

Review

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Review

Non-Fasting Glucose Measures and Their Clinical Significance

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Abstract

Several lipid-management guidelines now favor non-fasting lipid measurements for cardiovascular risk assessment. In parallel, this review evaluated the potential clinical utility of non-fasting glucose measures for disease diagnosis and risk prediction. Postprandial plasma glucose measured 4–7.9 hours after a meal (PPG_{4–7.9h}) shows relative stability within this window and appears to be a promising marker for diagnosing diabetes and predicting mortality from cardiovascular disease (CVD) and cancer. Similarly, 2-hour plasma glucose during an oral glucose tolerance test performed 4–7.9 hours after a meal (2-h PG_{OGTT4–7.9h}) demonstrates diagnostic and prognostic value, particularly for diabetes and cardiovascular mortality. Notably, the diagnostic and predictive performance of these non-fasting measures is not inferior to that of traditional fasting glucose assessments. Mechanistically, postprandial hyperglycemia may contribute to CVD through increased oxidative stress and inflammation, endothelial dysfunction, and promotion of atherogenesis and thrombogenesis. It may also increase cancer risk via oxidative stress, inflammation, and insulin-mediated cellular proliferation. In addition, it may enhance lipogenesis to form membrane lipids supporting tumor growth. Further research is required to establish the clinical applicability, optimal thresholds, and generalizability of these non-fasting glucose measures.

Keywords: diabetes; type 2 diabetes; prediabetes; postprandial; nonfasting; diagnosis; mortality; lipid; fatty acid

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex, chronic metabolic disorder characterized by persistent hyperglycemia resulting from a combination of insulin resistance and relative insulin deficiency [1,2]. T2DM accounts for approximately 90–95% of all diabetes cases worldwide and represents a substantial and growing global health burden [3–5]. The global prevalence of T2DM has increased markedly over recent decades, driven by population ageing, urbanization, sedentary lifestyle, and rising rates of overweight and obesity [5–7].

Chronic hyperglycemia in T2DM is associated with long-term microvascular complications, including retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as coronary heart disease, stroke, and peripheral arterial disease [8–12]. In addition, T2DM is associated with an increased risk of cancer incidence [13–15] and cancer-related mortality [16–19].

Globally, an estimated 240 million individuals (44.7%) with diabetes remained undiagnosed in 2021 [20]. Current diagnostic criteria predominantly rely on measurements of glycated hemoglobin (HbA_{1c}), fasting plasma glucose, or 2-hour (2-h) plasma glucose following an oral glucose tolerance test (OGTT). Recently, 1-h plasma glucose following an OGTT after fasting has been recognized as a

diagnostic criterion [21]. However, these approaches have some limitations. HbA_{1c} lacks sensitivity for detecting acute hyperglycemia in newly diagnosed diabetes [22] and identifies only a minority of total diabetes cases (approximately 30%) [23]. In addition, fasting plasma glucose testing and OGTT require fasting, which may be inconvenient and potentially hazardous for vulnerable individuals, particularly those at risk of hypoglycemia while awaiting blood collection [24].

In contrast, several lipid-management guidelines now recommend non-fasting lipid measurements over fasting tests for cardiovascular risk assessment [24–27]. These non-fasting assessments include total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. This paradigm shift reflects evidence that non-fasting tests are more convenient and acceptable to patients and are comparable or superior to fasting measurements in predicting cardiovascular disease (CVD) risk [24] and mortality [28].

In line with this shift, it may be clinically valuable to explore the potential utility of non-fasting postprandial plasma glucose (PPG), defined as glucose measured within <8 h of fasting according to the American Diabetes Association [3,4]. In this review, we first describe temporal patterns of non-fasting PPG and then focus on emerging evidence highlighting the clinical significance of the postprandial window 4–7.9 h after a meal. During this interval, PPG (PPG_{4–7.9h}) and 2-h plasma glucose measured during OGTT (2-h PG_{OGTT4–7.9h}) appear to have relevance for diabetes diagnosis and for predicting mortality from CVD and cancer. Finally, we examine the molecular mechanisms through which postprandial hyperglycemia may contribute to increased cardiovascular and cancer risk.

2. Plasma Glucose with a Postprandial Time of Less Than 4 h

2.1. Plasma Glucose Returns to Baseline Within 4 h After a Meal

Postprandial glucose excursions reflect the balance between the rate of exogenous glucose appearance from ingested nutrients and the efficiency of glucose disposal by metabolically active tissues, primarily skeletal muscle and adipose tissue [29,30]. The shape of the postprandial glucose curve therefore represents the dynamic interplay between intestinal glucose absorption, insulin secretion, peripheral insulin sensitivity, and suppression of endogenous glucose production over time [31]. In the early postprandial phase, glucose levels are largely determined by the rate of gastric emptying and intestinal carbohydrate absorption [32,33].

In healthy individuals, PPG rises following meal ingestion, typically peaking within 0.5–1 h, and subsequently declines over the next 2–3 h [3,34]. PPG levels generally return to baseline approximately 4 h post-meal (Figure 1) [34].

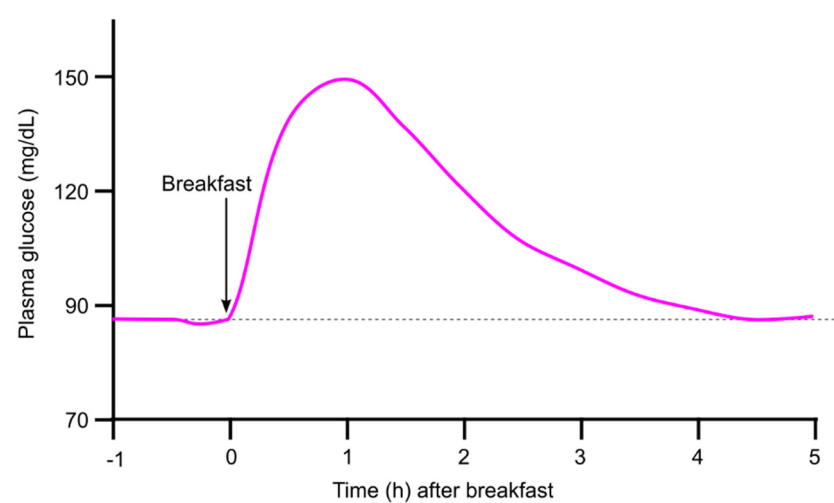


Figure 1. Postprandial plasma glucose (PPG) response in healthy individuals. Fifteen healthy participants consumed a standardized breakfast beginning at 10:00 AM, which was ingested within 5 minutes. The meal

consisted of a cheese omelet and a dextrose-containing beverage, providing an average of 84 g glucose, 10 g fat, and 26 g protein. The data was derived from [34].

Eichenlaub et al. [35] examined PPG dynamics in healthy individuals following consumption of three identical meals. Participants consumed either a standard diet or a high-carbohydrate diet (Figure 2). PPG levels returned to baseline within 3 h after the standard diet, whereas normalization occurred within 4 h following the high-carbohydrate diet. These findings suggest that plasma glucose generally reaches a homeostatic state approximately 4 h after meal intake in healthy individuals, regardless of meal timing or macronutrient composition. Supporting this concept, a large population-based study of 34,907 US adults from the general population demonstrated that PPG attained a relatively stable level 4 h post-meal [36].

