diabetology

MDPI

Review

Metabolic Rejuvenation in Type 2 Diabetes: A Network Biology Perspective on Functional Restoration and Disease Modification

Hiroshi Yamamoto [1,*], Yoshikazu Yonei [2] and Teruyoshi Tanaka [3,4]

[1] Department of Metabolic and Bariatric Surgery, JCHO Shiga Hospital, 1-24 Fujimi, Otsu 520-0846, Shiga, Japan
[2] Faculty of Life and Medical Sciences, Doshisha University, Kyotanabe 610-0394, Kyoto, Japan; yyonei@mail.doshisha.ac.jp
[3] Department of Fisheries, Faculty of Agriculture, Kindai University, 3327-204 Nakamachi, Nara 631-8505, Japan; t-tanaka@nara.kindai.ac.jp
[4] Agricultural Technology and Innovation Research Institute, Kindai University, 3327-204 Nakamachi, Nara 631-8505, Japan
* Correspondence: yhiroshi@belle.shiga-med.ac.jp; Tel.: +81-77-537-3101

Abstract

Type 2 diabetes (T2D) is increasingly recognized as a systemic network disorder in which impaired communication among endocrine, neural, immune, and microbial systems drives metabolic dysfunction and accelerates biological aging. Extending DeFronzo's "Ominous Octet," contemporary advances in immunometabolism, mitochondrial biology, circadian physiology, and incretin signaling demonstrate that metabolic homeostasis depends on the structural and functional integrity of dynamic inter-organ networks. Their progressive disruption contributes not only to classical insulin resistance and β-cell failure, but also to chronic low-grade inflammation (inflammaging), mitochondrial decay, autonomic dysregulation, and epigenetic age acceleration. Crucially, modern disease-modifying interventions—including multi-incretin receptor agonists, SGLT2 inhibitors, metabolic/bariatric surgery, and circadian-aligned lifestyle programs—produce pleiotropic benefits that extend far beyond simple glycemic control. These convergent effects suggest partial restoration of impaired metabolic networks rather than isolated correction of glucose abnormalities. In this review, we propose "Metabolic Rejuvenation" as a novel, unifying operational framework describing the systemic restoration of metabolic network integrity, physiological resilience, and biological adaptability. Mechanistically, we discuss how reactive aldehyde-driven glycative stress operates within a multifactorial cascade—together with chronic inflammation and organelle dysfunction—to drive metabolic network collapse and accelerate biological aging. Finally, we outline a multidimensional assessment framework spanning five measurable domains (Inflammatory, Energetic & Mitochondrial, Autonomic & Neuroendocrine, Clinical & Metabolic, and Digital & Behavioral) to quantify disease modification, β-cell preservation, and diabetes remission potential toward healthy metabolic longevity.

Keywords: type 2 diabetes; Metabolic Rejuvenation; network biology; inter-organ communication; biological aging; glycative stress; disease modification

Check for updates

Academic Editor: Bogdan Timar

Received: 3 August 2026
Revised: 24 September 2026
Accepted: 28 September 2026
Published: 9 October 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Type 2 diabetes mellitus (T2D) has historically been defined as a chronic metabolic disorder driven by peripheral insulin resistance and progressive pancreatic β-cell failure [1]. While glucose-centric management strategies successfully mitigate acute hyperosmolar

states and microvascular damage, they often fail to arrest systemic multi-organ deterioration [1]. The transition from DeFronzo's "Ominous Octet" model [1] to contemporary systems biology has revealed that T2D is fundamentally a network disease—a breakdown in bidirectional communication across endocrine, immune, neural, microbial, and metabolic axes [1,2]. In this review, we synthesize recent advances in immunometabolism [3,4], mitochondrial quality control [5,6], circadian physiology [7,8], and biological aging [9,10] to establish "Metabolic Rejuvenation" as a proposed operational framework for modern disease-modifying therapies.

The "Ominous Octet" expanded the diabetes paradigm by demonstrating that hyperglycemia stems from co-existing defects across multiple organs [1] (Figure 1). Since then, multidisciplinary breakthroughs in immunometabolism [3,4], mitochondrial biology [5,6], circadian physiology [7,8], network medicine [2], nutrient-sensing pathways [11,12], and incretin biology [13,14] have highlighted that metabolic homeostasis is an emergent property of interconnected systems. Disruption of these inter-organ networks extends well beyond glucose dysregulation, accelerating chronic low-grade inflammation ("inflammaging") [9,15], mitochondrial decay [5,6], autonomic nervous system imbalance [16], gut microbiota dysbiosis [17], and epigenetic age acceleration [10]—all recognized hallmarks of accelerated biological aging (Figure 2).

