

Parasympathetic Regulation of Insulin Pulsatility: A Missing Link in Early Type 2 Diabetes

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ABSTRACT

Background: Early type 2 diabetes (T2D) is conventionally defined by insulin resistance and progressive β -cell failure. However, this framework does not fully explain the frequent observation of preserved or elevated insulin levels during early disease despite impaired metabolic control. Insulin is physiologically secreted in coordinated oscillatory pulses that optimize hepatic insulin signaling.

Methods: We synthesized evidence from human and experimental studies of insulin pulsatility, β -cell network dynamics, and autonomic regulation to develop a conceptual model integrating temporal aspects of insulin secretion with early T2D pathophysiology.

Findings: Disruption of insulin pulsatility—characterised by reduced amplitude, impaired synchronisation, and loss of early-phase secretion—occurs early in prediabetes and T2D, often preceding overt hyperglycaemia and substantial β -cell loss. Experimental evidence indicates that pulsatile insulin delivery is metabolically more effective than continuous exposure. Loss of pulsatile insulin dynamics reduces hepatic signalling efficiency, necessitating compensatory hyperinsulinaemia despite preserved insulin production.

Interpretation: Early T2D may be fundamentally a disorder of insulin signal timing rather than insulin deficiency. This temporal framework integrates β -cell biology, autonomic regulation, and hepatic insulin action, and reframes hyperinsulinaemia as a consequence of signalling inefficiency. Restoring physiological insulin pulsatility—through behavioural, pharmacological, or technological approaches—may represent a novel strategy for early disease modification.

Keywords

Insulin pulsatility, Type 2 diabetes, Hepatic insulin resistance, Parasympathetic nervous system, β -cell function, Hyper-insulinemia.

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Introduction

Early type 2 diabetes (T2D) is conventionally defined by insulin resistance and progressive β -cell failure. Early type 2 diabetes (T2D) is widely conceptualised as a disorder driven by insulin

resistance and progressive β -cell failure. Within this framework, hyperglycaemia emerges when β -cells fail to compensate for increased metabolic demand. However, this model does not fully account for a consistent clinical observation: during the early

stages of T2D, insulin levels are often normal or elevated, and β -cell secretory capacity remains relatively preserved, yet hepatic insulin resistance and dysglycaemia are already present.

However, accumulating physiological and clinical evidence suggests that abnormalities in insulin secretion dynamics—rather than absolute insulin deficiency—are among the earliest detectable defects [1,2]. In healthy individuals, insulin is secreted in coordinated oscillatory pulses that optimize hepatic insulin signalling [3,4]. In prediabetes and early T2D, this temporal organisation is disrupted despite preserved insulin production [5,6]. We propose that early T2D is fundamentally a disorder of insulin signal timing, characterised by loss of pulsatile efficiency and compensatory hyperinsulinaemia [7,8].

This apparent mismatch between insulin quantity and metabolic effectiveness suggests that defects in insulin action may not be explained solely by reduced hormone availability. Instead, growing evidence indicates that insulin should be understood not only as a hormone defined by concentration, but also as a signal defined by its temporal pattern. In healthy individuals, insulin is secreted in coordinated oscillatory pulses, generating rhythmic fluctuations in the portal circulation that enhance hepatic insulin receptor activation, promote receptor recycling, and optimise suppression of hepatic glucose production [2,4,9-12]. Experimental studies have demonstrated that pulsatile insulin delivery is more effective than continuous exposure, even when total insulin levels are equivalent [2,11].

Notably, abnormalities in insulin pulsatility are detectable early in the course of metabolic dysfunction. Individuals with prediabetes exhibit reduced pulse amplitude, irregular oscillatory patterns, and impaired synchronisation of insulin secretion despite preserved overall insulin output [13,18-20]. Loss of early-phase insulin secretion—traditionally interpreted as a marker of β -cell dysfunction—may instead reflect disruption of coordinated pulsatile signalling [15,18]. These observations suggest that early T2D may involve a qualitative defect in insulin signalling dynamics rather than an initial quantitative deficiency.

In parallel, increasing recognition of neuro–metabolic integration highlights the role of autonomic regulation in shaping insulin secretion. Parasympathetic (vagal) input contributes to the initiation and synchronisation of early insulin bursts, and alterations in autonomic tone associated with modern metabolic environments may disrupt this regulation [6,9,17,21,22]. This provides a mechanistic link between environmental factors, neural control, and β -cell function in early disease.

