Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(12): 46323
https://doi.org/10.31083/FBL46323

Review

Beyond Cyclic Nucleotides: Emerging Roles of Phosphodiesterases in Metabolic Disorders

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Academic Editor: Xiaolei Tang
Submitted: 4 September 2025 Revised: 13 October 2025 Accepted: 21 October 2025 Published: 19 December 2025

Abstract

Phosphodiesterases (PDEs) are a huge superfamily of enzymes that fine-tune the intracellular levels of cyclic nucleotides —cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)—thus playing a pivotal role in the control of many cellular processes. While traditionally studied in the context of cardiovascular and neurological systems, mounting evidences highlight a crucial involvement of PDEs in metabolic homeostasis. This review explores the expanding landscape of PDEs function beyond classical cyclic nucleotide degradation, focusing on their roles in glucose and lipid metabolism and their implications in metabolic disorders, including obesity, type 2 diabetes (T2DM), and metabolic syndrome (MetS). Starting from an overview of the PDE superfamily, this work deeply examines the compartmentalized actions of cAMP-dependent protein kinase A (PKA) and cGMP-dependent protein kinase G (PKG) signaling pathways in key metabolically active tissues integrating PDE activities across different organs and disease states to offer a holistic view of their metabolic relevance. Special attention is given to the therapeutic relevance of PDE inhibitors (PDEi), distinguishing between established applications and emerging strategies targeting specific PDE isoforms in metabolic disease contexts to underscore the evolving concept that PDEs act as dynamic regulators of metabolic signaling networks. Understanding their isoform-specific and tissue-specific actions could thus open new avenues for therapeutic intervention in complex metabolic disorders.

Keywords: cyclic nucleotide phosphodiesterases; phosphodiesterase inhibitors; obesity; diabetes mellitus; metabolic syndrome

1. Introduction

Metabolic disorders, including obesity, type 2 diabetes (T2DM), and metabolic syndrome (MetS), represent a growing global health burden with profound clinical, social, and economic implications [1]. According to recent epidemiological estimates, over 1 billion people worldwide are affected by overweight or obesity, and the prevalence of T2DM continues to rise, particularly in low and middle-income countries [2]. These conditions are not only closely linked to increased cardiovascular morbidity and mortality but also contribute to a wide range of comorbidities including hepatic steatosis and renal dysfunction [3].

At the core of these disorders lies a complex interplay of molecular and cellular mechanisms, with insulin resistance and chronic low-grade inflammation playing central roles in the pathogenesis of metabolic dysregulation [4]. Although lifestyle interventions such as caloric restriction and physical activity remain the cornerstone of prevention and treatment, their long-term efficacy is often limited by poor adherence and compensatory metabolic adaptations [5,6]. Pharmacological agents such as metformin, Glucagon-Like Peptide-1 (GLP-1) receptor agonists, and thiazolidinediones have demonstrated benefits in improving glycemic control and insulin sensitivity, yet the need for safer and more durable therapies remains largely unmet [7,8].

In recent years, cyclic nucleotides signaling pathways have emerged as critical regulators of metabolic homeostasis [9,10]. The second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) govern a broad array of physiological processes, including mitochondrial biogenesis, lipolysis, insulin secretion, inflammation, vascular tone, and thermogenesis across metabolically active tissues such as adipose tissue, liver, skeletal muscle, and heart [11]. The intracellular levels of cAMP and cGMP are tightly controlled by phosphodiesterases, a superfamily of enzymes that hydrolyze these second messengers [12].

Among the phosphodiesterase (PDE) families, several isoforms, most notably PDE3, PDE4, and PDE5, have been identified as key modulators of metabolic signaling cascades [13–15]. These enzymes contribute to the spa-

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tial and temporal compartmentalization of cyclic nucleotide responses, providing tissue- and context-specific regulation of metabolic pathways. Pharmacological inhibition of PDEs offers a unique opportunity to selectively amplify beneficial cAMP- or cGMP-dependent signaling events. Notably, PDE5 inhibitors, historically used for the treatment of erectile dysfunction and pulmonary hypertension, have shown favorable effects on insulin sensitivity, endothelial function, and lipid metabolism in both preclinical and clinical studies [16–19]. Similarly, PDE3 and PDE4 inhibitors have been investigated for their potential to modulate inflammation, lipolysis, and adipocyte function [20].

Finally, beyond their classical role in cyclic nucleotide degradation, both PDE3 and PDE4 have been shown to assemble into multiprotein macrocomplexes with A-kinase anchoring proteins (AKAPs), sarcoplasmic reticulum Ca^{2+}-ATPase 2 (SERCA2), phospholamban (PLB), and the 5-hydroxytryptamine 4 (5-HT_4) receptor, thereby modulating distinct signaling pathways in a tissue-specific manner [21–23].

In this context, targeting cyclic nucleotide signaling through PDE inhibition could represent a promising therapeutic avenue for the management of metabolic diseases. This review aims to explore the molecular mechanisms by which the cAMP-dependent protein kinase A (PKA) and cGMP-dependent protein kinase G (cGMP-PKG) pathways regulates glucose and lipid metabolism, assess the current clinical evidence supporting their use, and discuss emerging insights into isoform-specific and tissue-targeted pharmacological strategies.

2. Methodology

Different databases, including PubMed, Web of Science, Scopus and Google Scholar, were used for the keywords of “Phosphodiesterases, Obesity, Type 2 Diabetes, Metabolic syndrome, Phosphodiesterases Inhibitors, Phosphodiesterases knockout mouse models”.

Inclusion criteria included all of the following keywords: “PDEs and obesity, PDEs and T2DM, PDEs and MetS, PDEi and metabolic disorders, PDEs knockout mouse models and metabolic disorders”.

Exclusion criteria were metabolic diseases apart from “obesity, T2DM and MetS”.

3. cAMP-PKA Signaling in Glucose and Lipid Metabolism

The cAMP–dependent PKA signaling cascade is a central regulatory pathway in cellular energy metabolism, integrating hormonal signals to coordinate glucose and lipid homeostasis across metabolically active tissues [24].

Signal initiation begins with the activation of a G protein-coupled receptor (GPCR), which stimulates adenylyl cyclase (AC) activity, catalyzing the conversion of adenosine triphosphate (ATP) into cAMP. Rapid increase in intracellular cAMP levels activates PKA, which phosphorylates a broad range of downstream effectors, thereby modulating lipolysis, gluconeogenesis, mitochondrial function, and thermogenesis [25] (Fig. 1).

To ensure signaling specificity, cAMP–PKA activity is compartmentalized into subcellular domains, primarily orchestrated by AKAPs. These scaffold proteins tether PKA in close proximity to both substrates and key regulators, including AC and PDEs, such as PDE4 [24].

In parallel to the canonical PKA pathway, cAMP also activates exchange protein directly activated by cAMP (EPAC), a guanine nucleotide exchange factor that regulates small GTPases [26]. This PKA-independent pathway has been implicated in the modulation of key metabolic processes, including glucose metabolism, insulin secretion, and energy homeostasis [27].