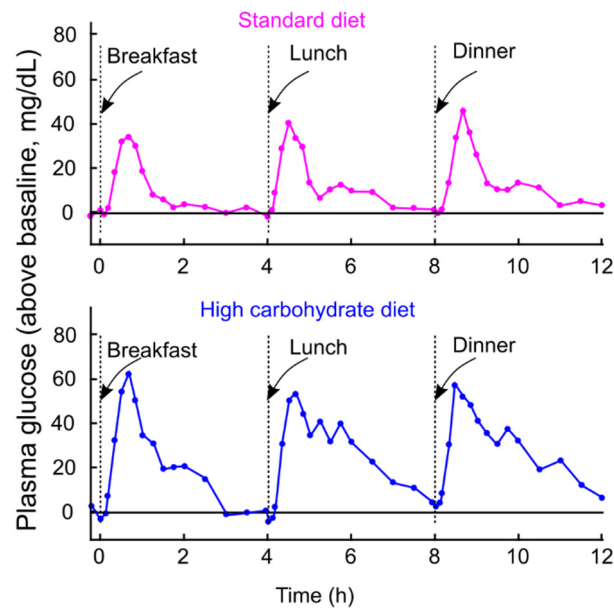


Figure 2. Postprandial glucose responses in healthy individuals following three identical meals. Participants consumed the same standardized meal for breakfast, lunch, and dinner, with meals separated by 4 h. **Upper panel:** Twelve participants consumed a standard diet with a macronutrient composition of 40% carbohydrate, 49% fat, and 11% protein. **Lower panel:** Ten participants consumed a high-carbohydrate diet with a macronutrient composition of 63% carbohydrate, 27% fat, and 10% protein. The figure is modified from [35], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 1 March 2026).

2.2. PPG Within 4 h After a Meal for Risk Prediction

Non-fasting plasma glucose has been proposed as a marker for risk prediction [37]. Several studies have reported that elevated PPG levels measured 1 or 2 h after breakfast [38–41] or 2 h after lunch [42] are associated with an increased risk of all-cause mortality. Similarly, higher PPG levels at 1 or 2 h after breakfast [38,39] or 2 h after lunch [42,43] have been linked to an elevated risk of CVD events.

Despite these associations, PPG measurements obtained 1 or 2 h after a meal have limited practicality for large-scale screening and routine clinical use. First, dietary variation in meal composition and quantity can alter PPG levels by more than 20 mg/dL, introducing substantial measurement variability [35]. Second, accurate timing of blood sampling at exactly 1 or 2 h after a meal is difficult to achieve in real-world settings, and even modest deviations (e.g., ± 0.5 h [41]) may lead to clinically meaningful differences, given the rapid fluctuations in glucose concentration during the early postprandial period [35]. Third, interindividual differences in digestion and metabolism,

combined with the absence of a universally accepted meal protocol for routine testing [44], further limit the interpretability and utility of PPG measured at 1 or 2 h post-meal. Consistent with these limitations, PPG measured at variable times within 0–3.9 hours after a meal was not associated with cardiovascular or cancer mortality in US adults from the general population [36,45].

3. PPG Levels Are Stable Between 4 and 7.9 h After a Meal

Postprandial glucose concentrations 4 h after meal ingestion are increasingly influenced by peripheral insulin sensitivity and hepatic glucose output, including both gluconeogenesis and glycogenolysis. Although in most individuals, intestinal glucose absorption is largely complete within 4 h, delayed gastric emptying can prolong carbohydrate delivery to the intestine and extend the contribution of exogenous glucose to circulating levels in a subset of individuals [32,46].

Postprandial plasma glucose levels measured between 4 and 7.9 h (PPG_{4-7.9h}) exhibit relative stability during this interval (Figure 3) [45,47,48]. Consequently, this late postprandial, non-fasting time window may offer a distinct and practical opportunity for glucose assessment and cardiometabolic risk stratification.

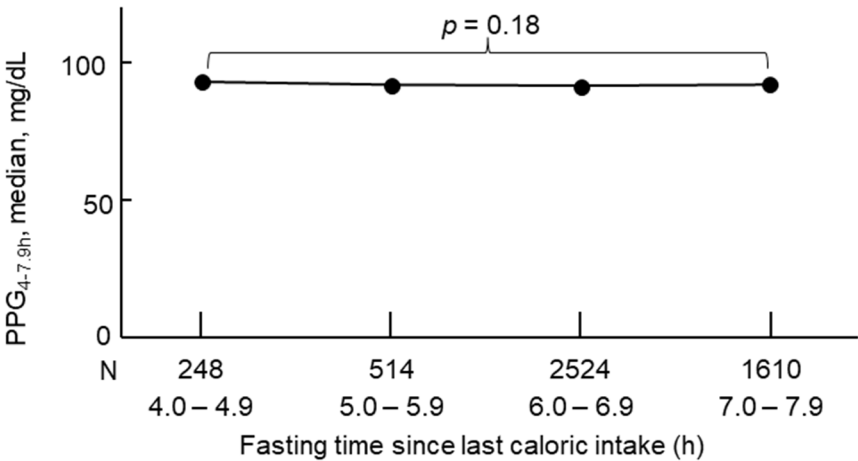


Figure 3. Hourly average of PPG_{4-7.9h}. PPG_{4-7.9h}, postprandial plasma glucose measured 4–7.9 h after a meal. The figure is from [48], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 1 March 2026).

4. Clinical Significance of PPG_{4-7.9h}

4.1. PPG_{4-7.9h} for Diabetes Diagnosis

The diagnostic utility of PPG_{4-7.9h} remains to be fully established. A recent study evaluated whether estimated PPG_{4-7.9h} could be used for diabetes diagnosis [47]. In that study, two participant groups were analyzed. Group 1 (*n* = 4420) had measured PPG_{4-7.9h} values, whereas Group 2 (*n* = 8422) lacked PPG_{4-7.9h} measurements but had complete data for traditional diabetes diagnostic tests [47]. Using data from Group 1, a multiple linear regression model was developed to estimate PPG_{4-7.9h}, achieving an accuracy within 11 mg/dL in 80% of participants. This model was subsequently applied to Group 2 to generate estimated PPG_{4-7.9h} values for each individual. Receiver operating characteristic analysis demonstrated that estimated PPG_{4-7.9h} identified diabetes with an overall accuracy of 87.3%, a sensitivity of 75.1%, a specificity of 84.1%, and an optimal cutoff value of 102.5 mg/dL (Figure 4) [47]. This performance falls within the “excellent” diagnostic accuracy range of 80–90% [49,50].

By comparison, the diagnostic accuracy of HbA_{1c} for diabetes has been reported to be approximately 65% [51], and an HbA_{1c} threshold ≥6.5% yields sensitivities ranging from 35% to 50% [52,53]. Similarly, a fasting plasma glucose threshold ≥126 mg/dL detects OGTT-diagnosed diabetes with sensitivities between 40% and 70% [54–56]. Importantly, PPG_{4-7.9h} is a non-fasting measure,

offering greater convenience than fasting tests, and its measurement is less costly than HbA_{1c} testing [57,58]. Collectively, these findings suggest that establishing PPG_{4-7.9h} as an additional diagnostic marker for diabetes may have meaningful clinical relevance [47].