In this Personal View, we propose a unifying framework in which early T2D is fundamentally a disorder of insulin signal timing. We integrate evidence from β -cell physiology, pulsatile insulin dynamics, and autonomic regulation to argue that loss of temporal organisation reduces hepatic signalling efficiency, leading to compensatory hyperinsulinaemia and subsequent metabolic stress [11,12]. This perspective reframes early disease pathophysiology,

highlights limitations of current models based on static insulin measurements, and identifies new opportunities for early diagnosis and therapeutic intervention.

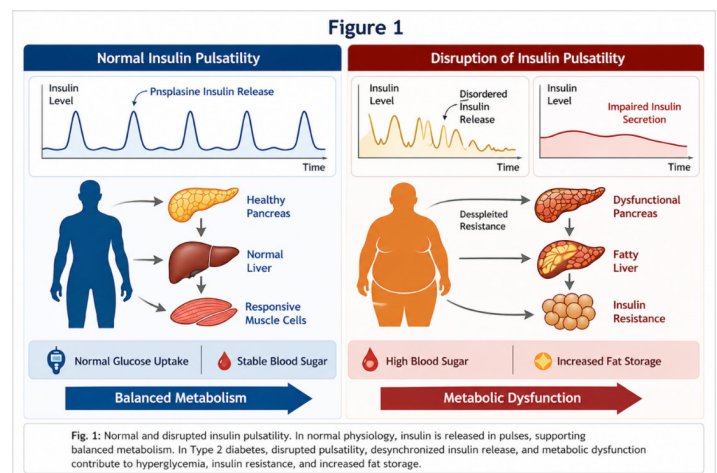
The clinical paradox in early type 2 diabetes

Early T2D presents a longstanding paradox: insulin levels are often normal or elevated, β -cell mass is relatively preserved, yet hepatic insulin resistance and dysglycaemia emerge [6,9]. We argue that this mismatch reflects a qualitative defect in insulin signalling, rooted in the loss of its physiological temporal structure [7,8].

Physiology of Insulin Pulsatility (Figure 1)

Insulin secretion is intrinsically pulsatile and organized across multiple time scales. **Fast oscillations** (~4–6 minutes) arise from intrinsic β -cell electrical and calcium oscillators and coordinated islet activity. These oscillations are highly synchronized and generate rhythmic portal insulin peaks that maximize hepatic signaling efficiency [11].

Superimposed on basal oscillations are early postprandial insulin bursts, which are amplified and temporally coordinated by parasympathetic (vagal) input [6,9,17]. These feed-forward signals occur during the cephalic and early absorptive phases and exert disproportionate metabolic effects despite small insulin mass [9].



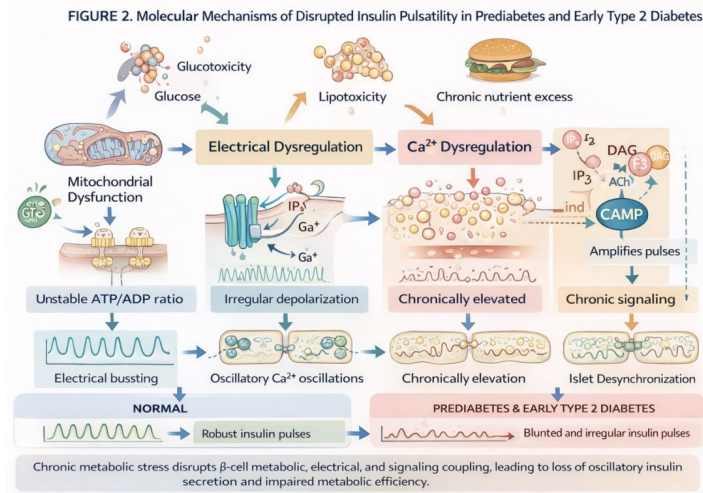
Slower ultradian oscillations (60–120 minutes) reflect feedback interactions between insulin secretion, plasma glucose, and hepatic glucose output [5,16]. While physiologically relevant, they are less central to early-phase insulin action.

The functional significance of pulsatility lies in its ability to generate high peak-to-trough insulin contrast in the portal circulation. This oscillatory exposure enhances receptor responsiveness and downstream signaling compared with continuous insulin delivery, even when total insulin exposure is equivalent [11,12].