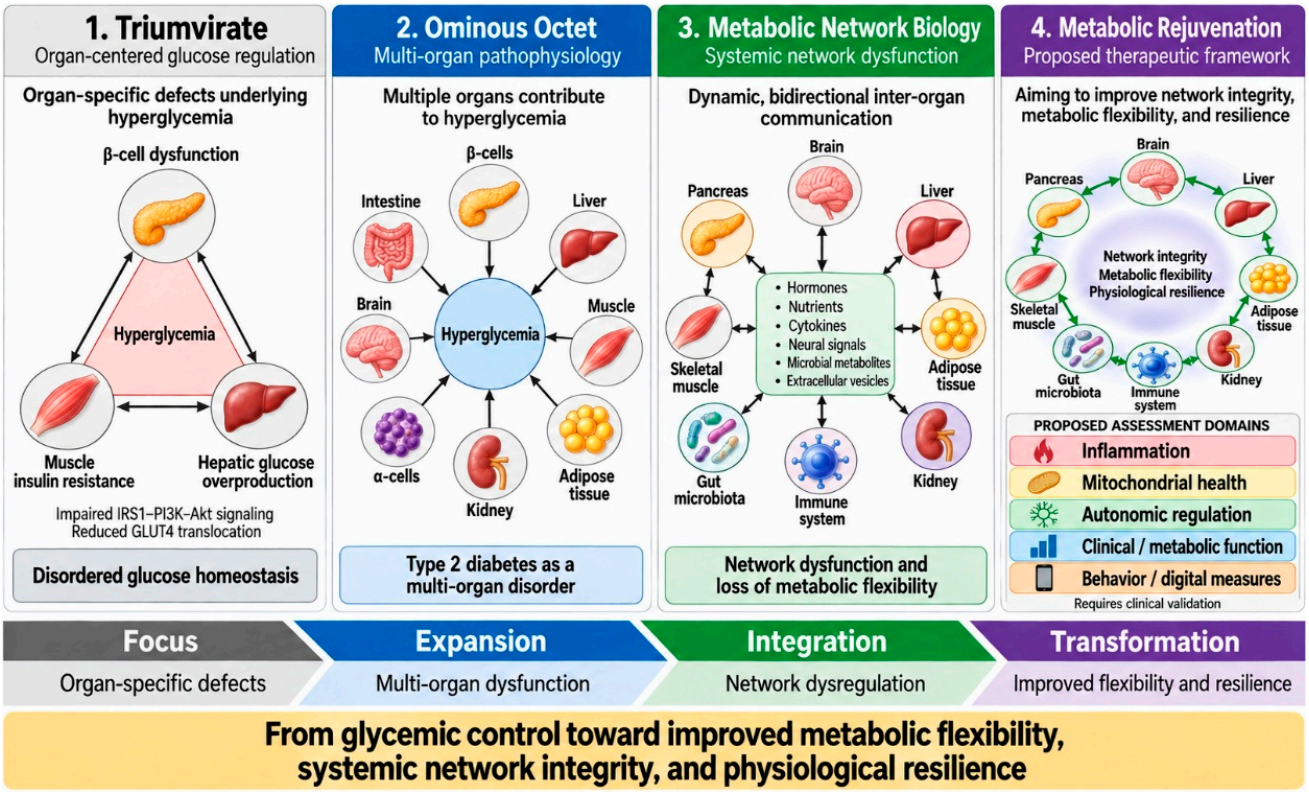


Figure 1. Conceptual evolution from the classical Triumvirate to Metabolic Rejuvenation.

It is widely established that lifestyle modifications—principally dietary energy restriction, structured physical activity, and subsequent body weight reduction—represent the primary cornerstone of T2D management [1]. Weight loss achieved through lifestyle optimization directly alleviates systemic nutrient overload, relieves cellular metabolic stress, and serves as the essential first-line means to re-establish metabolic homeostasis, restore physiological insulin sensitivity, and achieve normoglycemia [1,2]. Within this conceptual landscape, modern disease-modifying pharmacotherapies and metabolic surgery do not replace these fundamental interventions; rather, they serve to complement and

reinforce these physiological processes across interconnected inter-organ networks [1,2,13], particularly when lifestyle measures alone prove insufficient to fully reverse or arrest disease progression.

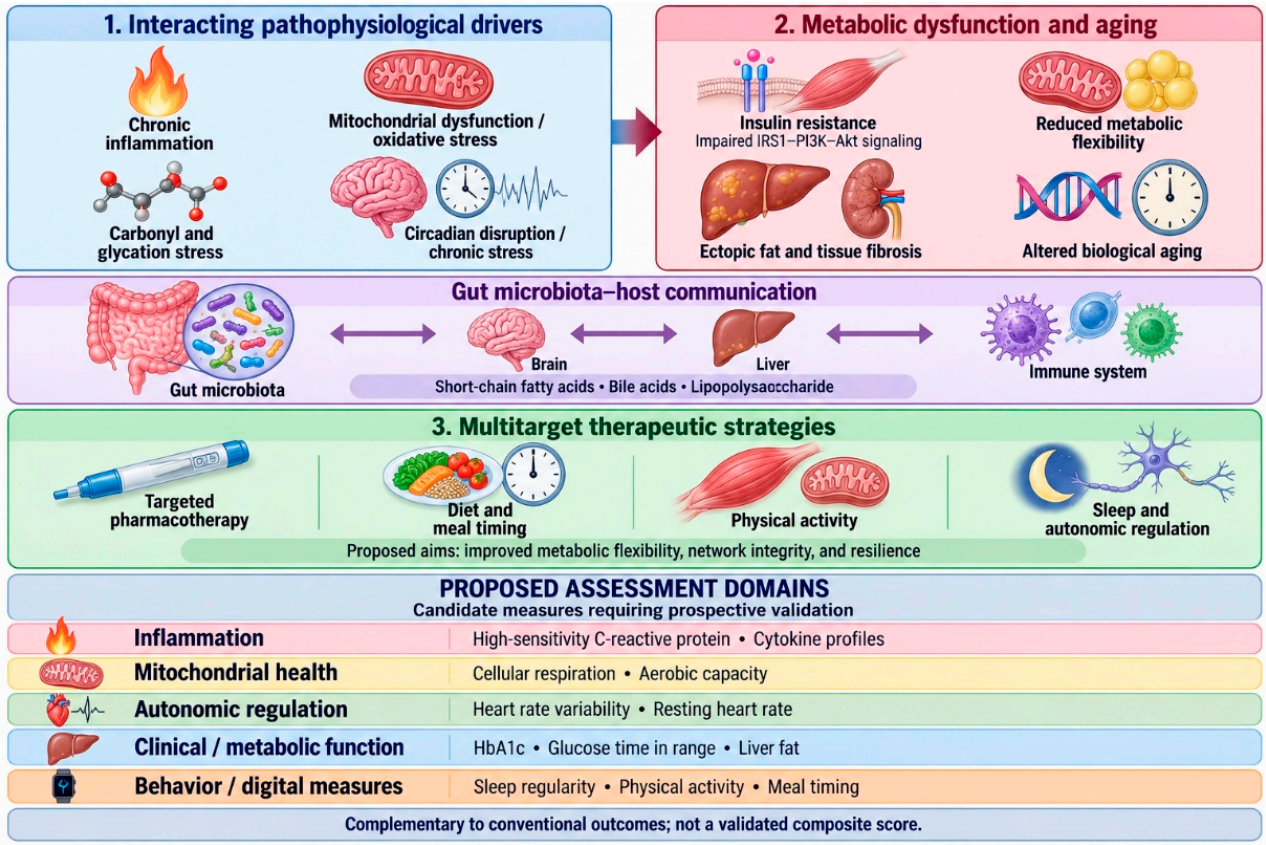


Figure 2. Integrated pathophysiological framework of network disruption, multi-target interventions, and the multidimensional assessment of Metabolic Rejuvenation. Abbreviations used in Figure 2 (in alphabetical order): Akt: Protein Kinase B; HbA1c: Glycated Hemoglobin A1c; IRS1: Insulin Receptor Substrate 1; PI3K: Phosphoinositide 3-Kinase.