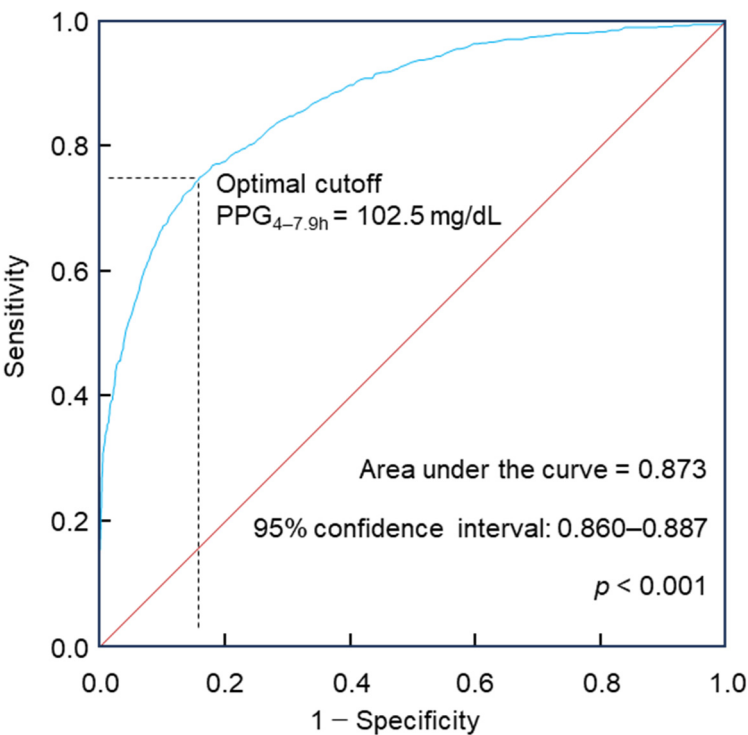


Figure 4. The predictive value of estimated PPG_{4-7.9h} for diabetes. PPG_{4-7.9h}, postprandial plasma glucose measured 4–7.9 h after meal consumption. The figure is from [47], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 1 March 2026).

Notably, the optimal cutoff value of 102.5 mg/dL for estimated PPG_{4-7.9h} is substantially lower than the current fasting plasma glucose threshold of 126 mg/dL used for diabetes diagnosis [3,59]. This finding is consistent with prior reports. For example, Peter et al. [60] observed mean PPG_{4-7.9h} (measured 4 h post-meal) and fasting plasma glucose concentrations of 102 mg/dL and 127 mg/dL, respectively, in individuals with mild type 2 diabetes. Similarly, Avignon et al. [61] reported corresponding values of 104 mg/dL for PPG_{4-7.9h} and 133 mg/dL for fasting plasma glucose in patients with mild type 2 diabetes, with PPG_{4-7.9h} assessed 5 h after lunch. Collectively, these data indicate that the proposed PPG_{4-7.9h} cutoff of 102.5 mg/dL aligns closely with the reported range of 102–104 mg/dL observed in individuals with early-stage type 2 diabetes [60,61].

The physiological basis for the higher fasting plasma glucose levels relative to PPG_{4-7.9h} remains incompletely understood. However, this difference may be partially attributable to the “dawn phenomenon” [62], characterized by a transient early-morning rise in glucose levels driven by increased hepatic glycogenolysis and gluconeogenesis in individuals with diabetes [63].

4.2. PPG_{4-7.9h} for Mortality Risk Prediction From CVD and Diabetes

The prognostic value of PPG_{4-7.9h} for mortality risk was evaluated in 4896 US adults [48]. Higher PPG_{4-7.9h} levels were positively associated with mortality from hypertension, diabetes, and CVD (Figure 5). Importantly, the associations with hypertension- and CVD-related mortality remained significant after adjustment for HbA_{1c}. In contrast, the association between PPG_{4-7.9h} and diabetes-related mortality was attenuated after adjustment for HbA_{1c} (Figure 5).

Notably, similar associations were observed among participants without a prior diagnosis of myocardial infarction or stroke, supporting the hypothesis that elevated PPG_{4-7.9h} may contribute to the development of incident CVD rather than merely reflecting established pathology.

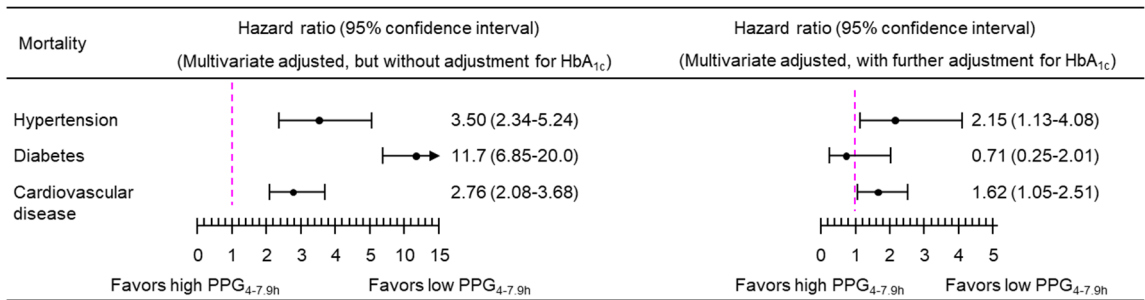


Figure 5. A one-natural-log-unit increase in PPG_{4-7.9h}-associated mortality risk in 4896 participants. HbA_{1c}, hemoglobin A_{1c}; PPG_{4-7.9h}, postprandial plasma glucose measured 4–7.9 h after a meal. The image is from [48], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 1 March 2026).

4.3. PPG_{4-7.9h} for Mortality Risk Prediction From Cancer

The prognostic value of PPG_{4-7.9h} for cancer mortality was evaluated in 4648 US adults from the general population [45]. Higher PPG_{4-7.9h} levels were significantly associated with an increased multivariable-adjusted risk of cancer mortality, with a 1-natural-log-unit increase corresponding to a hazard ratio of 2.00 (95% confidence interval, 1.09–3.67). In contrast, fasting plasma glucose, PPG measured within 0–3.9 h after a meal, HbA_{1c}, and insulin were not associated with cancer mortality in this cohort [45]. Notably, the association between PPG_{4-7.9h} and cancer mortality remained robust after additional adjustment for HbA_{1c}, indicating superior predictive capacity of PPG_{4-7.9h} for cancer mortality.

The same study also identified PPG_{4-7.9h} thresholds for cancer risk stratification according to HbA_{1c} categories (<5.7%, 5.7–6.4%, ≥6.5%). The corresponding PPG_{4-7.9h} categories were defined as <94 mg/dL (normal), 94–100 mg/dL (borderline high), and ≥101 mg/dL (high) [45]. Compared with individuals with normal PPG_{4-7.9h}, those with high PPG_{4-7.9h} (≥101 mg/dL) exhibited a 41% higher risk of cancer mortality [45].

Moreover, elevated PPG_{4-7.9h} appeared to be related to the development of new cancers. Among participants without a prior cancer diagnosis, high PPG_{4-7.9h} was associated with a 45% higher risk of cancer mortality relative to normal PPG_{4-7.9h}. In contrast, among the 413 participants with a prior cancer diagnosis, PPG_{4-7.9h} was associated with a non-significant increase in cancer mortality (high vs. normal PPG_{4-7.9h}: hazard ratio, 1.64; 95% confidence interval, 0.88–3.07; p = 0.12) [45], likely reflecting limited statistical power due to small sample size.

5. Two-hour Plasma Glucose During OGTT Performed Between 4 and 7.9 h After a Meal (2-h PG_{OGTT@4-7.9h})

5.1. 2-h PG_{OGTT@4-7.9h} for Diabetes Diagnosis

An OGTT is typically performed after at least 8 h of fasting. A recent study examined the potential clinical utility of 2-h plasma glucose during an OGTT performed 4–7.9 h postprandially (termed 2-h PG_{OGTT@4-7.9h}), in a cohort of 2347 US adults [64]. In that study, 2-h PG_{OGTT@4-7.9h} exhibited a linear association with HbA_{1c} and was positively associated with an increased adjusted risk of HbA_{1c}-defined diabetes [64]. Receiver operating characteristic curve analysis demonstrated that 2-h PG_{OGTT@4-7.9h} predicted HbA_{1c}-diagnosed diabetes with an accuracy of 92% and an optimal cutoff value of 206.8 mg/dL (Figure 6), comparable to the performance of fasting 2-h OGTT glucose (accuracy =

95%, optimal cutoff = 203.6 mg/dL) [64]. Notably, diabetes was defined solely by HbA_{1c} in this analysis. Therefore, further studies incorporating comprehensive diagnostic criteria are warranted to determine whether 2-h PG_{OGTT@4-7.9h} can be reliably used for diabetes diagnosis.