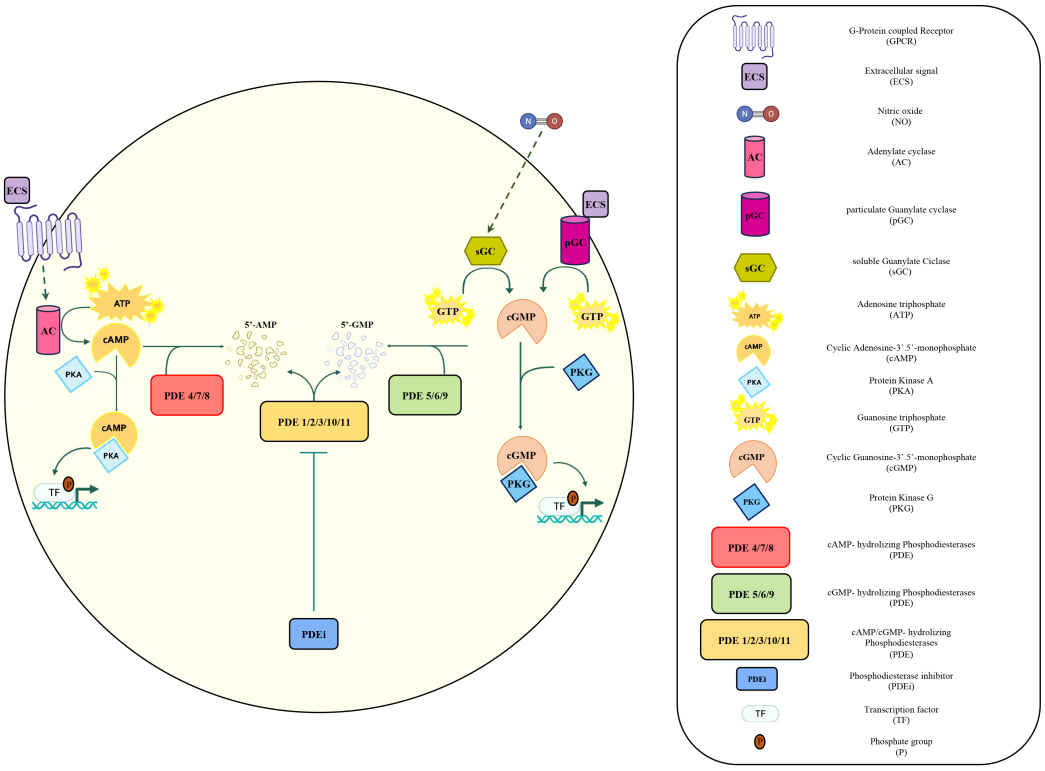
Data obtained from mouse models have demonstrated that targeted disruption of specific PKA subunits confers protection against diet-induced obesity and metabolic dysfunction. In this regard, knockout of PKA regulatory subunit RIIα results in reduced adiposity and improved glucose homeostasis via differential effects on PKA activity in liver and adipose tissue, while RIIβ-null mice exhibit resistance to diet-induced obesity and hyperglycemia [28,29]. In humans, obesity is associated with a significant reduction in PKA regulatory subunit RIIβ expression in both visceral and subcutaneous adipose tissue, which correlates inversely with body mass index (BMI), insulin resistance, and homeostasis model assessment of insulin resistance (HOMA-IR): functionally, this is accompanied by blunted cAMP-induced PKA activity, particularly in visceral adipocytes.

In the liver, the cAMP–PKA axis plays a crucial role in promoting glucose production during fasting [30]. Upon glucagon stimulation, elevated cAMP levels activate PKA, which phosphorylates and activates key transcription factors such as cAMP response element–binding protein (CREB). This induces the expression of gluconeogenic genes including phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), often in concert with the CREB regulated transcription coactivator 2 (CRTC2), thereby enhancing hepatic gluconeogenesis and contributing to systemic glucose availability during fasting states [31].

PKA also phosphorylates and inhibits acetyl-CoA carboxylase (ACC), reducing malonyl-CoA levels and promoting fatty acid oxidation (FAO), while simultaneously suppressing de novo lipogenesis [32].

Glucose production can be influenced by PKA also through post-translational mechanisms, including phosphorylation of bifunctional enzymes that modulate glycolysis and gluconeogenesis: dysregulation of these pathways contributes to hyperglycemia in T2DM, highlighting its potential as a therapeutic target [33].

In white adipose tissue (WAT), the cAMP-PKA signaling cascade exerts dual regulatory control over both adipogenesis and lipolytic processes [34]. PKA-



	WAT	BAT	Liver	Skeletal muscle	Heart	Kidney	Pancreas
PDE1i	N/A	N/A	N/A	N/A	↑ Cardiac Output ↓ Arterial resistance ↑ Contractility	N/A	↑ Glucose-stimulated insulin secretion
PDE3i	↑ WAT browning ↓ Inflammation	N/A	N/A	N/A	↑ Cardiac Output ↓ Arterial resistance ↑ Contractility	↓ Proteinuria	↑ β-cell function
PDE4i	↓ Body weight ↓ Adipocyte size ↓ Macrophage infiltration	N/A	↓ Steatohepatitis	↓ Muscle mass loss	N/A	N/A	↑ Insulin release
PDE5i	↑ Adipogenesis ↑ Browning ↑ Mitochondrial Function ↑ Inflammation	↑ Thermogenic gene expression ↑ Glucose Tolerance	↑ Insulin Sensitivity	↑ Insulin Sensitivity	↑ Vasodilation ↑ Endothelial Function ↑ Cardiac Function ↑ Cardiac Remodelling	↓ Albumin Excretion	↑ Insulin Sensitivity ↑ β-cell Compensation ↑ β-cell Function
PDE9i	↑ Lipid Oxidation ↑ Mitochondrial Biogenesis	N/A	↓ Steatohepatitis ↑ Glucose Homeostasis	↑ Insulin Sensitivity	N/A	N/A	↑ Insulin Sensitivity
PDE10i	↓ Adiposity ↑ WAT browning ↑ Insulin sensitivity	↑ Thermogenic capacity ↑ Mitochondrial biogenesis	N/A	N/A	N/A	N/A	N/A

Fig. 1. Overview of the cAMP and cGMP signalling pathways and known effects of PDEi on key metabolically active tissues. The activation of the cAMP signalling pathway is initiated by the binding of an extracellular ligand (e.g., peptide hormones, catecholamines, neurotransmitters) to a GPC receptor which activates AC that in turn catalyses the conversion of ATP into cAMP. The resulting increase in intracellular cAMP levels leads to the activation of the PKA, a tetrameric enzyme that exerts its biological function through the serine/threonine phosphorylation of specific downstream protein substrates, including TFs, thereby modulating specific cellular responses and gene expression. PDEs catalyses the hydrolysis of cAMP, resulting in its degradation. PDEi act by selectively blocking the catalytic activity of PDEs, thereby prolonging and compartmentalizing cAMP levels and potentiating the downstream effects of PKA. In the cGMP signalling pathway, the binding of NO activates sGC, and the binding of extracellular ligands activates pGC. Both sGC and pGC catalyse the conversion of GTP into cGMP. Increased intracellular cGMP activates PKG, which in turn phosphorylates downstream targets. PDEs catalyse the hydrolysis of cAMP to 5′-AMP and cGMP to 5′-GMP, resulting in their degradation. Known effects of PDEi on key metabolically active tissues are summarized in the table. ↑ and ↓ symbols denote positive (increase, improvement) and negative (decrease, impairment) changes, respectively. PDE, phosphodiesterase; WAT, white adipose tissue; BAT, brown adipose tissue; N/A, not applicable; NO, nitric oxide; GPCR, G protein-coupled receptor; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; PKA, protein kinase A; TF, transcription factor; PDEi, phosphodiesterase inhibitor; sGC, soluble guanylate cyclase; pGC, particulate guanylate cyclase; GTP, guanosine triphosphate; cGMP, guanosine monophosphate; PKG, protein kinase G.

dependent phosphorylation triggers the activation of activating transcription factor (ATF)/CREB transcription factors, which subsequently drives the transcriptional induction of key adipogenic master regulators, including peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT enhancer binding proteins (C/EBPs), thereby promoting preadipocyte differentiation [35]. In mature adipocytes, cAMP promotes lipolysis via phosphorylation and activation of key enzymes such as hormone-sensitive lipase (HSL), adipose triglyceride lipase (ATGL), and perilipin-1, while also promoting thermogenesis via induction of uncoupling protein 1 (UCP1) [36].

Brown adipose tissue (BAT), by contrast, utilizes cAMP signaling to regulate thermogenesis. Cold-induced sympathetic stimulation activates β-adrenergic receptors, leading to cAMP production, PKA activation, and transcription of thermogenic genes via CREB, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), and PR domain-containing 16 (PRDM16) [37, 38]. These pathways also promote mitochondrial biogenesis and increased substrate oxidation, essential steps that collectively culminate in the expression and activation of UCP1.

Interestingly, cAMP also contributes to "WAT browning", a transdifferentiation process by which white adipocytes adopt BAT-like features becoming beige/brite adipocytes, representing a promising strategy to fight obesity [39,40].

Although less pronounced than in adipose and hepatic tissue, cAMP-PKA signaling also contributes to muscle glycogenolysis through phosphorylation of phosphorylase kinase, which activates glycogen phosphorylase to induce glucose release from glycogen stores during exercise. Moreover, PKA signaling has been implicated in enhancing glucose uptake through insulin-independent pathways under certain physiological contexts, although this remains less well-characterized [41]. In skeletal muscle, cAMP is also involved in acute regulation of contraction via modulation of calcium handling and long-term adaptation through enhanced glycolytic capacity and myofiber hypertrophy [42]. Moreover, epinephrine-induced cAMP production facilitates glycogenolysis during exercise and may help mitigate muscle atrophy under pathological conditions [43].