Disruption of Insulin Pulsatility in Pre-diabetes and Early Type 2 Diabetes (Figure 2)

The transition from normal glucose tolerance to early T2D is characterized by progressive disruption of insulin temporal

organization rather than an initial loss of insulin production [18,20].



In prediabetes, fast oscillations become irregular, with reduced amplitude and impaired inter-islet synchronization [13]. Parasympathetic-modulated early bursts are delayed or fragmented, and first-phase insulin secretion becomes blunted despite preserved β -cell capacity [15,18].

In early T2D, pulsatility is markedly disrupted. Oscillations lose regularity, amplitude is attenuated, and parasympathetic feed-forward signaling is impaired [13,20]. First-phase insulin secretion becomes undetectable in systemic measurements [15], while basal and late-phase insulin secretion increase, resulting in hyperinsulinemia [18].

This progression reflects a shift from efficient, temporally coordinated insulin delivery to inefficient, excessive insulin exposure. Importantly, systemic insulin levels may remain normal or elevated despite impaired hepatic signaling, highlighting a mismatch between insulin quantity and effectiveness (Table 1).

Table 1: Side by side summary of the characteristic features of progression from normal to pre-diabetics and early type 2 diabetes mellitus.

Feature	Normal	Pre-diabetes	Early T2DM
Fast pulsatility	Regular (4–6 min)	Irregular	Largely lost
Islet synchrony	High	Reduced	Severely reduced
Parasympathetic bursts	Intact, rapid	Blunted/delayed	Markedly impaired
First-phase insulin	Present	Blunted	Absent systemically
C-peptide capacity	Normal	Near-normal	Often preserved
Systemic insulin	Normal	Normal–high	High
Dominant defect	None	Timing	Coordination & timing

A Temporal Signaling Model of Early Type 2 Diabetes

We hypothesize a staged model in which disruption of insulin temporal dynamics represents an initiating mechanism in T2D pathogenesis: First; **attenuation of pulsatile amplitude** reduces portal insulin peak-to-trough contrast [11,12]. Second, **impaired**

hepatic receptor entrainment decreases signaling efficiency [11]. Third, **compensatory hyper-insulinemia** develops to maintain glucose homeostasis [12]. Finally, **Progressive metabolic stress** promotes lipid accumulation and intracellular insulin resistance [6].

Within this framework, early metabolic dysfunction arises from qualitative defects in insulin signaling rather than quantitative insulin deficiency. Loss of pulsatility lowers the threshold for hepatic insulin resistance, which is later reinforced by lipid-mediated intracellular pathways.

Parasympathetic Modulation and Neuro-Metabolic Dysfunction (Table 1)

Parasympathetic input plays a critical role in amplifying and synchronizing early insulin bursts [16,17]. Under physiological conditions, vagal signaling is phasic and tightly coupled to meal initiation [9]. In modern metabolic environments characterized by frequent feeding and caloric excess, parasympathetic signaling may shift from phasic to more sustained patterns. This transition can impair β -cell oscillatory coupling, reduce burst amplitude [6,17], and promote desynchronization of insulin secretion [16].

Visceral adiposity further alters autonomic balance and afferent signaling, contributing to impaired neural–islet communication. These changes provide a plausible neuro–metabolic mechanism linking environmental factors to early disruption of insulin pulsatility [16–18], leading to impaired β -cell synchrony and reduced pulsatile amplitude [19–21].

What current models overlook (Figure 3)

Insulin is not secreted continuously. Under physiological conditions, it is released in coordinated pulses (every 4–6 minutes), generating oscillatory portal insulin exposure [3,4]. This pulsatility enhances receptor activation, promotes receptor recycling, and improves suppression of hepatic glucose production [7,8]. Experimental studies show that pulsatile insulin delivery is more effective than continuous exposure, even when total insulin levels are identical [10,11]. Loss of insulin pulsatility reduces signalling efficiency at the hepatic level, necessitating compensatory increases in insulin secretion [7–9]. Therefore, the **proposed sequence** is first, reduced pulsatile amplitude and coordination [5,6]; second, impaired hepatic receptor entrainment [7,8]; third, decreased signalling efficiency; fourth, compensatory hyperinsulinaemia [9]; finally resulting in secondary metabolic stress and insulin resistance [12,13].