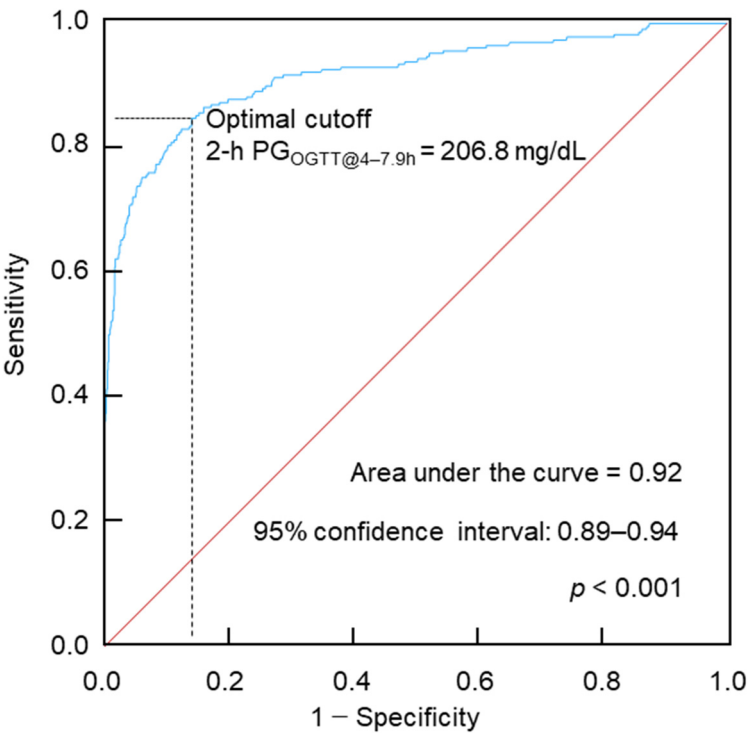


Figure 6. The predictive value of 2-h PG_{OGTT@4-7.9h} for diabetes (defined as hemoglobin A_{1c} ≥ 6.5%). The sensitivity was 84.8%, and the specificity was 86.1%, with an optimal cutoff of 206.8 mg/dL. 2-h PG_{OGTT@4-7.9h}, 2-h plasma glucose during an OGTT performed between 4 and 7.9 h after meal consumption. The image is from [64], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 19 January 2025).

5.2. 2-h PG_{OGTT@4-7.9h} for Prediabetes Risk

Based on the American Diabetes Association Criteria, individuals with an HbA_{1c} level between 5.7% and 6.4% can be defined as prediabetes. A one-square-root increase in 2-h PG_{OGTT@4-7.9h} was associated with a 13% higher adjusted risk of prediabetes defined by HbA_{1c} [64]. When analyzed as a dichotomous variable using a cutoff of 140 mg/dL, individuals with 2-h PG_{OGTT@4-7.9h} ≥140 mg/dL had a 29% higher adjusted risk of prediabetes compared with those with values <140 mg/dL [64]. Collectively, these findings suggest that 2-h PG_{OGTT@4-7.9h} may be a useful marker for identifying individuals at elevated risk of prediabetes.

5.3. 2-h PG_{OGTT@4-7.9h} for Mortality Risk Prediction

A one-square-root increase in 2-h PG_{OGTT@4-7.9h} was associated with a 6%, 46%, and 7% higher risk of mortality from all causes, diabetes, and CVD, respectively (Table 1) [64]. The associations between 2-h PG_{OGTT@4-7.9h} and both all-cause and diabetes-related mortality remained significant after adjustment for HbA_{1c}. In contrast, the association with CVD mortality was attenuated after adjustment for HbA_{1c}. No significant association was observed between 2-h PG_{OGTT@4-7.9h} and cancer mortality (Table 1).

Notably, the predictive performance of 2-h PG_{OGTT@4-7.9h} for CVD mortality was comparable to that of fasting 2-h OGTT glucose (Table 1). Moreover, 2-h PG_{OGTT@4-7.9h} appeared to be a stronger predictor of diabetes-related mortality than its fasting counterpart (hazard ratio, 1.46 vs. 1.29; Table 1) [64], highlighting its potential clinical value as a non-fasting prognostic marker.

Table 1. Association between 2-h plasma glucose during OGTT¹ with mortality, with or without adjustment for HbA_{1c}.

Mortality	Multivariate adjusted, without adjustment for HbA _{1c}			Multivariate adjusted, with further adjustment for HbA _{1c}		
	Hazard ratio	95% CI	<i>p</i>	Hazard ratio	95% CI	<i>p</i>
2-h PG _{OGTT@4–7.9h}						
All-cause mortality	1.06	1.04–1.08	<0.001	1.04	1.02–1.07	0.003
Diabetes mortality	1.46	1.33–1.61	<0.001	1.39	1.17–1.65	<0.001
CVD mortality	1.07	1.03–1.11	<0.001	1.03	0.98–1.08	0.26
Cancer mortality	1.00	0.95–1.05	1.00	1.02	0.96–1.07	0.58
2-h PG during OGTT after fasting						
All-cause mortality	1.06	1.04–1.07	<0.001	1.04	1.02–1.06	<0.001
Diabetes mortality	1.29	1.21–1.38	<0.001	1.26	1.12–1.43	<0.001
CVD mortality	1.06	1.03–1.09	<0.001	1.01	0.97–1.04	0.77
Cancer mortality	1.00	0.97–1.04	0.80	1.00	0.96–1.05	0.85

¹, square root transformed. 2-h PG_{OGTT@4–7.9h}, 2-h plasma glucose during an OGTT between 4 and 7.9 h after a meal; CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; OGTT, oral glucose tolerance test; PG, plasma glucose. The table is from [64], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 19 January 2025).

6. Mechanisms Linking Postprandial Hyperglycemia to Cardiovascular Disease

6.1. Postprandial Hyperglycemia Induces Changes in Glucose Metabolism

Postprandial hyperglycemia enhances glycolytic flux and induces excessive mitochondrial superoxide production [65]. The resulting increase in reactive oxygen species (ROS) inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thereby diverting glucose metabolites into alternative pathogenic pathways (Figure 7). These include: (1) the diacylglycerol (DAG) pathway, in which dihydroxyacetone phosphate is metabolized to generate increased levels of DAG, a key second-messenger molecule that activates protein kinase C signaling [66–71]; (2) the polyol pathway, in which glucose is reduced to sorbitol at the expense of reduced nicotinamide adenine dinucleotide phosphate (NADPH)—a critical cofactor for glutathione (GSH) recycling—thereby impairing cellular antioxidant defenses [72]. Flux through this pathway also promotes formation of the reactive carbonyl 3-deoxyglucosone [73,74], which contributes to the generation of advanced glycation end products (AGEs) [75,76]; (3) the methylglyoxal pathway, in which dihydroxyacetone phosphate is converted to methylglyoxal by methylglyoxal synthase [77,78], leading to AGE formation; and (4) the hexosamine biosynthetic pathway, which produces uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) [65,79]. UDP-GlcNAc serves as a substrate for protein O-GlcNAcylation, a post-translational modification that modulates cell signaling and gene transcription [80].