Crucially, modern therapeutic breakthroughs—including long-acting GLP-1 receptor agonists (GLP-1RAs) [13,14], dual/triple incretin receptor agonists [18,19], SGLT2 inhibitors [20], and bariatric/metabolic surgery [21,22]—demonstrate systemic organ protection and disease-modifying effects that transcend conventional glycemic reduction. These pleiotropic outcomes indicate that modern interventions succeed by restoring network connectivity, flexibility, and resilience rather than merely correcting an isolated biochemical defect.

To bridge systems biology, geroscience, and clinical therapeutics, this review introduces "Metabolic Rejuvenation" as a unifying operational framework and therapeutic objective [1,2] (Figure 1). Mechanistically, we discuss how reactive aldehyde-driven glycative stress operates as a key contributing factor within a broader multifactorial cascade—alongside chronic inflammation [3,9], mitochondrial decay [5,6], and autonomic dysregulation [16]—to drive network collapse [10,23] (Figures 2 and 3). Finally, we outline a simplified, multidimensional assessment framework spanning five measurable domains (Inflammatory, Energetic & Mitochondrial, Autonomic & Neuroendocrine, Clinical & Metabolic, and Digital & Behavioral) to quantify disease modification, β-cell preservation, and diabetes remission potential toward healthy metabolic longevity (Figure 2).

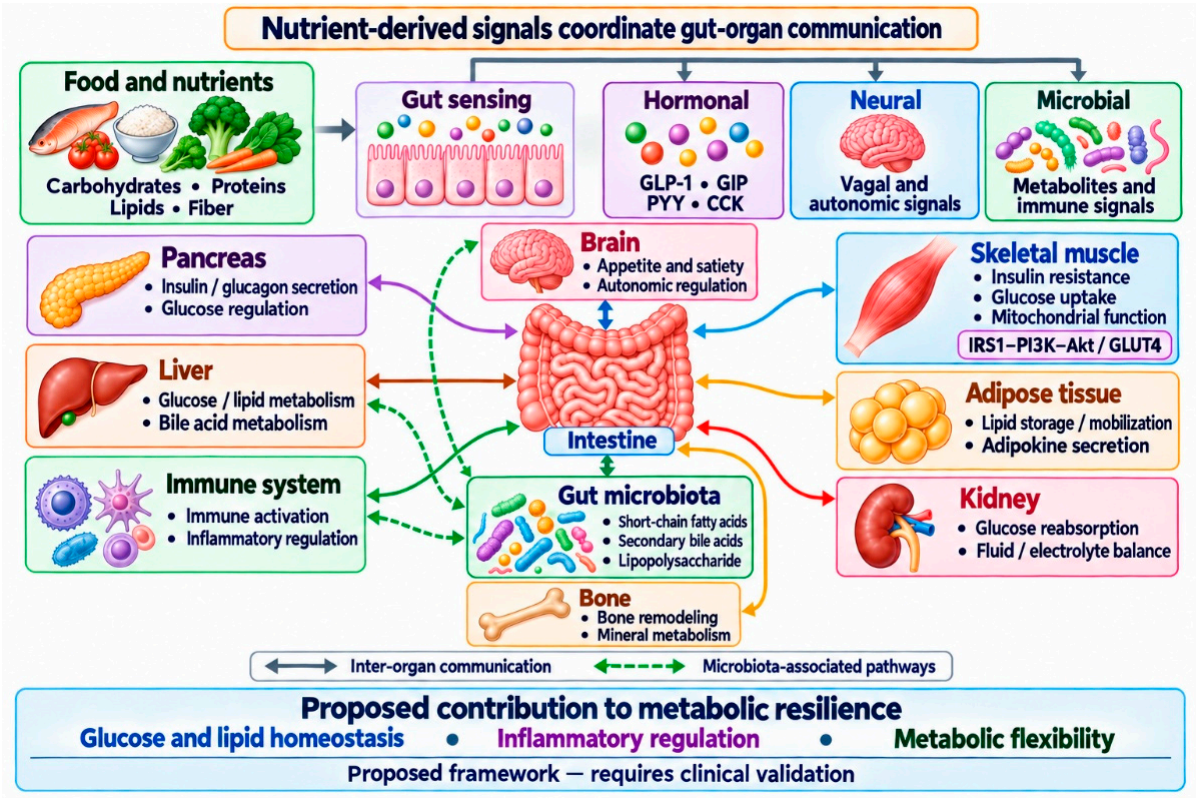


Figure 3. Nutrient-derived signaling pathways and inter-organ network communication in metabolic homeostasis. Abbreviations used in Figure 3 (in alphabetical order): Akt: Protein Kinase B; CCK: Cholecystokinin; GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide-1; GLUT4: Glucose Transporter Type 4; IRS1: Insulin Receptor Substrate 1; PI3K: Phosphoinositide 3-Kinase; PYY: Peptide YY.

Schematic representation of the conceptual milestones in type 2 diabetes (T2D) pathophysiology and therapeutic strategies: (1) Traditional Triumvirate (glucose-centric model focused on insulin resistance, β-cell dysfunction, and hepatic glucose overproduction); (2) DeFronzo's Ominous Octet (expansion of pathophysiological drivers across eight distinct organs); (3) Metabolic Network Biology (current systems-medicine paradigm recognizing T2D as an emergent property of disrupted, bidirectional, and inter-organ networks including endocrine, neural, immune, microbial, and metabolic axes); and (4) Metabolic Rejuvenation (a proposed therapeutic framework aiming beyond simple glycemic control to restore systemic network integrity, cellular resilience, and biological adaptability). The bottom panel illustrates the paradigm shift from isolated symptom/glucose control toward functional restoration and healthy metabolic longevity.

No non-standard abbreviations are used in Figure 1.