In pancreatic β-cells, cAMP signaling plays a dual role in enhancing insulin secretion and supporting β-cell mass and survival. Incretins such as GLP-1 and gastric inhibitory polypeptide (GIP) stimulate cAMP production via Gs-coupled receptors, enhancing glucose-stimulated insulin secretion via both PKA and EPAC-mediated pathways [27]. Importantly, dysregulation of cAMP signaling in β-cells contributes to glucolipotoxicity and β-cell failure in T2DM, further underscoring its therapeutic relevance.

Given the widespread metabolic impact of the cAMP pathway, its regulation is subject to intricate control mechanisms. A pivotal mechanism integrating the intracellular dynamics of cyclic nucleotides is the well-characterized cross-talk between the cAMP and cGMP pathways, primarily mediated by the dual-substrate phosphodiesterase 2 (PDE2). This enzyme hydrolyzes cAMP and is allosterically activated by cGMP, thereby establishing a robust negative feedback loop where elevated cGMP levels effectively limit cAMP accumulation [44,45].

Such regulatory interplay has been extensively investigated in cardiac physiology, embryonic development, and vascular homeostasis, where tightly controlled cyclic nucleotide dynamics are crucial for functional integrity [46,47].

Notwithstanding the established regulatory capacity of the PDE2-mediated cross-talk, the enzyme's specific role in metabolic homeostasis remains a significant knowledge gap. Current evidence suggesting PDE2 involvement in metabolic regulation is tenuous, primarily stemming from a singular report that documented its expression and modulation within adipose tissue, correlating with obesity-related phenotypes in rodent models [48]. Crucially, this preliminary investigation did not include functional metabolic assessments, lacking data on the effects of PDE2 inhibition on key processes such as lipolysis rates, glucose uptake, or insulin sensitivity, thus leaving its direct contribution to adipocyte function largely unsubstantiated.

Together, these findings underscore the critical role of PKA in maintaining metabolic homeostasis and support its potential as a therapeutic target for the treatment of obesity and related metabolic disorders.

4. cGMP-PKG Signaling in Glucose and Lipid Metabolism

The cGMP-PKG signaling pathway plays a pivotal role in regulating energy homeostasis and glucose and lipid metabolism [10].

Upon cGMP elevation, PKG is activated and phosphorylates downstream effectors that influence energy balance, mitochondrial function, adipogenesis, and insulin sensitivity across multiple tissues [10,12] (Fig. 1).

Emerging evidence indicates that modulation of this pathway influences both the development and thermogenic activity of adipocytes, with direct implications for metabolic health and resistance to obesity [15]. Loss of PKG impairs brown adipose tissue thermogenic function, as evidenced by decreased UCP1 expression and reduced mitochondrial content in PKG-I knockout mice [49]. Brown preadipocytes isolated from these mice also show defective differentiation with downregulation of thermogenic markers including PPARγ, UCP1, and PGC-1α. Conversely, PKG overexpression confers resistance to diet-induced obesity, enhancing insulin sensitivity, energy expenditure, BAT mitochondrial content, and expression of UCP1 and PGC-1α [50]. Notably, cGMP pathway activation also promotes

adipogenic and thermogenic programs in cultured human adipocytes [51].

Recent findings suggested that activation of the cGMP-PKG pathway in adipocytes promotes lipolysis, adiponectin secretion, and WAT browning, leading to enhanced thermogenesis and energy expenditure [15,52].In addition, natriuretic peptides promote mitochondrial biogenesis and expression of UCP1 via PKG-dependent activation of p38 MAPK and PGC-1α [53]. Moreover, PKG phosphorylates and activates HSL and perilipin, thereby facilitating lipolysis in a fashion complementary to β-adrenergic–cAMP–PKA signaling [54,55]. cGMP-induced lipolysis has been demonstrated to occurs also in cardiac tissue where cGMP signaling is able to modulate cardiac energy metabolism in a cardiomyocyte-specific manner by promoting HSL-dependent lipolysis. This action facilitates triglycerides turnover and lipid compartmentalization, thereby limiting their accumulation particularly under fasting conditions [56]. In skeletal muscle, cGMP signaling improves glucose uptake, vascular perfusion, and mitochondrial respiration. Here, PKG enhances insulin sensitivity through vasodilation-mediated increases in skeletal muscle blood flow, thereby facilitating glucose delivery and disposal [57]. Although less extensively characterized, hepatic cGMP-PKG signaling has been shown to suppress gluconeogenesis and promote fatty acid oxidation [58]. PKG activation decreases the expression of key gluconeogenic enzymes, such as PEPCK and G6Pase, and promotes phosphorylation of transcriptional co-regulators like forkhead box protein O1 (FOXO1), reducing hepatic glucose output [59,60]. cGMP–PKG signaling supports β-cell function and insulin secretion, particularly through enhancement of islet blood flow and protection from oxidative stress. Finally, in cardiometabolic disease models, PDE5 inhibition improves endothelial function, reduces cardiac hypertrophy, and enhances insulin signaling, highlighting overall systemic metabolic benefits [17,61,62].

Although the cAMP-PKA signaling pathway holds a preeminent role in governing central metabolic functions, including the rapid regulation of lipolysis, glycogenolysis, and thermogenesis, emerging literature suggests that cGMP-PKG signaling is crucial for metabolic adaptation, exerting a key influence on processes such as mitochondrial biogenesis, glucose uptake, and the modulation of insulin action. This necessitates an integrated view wherein the two signaling systems converge to ensure systemic metabolic flexibility. The convergence of these pathways is highlighted by a critical heterologous cross-talk mechanism, prominently featuring the cyclic nucleotide phosphodiesterases (e.g., PDE3-PDE5) [15].

5. Established and Emerging Therapeutic Use of PDE Inhibitors in Metabolic Disorders

Phosphodiesterase inhibitors are a diverse class of pharmacological agents that exert their effects by preventing the enzymatic hydrolysis of the second messengers cAMP and cGMP, thereby prolonging and amplifying cyclic nucleotide–mediated signaling [63]. PDE enzymes are divided into 11 families (PDE1–PDE11) based on their substrate specificity, regulatory mechanisms, and tissue distribution. Each isoform fine-tunes local cyclic nucleotide pools within specific subcellular microdomains, contributing to the spatial and temporal regulation of intracellular signaling networks [64]. Historically, PDEi have been developed and approved for non-metabolic indications, most notably, PDE5 inhibitors for erectile dysfunction and pulmonary hypertension, and PDE4 inhibitors for chronic obstructive pulmonary disease and inflammatory disorders [65–67].

Recent evidence has highlighted the broad expression of PDEs in key metabolically active tissues including adipose tissue, liver, skeletal muscle, pancreatic β-cells, and the cardiovascular system, underscoring their critical role in the regulation of glucose and lipid metabolism, mitochondrial function, and immunoinflammatory responses [68,69]. As such, PDEi are emerging as attractive candidates for the management of metabolic disorders, including obesity, T2DM, MetS, and non-alcoholic fatty liver disease (NAFLD).

Chronic low-grade inflammation within adipose tissue represents a pivotal driver of the pathophysiology of MetS. Hypertrophic adipocytes and infiltrating immune cells, particularly pro-inflammatory macrophages, establish a sustained inflammatory milieu characterized by increased secretion of cytokines such as TNF-α, IL-6, and monocyte chemoattractant protein 1 (MCP-1) [70]. This pro-inflammatory signaling disrupts insulin receptor signaling through serine phosphorylation of IRS proteins and promotes systemic insulin resistance. In parallel, inflammation-driven remodeling of the extracellular matrix and dysregulated adipokine secretion (e.g., decreased adiponectin, increased leptin and resistin) further impair metabolic homeostasis [71]. The chronic activation of nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways within adipose tissue not only perpetuates local inflammation but also contributes to ectopic lipid deposition in the liver and skeletal muscle, fueling lipotoxicity, mitochondrial dysfunction, and systemic metabolic derangements [72]. Consequently, adipose tissue inflammation is now considered not merely a bystander but a central pathogenic mechanism underlying the development and progression of MetS and its cardiovascular and metabolic complications.

MetS itself is therefore defined as a cluster of interrelated cardiometabolic abnormalities (insulin resistance, abdominal obesity, dyslipidemia, hypertension, and hyperglycemia) that synergistically increase the risk of cardiovascular events and T2DM [73]. These pathological features are deeply connected to cyclic nucleotide-regulated signaling pathways, positioning PDEs as key molecular targets in

these contexts. Preclinical studies investigating the effect of PDE blockade in metabolic disorders are summarized in Table 1 (Ref. [15,18,52,74–86]).