In parallel, hyperglycemia suppresses the pentose phosphate pathway (PPP). Hyperglycemia-induced oxidative stress inhibits glucose-6-phosphate dehydrogenase, the rate-limiting enzyme of the PPP [81,82]. As the PPP is a major source of cellular NADPH, its inhibition further compromises redox homeostasis and antioxidant capacity under hyperglycemic conditions (Figure 7).

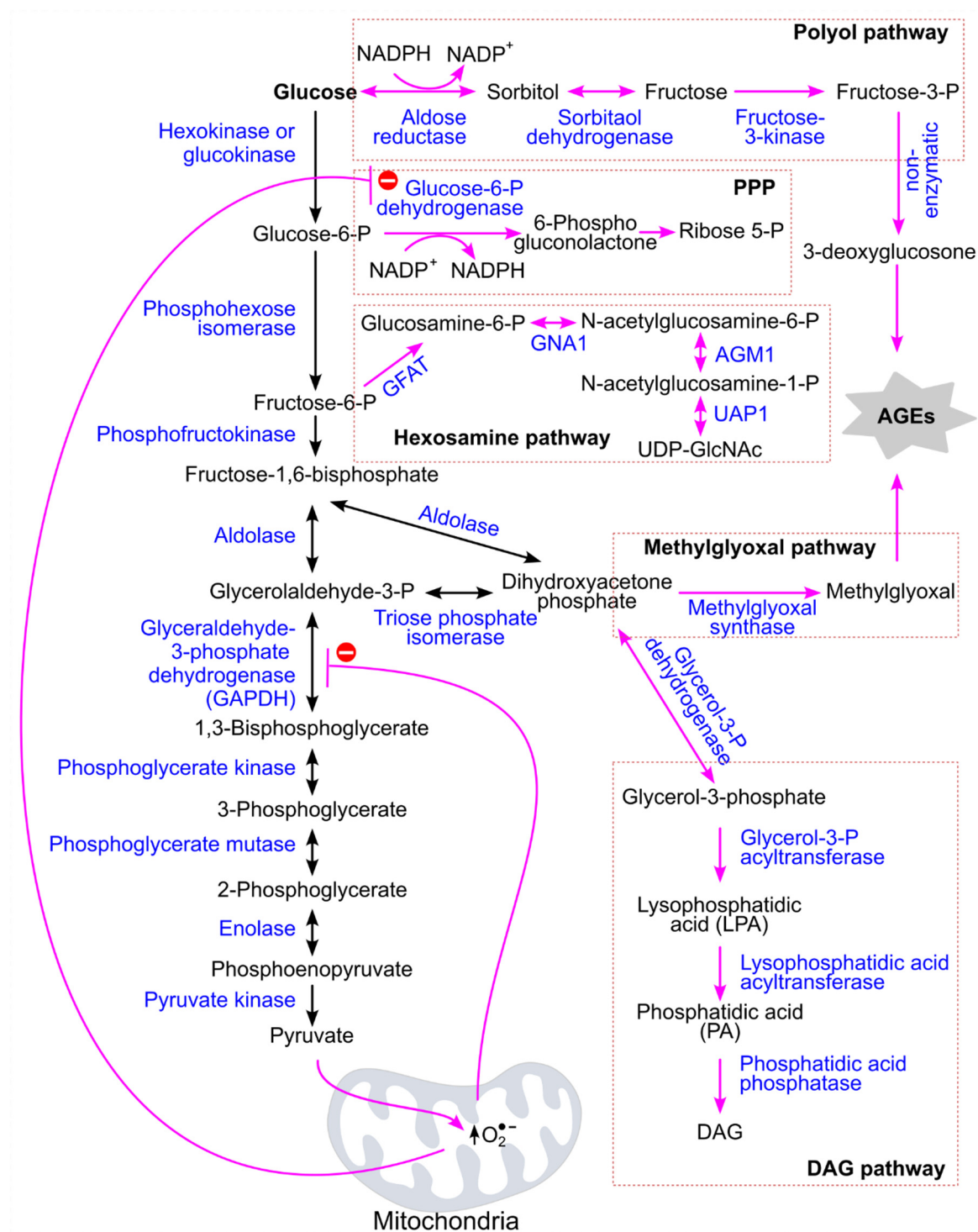


Figure 7. Glucose metabolism and alteration under postprandial hyperglycemia. Under normal conditions, most of the glucose undergoes glycolysis to produce pyruvate (left side of the figure), and the latter then enters mitochondria for the citric acid cycle reaction and ATP production. Under postprandial hyperglycemia, excess superoxide is generated in mitochondria, which then inhibits the enzyme GAPDH, decreasing glycolysis. Consequently, glucose metabolism is diverted to other pathways, including the polyol pathway, the hexosamine pathway, the methylglyoxal pathway, and the DAG pathway. In addition, increasing oxidative stress under the hyperglycemic condition inhibits glucose-6-phosphate dehydrogenase, and thus inhibits the pentose phosphate pathway, leading to decreased production of NADPH. Fuchsia colored arrows represent altered metabolism pathways due to hyperglycemia. Double-headed arrows indicate reversible reactions. Blue text represents enzymes for each reaction. AGEs, advanced glycation end products; AGM1, phosphoacetylglucosamine mutase; DAG, diacyl glycerol; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GFAT, glutamine:fructose-6-

phosphate aminotransferase; GNA1, glucosamine-6-phosphate acetyltransferase; LPA, lysophosphatidic acid; NADP⁺, oxidized nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate; P, phosphate; PA, phosphatidic acid; PPP, pentose phosphate pathway; UAP1, UDP-GlcNAc pyrophosphorylase; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine. The image is adapted from [83], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 1 March 2026).

6.2. Mechanisms Underlying Postprandial Hyperglycemia-Induced Increase in CVD Risks

PPG excursions contribute to CVD through mechanisms involving enhanced oxidative stress, inflammation, endothelial dysfunction, accelerated atherogenesis, and pro-thrombotic changes.

6.2.1. Postprandial Hyperglycemia Increases Oxidative Stress

Postprandial hyperglycemia promotes mitochondrial superoxide overproduction, thereby increasing oxidative stress [65,84]. Concurrently, hyperglycemia activates several metabolic pathways that generate reactive carbonyl species. Activation of the polyol pathway and the methylglyoxal pathway results in the overproduction of 3-deoxyglucosone [73,74] and methylglyoxal, respectively, both of which are highly reactive carbonyl compounds. In addition, postprandial hyperglycemia facilitates the formation of glyoxal through glucose auto-oxidation, contributing further to the cellular reactive carbonyl burden [85]. These reactive carbonyls readily modify intracellular and extracellular proteins by reacting with amino groups, leading to the formation of AGEs [75,76]. Subsequent engagement of AGEs with their cognate receptors (RAGEs) amplifies oxidative stress and triggers pro-inflammatory signaling cascades [76].

Postprandial hyperglycemia also disrupts cellular antioxidant defenses by reducing intracellular GSH levels (Figure 8), the cell's primary endogenous antioxidant. GSH directly neutralizes ROS and reactive nitrogen species (RNS)—including superoxide, hydrogen peroxide, hydroxyl radicals, nitric oxide, and peroxynitrite—via its redox-active thiol group [86,87]. The pentose phosphate pathway (PPP; Figure 7) plays a critical role in maintaining redox homeostasis as the principal source of nicotinamide adenine dinucleotide phosphate (NADPH) [88]. Hyperglycemia suppresses PPP activity, thereby reducing NADPH production [81,82]. Simultaneously, increased flux through the polyol pathway further depletes NADPH due to its high reductive demand. The resulting NADPH deficiency compromises the capacity of glutathione reductase to regenerate reduced GSH from oxidized glutathione (GSSG) [89]. Consequently, intracellular GSH levels decline (Figure 8), leading to impaired antioxidant capacity and redox imbalance [90]. This failure of antioxidant defenses permits excessive accumulation of ROS, such as superoxide and hydrogen peroxide, thereby exacerbating cellular oxidative damage.