Schematic representation mapping the proposed mechanistic continuum from upstream drivers of metabolic network collapse to multi-target therapeutic restoration and quantitative clinical assessment. (1) Upstream Stressors & Multifactorial Drivers: Multiple interacting processes—including chronic metaflammation, mitochondrial reactive oxygen species (ROS) production and organelle decay, reactive aldehyde-driven glycative stress (forming advanced glycation end-products [AGEs]), circadian disruption, and autonomic dysregulation (parasympathetic withdrawal)—act interactively within a multifactorial cascade rather than through a single linear pathway. (2) Downstream Metabolic Dysfunction & Accelerated Aging: Cumulative systemic stress drives organ steatosis, tissue fibrosis, severe insulin resistance, glucolipotoxicity, and accelerated epigenetic aging. (3) Multi-Target Management & Therapeutic Interventions: Convergent multi-target modal-

ities (e.g., multi-incretin pharmacotherapy, SGLT2 inhibitors, time-restricted eating, exercise prescriptions, and autonomic modulation via vagus nerve stimulation [VNS]) aim to restore network connectivity and cellular resilience. (4) Quantitative Operational Blueprint (5 Measurable Domains): A theoretical, proposed framework requiring prospective clinical validation to measure functional restoration across five distinct domains: Inflammatory, Energetic & Mitochondrial, Autonomic & Neuroendocrine, Clinical & Metabolic, and Digital & Behavioral.

2. From Ominous Octet to Metabolic Network Biology

Building upon DeFronzo's "Ominous Octet" paradigm [1], contemporary systems biology recognizes metabolic homeostasis as an emergent property of dynamic, bidirectional, and multilayered communication networks encompassing endocrine, immune, neural, microbial, and nutritional systems [2] (Figure 1).

At the cellular and molecular level, peripheral insulin resistance centers on impairment of the canonical Insulin Receptor Substrate 1 (IRS1) → PI3K → Akt pathway in skeletal muscle, liver, and adipose tissue [6,15]. Sustained nutrient excess drives accumulation of intracellular lipid metabolites (diacylglycerols, ceramides), proinflammatory cytokines (TNF-α, IL-6), and reactive oxygen species, which promote inhibitory serine phosphorylation of IRS1 and block downstream Akt activation, thereby reducing GLUT4 translocation and glucose uptake [15,24,25]. This molecular blockade undermines metabolic flexibility—the ability of tissues to switch between fatty acid oxidation and glucose utilization in response to feeding and fasting [6,24]. Within a network medicine framework, impaired Akt signaling functions as a critical nodal disruption that is continuously amplified by systemic inputs (inflammation, lipotoxic intermediates, autonomic and neuroendocrine alterations), linking cell-autonomous defects to whole-body metabolic collapse [2,3,15].

Immunometabolism has established that chronic low-grade tissue inflammation—characterized by M1-like macrophage polarization and elevated pro-inflammatory cytokines (TNF-α, IL-6)—directly impairs intracellular insulin signaling and tissue remodeling [3,4,15] (Figure 3). Mitochondrial biology reveals that defective oxidative phosphorylation, excessive reactive oxygen species (ROS) generation, and impaired mitophagy cause cellular metabolic inflexibility and β-cell exhaustion [5,6,24–26].

Circadian rhythms synchronize systemic nutrient disposal with environmental cycles via autonomous molecular clocks (CLOCK, BMAL1) [7,8]; modern circadian disruption destabilizes counter-regulatory hormone dynamics and autonomic tone [11,27].

At the islet level, sustained nutrient overload and systemic metabolic stress induce progressive pancreatic β-cell failure through organelle dysfunction and cellular identity loss. Sustained insulin demand dramatically accelerates proinsulin biosynthesis, which overwhelms the folding capacity of the endoplasmic reticulum (ER) [28]. This induces chronic ER stress, misfolded proinsulin accumulation, and prolonged activation of the unfolded protein response (UPR) [28]. Coupled with glucolipotoxicity and mitochondrial reactive oxygen species (ROS) generation [5,6,24], persistent ER stress leads to the downregulation of core lineage-defining transcription factors (such as PDX1, MAFA, and NKX6-1) [28]. Consequently, β-cells undergo dedifferentiation into progenitor-like states or transdifferentiation into other islet cell phenotypes rather than absolute apoptotic depletion alone [28,29].

Restoring cellular bioenergetics and alleviating ER stress are thus critical for preserving β-cell identity and function, and potentially achieving diabetes remission [28,30].

Furthermore, cellular nutrient-sensing pathways driven by AMPK and mTOR integrate micro-nutrient availability with whole-body metabolic adaptation [12]. Incretin hormones (GLP-1, GIP) serve as key physiological interfaces linking intestinal nutrient sensing with central neural and peripheral organ regulation [13,14] (Figure 3). Concurrently, the

gut microbiota acts as an active regulatory node; microbial short-chain fatty acids (SCFAs), secondary bile acids, and lipopolysaccharides (LPSs) dynamically regulate incretin release, FXR/TGR5 signaling, and intestinal barrier integrity [17,31,32]. Restoration of metabolic health requires moving beyond organ-specific defect correction toward rebuilding the integrity, adaptability, and resilience of the interconnected metabolic network (Figure 1).

Detailed illustration of the dynamic, multidirectional food–hormone–organ–neural–microbial communication network regulating systemic metabolism. Nutrient ingestion (Panel 1) triggers specialized enteroendocrine and nutrient sensors in the gut mucosa (Panel 2), stimulating gut-derived hormonal secretion (Panel 3; e.g., GLP-1, GIP, PYY, CCK) and neural afferent signaling via the vagus nerve (Panel 4). Circulating signals and systemic mediators (Panel 5) coordinate integrated homeostatic responses across target organs (Panel 6; Pancreas, Liver, Immune system, Gut microbiota, Bone, Kidney, Adipose tissue, Skeletal muscle, and Brain). Gut Microbiota Integration: The gut microbiota functions as an independent, core regulatory hub directly communicating with the liver, brain, immune system, and adipose tissue via short-chain fatty acids (SCFAs), secondary bile acids, lipopolysaccharides (LPSs), and microbe-associated molecular patterns (MAMPs), independently of and in coordination with mucosal incretin secretion. Reconstruction and maintenance of this inter-organ network integrity support Metabolic Rejuvenation by retarding biological aging and restoring physiological flexibility.