Among PDEi, PDE5 inhibitors (PDE5i) such as sildenafil and tadalafil, promote nitric oxide (NO)-dependent vasodilation by blocking cGMP degradation in vascular smooth muscle [87]. Beyond their vascular effects, PDE5i enhance adipogenesis, induce browning of WAT, and improve mitochondrial respiration [88–90]. In preclinical and clinical settings, PDE5i have been demonstrated to improve insulin sensitivity, reduce systemic inflammation, and enhance endothelial function, mechanisms of paramount importance in MetS and T2DM [91,92]. A randomized controlled trial using sildenafil (25 mg three times daily for three months) in individuals with pre-diabetes revealed significant improvement in insulin sensitivity, enhanced fibrinolytic balance, and reduction of urinary albumin excretion, although without augmentation of glucose-stimulated insulin secretion [61]. Similarly, 20 mg tadalafil daily administered to obese insulin-resistant patients improved β-cell compensation, particularly in those with severe obesity [93]. Preclinical studies showed that chronic administration of sildenafil improves insulin sensitivity, reduces inflammation, and preserves β-cell function via cGMP-PKG signaling, although context-specific effects have been reported, such as impaired glucose tolerance and lack of thermogenic gene induction in brown adipose tissue [83,94]. Udenafil also enhanced mitochondrial oxidative phosphorylation, fatty acid oxidation, and PGC-1α expression, promoting insulin sensitivity [89].

PDE3 inhibitors (PDE3i), including milrinone and cilostazol, modulate both cAMP and cGMP levels. While their approved uses are related to heart failure and intermittent claudication, PDE3B, highly expressed in adipocytes, liver, and pancreatic islets, has been implicated in energy homeostasis [95,96]. Mice overexpressing *Pde3b* exhibit glucose intolerance and β-cell dysfunction, whereas *Pde3b-deficient* mice are protected from diet-induced obesity and display *white-to-beige* conversion of adipocytes [97,98]. Genetic ablation of *Pde3b* also reduces inflammation via diminished NLRP3 inflammasome activation, enhances insulin sensitivity, and confers resistance to HFD-induced weight gain [99].

PDE1 inhibitors (PDE1i) regulate both cAMP and cGMP via a Ca^{2+}/calmodulin-dependent mechanism. PDE1C inhibition enhances glucose-stimulated insulin secretion in pancreatic β-cells [100]. Moreover, chronic exposure to the highly selective PDE1i lenrispodun improves cardiac output, reduces arterial resistance, and enhances contractility in both animal models and clinical trials, supporting PDE1 relevance in cardiometabolic diseases [101,102].

PDE4 inhibitors (PDE4i), including roflumilast and apremilast, are potent anti-inflammatory agents, modulating immune cell activity and cytokine release. In HFD-fed mice, roflumilast reduced weight gain, enhanced energy expenditure, improved glucose tolerance and insulin sensitivity, and attenuated steatohepatitis via PKA/CREB activation and PGC-1α induction [77]. In psoriasis patients, roflumilast reduced BMI by ~4% over 24 weeks [103]. Additional human study support early fat mass loss and insulin sensitivity gains [104]. Apremilast, an orally administered phosphodiesterase-4 inhibitor currently in phase 2 clinical studies of psoriasis and other chronic inflammatory diseases, inhibits cytokines such as IL-4, IL-5, TNF-α, and IFN-γ, ameliorating systemic inflammation and insulin resistance [105].

PDE9 inhibitors (PDE9i) represent a novel class targeting natriuretic peptide-derived cGMP signaling and PDE9 is highly expressed in heart and adipose tissue modulating pathways involved in lipid oxidation and mitochondrial biogenesis [106]. Genetic deletion or pharmacological inhibition of PDE9 improves glucose homeostasis, enhances insulin sensitivity, and reduces hepatic steatosis in obese and diabetic mice and these effects are mediated via PKG activation and upregulation of mitochondrial and oxidative genes [52,85].

Pharmacological blockade of PDE10A using the highly selective PDE10i MP-10 has been shown to activate BAT and enhance thermogenic capacity *in vivo*. In murine models of diet-induced obesity, chronic treatment with MP-10 promotes body weight reduction through elevated whole-body energy expenditure, concomitant with the induction of browning programs in WAT and an improvement in systemic insulin sensitivity [107].

Clinical studies testing the use of PDEi in metabolic disorders have predominantly focused on selective pharmacological agents that offer mechanistic precision. These include, but are not limited to, PDE5 inhibitors (e.g., sildenafil, tadalafil) and PDE4 inhibitors (e.g., roflumilast), which precisely modulate specific cyclic nucleotide signaling pathways governing lipolysis, insulin sensitivity, and energy expenditure. In sharp contrast, a minority of studies have explored the utility of non-selective or naturally derived modulators, such as caffeine and polyphenols, often tested in combination with other treatments. These natural compounds typically exert a broader, yet milder, spectrum of PDE inhibition alongside inherent thermogenic, antioxidant, and anti-inflammatory properties. While the selective inhibitors provide critical translational insights into the role of specific signaling cascades, the non-selective approach demonstrates that weaker, pleiotropic PDE modulation, particularly when synergized with other biological activities, can still significantly influence metabolic regulation. Both complementary approaches are vital, offering a broader and more nuanced understanding of the therapeutic potential of PDE-targeted strategies against metabolic dysfunction.

As summarized in Table 2, the majority of registered clinical trials (RCTs) investigating PDEi in obesity and re-

Table 1. Preclinical studies investigating the effect of PDE inhibition/ablation in metabolic disorders.

Gene	Substrate selectivity	Experimental model	Phenotype/outcomes	Reference
PDE3	cAMP-specific, cGMP-inhibited	C57BL/6J male mice fed with HFD + 0.15% cilostazol for 16 weeks	Improvement in glucose tolerance and lipid profile, WAT browning	[74]
		Pde3b$^{-/-}$ mice	Increases in respiratory uncoupling and FAO, improvement in energy homeostasis and insulin sensitivity, reduction in circulating FFA levels	[75]
PDE4	cAMP-specific	Sprague–Dawley male rats fed with HFD + 1 mg/kg rolipram for 2 weeks	HFD-induced obesity impairs PDE4 increase in response to NA stimulation	[76]
		C57BL/6J male mice fed with HFD + 21 mg/kg roflumilast for 12 weeks	PDE4 inhibition reduces weight gain, improved glucose tolerance and insulin sensitivity	[77]
		Pde4b$^{-/-}$ mice	*Pde4b*$^{-/-}$ mice with HFD showed lower weights, smaller adipocytes, and decreased serum leptin levels suppressed macrophage infiltration in white adipose tissue	[78]
		C57BL/6J male mice	In HFD-induced obese mice, PDE4 inhibition decreased the animals' body weight, visceral adipose tissue weight, and adipocyte size	[79]
		Male mice	In diabetic nephropathy, PDE4 inhibition showed suppressive effects on glycosylated hemoglobin, urinary albumin/creatinine ratio, suppressed pro-fibrotic and pro-inflammatory marker mRNAs and increased anti-reactive oxygen species marker mRNAs in the kidneys	[80]
		Female db/db mice	PDE4 inhibition abolished the increase in blood glucose, reduced the increment in glycosylated hemoglobin, and induced insulin release in primary islets	[81]
		Male Wistar rats	PDE4 inhibition decreased the loss of skeletal muscle mass in diabetic rats	[82]
PDE5	cGMP-specific	C57BL/6J male mice fed with HFD + 12 mg/kg Sildenafil for 12 weeks	Chronic PDE5 inhibition improves insulin action and energy balance	[83]
		Pde5a$^{-/-}$ mice	Improved glucose metabolism and white to beige adipocytes conversion, enhanced thermogenic capacity, reduced hepatic fat content	[15]
		Adult mice	In T2DM model, PDE5 upregulation and lower cGMP levels were associated with insulin resistance and endothelial dysfunction	[84]
		Male CD1 mice	PDE5 inibition expanded tissue anti-inflammatory TEMs, which are known to limit inflammation and promote tissue repair	[18]
PDE9	cGMP-specific	*Pde9a*$^{-/-}$ mice	*Pde9a*$^{-/-}$ mice were resistant to HFD-induced obesity	[52]
		C57BL/6N male and female mice	In HFD-induced obesity, PDE9 inhibition reduced body fat, enhanced mitochondrial activity and improved metabolic syndrome markers	[85]
PDE10	cAMP-specific, cGMP-sensitive	Adult female CD1 and C57BL/6 mice	PDE10 inhibition in HFD-induced obese mice resulted in weight loss, browning of WAT, and improved insulin sensitivity	[84]
		C57Bl/6N Tac mice	In HFD-induced obesity, PDE10 inhibition showed lower fat fraction in white and brown adipose tissue an upregulation of marker genes involved in WAT beigeing	[86]

$^{-/-}$, knockout; HFD, high fat diet; WAT, white adipose tissue; FAO, fatty acid oxidation; FFA, free fatty acid; NA, norepinephrine; TEM, TIE2-expressing monocytes; T2DM, type 2 diabetes; cGMP, guanosine monophosphate; cAMP, cyclic adenosine monophosphate.