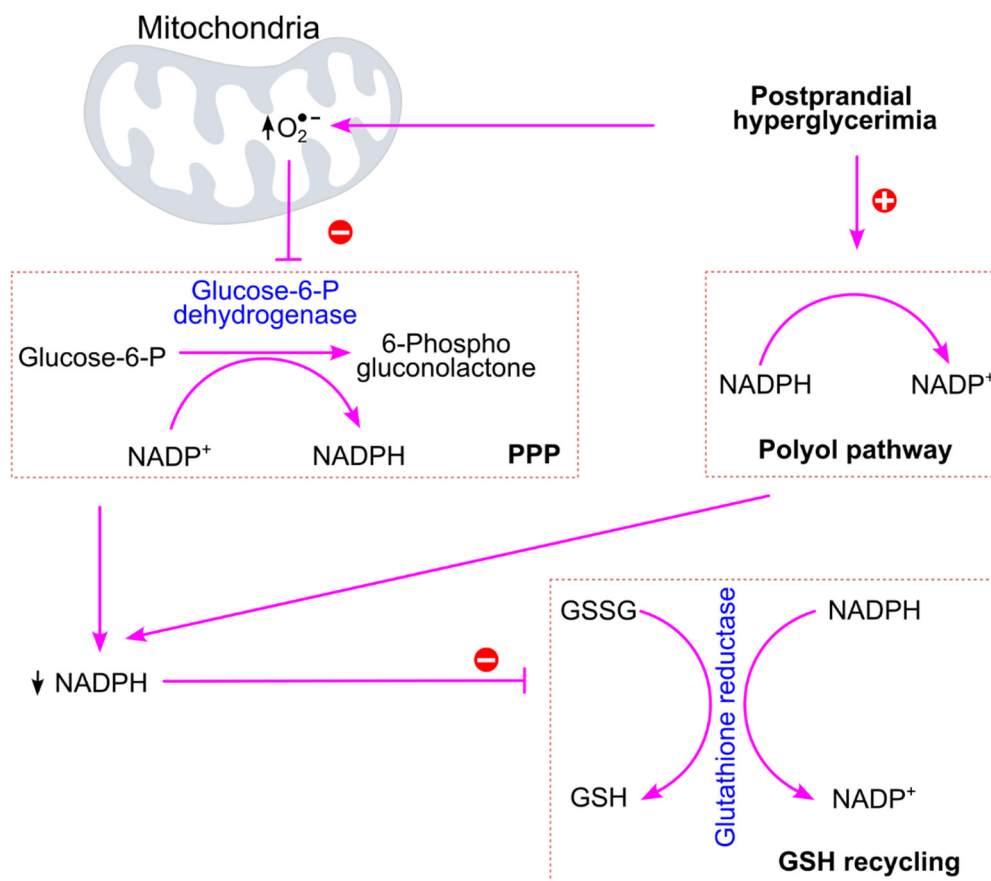


Figure 8. Postprandial hyperglycemia decreases cellular antioxidant capacity. Postprandial hyperglycemia inhibits the pentose phosphate pathway and consequently decreases NADPH production. In addition, it increases the polyol pathway and thus increases NADPH consumption. Therefore, postprandial hyperglycemia leads to NADPH deficiency, consequently decreasing cellular levels of GSH and cellular antioxidant capacity. Blue text represents enzymes for each reaction. GSH, reduced glutathione; GSSG, glutathione disulfide; NADP⁺, oxidized nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate; O₂^{•-}, superoxide; P, phosphate; PPP, pentose phosphate pathway.

6.2.2. Postprandial Hyperglycemia Leads to Activation of Inflammatory Pathways

Postprandial hyperglycemia increases inflammation in humans, as indicated by an increase in high-sensitivity C-reactive protein [91,92]. Hyperglycemia increases superoxide production, which activates nuclear factor- κ B (NF- κ B) [93], a transcriptional factor, in endothelial and mononuclear cells [94,95], upregulating adhesion molecules such as monocyte chemoattractant protein 1 (MCP-1), vascular cell adhesion protein 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1) [96,97]. In addition, NF- κ B increases the transcription of inflammatory mediators [e.g., interleukin-1 (IL-1), IL-6, and tumor necrosis factor- α (TNF- α)] and increases their circulating concentrations [98,99].

Postprandial hyperglycemia activates the DAG-protein kinase C pathway [100–102], AGE pathways [103], and the hexosamine pathway [80]. These pathways can activate NF- κ B, leading to leukocyte adhesion and inflammation.

6.2.3. Postprandial Hyperglycemia Leads to Endothelial Dysfunction

Spikes of postprandial glucose can induce endothelial dysfunction in both healthy [104,105] and diabetic individuals [106]. The high glucose-induced endothelial dysfunction is due to increased ROS production, as endothelial dysfunction is prevented by ROS scavengers such as GSH [104], superoxide dismutase, and catalase [107,108]. Acute glucose excursion-induced endothelial dysfunction may involve a reduced availability of nitric oxide (NO), as this dysfunction could be

alleviated by arginine [109]. Therefore, the underlying mechanism for hyperglycemia-induced endothelial dysfunction is largely derived from an increase in ROS production and a decrease in cellular antioxidant capacity.

6.2.4. Postprandial Hyperglycemia Promotes Atherogenesis

Postprandial hyperglycemia leads to endothelial dysfunction, and the latter contributes to atherosclerosis [66,110]. It also promotes LDL oxidation [104,111,112], resulting from excessive ROS production [106,111]. Oxidized LDL is a major driver of atherosclerosis [113]. Postprandial hyperglycemia increases the production of reactive carbonyl species via the polyol pathway [73,74] and the methylglyoxal pathway [77,78]. The increase in reactive carbonyl species results in the production of AGEs, and the latter bind to RAGEs and amplify oxidative stress and inflammation, thus promoting atherosclerosis [114]. Postprandial hyperglycemia may predict atherosclerosis better than its fasting counterpart or HbA_{1c} [115].

6.2.5. Postprandial Hyperglycemia Enhances Thrombotic Events

Postprandial hyperglycemia leads to a prothrombotic state, which has been reviewed previously [116]. In summary, postprandial hyperglycemia can result in platelet hypersensitivity, enhanced levels of pro-coagulation mediators (e.g., tissue factor and thrombin), and decreased fibrinolysis [116]. Therefore, postprandial hyperglycemia could lead to the development of fibrinolysis-resistant clots and increase the risk of CVD. Postprandial hyperglycemia may be a stronger predictor of thrombotic events than fasting plasma glucose [96].

7. Mechanisms Linking Postprandial Hyperglycemia to Cancer

Diabetes is associated with high mortality in patients with various cancers [16–19]. Cancer incidence is increasing in people with diabetes [13–15]. It has been reported that PPG is a better predictor of cancer mortality than fasting glucose or HbA_{1c} [45], highlighting the danger of post-meal spikes. The mechanisms underlying hyperglycemia-associated increase in cancer risk are not well understood, but it may result from an increase in oxidative stress, circulating insulin, and lipogenesis [117].

7.1. Postprandial Hyperglycemia Increases ROS Production and Inflammation

Postprandial hyperglycemia increases ROS production via mitochondria, which results in DNA damage, contributing to cancer formation [15,118]. Hyperglycemia can increase the formation of AGEs, and the latter increase cancer risk [119]. AGEs bind to RAGEs, leading to activation of NADPH oxidase. Activated NADPH oxidase promotes ROS production [120], causing DNA damage and mutation, and promoting tumorigenesis [121,122]. In addition, activation of NADPH oxidase leads to activation of transcriptional factor NF- κ B, which increases gene expression of proinflammatory cytokines and chemokines such as IL-6, TNF- α , and MCP-1 [121,123,124], and forms a chronic inflammatory microenvironment to facilitate cancer cell proliferation (Figure 9).