3. Inter-Organ Communication in Metabolic Networks

Metabolic homeostasis is maintained through continuous, multidirectional communication among peripheral organs and central control systems (Figure 3). The gastrointestinal tract occupies a foundational position as a primary sensing interface and endocrine hub [14]. Specialized enteroendocrine cells detect luminal nutrients via specialized receptors (T1R/T2R, SGLT1, PepT1, GPR120, GPR119, CaSR, FFARs, TGR5), triggering the rapid release of peptide hormones including GLP-1, GIP, PYY, and CCK [13,14] (Figure 3).

This nutrient–hormone–organ axis coordinates multiple inter-organ communication loops:

- Gut–Pancreas Axis: Incretin hormones potentiate glucose-stimulated insulin secretion, suppress glucagon release, and promote β-cell survival [13,14] (Figure 3).
- Gut–Brain Axis: Circulating GLP-1 and vagal afferent signaling engage hypothalamic and brainstem circuits to regulate satiety, autonomic output, and systemic energy expenditure [13,33] (Figure 3).
- Gut–Liver Axis: Bile acids and microbial SCFAs modulate hepatic gluconeogenesis and lipogenesis via FXR and TGR5 pathways [31,32] (Figure 3).
- Adipose and Bone Communication: Adipokines (adiponectin, leptin) [34] and bone-derived factors (osteocalcin, FGF23) [35] actively regulate central appetite, systemic insulin sensitivity, and mineral–energy homeostasis (Figure 3).

Disruption of any single node in this interconnected network compromises whole-body resilience, providing a mechanistic rationale for multi-target restorative interventions.

4. Obesity and Diabetes Accelerate Biological Aging

Obesity and T2D represent systemic conditions characterized by accelerated biological aging [10,29]. Sustained nutrient excess and chronic metabolic stress disrupt network integrity, triggering pathological mechanisms that mirror chronological senescence (Figure 2):

- Inflammaging: Persistent nutrient excess drives innate immune cell infiltration in adipose tissue and liver, sustaining pro-inflammatory cytokine cascades (TNF-α, IL-6, MCP-1) that impair proximal insulin signaling and tissue regeneration [3,9,15,36,37] (Figure 2).

- Mitochondrial Decay: Impaired oxidative phosphorylation, elevated ROS, and defective mitophagy promote cellular metabolic inflexibility and cellular senescence [5,6,24–26,29] (Figure 2).
- Immune and Autonomic Remodeling: T2D induces immunosenescence-like immune cell shifts [3] and central autonomic dysregulation, impairing bidirectional organ cross-talk [16] (Figure 2).
- Epigenetic Age Acceleration: Epigenetic clocks confirm that chronic metabolic stress and nutrient excess accelerate DNA methylation age [10,38]. Rather than providing definitive proof of chronological or biological age reversal, emerging evidence suggests that effective metabolic restoration (e.g., significant weight loss or metabolic surgery) may decelerate or attenuate this epigenetic clock acceleration, functioning as a sensitive biomarker of overall metabolic system recovery [10,21,22,38] (Figure 2).
- Microbiota Dysbiosis: Loss of gut barrier integrity permits systemic endotoxin (LPS) translocation, amplifying neuroimmune and systemic inflammation [17] (Figure 2).

These self-reinforcing loops form a continuous cycle of network deterioration, reducing physiological resilience and accelerating biological age (Figure 2).

5. Therapeutic Restoration of Metabolic Networks

Modern diabetes therapies exert effects across multiple metabolic and organ systems, and these pleiotropic effects may be interpreted within a network-based framework of functional restoration (Figure 2).

5.1. Incretin-Based Therapies

GLP-1RAs improve glycemia, reduce body weight, lower cardiovascular events, and alleviate hepatic steatosis [13,14]. Systemic GLP-1 signaling modulates central autonomic tone, suppresses neuroinflammation, and dampens systemic inflammatory cascades [13,33]. Next-generation dual (GLP-1/GIP) and triple (GLP-1/GIP/glucagon) receptor agonists [18,19] achieve unprecedented metabolic efficacy by simultaneously engaging complementary evolutionary signaling pathways (Figure 2).

5.2. SGLT2 Inhibitors and Metabolic Surgery

SGLT2 inhibitors provide cardiorenal protection by promoting glucosuria/natriuresis, reducing arterial stiffness, shifting substrate utilization toward ketone bodies, and suppressing tissue oxidative stress [20]. Bariatric/metabolic surgery induces rapid, weight-independent improvements in insulin sensitivity, postprandial incretin secretion, bile acid dynamics, and gut microbiota structure, resetting gut–brain–liver–pancreas cross-talk and achieving high rates of T2D remission [21,22]. Intensive weight management programs further demonstrate T2D remission via metabolic remodeling [30].

5.3. Lifestyle Interventions as the Foundational Network Restorer

Undeniably, lifestyle optimization—encompassing caloric restriction, healthy dietary pattern composition, and regular exercise—remains the indispensable bedrock for restoring metabolic homeostasis in type 2 diabetes [1,39]. From a network biology perspective, substantial weight loss acts as a powerful broad-spectrum intervention that concurrently reduces ectopic lipid deposition, restores insulin signaling across target tissues (liver, skeletal muscle, and adipose tissue), and suppresses systemic low-grade inflammation [2,9,40] (Figure 2). By relieving tissue-level nutrient stress, lifestyle-induced weight reduction initiates a cascade of convergent molecular events that re-establish systemic normoglycemia and functional homeostasis [1,39,40]. Within the Metabolic Rejuvenation framework, lifestyle modification serves as the primary, non-pharmacological foundation upon which advanced

pharmacotherapies and metabolic surgical approaches build to further stabilize and repair multi-organ organelle stress and network communication [13,21] (Figure 2).

6. Metabolic Rejuvenation: Operational Framework

We propose "Metabolic Rejuvenation" as a conceptual and operational framework for integrating established biological processes and as a therapeutic objective that describes the systemic restoration of metabolic network integrity, organelle quality control, and biological resilience [1,2,41] (Figures 1 and 2). Rather than implying chronological age reversal, Metabolic Rejuvenation refers to the measurable recovery of physiological adaptability and functional capacity compromised by chronic metabolic stress and disease progression [1,2].

To clarify the novel conceptual and clinical value of this paradigm, it is necessary to explicitly distinguish Metabolic Rejuvenation from established constructs in metabolic medicine (Table 1):

Table 1. Conceptual distinctions between Metabolic Rejuvenation and established biological constructs.