Insulin is physiologically secreted as a coordinated, time-encoded pulsatile signal that optimises hepatic insulin signalling efficiency [2,7,12]. In early type 2 diabetes (T2D), this temporal organisation is progressively disrupted, with reduced pulse amplitude, irregular oscillations, and loss of β -cell synchrony occurring before substantial decline in insulin secretion [5,14,20]. Neuro–metabolic regulation, particularly parasympathetic (vagal) input, plays a key role in synchronising insulin release, and its dysregulation

contributes to impaired pulsatility [6,16,17]. This loss of temporal structure reduces portal peak-to-trough insulin contrast, leading to impaired hepatic signalling, compensatory hyperinsulinaemia, and subsequent metabolic stress and insulin resistance [2,9,18].

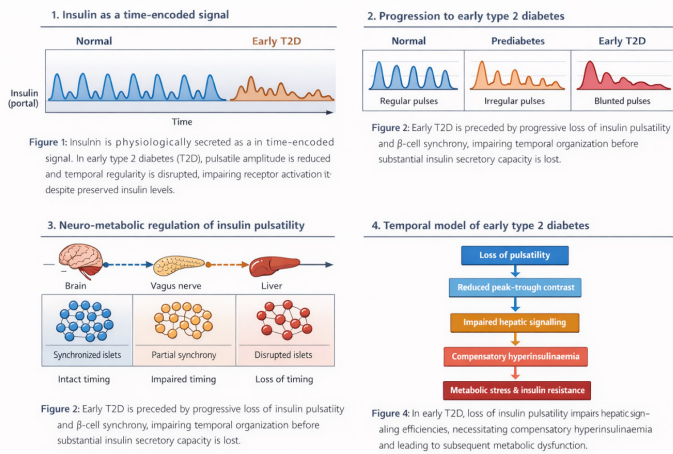


Figure 3:

We propose a shift from a **quantity-based model** to a **signal-based model**:

Traditional model	Temporal model
Insulin resistance	Insulin signalling inefficiency
β-cell failure	Loss of pulsatility and synchrony
Hyperinsulinaemia (as cause)	Hyperinsulinaemia as compensation (as result)

Evidence supporting a temporal defect

- **Early disruption precedes hyperglycaemia**
Studies in prediabetes demonstrate reduced pulse amplitude, irregular oscillatory patterns, and impaired inter-islet synchrony [5,6,14]. These abnormalities occur before overt hyperglycaemia [6,15].
- **Loss of first-phase insulin as a timing failure**
The early insulin response to meals may reflect impaired parasympathetic signalling and loss of coordinated pulsatile bursts [16-18].
- **Pulsatility determines metabolic effectiveness**
Pulsatile insulin delivery improves hepatic glucose suppression, whereas continuous insulin leads to receptor desensitisation [10,11].

Implications for clinical practice

Reframing early type 2 diabetes as a disorder of insulin signal timing has practical implications for both diagnosis and management. Reliance on static measures of insulin concentration may overlook early dysfunction, as preserved or elevated insulin levels can coexist with impaired pulsatile signalling. Loss of first-phase insulin secretion should be interpreted as a defect in temporal coordination rather than solely β-cell failure. Clinically, this perspective supports earlier identification of metabolic dysfunction through dynamic assessment of insulin responses and highlights the potential value

of interventions that restore physiological patterns of insulin secretion. Strategies such as optimising meal timing and frequency, targeting autonomic balance, and developing pulsatile insulin delivery approaches may improve metabolic efficiency and delay disease progression in at-risk individuals.

Limitations

Direct measurement of portal insulin pulsatility remains challenging [2,7]. Causality between pulsatility loss and insulin resistance requires further study [12,13].

Conclusion

Early type 2 diabetes may be better understood as a disorder of insulin signaling dynamics rather than insulin deficiency. Disruption of insulin pulsatility reduces hepatic signaling efficiency and promotes compensatory hyper-insulinemia [7,12], preceding overt metabolic failure. Attenuation of pulsatile amplitude—potentially driven by altered parasympathetic modulation—provides a unifying mechanism linking modern metabolic stressors to early disease pathogenesis. Targeting insulin temporal dynamics may represent an under-recognized opportunity for early intervention [7-9].

A focus on insulin pulsatility shifts the conceptual framework of early type 2 diabetes from one of deficiency to one of disordered signaling. Interventions that restore temporal organization of insulin secretion may offer a previously unrecognized opportunity to modify disease progression.

Author Contributions

W.F.N. conceptualized the study. M.W.N. contributed to literature review and drafting. O.W.N. drafted and revised the manuscript. All authors approved the final version.

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