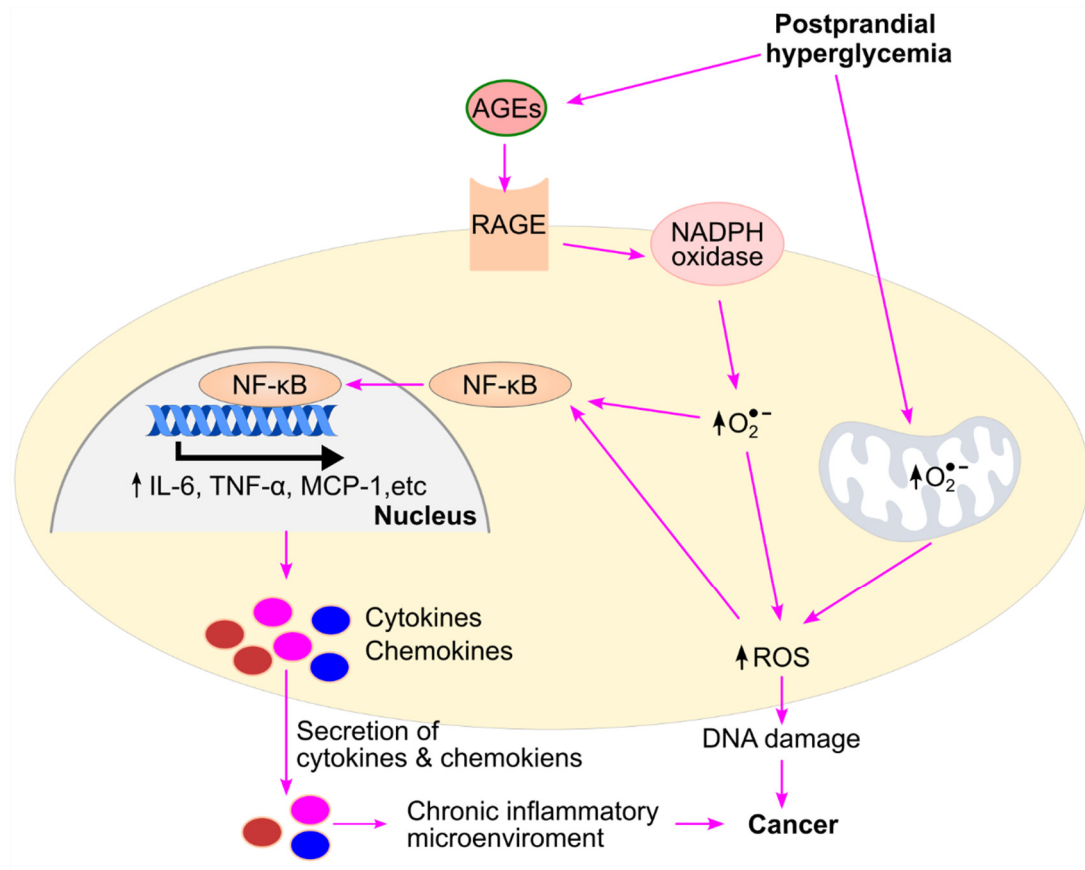


Figure 9. Postprandial hyperglycemia promotes cancer formation via increasing ROS production. ↑, increase; AGE, advanced glycation end product; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NF- κ B, nuclear factor- κ B; $O_2^{\bullet-}$, superoxide; RAGE, receptor for advanced glycation end-product; ROS, reactive oxygen species; TNF- α , tumor necrosis factor-alpha.

7.2. Postprandial Hyperglycemia Promotes Cancer Proliferation Through Increased Circulating Insulin

Postprandial hyperglycemia leads to an increase in circulating insulin, which acts via insulin receptors to directly promote tumor growth [125]. Activation of the insulin receptor leads to the activation of the phosphatidylinositol 3-kinase/protein kinase B/ mammalian target of rapamycin (PI3K/AKT/ mTOR) pathway, leading to cancer cell proliferation [126–128]. Activation of the insulin receptor can also activate Ras/MAPK (mitogen-activated protein kinase) cascade and promote cancer cell proliferation [129]. Moreover, high insulin can increase the levels of insulin-like growth factor-1, and the latter can also activate Ras/MAPK cascade to promote cancer cell proliferation [130].

7.3. Postprandial Hyperglycemia Drives Lipogenesis to Support Cancer Cell Proliferation

Excess postprandial glucose is converted into fatty acids and triglycerides [83]. High triglycerides are positively associated with diabetes incidence and mortality [131–133]. In addition, higher mortality risks for certain cancers, such as gastric cancer [18]. In addition, increased fatty acid formation promotes the formation of membrane lipids such as phospholipids and glycolipids (Figure 10). Thus, postprandial hyperglycemia may be a significant driver of cancer progression by providing necessary components for cell membrane formation, which are critical for the uncontrolled growth of cancer cells. Postprandial hyperglycemia can enhance lipogenesis via transcriptional regulation, which has been reviewed recently and summarized in Figure 11 [83]. Importantly, hyperglycemia can activate two transcriptional factors—sterol regulatory element-binding protein (SREBP) and carbohydrate response element-binding protein (ChREBP)—to enhance expression of genes involved

in fatty acid synthesis, including acetyl-CoA carboxylase, ATP citrate lyase, fatty acid synthase [127,128].

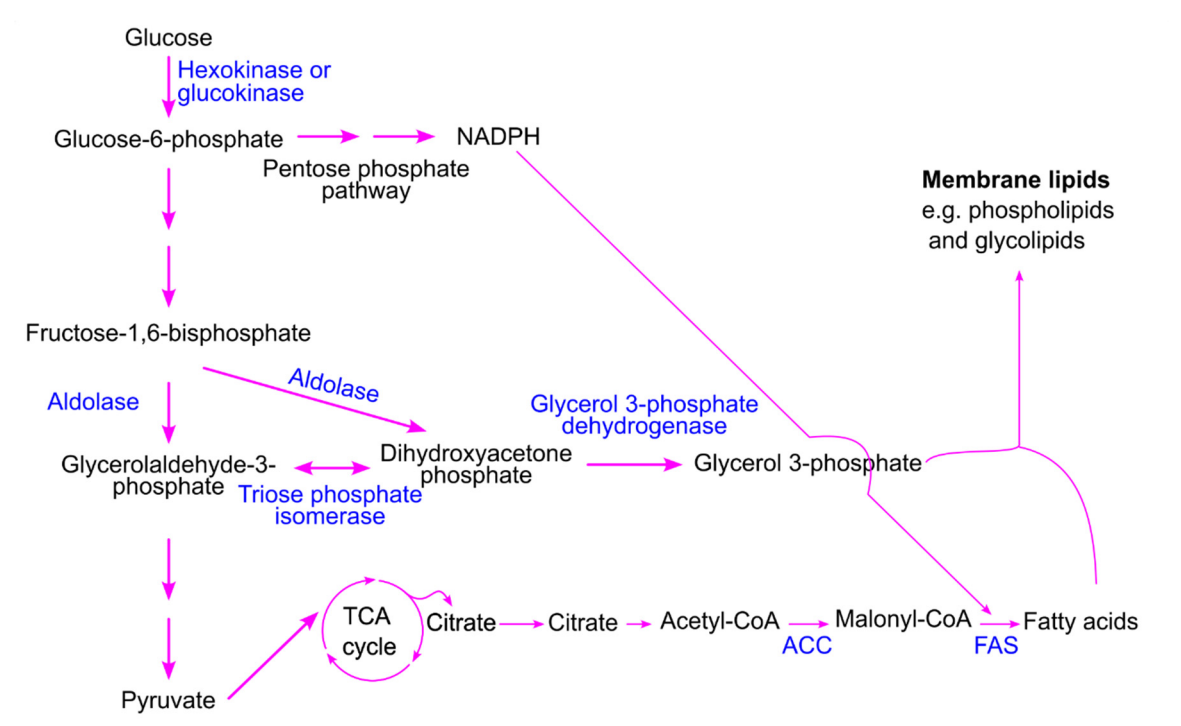


Figure 10. Cellular conversion of excess glucose to membrane lipids. ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; NADPH, reduced nicotinamide adenine dinucleotide phosphate; TCA, tricarboxylic acid. Blue text represents enzymes. The image is adapted from [83], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 1 March 2026).