Conceptual Construct	Core Definition	Key Difference from Metabolic Rejuvenation	Representative Clinical/Biological Endpoint
Diabetes Remission	Normoglycemia (HbA1c < 6.5%) without glucose-lowering drugs for ≥3 months.	Glycemia-centric outcome; does not inherently imply network or organelle repair.	HbA1c, fasting glucose, medication-free status.
Metabolic Flexibility	Capacity of tissues to adapt substrate oxidation to availability and demand.	Tissue-level bioenergetic property; serves as a functional component of rejuvenation.	Respiratory quotient (RQ), substrate oxidation rates, VO_2 kinetics.
Physiological Resilience	Capacity to resist, buffer, or recover from acute homeostatic stressors.	Dynamic stress-response metric; focuses on acute recovery kinetics rather than chronic structural repair.	HRV dynamics, acute metabolic challenge recovery, stress reactivity.
Disease Modification	Slowing, halting, or reversing the underlying clinical progression of diabetes.	Clinical trajectory endpoint; does not explicitly specify underlying network or cellular mechanisms.	β-cell decline rate, eGFR slope, cardiovascular event reduction.
Biological Aging	Progressive accumulation of systemic cellular/organellar damage and epigenetic acceleration.	Broad biological aging construct; acts as a mechanistic target rather than a therapeutic protocol.	DNA methylation age, senescent cell markers, SASP factors.
Metabolic Rejuvenation (*proposed*)	Systemic restoration of metabolic network integrity, organelle quality, and physiological resilience.	Unifying operational framework integrating multi-organ network repair, organelle health, and functional adaptability.	Composite 5-Domain Index (Inflammatory, Energetic/Mitochondrial, Autonomic, Clinical/Metabolic, Digital/Behavioral).

By serving as an integrative concept bridging systems biology and precision medicine, the Metabolic Rejuvenation framework establishes a clear, measurable path toward restoring physiological longevity in type 2 diabetes [1,2,41].

7. Reactive Aldehydes and Glycative Stress in Progressive Metabolic Decay and Complications

Metabolic network disruption in type 2 diabetes arises from multiple, interacting processes, including nutrient and energy excess, hyperglycemia, lipotoxicity, oxidative stress, and chronic low-grade inflammation. Within this multifactorial network, reactive aldehyde-driven glycative stress may serve as an important biochemical amplifier that links metabolic overload to progressive molecular damage and loss of cellular and tissue homeostasis [23].

Hyperglycemia, increased glucose flux, lipid peroxidation, and oxidative stress promote the generation of diverse reactive carbonyl and aldehyde species, including methylglyoxal (MGO), glyoxal (GO), 3-deoxyglucosone (3-DG), glyceraldehyde (GA), 4-hydroxynonenal (4-HNE), and malondialdehyde (MDA) [23]. These highly reactive species can directly modify proteins, lipids, and other cellular components, impairing their structure and function, while also promoting the formation and accumulation of Advanced Glycation End-products (AGEs) [23]. Through both direct carbonyl-mediated molecular damage and AGE-dependent signaling and cross-linking, glycative stress may contribute to progressive metabolic dysfunction across multiple tissues and organ systems. Major consequences include those detailed below.

7.1. Metaflammation and Vascular Injury

Reactive aldehydes can directly modify cellular and extracellular proteins, while accumulated AGEs activate RAGE-mediated NF-κB signaling. Together, these processes promote oxidative stress and chronic low-grade inflammation, contributing to endothelial dysfunction, vascular remodeling, and arterial stiffness [3,23].

7.2. Skeletal Muscle Dysfunction and Sarcopenia

Reactive aldehyde-mediated protein modification and AGE accumulation may impair skeletal muscle function through alterations in intracellular proteins and extracellular matrix properties. AGE cross-linking can increase tissue stiffness and, together with chronic inflammation and metabolic dysfunction, may contribute to impaired muscle quality and the progression of sarcopenia in T2D [23,42].

7.3. Organelle Decay and Long-Term Complications

Intracellular accumulation of reactive dicarbonyls and aldehydes can modify mitochondrial and endoplasmic reticulum proteins, impairing cellular bioenergetics and protein quality control. Coupled with AGE-mediated inflammation and vascular injury, these organellar perturbations may contribute to the development and progression of diabetic microvascular (nephropathy, retinopathy, neuropathy) and macrovascular complications [5,28].

Thus, mitigating the reactive aldehyde burden—through suppression of their generation, enhancement of enzymatic detoxification, and limitation of AGE formation and accumulation—may represent a promising therapeutic strategy to attenuate cumulative tissue damage and preserve metabolic network integrity [5,23,28].

8. How Should We Measure Metabolic Rejuvenation? A Practical Clinical Framework

Evaluating Metabolic Rejuvenation in clinical practice requires transitioning from single glycemic metrics toward a practical, multidimensional assessment [1,2,41]. To ensure clinical feasibility, we prioritize routinely accessible laboratory and clinical parameters, while reserving complex physiological tests for exploratory research (Figure 2):

Inflammatory Domain: High-sensitivity C-reactive protein (hs-CRP) and neutrophil-to-lymphocyte ratio (NLR) [3,9,15].

Energetic & Mitochondrial Domain: HbA1c, continuous glucose monitoring time-in-range (TIR; 70–180 mg/dL), HOMA-IR, HOMA-β, and selected indicators of mitochondrial and metabolic function [5,6,41,43].

Autonomic & Neuroendocrine Domain: Resting heart rate, standard heart rate variability (HRV) measures, and clinically feasible indicators of autonomic and neuroendocrine function [16].

Clinical & Metabolic Domain: Body weight or waist circumference, blood pressure, triglyceride-to-HDL ratio, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and the FIB-4 index [20,41,44].

Digital & Behavioral Domain: Physical activity, sleep–wake regularity, continuous glucose monitoring metrics, and dietary patterns assessed using clinically feasible digital or behavioral measures [7,8,27,39,40].

Future Validation and Standardization

It is essential to emphasize that the proposed Composite Metabolic Resilience Index is currently a theoretical operational framework. Translational implementation will require prospective clinical validation studies to standardize measurement protocols, determine appropriate weighting of individual domains, and establish normative cutoff values across diverse patient populations [41].