Table 2. Registered clinical trials investigating the use of selective PDE inhibitors in the context of obesity.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	Sponsor
NCT00685945	Renin-Angiotensin Aldosterone System and Fibrinolysis Interaction in Humans	Both	24 adults, older	Completed	Yes	Bradykinin, L-NMMA + bradykinin, Isosorbide + L-NMMA + bradykinin, Sildenafil + L-NMMA + bradykinin	NA	Randomized	t-PA Release	Vanderbilt University
NCT01444651	A Trial of Tadalafil and Glycemic Traits	Both	73 adults	Completed	Yes	Tadalafil, placebo	3	Randomized	Insulin resistance	Dr. Thomas J. Wang
NCT01862029	Effects of Roflumilast on Insulin and Blood Sugar Levels in Prediabetic Overweight and Obese Individuals	Both	24 adults, older	Completed	Yes	Roflumilast	2	Single-group assignment	Insulin Sensitivity	National Heart, Lung, and Blood Institute (NHLBI)
NCT02524184	Sildenafil Activates Browning of White Adipose Tissue and Improves Insulin Sensitivity	Male	11 adults	Unknown	No	Sildenafil, placebo	4	Randomized	WAT browning	Dr. Xiang Guang-da
NCT02554045	Daily Tadalafil on Body Fat and Lean Mass	Male	20 adults, older	Completed	No	Tadalafil, placebo	4	Randomized	Variation in lean and fat mass	La Sapienza University of Rome
NCT02595684	Effect of Tadalafil on Insulin Secretion and Insulin Sensitivity in Obese Men	Male	18 adults	Completed	Yes	Tadalafil, placebo	4	Randomized	Fasting Glucose	University of Guadalajara
NCT02819440	PDE5i for Obesity-Related Cardiometabolic Dysfunction	Both	141 adults	Completed	Yes	Tadalafil, Placebo	2	Randomized	Resting Energy Expenditure	Vanderbilt University Medical Center
NCT03905018	Effect of Tadalafil Administration on Vasodilatation Mediated by Flow in Patients with Obesity Grade I-II	Male	80 adults	Unknown	No	Tadalafil	3	Randomized	Vasodilatation	Centro Universitario de Ciencias de la Salud, Mexico
NCT04623840	Combined Effect of Continuous and Interval in Addition to Tadalafil on Erectile Dysfunction	Male	60 adults	Unknown	No	Tadalafil	NA	Randomized	Five-Item Version of International Index of Erectile Function	Cairo University
NCT04684589	Effect of PDE5 Inhibition on Adipose Metabolism in Humans	Both	100 adults	Recruiting	No	Tadalafil, Placebo	2	Randomized	Thermoneutral FSF of WAT	Vanderbilt University Medical Center
NCT05051436	The Effects of Mirabegron and Tadalafil on Glucose Tolerance in Prediabetics	Both	96 adults, older	Recruiting	No	Mirabegron, Tadalafil, Placebo	4	Randomized	Oral glucose tolerance test	Philip Kern
NCT06125665	Aminophylline on Perioperative Lung Mechanics in COPD Morbidly Obese Patients Undergoing Laparoscopic Bariatric Surgery	Both	60 adults	Recruiting	No	Aminophylline-Dexmedetomidine	NA	Randomized	Static lung compliance	Tanta University

NA, not assigned; tPA, tissue plasminogen activator; L-NMMA, L-NG-monomethylarginine, acetate salt; COPD, chronic obstructive pulmonary disease; FSF, fat signal fraction; WAT, white adipose tissue.

Table 3. Registered clinical trials investigating the use of non-selective/naturally derived PDE inhibitors in the context of obesity.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	Sponsor
NCT00302289	B181 Stimulation of Thermogenesis by Bio-Active Food Ingredients	Male	12 adults	Completed	No	Tyrosine, green tea, caffeine	1	Randomized	Energy expenditure, appetite ratings and energy intake	University of Copenhagen
NCT00377975	"Pecos" B-adrenergic and PPAR-G Stimulation Upregulates Lipid Metabolism in Human Subcutaneous Fat	Both	96 adults	Completed	No	Ephedrine, pioglitazone, caffeine	2	Randomized	Fat percentage, UCP1 gene expression, visceral adiposity	Pennington Biomedical Research Center
NCT00611416	The Role of Tea Catechins and Caffeine in Relation to Energy Metabolism	Male	15 adults	Completed	No	Green tea, mix of catechins and caffeine, EGCG, EGC, Caffeine, Placebo	NA	Randomized	Resting Energy Expenditure	University of Copenhagen
NCT00681733	Pentoxifylline Versus Pioglitazone In Non-Alcoholic Steatohepatitis (NASH)	Both	20 adults, older	Unknown	No	Pioglitazone, pentoxifylline	NA	Randomized	Improvement in metabolic profile and histology	Govind Ballabh Pant Hospital
NCT00692731	Efficacy of a Tea Catechin Sports Drink for Enhancing Exercise-Induced Fat Loss	Both	132 adults, older	Completed	No	Catechins, caffeine	NA	Perspective	Body fat mass	Provident Clinical Research
NCT00770328	The Effects of Pentoxifylline on PAI-1 in an Obese Population	Both	37 adults, older	Completed	Yes	Pentoxifylline, placebo	4	Randomized	PAI-1 levels	Vanderbilt University
NCT01556321	Long-term Effects of Green Tea on Gut Flora, Fat Absorption, Body Composition and Resting Energy Expenditure	Both	70 adults	Completed	No	Placebo, green tea	NA	Randomized	Gut flora composition	Maastricht University Medical Center
NCT01596907	Treatment of Low Metabolic Rate Following Bariatric Surgery	Both	218 adults, older	Completed	No	Ephedrine sulfate with caffeine, cellulose	NA	Randomized	Resting Energy	Oregon Weight Loss Surgery, LLC
NCT01691196	Inflammation in Peritoneal Dialysis Patients Effect of Obesity	Both	Unknown	Withdrawn	No	Unknown	NA	Perspective	Levels of inflammatory cytokines	University of Illinois at Chicago
NCT01710722	The Effect of Leptin A-200, Caffeine/Ephedrine and Their Combination Upon Weight Loss and Body Composition in Man	Both	45 adults	Completed	No	Caffeine and ephedrine, Leptin A, caffeine, ephedrine, and leptin A	NA	Randomized	Percent loss of total body fat to visceral fat	Pennington Biomedical Research Center
NCT01815203	Caffein Consumption and Response Inhibition	Male	21 adults	Completed	No	Caffeine, placebo	NA	Randomized	Insulin Sensitivity	Uppsala University
NCT02048215	Effect on Energy Metabolism at Cellular Level of Diet Plus Treatment with Ephedrine and Caffeine in Obesity	Female	13 adults	Completed	No	Caffeine, placebo, ephedrine, hypocaloric diet	3	Randomized	Resting energy expenditure	Istituto Auxologico Italiano
NCT02157974	Liver and Fat Regulation in Overweight Adolescent Girls	Female	92 children, adults	Completed	Yes	Byetta exenatide	3	Non randomized	Hepatic Glucose Release	University of Colorado, Denver