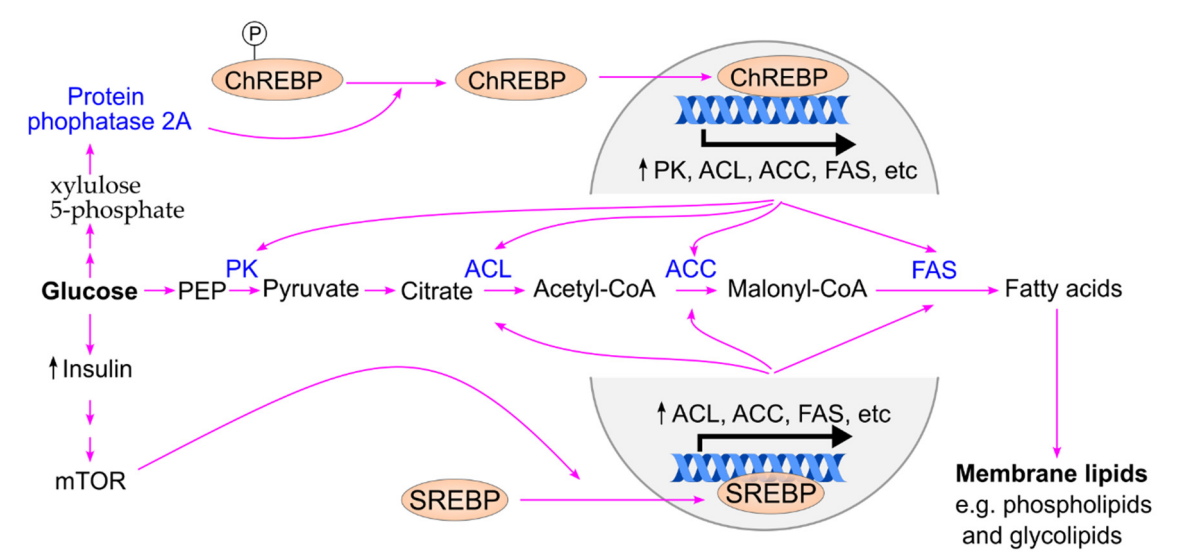


Figure 11. Chronic high postprandial glucose levels promote membrane lipid synthesis via transcriptional regulation. Elevated glucose stimulates the expression of genes involved in lipid synthesis by activating two transcriptional factors: carbohydrate response element binding protein (ChREBP) and sterol regulatory element binding protein (SREBP). ↑, increase; ACC, acetyl-CoA carboxylase; ACL, ATP citrate lyase; FAS, fatty acid synthase; mTOR, mammalian target of rapamycin; P, phosphate; PEP, phosphoenopyruvate; PK, pyruvate kinase. Blue text represents enzymes. The image is adapted from [83], which was published under the terms of the Creative Commons CC BY 4.0 DEED (<https://creativecommons.org/licenses/by/4.0/>, accessed on 1 March 2026).

8. Future Research

More research needs to be conducted to diagnose, prevent, and treat diabetes and diabetes associated complications [134–136]. The true diagnostic performance of PPG_{4–7.9h} and 2-h PG_{OGTT@4–7.9h} remains uncertain. To date, the diagnostic accuracy of PPG_{4–7.9h} has been evaluated using estimated rather than directly measured values, while the performance of 2-h PG_{OGTT@4–7.9h} has been examined using HbA_{1c}-defined diabetes as the reference standard. Consequently, definitive conclusions regarding their diagnostic validity cannot yet be drawn. Future investigations should employ more rigorous study designs, ideally incorporating cohorts in which each participant undergoes comprehensive assessment with all established diabetes diagnostic tests alongside these two non-fasting glucose measures. In addition, further research is required to determine whether PPG_{4–7.9h} and 2-h PG_{OGTT@4–7.9h} can reliably identify individuals at high risk of prediabetes.

Both PPG_{4–7.9h} and 2-h PG_{OGTT@4–7.9h} have demonstrated associations with cardiovascular mortality risk in US adults. However, the generalizability of these findings to other populations remains unknown and this warrants investigation. Moreover, whether these non-fasting glucose measures can predict incident CVD and cancer has yet to be established and should be addressed in future prospective studies.

9. Conclusions

Recent evidence indicates that the postprandial interval of 4–7.9 hours may represent a critical window for diabetes diagnosis and for stratifying risk of CVD and cancer. Nevertheless, these observations require confirmation in studies employing more rigorous designs and encompassing diverse populations. Notably, several clinical guidelines have shifted from fasting lipid measurements toward non-fasting testing paradigms [24–27,137]. In this context, evaluating the clinical utility of non-fasting glucose measures—specifically PPG_{4–7.9h} and 2-h PG_{OGTT@4–7.9h}—has substantial translational relevance.

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Abbreviations

The following abbreviations are used in this manuscript:

2-h PG _{OGTT@4–7.9h}	2-hour plasma glucose during an OGTT performed between 4 and 7.9 hours after a meal
ACC	acetyl-CoA carboxylase
ACL	ATP citrate lyase
AGE	advanced glycation end product
AGM1	phosphoacetylglucosamine mutase
CI	confidence interval
CVD	cardiovascular disease

DAG	diacyl glycerol
FAS	fatty acid synthase
GSH	reduced glutathione
GSSG	glutathione disulfide
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GFAT	glutamine:fructose-6-phosphate aminotransferase
GNA1	GlcN-6P acetyltransferase
h	hour
HbA _{1c}	hemoglobin A _{1c}
HDL	high-density lipoprotein
HR	hazard ratio
ICAM-1	intercellular adhesion molecule 1
IL	interleukin
LDL	low-density lipoprotein
LPA	lysophosphatidic acid
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein-1
mTOR	mammalian target of rapamycin
NADP ⁺	oxidized nicotinamide adenine dinucleotide phosphate
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NF-κB	nuclear factor-κB
O ₂ •	superoxide
NO	nitric oxide
OGTT	oral glucose tolerance test
P	phosphate
PA	phosphatidic acid
PEP	phosphoenopyruvate
PK	pyruvate kinase
PPG	postprandial plasma glucose
PPG _{4-7.9h}	postprandial plasma glucose measured 4–7.9 hours after a meal
PPP	pentose phosphate pathway
RAGE	receptor for advanced glycation end-product
ROS	reactive oxygen species
T2DM	type 2 diabetes mellites
TCA	tricarboxylic acid
TNF-α	tumor necrosis factor-alpha
UAP1	UDP-GlcNAc pyrophosphorylase
UDP-GlcNAc	uridine diphosphate N-acetylglucosamine
VCAM-1	vascular cell adhesion protein 1

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