9. Future Perspectives and Conclusions

Translating Metabolic Rejuvenation into routine practice will require longitudinal studies integrating clinical phenotyping with multi-omics approaches, network-based modeling, and standardized assessment platforms. Targeting dicarbonyl stress together with convergent metabolic, inflammatory, mitochondrial, autonomic, and behavioral pathways may provide a useful framework for investigating mechanisms of disease modification and functional recovery [2,23].

In conclusion, type 2 diabetes can be understood not only as a disorder of glucose regulation but also as a systemic disorder involving interconnected metabolic, inflammatory, mitochondrial, neural, and endocrine networks. Metabolic Rejuvenation is proposed as a conceptual framework for integrating these processes and for organizing multidimensional measures of metabolic function, physiological resilience, and clinical outcomes. Whether this framework can improve the identification or prediction of diabetes remission, preservation of β-cell function, or long-term metabolic health remains to be determined through prospective clinical validation (Figures 1 and 2).

Author Contributions: Conceptualization, H.Y. and Y.Y. and T.T.; Methodology, H.Y.; Investigation, H.Y.; Writing—original draft prepara-tion, H.Y.; Writing—review and editing, H.Y., Y.Y., and T.T.; Visualization, H.Y. and T.T.; Supervision, Y.Y. and T.T. All authors have read and agreed to the published version of the manuscript.

Funding: This work was partially supported by JSPS KAKENHI (Grant Numbers 20K10320 and 25K13460) and the Japan Community Health care Organization (JCHO) Research Grant (Grant Number R05-02-002).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: During the preparation of this manuscript, the authors used ChatGPT (GPT6, OpenAI, San Francisco, CA, USA) for figure generation for figure preparation and refinement. The

authors reviewed and edited all generated materials and take full responsibility for the final content of the publication.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. DeFronzo, R.A. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* **2009**, *58*, 773–795. [CrossRef] [PubMed]
2. Barabási, A.L.; Gulbahce, N.; Loscalzo, J. Network medicine: A network-based approach to human disease. *Nat. Rev. Genet.* **2011**, *12*, 56–68. [CrossRef] [PubMed]
3. Hotamisligil, G.S. Inflammation, metaflammation and immunometabolic disorders. *Nature* **2017**, *542*, 177–185. [CrossRef] [PubMed]
4. Mathis, D.; Shoelson, S.E. Immunometabolism: An emerging frontier. *Nat. Rev. Immunol.* **2011**, *11*, 81. [CrossRef] [PubMed]
5. Picard, M.; Shirihai, O.S. Mitochondrial signal transduction. *Cell Metab.* **2022**, *34*, 1620–1653. [CrossRef] [PubMed]
6. Szendroedi, J.; Phielix, E.; Roden, M. The role of mitochondria in insulin resistance and type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **2011**, *8*, 92–103. [CrossRef] [PubMed]
7. Panda, S. Circadian physiology of metabolism. *Science* **2016**, *354*, 1008–1015. [CrossRef] [PubMed]
8. Stenvers, D.J.; Scheer, F.A.J.L.; Schrauwen, P.; la Fleur, S.E.; Kalsbeek, A. Circadian clocks and insulin resistance. *Nat. Rev. Endocrinol.* **2019**, *15*, 75–89. [CrossRef] [PubMed]
9. Franceschi, C.; Campisi, J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J. Gerontol. A Biol. Sci. Med. Sci.* **2014**, *69*, S4–S9. [CrossRef] [PubMed]
10. Horvath, S.; Raj, K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat. Rev. Genet.* **2018**, *19*, 371–384. [CrossRef] [PubMed]
11. Asher, G.; Sassone-Corsi, P. Time for food: The intimate interplay between nutrition, metabolism, and the circadian clock. *Cell* **2015**, *161*, 84–92. [CrossRef] [PubMed]
12. Hardie, D.G. AMPK: A target for drugs and natural products with effects on both diabetes and cancer. *Diabetes* **2013**, *62*, 2164–2172. [CrossRef] [PubMed]
13. Drucker, D.J. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab.* **2018**, *27*, 740–756. [CrossRef] [PubMed]
14. Holst, J.J. The physiology of glucagon-like peptide 1. *Physiol. Rev.* **2007**, *87*, 1409–1439. [CrossRef] [PubMed]
15. Saltiel, A.R.; Olefsky, J.M. Inflammatory mechanisms linking obesity and metabolic disease. *J. Clin. Investig.* **2017**, *127*, 1–4. [CrossRef] [PubMed]
16. Thayer, J.F.; Yamamoto, S.S.; Brosschot, J.F. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int. J. Cardiol.* **2010**, *141*, 122–131. [CrossRef] [PubMed]
17. Cani, P.D.; Amar, J.; Iglesias, M.A.; Poggi, M.; Knauf, C.; Bastelica, D.; Neyrinck, A.M.; Fava, F.; Tuohy, K.M.; Chabo, C.; et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **2007**, *56*, 1761–1772. [CrossRef] [PubMed]
18. Müller, T.D.; Blüher, M.; Tschöp, M.H.; DiMarchi, R.D. Anti-obesity drug discovery: Advances and challenges. *Nat. Rev. Drug Discov.* **2022**, *21*, 201–223. [CrossRef] [PubMed]
19. Jastreboff, A.M.; Aronne, L.J.; Ahmad, N.N.; Wharton, S.; Connery, L.; Alves, B.; Kiyosue, A.; Zhang, S.; Liu, B.; Bunck, M.C.; et al. Tirzepatide once weekly for the treatment of obesity. *N. Engl. J. Med.* **2022**, *387*, 205–216. [CrossRef] [PubMed]
20. Heerspink, H.J.L.; Stefánsson, B.V.; Correa-Rotter, R.; Chertow, G.M.; Greene, T.; Hou, F.F.; Mann, J.F.E.; McMurray, J.J.V.; Lindberg, M.; Rossing, P.; et al. Dapagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **2020**, *383*, 1436–1446. [CrossRef] [PubMed]
21. Schauer, P.R.; Bhatt, D.L.; Kirwan, J.P.; Wolski, K.; Aminian, A.; Brethauer, S.A.; Navaneethan, S.D.; Singh, R.P.; Pothier, C.E.; Nissen, S.E.; et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N. Engl. J. Med.* **2017**, *376*, 641–651. [CrossRef] [PubMed]
22. Mingrone, G.; Panunzi, S.; De Gaetano, A.; Guidone, C.; Iaconelli, A.; Nanni, G.; Castagneto, M.; Bornstein, S.R.; Rubino, F. Bariatric-metabolic surgery versus conventional medical therapy in obese patients with type 2 diabetes: 10 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* **2021**, *397*, 293–304. [CrossRef] [PubMed]
23. Yonei, Y.; Yagi, M.; Sato, K.; Ogura, M. Glycative stress: Molecular impacts and defense mechanisms. *Glycative Stress Res.* **2023**, *10*, 145–158. [CrossRef] [PubMed]
24. Montgomery, M.K.; Turner, N. Mitochondrial dysfunction and insulin resistance: An update. *Endocr. Connect.* **2015**, *4*, R1–R15. [CrossRef] [PubMed]
25. Rovira-Llopis, S.; Bañuls, C.; Diaz-Morales, N.; Hernandez-Mijares, A.; Rocha, M.; Victor, V.M. Mitochondrial dynamics in type 2 diabetes: Pathophysiological implications. *Redox Biol.* **2017**, *11*, 637–645. [CrossRef] [PubMed]