Table 3. Continued.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	Sponsor
NCT02185638	Appetite Suppression Effects of an Herbal Combination of Yerba matè, Guarana, Damiana (YGD), and 12 Other Herbal Components, Versus YGD Alone	Female	19 adults	Completed	No	Yerba maté, guarana and damiana (YGD) and Akavar (A20-50)	NA	Randomized	Appetite sensations	University of Copenhagen
NCT02740660	Body Composition Changes with Albuterol and Caffeine Versus Placebo in Adolescents	Both	12 children	Completed	Yes	Caffeine, albuterol, placebo	NA	Randomized	Fat Mass	Pennington Biomedical Research Center
NCT02751840	Effects of Caffeine and Coffee on Resting Metabolic Rate, Comparing Normal Weight Men to Obese Men	Male	33 adults	Completed	No	Caffeine, placebo, decaffeinated	3	Randomized	Resting metabolism	Tel Hai College
NCT02758990	Interventional Testing of Gene-environment Interactions Via the Verifomics Mobile Application	Both	16 adults, older	Terminated	No	Vitamin A, Vitamin B6, Vitamin C, Nicotinamide, Vitamin D3, Vitamin, Broccoli, Spinach, Caffeine, Coffee, Chocolate	NA	Non Randomized	Frequency of correct predictions	Verifomics LLC
NCT03512496	Metabolic and Genetic Impacts of Energy Drinks in Youth	Both	Unknown	Withdrawn	No	Acute energy drink, Placebo Acute energy drink, Caffein Acute energy drink, Decaf	NA	Randomized	Glucose tolerance	University of Calgary
NCT03717935	Oral Amino Acid Nutrition to Improve Glucose Excursions in PCOS	Female	27 child, adults	Completed	Yes	Essential Amino Acid, Placebo	NA	Randomized	Hepatic Fat Fraction	University of Colorado, Denver
NCT04025060	Reducing Sugar-sweetened Beverage Consumption Among Children	Both	29 children	Completed	No	Caffeine-free soda, Carbonated water, Regular soda	NA	Randomized	Adherence	George Washington University
NCT05445232	An Interaction (DDI) Study of LY3437943 in Obese Participants	Both	32 adults, older	Completed	No	Midazolam, Warfarin, Caffeine	1	Non randomized	Pharmacokinetics	Eli Lilly and Company
NCT06564441	A Study to Test Whether BI 456906 (Survodutide) Influences the Amount of Bupropion, Caffeine and Midazolam in the Blood in People with Overweight or Obesity	Both	34 adults	Active not recruiting	No	Survodutide, Bupropion, Caffeine, Midazolam	1	Interventional	AUC bupropion in plasma	Boehringer Ingelheim

NA, not assigned; UCP1, uncoupling protein 1; EGCG, epigallocatechin-3-gallate; EGC, epigallocatechin; PAI-1, plasminogen activator inhibitor-1; PCOS, polycystic ovary syndrome; AUC, area under the curve.

Table 4. Registered clinical trials investigating the use of selective PDE inhibitors in the context of T2DM.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	S Sponsor
NCT00527995	Acute Effects of Sildenafil on Endothelial Function in People With Diabetes	Male	40 adults, older	Completed	No	Sildenafil	3	Randomized	Improvement of flow mediated dilatation of the brachial artery	Ruhr University of Bochum
NCT00645268	A Multicenter, Double-blind Study to Evaluate the Effect of Pretreatment With a Daily Dose of Sildenafil on the As-Needed Efficacy of Viagra in Men With Erectile Dysfunction and Type 2 Diabetes	Male	300 adults, older	Completed	No	Sildenafil, Placebo	4	Randomized	The IIEF Erectile Function Domain score	Viatris Inc.
NCT00692237	Cardiovascular Effects of Chronic Sildenafil in Men With Type 2 Diabetes	Male	59 adults, older	Completed	Yes	Sildenafil, Placebo	4	Randomized	Left Ventricular Torsion	La Sapienza University of Rome
NCT00823849	Study of Cilostazol and Probucol to Assess Their Effects on Atherosclerosis Related Biomarker	Both	200 adults, older	Completed	No	Cilostazol, Probucol, Cilostazol + Probucol	4	Randomized	Primary Efficacy Evaluation	Otsuka Beijing Research Institute
NCT00886574	Cilostazol Versus Aspirin for Primary Prevention of Atherosclerotic Events	Both	400 adults, older	Unknown	No	Cilostazol, Aspirin	4	Randomized	Maximal and mean IMT of both common carotid arteries	Hanyang University
NCT01076478	Asian Study on Cilostazol Effectivity in Neuropathies of Diabetes Mellitus Type 2-A Pilot Study in the Philippines	Both	47 adults, older	Completed	No	Cilostazol	4	Randomized	Subjective neuropathy assessment by NSS	Otsuka Pharmaceutical, Inc., Philippines
NCT01084369	Effect of Testosterone on Endothelial Function and Microcirculation in Type 2 Diabetic Patients with Hypogonadism	Male	22 adults, older	Terminated	No	Testosterone	4	NA	Improvement in endothelial dependent and endothelial-independent vasodilatation and function	Tameside Hospital NHS Foundation Trust
NCT01180283	Efficacy and Safety of Lodenafil Carbonate in the Treatment of Erectile Dysfunction in Patients with Diabetes	Male	Adults, older	Completed	No	lodenafil carbonate	4	Non randomized	Erectile function	Cristália Produtos Químicos Farmacêuticos Ltda.
NCT01200394	A Phase 2, Placebo-Controlled Study to Evaluate The Efficacy And Safety Of PF-00489791 In Patients With Type 2 Diabetes And Overt Nephropathy	Both	256 adults, older	Completed	Yes	PF-00489791, Placebo	2	Randomized	Change From Baseline in UACR	Pfizer
NCT01238224	Effects of PDE-5 Inhibition on Postprandial Hyperglycemia in Type 2 Diabetes	Both	22 adults, older	Terminated	No	Tadalafil	1	Randomized	Capillary recruitment, muscle glucose uptake and circulating glucose levels	Vastra Gotaland Region
NCT01566006	Mycophenolate Mofetil, Carnitine and PDE5 Inhibitor, Three Potential Treatments for Resistant Proteinuria Slowing Diabetic Nephropathy Deterioration	Both	80 adults, older	Unknown	No	Mycophenolate Mofetil (MMF), Phosphodiesterase 5 inhibitors, Carnitine	NA	Randomized	Proteinuria	The Nazareth Hospital, Israel

Table 4. Continued.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	S Sponsor
NCT01803828	REmodelling in Diabetic CardiOmapathy: Gender Response to PDE5i InhibiTOrs	Both	120 adults, older	Completed	No	Tadalafil, Placebo	4	Randomized	Change from Baseline in Left Ventricular torsion	La Sapienza University of Rome
NCT02219646	Diabetes & Vardenafil	Male	54 adults, older	Completed	No	Vardenafil, Placebo	2	Randomized	Endothelin-1 levels	Azienda USL Modena
NCT02266030	Effect of Cilostazol on Coronary Artery Stenosis and Plaque Characteristics in Patients with T2DM	Both	100 adults, older	Completed	No	Cilostazol, Aspirin	3	Randomized	Coronary artery stenosis	Seoul National University Bundang Hospital
NCT02601989	Effects on Insulin Resistance with Tadalafil in Type 2 Diabetes: a Double-blind, Placebo-controlled Crossover Study	Both	23 adults, older	Completed	No	Tadalafil, Placebo	2	Randomized	Insulin sensitivity	Goteborg University
NCT02933788	Effect of aSpirin Versus CilOstazol for Inhibition of Antiplatelet aggRegaTion in Type 2 DM Patients	Both	116 adults, older	Unknown	No	Cilostazol, Acetylsalicylic acid	4	Randomized	Platelet reactivity testing	Kangbuk Samsung Hospital
NCT02983214	Diabetic Artery Obstruction: is it Possible to Reduce Ischemic Events with Cilostazol?	Both	826 adults, older	Completed	No	Clopidogrel, Cilostazol	4	Randomized	Acute ischemic stroke/TIA, MI, or death from vascular cells	University of Ioannina
NCT03248401	Effect of Cilostazol on Carotid Atherosclerosis Estimated by 3D Ultrasound in Patients with Type 2 Diabetes	Both	50 adults, older	Completed	No	Cilostazol, Aspirin	4	Randomized	Change of carotid artery atherosclerosis, plaque composition	Seoul National University Bundang Hospital
NCT03462017	Pharmacodynamic Study to Assess the Effects of Repeated Dosing of SAR247799 on Endothelial Function in Patients with Type 2 Diabetes Mellitus	Both	54 adults	Completed	No	SAR247799, Placebo, Sildenafil, Acetylcholine	1	Randomized	Change in Flow Mediated Dilation	Sanofi
NCT04170790	Evaluation of Drug Interactions of Saxagliptin with Sildenafil in Healthy Volunteers	Male	18 adults	Unknown	No	Saxagliptin, Sildenafil	NA	Interventional	Maximum Plasma Concentration	Ain Shams University
NCT05487755	Investigational and Comparative Study in the Management of Diabetic Nephropathy	Both	90 adults, older	Completed	No	Tadalafil Oral Tablet, Pentoxifylline Oral Tablet	3	Randomized	Change in Urinary albumin/creatinine ratio	Tanta University
NCT06402747	Clopidogrel Versus Cilostazol on Vessels	Both	120 adults, older	Recruiting	No	Clopidogrel, Cilostazol	4	Randomized	Changes of carotid intima-media thickness	Seoul National University Bundang Hospital
NCT06989697	Cilostazol-Ginkgo for Cognitive Function in Elderly Diabetes	Both	80 adults, older	Recruiting	No	Cilostazol, Ginko Leaf Dried Ext., Placebo	3	Randomized	Change in MMSE Score	Seoul National University Bundang Hospital

NA, not assigned; IIEF, international index of erectile function; IMT, intima media thickness; NSS, neuropathy symptom score; UACR, urinary albumin creatinine ratio; TIA, transient ischemic attack; MI, myocardial infarction; MMSE, mini-mental state examination.

