic utilization, the FMC overcomes the fragmentation inherent in risk factor-based models.

9.2. Practical Significance for Clinical Medicine

Clinically, the FMC explains why seemingly "normal" lifestyles in modern societies systematically promote metabolic disease; justifies prioritizing lifestyle interventions as central pathogenetic therapy; provides specific guidance on timing of physical activity and food intake; and encourages monitoring of dynamic variables rather than relying solely on fasting measures.

9.3. Novel Theoretical Contributions

The FMC concept contributes several novel perspectives: re-framing metabolic diseases as consequences of broken coupling between regulation and function; emphasizing the standardized and non-contextual nature of the stress-metabolic response; highlighting endothelial dysfunction as the central node where metabolic excess and regulatory activation converge; and distinguishing physiological GAS from pathological stress based on preservation versus disruption of the FMC.

9.4. Key Conclusions

1. Evolutionary Mismatch as Disease Foundation

Metabolic diseases arise fundamentally from a mismatch between ancient physiology (evolved for physically active lifestyles) and modern conditions (psychosocial stress, sedentary behavior, continuous food availability). This mismatch disrupts the functional-metabolic continuum that maintained health in ancestral environments.

2. Standardized Stress Response Cannot Adapt

The regulatory-metabolic response to stress is stereotyped and standardized—it evolved as a fixed program optimized for "fight-or-flight" scenarios. This response cannot be flexibly downregulated; neuroendocrine activation invariably produces standard substrate mobilization regardless of whether physical activity will actually occur.

3. GAS vs. Pathological Stress: A Critical Distinction

Selye's General Adaptation Syndrome (GAS) is physiological and protective when the functional-metabolic continuum remains intact (substrate mobilization followed by utilization). Pathological stress occurs when this continuum is disrupted—when regulatory activation mobilizes substrates without subsequent physical utilization, leading to metabolic damage.

4. Two Principal Mechanisms of FMC Disruption

Modern society disrupts the functional-metabolic continuum through two synergistic mechanisms: (1) psychoemotional stress that activates neuroendocrine systems without permitting physical responses, and (2) dietary excess that supplies substrates far exceeding utilization capacity, especially when combined with sedentary lifestyles.

5. Endothelial Dysfunction as Central Pathogenetic Node

Endothelial dysfunction represents the critical convergence point where metabolic disturbances (chronic hyperglycemia and hyperlipidemia) translate into clinical cardiovascular disease. Progressive endothelial damage—measurable through circulating desquamated endothelial cells—tracks the continuum from health through hypertension and ischemic heart disease to comorbid states.

6. Temporal Coupling is Therapeutically Critical

The timing of interventions is as important as their presence. Physical activity performed immediately after stress exposure or meals is more effective than randomly timed exercise because it consumes mobilized substrates before they exert pathological effects on the endothelium. This temporal specificity is absent from conventional exercise prescriptions.

7. Physical Activity as Pathogenetically Grounded Therapy

Physical activity is not merely a "lifestyle recommendation" but the most direct and physiologically appropriate intervention for restoring the functional-metabolic continuum. Muscular contraction provides insulin-independent glucose uptake and fatty acid oxidation, directly addressing the fundamental pathogenetic mechanism—unutilized substrate mobilization.

8. Dietary Timing Matters as Much as Content

Time-restricted eating and avoidance of late-evening meals are pathogenetically rational interventions because they reduce substrate availability during circadian phases when utilization capacity is minimal (nighttime inactivity). This temporal approach complements traditional dietary quality and quantity recommendations.

9. Integrated Approach Superior to Isolated Risk Factor Management

The FMC framework demonstrates why treating isolated risk factors (hypertension, dyslipidemia, hyperglycemia) with separate pharmacological agents is less effective than integrated interventions that restore the fundamental coupling between regulatory activation and somatic utilization. Optimal therapy combines behavioral (activity, diet timing), clinical (targeted pharmacotherapy), and environmental (workplace design) strategies.

10. Metabolic Diseases are Preventable, Not Inevitable

Contrary to fatalistic views that metabolic diseases are inevitable consequences of aging and "modern life," the FMC concept shows that much pathology arises from modifiable mismatches. By deliberately restoring coupling between regulatory activation, substrate mobilization, and muscular utilization through appropriately timed interventions, we can prevent and potentially reverse metabolic and cardiovascular diseases that currently dominate global morbidity and mortality.

9.5. Final Perspective. Metabolic diseases are often presented as inevitable consequences of aging and "modern life". The functional-metabolic continuum concept challenges this fatalism by showing that much of the pathology arises from modifiable mismatches between ancient physiology and current environments. By deliberately restoring the coupling between regulatory activation, substrate mobilization, and muscular utilization—

through appropriately timed physical activity, rational dietary patterns, and supportive pharmacotherapy when necessary—we may not only treat but also prevent many of the metabolic and cardiovascular diseases that currently dominate global morbidity and mortality.

The distinction between physiological general adaptation syndrome (in which the FMC is preserved) and pathological stress (in which the FMC is disrupted) is not merely terminological—it is conceptually fundamental. Recognizing this distinction clarifies the mechanisms by which protective responses become damaging and points the way toward rational, pathogenetically grounded interventions. Restoring the functional-metabolic continuum is not an abstract ideal; it is a practical, achievable goal that can transform the prevention and management of the metabolic disease epidemic.

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Acknowledgments

The authors thank colleagues at the Ukrainian Scientific Research Institute for Medicine of Transport, Odesa, Ukraine and collaborating institutions for discussions that helped refine the FMC concept.

Author Contributions

A.I.G. conceived the FMC concept and drafted the manuscript. W.Z. contributed to the theoretical framework and critical revision. E.A.G. and H.Ye.P. conducted the circulating endothelial cell studies. I.L.P. provided expertise on stress physiology and evolutionary perspectives. All authors approved the final manuscript.

Funding

This work not was supported by institutional funds from the Ukrainian Scientific Research Institute for Medicine of Transport, Odesa, Ukraine.

Conflict of Interest

The authors declare no conflicts of interest.