26. Prasun, P. Mitochondrial dysfunction in metabolic syndrome. *Biochim. Biophys. Acta Mol. Basis Dis.* **2020**, *1866*, 165838. [CrossRef] [PubMed]
27. Gabriel, B.M.; Zierath, J.R. Circadian rhythms and exercise—Re-setting the clock in metabolic disease. *Nat. Rev. Endocrinol.* **2019**, *15*, 197–206. [CrossRef] [PubMed]
28. Back, S.H.; Kaufman, R.J. Endoplasmic reticulum stress and type 2 diabetes. *Annu. Rev. Biochem.* **2012**, *81*, 767–793. [CrossRef] [PubMed]
29. Palmer, A.K.; Tchkonia, T.; LeBrasseur, N.K.; Chini, E.N. Cellular senescence in type 2 diabetes: A therapeutic opportunity. *Diabetes* **2015**, *64*, 2289–2298. [CrossRef] [PubMed]
30. Lean, M.E.; Leslie, W.S.; Barnes, A.C.; Brosnahan, N.; Thom, G.; McCombie, L.; Peters, C.; Zhyzhneuskaya, S.; Al-Mrabeh, A.; Hollingsworth, K.G.; et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. *Lancet* **2018**, *391*, 541–551. [CrossRef] [PubMed]
31. Thomas, C.; Pellicciari, R.; Pruzanski, M.; Auwerx, J.; Schoonjans, K. Targeting bile acid signaling for metabolic diseases. *Nat. Rev. Drug Discov.* **2008**, *7*, 678–693. [CrossRef] [PubMed]
32. Wahlström, A.; Sayin, S.I.; Marschall, H.U.; Bäckhed, F. Intestinal crosstalk between bile acids and microbiota in metabolic homeostasis. *Cell Metab.* **2016**, *24*, 41–50. [CrossRef] [PubMed]
33. Thaler, J.P.; Yi, C.X.; Schur, E.A.; Guyenet, S.J.; Hwang, B.H.; Dietrich, M.O.; Zhao, X.; Sarruf, D.A.; Izgur, V.; Maravilla, K.R.; et al. Obesity is associated with hypothalamic injury in rodents and humans. *J. Clin. Investig.* **2012**, *122*, 153–162. [CrossRef] [PubMed]
34. Stern, J.H.; Rutkowski, J.M.; Scherer, P.E. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. *Cell Metab.* **2016**, *23*, 770–784. [CrossRef] [PubMed]
35. Ferron, M.; Wei, J.; Yoshizawa, T.; Del Fattore, A.; DePinho, R.A.; Teti, A.; Ducy, P.; Karsenty, G. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. *Cell* **2010**, *142*, 296–308. [CrossRef] [PubMed]
36. Reilly, S.M.; Saltiel, A.R. Adapting to obesity with adipose tissue inflammation. *Nat. Rev. Endocrinol.* **2017**, *13*, 633–643. [CrossRef] [PubMed]
37. Zatterale, F.; Longo, M.; Naderi, J.; Raciti, G.A.; Desiderio, A.; Miele, C.; Beguinot, F. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Front. Physiol.* **2019**, *10*, 1607. [CrossRef] [PubMed]
38. Oblak, L.; van der Zaag, J.; Higgins-Chen, A.T.; Levine, M.E.; Boks, M.P. A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration. *Ageing Res. Rev.* **2021**, *69*, 101348. [CrossRef] [PubMed]
39. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N. Engl. J. Med.* **2018**, *378*, e34. [CrossRef] [PubMed]
40. Pedersen, B.K.; Saltin, B. Exercise as medicine—Evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand. J. Med. Sci. Sports* **2015**, *25*, 1–72. [CrossRef] [PubMed]
41. Buse, J.B.; Wexler, D.J.; Tsapas, A.; Rossing, P.; Mingrone, G.; Mathieu, C.; D'Alessio, D.A.; Davies, M.J. 2019 Update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **2020**, *43*, 487–493. [CrossRef] [PubMed]
42. Cruz-Jentoft, A.J.; Bahat, G.; Bauer, J.; Boirie, Y.; Bruyère, O.; Cederholm, T.; Cooper, C.; Landi, F.; Rolland, Y.; Sayer, A.A.; et al. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* **2019**, *48*, 16–31. [CrossRef] [PubMed]
43. Battelino, T.; Danne, T.; Bergenstal, R.M.; Amiel, S.A.; Beck, R.; Biester, T.; Bosi, E.; Buckingham, B.A.; Cefalu, W.T.; Close, K.L.; et al. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the International Consensus on Time in Range. *Diabetes Care* **2019**, *42*, 1593–1603. [CrossRef] [PubMed]
44. Sterling, R.K.; Lissen, E.; Clumeck, N.; Sola, R.; Correa, M.C.; Montaner, J.; Seneviratne, S.; Soriano, V.; Inchausti, A.; Telfer, P.; et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* **2006**, *43*, 1317–1325. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.