Table 5. Registered clinical trials investigating the use of non-selective/naturally derived PDE inhibitors in the context of T2DM.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	S Sponsor
NCT00432887	Experimental Studies of the Effects of Caffeine on Glucose Regulation	Both	150 adults, older	Completed	No	Caffeine	1	Randomized	Postprandial glucose and insulin, fasting glucose and insulin, insulin resistance, glucose tolerance	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
NCT00663949	Assessment of the Effect of Captopril Versus Combination of Captopril and Pentoxifylline on Reducing Proteinuria in Type 2 Diabetic Nephropathy	Both	70 adults, older	Completed	No	Captopril, Captopril + Pentoxifylline	3	Randomized	Decreasing urinary protein	Shiraz University of Medical Sciences
NCT00950898	The Acute Effects of Coffee on Glucose Metabolism	Male	11 adults	Completed	No	Caffeine, Placebo	NA	Randomized	Plasma glucose levels	Brooklyn College of the City University of New York
NCT01030796	Quitting Caffeine for Better Glucose Metabolism	Both	25 adults, older	Completed	No	Caffeine	1	NA	Caffeine abstinence	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
NCT01382303	Effect of Pentoxifylline on Proteinuria in Korean Type 2 Diabetic Patients	Both	174 adults, older	Completed	Yes	Pentoxifylline, Placebo	4	Randomized	Percentage Change in Proteinuia, Changes of urine protein to creatinie ratio	Ajou University School of Medicine
NCT02291666	Evaluation of CYP450 Activities in Diabetic Patients vs. Non-diabetic Subjects	Both	73 adults, older	Completed	No	CRCHUM-MT cocktail	4	Non randomized	Metabolic ratio	Centre hospitalier de l'Universitè de Montrèal (CHUM)
NCT02929901	The Effects of Coffee Main Constituents (Caffeine and Chlorogenic Acid) Supplementation on Inflammatory, Metabolic Factors, Hepatic Steatosis and Fibrosis in NAFLD Patients with T2DM	Both	200 adults, older	Completed	No	Caffeine and chlorogenic acid, caffeine, chlorogenic acid, placebo	3	Randomized	Hepatic steatosis	National Nutrition and Food Technology Institute
NCT03006952	Add-on Pentoxifylline to Losartan Versus Increasing Dose of Losartan on NT-PRO BNP in Type 2 Diabetics with Nephropathy	Both	59 adults, older	Completed	No	Pentoxifylline, Losartan	4	Randomized	NT-pro BNP levels	Tehran University of Medical Sciences
NCT03664414	Pentoxifylline Effect in Patients with Diabetic Nephropathy.	Both	196 adults, older	Unknown	No	Pentoxifylline	4	Randomized	Change in the glomerular filtration rate	Maria Eugenia Galván Plata
NCT04243850	REGROUP: Renohemodynamic Effects empaGliflozin in vaRiOUs Populations	Both	Adults, older	Withdrawn	No	Empagliflozin, Placebo oral tablet, Caffeine	4	Randomized	Glomerular filtration rate	Amsterdam UMC
NCT04504045	Metformin's Effect on Drug Metabolism in Patients with Type 2 Diabetes	Both	10 adults, older	Terminated	No	Metformin, Caffeine, Efavirenz, Losartan, Omeprazol, Metoprolol, Midazolam	1	NA	Change from Baseline in Metabolic Rate	University of Southern Denmark
NCT04910178	Follow-up of NAFLD Patients With MRI-PDFF	Both	80 adults, older	Completed	No	Empagliflozin, Ursodeoxycholic acid, Pentoxifylline 400, placebo	4	Randomized	Liver fat content	Asmaa Abdelfattah Elsayed

NA, not assigned; NT-pro BNP, N-terminal pro-B-type natriuretic peptide.

Table 6. Registered clinical trials investigating the use of selective PDE inhibitors in the context of MetS.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	Sponsor
NCT00573950	Effects of Cilostazol on Plasma Adipocytokine and Arterial Stiffness	Both	48 adults	Unknown	No	Cilostazol, Placebo	4	Randomized	The effect on pulse wave velocity	Korea University Anam Hospital
NCT00738400	Study of Vardenafil in Patients Suffering From Erectile Dysfunction and Metabolic Syndrome	Male	150 adults	Completed	Yes	Vardenafil (Levitra, BAY38-9456), Placebo	4	Randomized	Change From Baseline in IIEF-EF	Bayer
NCT00750308	Renin Angiotensin Aldosterone System (RAAS) and Fibrinolysis in Humans: ACEi and PDE5i	Both	27 adults, older	Completed	Yes	Ramipril, Tadalafil, placebo	NA	Randomized	Beta cells function	Vanderbilt University
NCT01106118	Therapeutic Effectiveness of Vardenafil in Patients With Erectile Dysfunction and Metabolic Syndrome in Daily Clinical Practice	Male	2289 adults, older	Completed	No	Vardenafil (Levitra, BAY38-9456)	NA	Observational	Improvement in erectile function	Bayer
NCT01334554	Study of Sildenafil Citrate on Insulin Resistance in African American	Female	46 adults	Completed	Yes	Sildenafil, Placebo	2	Randomized	Insulin Sensitivity	Vanderbilt University
NCT02129725	Effect of Prolonged PDE-5 Inhibition on Insulin Signaling in Skeletal Muscle	Both	15 adults, older	Completed	Yes	Sildenafil citrate, Placebo	4	Randomized	Insulin-stimulated AKT Phosphorylation	Vanderbilt University
NCT02963454	Effects of Levosimendan on Cellular Metabolic	Both	50 adults, older	Unknown	No	Dobutamine, Levosimendan	NA	Randomized	Changes in the concentration of glucose in the extracellular fluid of the skeletal muscle	Military Hospital of Tunisy
NCT04383093	Tadalafil Plus Tamsulosin for Male LUTS and ED	Male	75 adults, older	Completed	No	Tadalafil	NA	Observational	Lower Urinary Tract Symptoms	University of Florence
NCT05292690	An Assistive Powered Wheelchair: Stage 2 Trial	Both	17 adults, older	Completed	No	Tadalafil	NA	Observational	Value of an Obstacle Alerting System	East Kent Hospitals University NHS Foundation Trust

NA, not assigned; IIEF-EF, International Index of Erectile Function - Erectile Function.

Table 7. Registered clinical trials investigating the use of non-selective/naturally derived PDE inhibitors in the context of MetS.

ID	Title	Sex	Enrollment	Status	Results	Interventions	Phase	Design	Outcome	S Sponsor
NCT00310323	Hepatic Drug Biotransformation in Children With Obstructive Sleep Apnea	Both	69 children	Completed	No	Dextromethorphan, Caffeine	NA	Non Randomized	Caffeine urinary molar ratio, Dextromethorphan urinary molar ratio	Virginia Commonwealth University
NCT02963454	Effects of Levosimendan on Cellular Metabolic	Both	50 adults, older	Unknown	No	Dobutamine, Levosimendan	NA	Randomized	Changes in the concentration of glucose in the extracellular fluid of the skeletal muscle	Military Hospital of Tunisy
NCT03041129	Post-Prandial Liver Glucose Metabolism in PCOS	Female	19 children, adults	Completed	Yes	NA	NA	Observational	Hepatic Fat Fraction measured by MRI	University of Colorado, Denver
NCT04278404	Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children Per Standard of Care (POPS)	Both	5000 children, adults	Recruiting	No	NA	NA	Observational	Clearance	Duke University
NCT04383093	Tadalafil Plus Tamsulosin for Male LUTS and ED	Male	75 adults, older	Completed	No	Tadalafil	NA	Observational	Lower Urinary Tract Symptoms	University of Florence
NCT05687474	Baby Detect: Genomic Newborn Screening	Both	6000 children	Recruiting	No	NA	NA	Observational	Acceptability	Centre Hospitalier Universitaire de Liege
NCT05713773	Pharmacodynamics and Pharmacokinetics of 3 New Developed Coated Glucose Beads in 20 Obese Healthy Subjects	Both	20 adults	Completed	No	Glucose, Caffeine	1	Randomized	GLP-1 levels	Aphaia Pharma US LLC
NCT06533007	PDE3B in Metabolic Regulation	Both	40 adults, older	Not yet recruiting	No	NA	NA	Observational	Lypolysis	Cambridge University Hospitals NHS Foundation Trust

NA, not assigned; MRI, magnetic resonance imaging; GLP-1, glucagon-like peptide-1.

lated metabolic disorders are early-phase, with relatively small sample sizes and variable study designs. A significant proportion of interventions evaluated indirect modulators of PDE signaling, such as caffeine, aiming to stimulate thermogenesis and enhance energy expenditure, though most failed to demonstrate consistent clinical benefits in terms of weight reduction or body composition (Table 3). More targeted approaches, including the use of pentoxifylline and roflumilast, have shown modest but measurable improvements in insulin sensitivity and inflammatory markers in obese or prediabetic populations, underscoring the translational potential of PDE blockade in metabolic disease.

A comparative assessment of the clinical trials involving the use of PDEi for the management of obesity and related metabolic dysfunctions highlights distinct features between selective and non-selective phosphodiesterase inhibition. Selective PDEi, particularly those targeting PDE5 and PDE4, exhibit more consistent and mechanistically defined effects, including improvements in insulin sensitivity, endothelial function, and systemic inflammation. These outcomes likely reflect their well-characterized pharmacokinetic and pharmacodynamic properties and tissue-specific modulation of cyclic nucleotide signaling. Conversely, studies investigating non-selective or naturally-derived PDE modulators, such as caffeine, tea catechins, and polyphenols, report broader, though less specific, metabolic effects often intertwined with antioxidant or thermogenic actions. While these agents show modest efficacy in weight reduction and metabolic improvement, their limited isoform selectivity complicates the interpretation of causal mechanisms.

The examination of RCTs involving the use of PDEi in the context of T2DM (Tables 4,5) highlights a heterogeneous body of evidence, with most studies being small, early-phase investigations focusing on surrogate endpoints such as vascular function, hemodynamic parameters, and markers of end-organ damage (e.g., albuminuria, intima-media thickness). Several randomized controlled trials with PDE5i primarily addressed improvements in endothelial function and cardiac remodeling—surrogate measures of clinical relevance in the T2DM population—supporting the notion of pleiotropic effects via the NO–cGMP pathway and myocardial mechanics. Other compounds, including pentoxifylline and cilostazol, were mainly evaluated for renal and anti-atherothrombotic outcomes, with some trials documenting reductions in proteinuria and favorable modulation of inflammatory biomarkers. Although these findings provide encouraging signals on intermediate endpoints, the methodological heterogeneity—differences in primary outcomes, limited treatment durations, and underpowered sample sizes—substantially limits generalizability and precludes firm conclusions regarding long-term clinical benefit in T2DM.

Comparison of the clinical studies analyzing the effect of PDEi for the treatment of T2DM reveals notable differences in the clinical impact and mechanistic scope of selective versus non-selective phosphodiesterase inhibition in T2DM management. Selective PDEi, particularly PDE5 and PDE3 inhibitors, have demonstrated significant benefits in improving endothelial function, insulin-mediated glucose uptake, and peripheral perfusion, reflecting their targeted modulation of cGMP or cAMP signaling in metabolic tissues. These agents also show favorable effects on cardiovascular risk markers, supporting their potential as adjunctive therapies for metabolic and vascular comorbidities in diabetes. In contrast, non-selective or naturally derived PDE modulators, such as methylxanthines, polyphenols, and catechins, exert milder but broader metabolic actions, often associated with enhanced mitochondrial function, antioxidant capacity, and lipid metabolism. However, their heterogeneous composition and lower PDE selectivity limit the ability to attribute observed benefits to specific cyclic nucleotide pathways. Overall, while selective PDEi provide stronger mechanistic and clinical evidence of metabolic improvement, non-selective modulators continue to offer valuable insights into the systemic regulation of energy metabolism and redox balance in diabetic conditions.

Most available clinical studies dissecting the effects of PDEi in MetS are early-phase, single-center investigations with relatively small sample sizes and variable primary outcomes, spanning from vascular function and arterial stiffness to insulin signaling and erectile function (Tables 6,7).

The comparison between the clinical trials designed to test the use of PDEi for the management of MetS underscores both the mechanistic specificity and the translational heterogeneity of phosphodiesterase inhibition in the context of MetS. Selective PDEi, particularly those acting on PDE5 and PDE4, demonstrate consistent improvements in key features of MetS (e.g., insulin resistance, dyslipidemia, endothelial dysfunction, and systemic inflammation) through targeted modulation of cAMP and cGMP signaling in vascular and metabolic tissues. Their efficacy profiles, supported by controlled pharmacokinetic parameters, suggest a promising therapeutic role in restoring metabolic and vascular homeostasis. Conversely, non-selective or naturally derived PDE modulators, including caffeine, theobromine, and polyphenolic compounds, exhibit broader systemic effects that integrate metabolic, antioxidant, and anti-inflammatory pathways. While their outcomes appear less predictable and mechanistically defined, these agents contribute to a more holistic understanding of cyclic nucleotide signaling in complex metabolic disorders. Taken together, selective PDE inhibitors provide stronger mechanistic evidence and translational potential, whereas non-selective modulators highlight complementary, lifestyle-associated strategies that may synergize with pharmacological interventions in managing MetS.

Notably, the majority of available RCTs investigated the effect of PDE5 inhibitors in MetS or in overlap-

ping cardiometabolic conditions such as T2DM and erectile dysfunction. These studies consistently demonstrated improvements in endothelial function, insulin sensitivity, and erectile function, supporting the concept of systemic metabolic and vascular benefits mediated via the NO–cGMP–PKG axis. However, most trials prioritized surrogate endpoints rather than long-term cardiometabolic outcomes.

Other PDE-targeting compounds have also been tested, albeit with limited translational relevance to MetS. Cilostazol, a PDE3 inhibitor, was evaluated for effects on adipokines and arterial stiffness, while levosimendan (a PDE3/4 modulator with inotropic effects) was tested in relation to skeletal muscle metabolism. More recently, exploratory observational protocols have focused on PDE3B in metabolic regulation, with ongoing studies aiming to delineate its role in lipolysis and energy balance.

Together, all preclinical and clinical data analyzed and discussed above, suggest that PDE inhibitors, by selectively modulating intracellular cyclic nucleotide signaling, can enhance insulin action, stimulate lipid oxidation, suppress adipogenesis, reduce ectopic lipid deposition, and improve endothelial-metabolic cross-talk. Nevertheless, metabolic outcomes vary by PDE isoform, dosing duration, and tissue context, and some unfavorable effects, such as sildenafil-induced glucose intolerance under obesity, underscore the complexity of chronic modulation. Consequently, large-scale, long-term trials with isoform-selective and tissue-restricted PDE targeting are warranted to establish therapeutic efficacy, tolerability, and personalized applications in metabolic disease.

6. Conclusions

Collectively, these findings underscore the potential of PDEi as versatile modulators of metabolic homeostasis, capable of fine-tuning adipocyte thermogenesis, β-cell insulin secretion, and systemic anti-inflammatory and vasodilatory pathways. Translating these insights into clinical practice requires careful consideration of several factors. Long-term safety and isoform specificity remain paramount, as off-target effects or prolonged modulation of cyclic nucleotide signaling can have significant consequences. Tissue heterogeneity, including sex differences and organ-specific expression patterns, further influences both efficacy and susceptibility to adverse events. In addition, effective dose–tissue exposure, shaped by pharmacokinetic and pharmacodynamic properties, is essential to achieve meaningful target engagement. Finally, the long-term metabolic and cardiovascular outcomes of PDE modulation are still incompletely characterized. Together, these considerations highlight the need for well-designed, longitudinal studies to fully realize the therapeutic promise of PDE-targeted strategies in metabolic disorders.

Author Contributions

FC designed the research. NB, MRA, FS, GD, FGK, MAV, AMI and FC performed literature research and analyzed the data. NB and GD contributed to figure design. MRA and FS participate in the design of the tables. All authors critically reviewed and revised the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by the Italian Ministry of Research (grant no. P2022CE79J).

Conflict of Interest

The authors declare no conflict of interest. Given her role as the Guest Editor, Federica Campolo had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Xiaolei Tang.

Declaration of AI and AI-Assisted Technologies in the Writing Process

Although ChatGPT-4o was used as a thesaurus and for minor textual refinement during the drafting of this article, the authors carefully reviewed the entire article and take full responsibility for its content.

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