One-Hour Postload Hyperglycemia: Implications for Prediction and Prevention of Type 2 Diabetes

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Context: Recently, a value of 1-hour postload glucose concentration (1-h-PG) ≥155 mg/dL (8.6 mmol/L) in individuals with normal glucose tolerance (NGT) has been found to be associated with an increased risk for future type 2 diabetes mellitus (T2DM). In this review, we analyze the implication of 1-h-PG determination in prediction of T2DM and cardiovascular disease.

Design: A literature search was performed using MEDLINE. We included all English studies published up to February 2018 in peer-reviewed journals that examined the relationship between 1-h-PG and diabetes, cardiometabolic alterations, organ damage, and cardiovascular disease.

Results: Several longitudinal studies have consistently shown that 1-h-PG ≥155 mg/dL can recognize individuals at increased risk for future T2DM among subjects with NGT. Additionally, we describe the pathophysiological abnormalities associated with 1-h-PG ≥155 mg/dL including impaired insulin sensitivity, β-cell dysfunction, and increased glucose intestinal absorption, which are known to be involved in T2DM pathogenesis. Importantly, numerous studies have demonstrated that a value of 1-h-PG ≥155 mg/dL in individuals with NGT is not only linked to an increased risk for future T2DM, but also able to identify those having a worse cardiovascular phenotype and an increased risk of adverse cardiovascular outcomes.

Conclusions: Although 1-h-PG determination is not currently recommended by the American Diabetes Association for identifying high-risk individuals, the available evidence indicates that a value of 1-h-PG ≥155 mg/dL may be a useful tool to recognize, among subjects with NGT, those at increased risk of T2DM and cardiovascular disease. (***J Clin Endocrinol Metab*** **103: 3131–3143, 2018)**

The prevalence of type 2 diabetes mellitus (T2DM) and of the related conditions of high risk of developing the disease (the so-called prediabetes) continues to increase worldwide (1). Early detection of individuals at risk for T2DM is critical not only because the progression to full-blown disease is preventable through lifestyle and/or pharmacologic interventions (2–4), but also to prevent or delay microvascular and cardiovascular complications associated with both T2DM and prediabetes (5, 6). Diagnostic criteria for prediabetes conditions have changed over time (7–9). In

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Abbreviations: 1-h-PG, 1-hour postload glucose concentration; 2-h-PG, 2-hour postload glucose concentration; 25(OH)D, 25-hydroxyvitamin D; ADA, American Diabetes Association; ALT, alanine aminotransferase; BMI, body mass index; CATAMERI, Catanzaro Metabolic Risk Factors; cIMT, carotid intima–media thickness; GGT, γ-glutamyltransferase; HbA1c, glycated Hb; HDL, high-density lipoprotein; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; Israel GOH Study, Israel Study of Glucose Intolerance, Obesity, and Hypertension; MPP, Malmö Preventive Project; NAFLD, nonalcoholic fatty liver disease; NGT, normal glucose tolerance; NGT-1h-high, normal glucose tolerance with 1-hour postload glucose concentration ≥155 mg/dL; NGT-1h-low, normal glucose tolerance with 1-hour postload glucose concentration <155 mg/dL; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; SGLT-1, sodium/glucose cotransporter 1; T2DM, type 2 diabetes mellitus.

2010, the American Diabetes Association (ADA) has revised criteria for the identification of individuals at increased risk for T2DM and proposed a glycated Hb (HbA1c) value of 5.7% to 6.4% (39 to 46 mmol/mol) as a new indicator of prediabetes, in addition to impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (9).

Recently, a large body of evidence has shown that higher levels of plasma glucose concentration at 1 hour during an oral glucose tolerance test (OGTT) are associated with an increased risk for future T2DM. In this regard, different 1-hour postload glucose concentration (1-h-PG) cut-off values have been proposed for identification of high-risk individuals, and a value of 1-h-PG ≥155 mg/dL (8.6 mmol/L) has emerged as a reliable glycemic marker capable to recognize among individuals with normal glucose tolerance (NGT) those at increased risk for future T2DM [NGT with 1-hour PG ≥155 mg/dL (NGT-1h-high)] (10–15).

Although determination of 1-h-PG values is not recommended by the current ADA criteria for identifying adults at increased risk of T2DM (9), the potential contribution of this parameter to the diagnosis of dysglycemic conditions was previously appreciated, as indicated by its inclusion in the 1979 National Diabetes Data Group criteria for the diagnosis of IGT and T2DM (16). Thereafter, the World Health Organization deemed this criterion unnecessary (17).

Taking into account the large and increasing number of studies demonstrating the link between 1-h-PG and future T2DM and cardiovascular disease, we carried out a review with the purpose to analyze the implication of measurement of 1-h-PG in prediction of T2DM and cardiovascular disease.

Materials and Methods

A literature search was performed using MEDLINE. Details regarding search strategy, inclusion/exclusion criteria, assessment of studies quality by the Newcastle-Ottawa Scale (18), and statistical analysis are described in Supplemental Materials.

Results

Epidemiology of 1-h-PG ≥155 mg/dL

Several observational studies in different ethnic groups have analyzed the frequency of 1-h-PG ≥155 mg/dL across glucose tolerance categories (Table 1) (10–12, 15, 19–27). In the population-based San Antonio Heart

Table 1. Proportion of Subjects With NGT and a 1-h-PG ≥155 mg/dL in Different Studies

Study Name	Population Characteristics	Number of Participants	Proportion of Individuals With NGT and 1-h Postload Plasma Glucose <155 mg/dL (%)	Proportion of Individuals With NGT and 1-h Postload Plasma Glucose ≥155 mg/dL (%)
San Antonio Heart Study (10)	Adult Mexican-American population	1611	83.3	16.7
Botnia Study (11)	Adult Scandinavian white population	2442	84.2	15.8
Chiba Foundation for Health Promotion and Disease Prevention (19)	Japanese nonindustrial workers	4970	89.2	10.8
CATAMERI study (20)	Adult white individuals carrying at least one cardiovascular risk factor	3020	74.6	25.4
Section of Endocrinology, University of Florence (21)	Adult white individuals	1062	76.0	24.0
Genetics, Physiopathology, and Evolution of Type 2 Diabetes (GENFIEV) (23)	Adult white individuals at high risk of T2DM	926	61.0	39.0
Israel GOH Study (15)	Adult individuals of mixed ethnic origin	853	74.6	25.4
Dr. Mohan's Diabetes Specialties Centre (12)	Asian Indian adults at high risk of T2DM	1179	57.5	42.5
New York University Langone Diabetes and Endocrine Associates (24)	Adult individuals at high risk of T2DM	236	71.1	28.9
MPP (25)	Adult white men	4934	66.8	33.2
Study of Latino Adolescents at Risk (SOLAR) study (26)	Latino children with obesity	233	74.8	35.2
Endocrinology and Diabetology Unit, Bambino Gesu Children's Hospital (27)	Italian youth who are overweight/with obesity (≤18 y)	1038	89.0	11.0

Abbreviations: CATAMERI, Catanzaro Metabolic Risk Factors; Israel GOH Study, Israel Study of Glucose Intolerance, Obesity, and Hypertension; MPP, Malmö Preventive Project.

Study comprising 1611 Mexican-Americans, a 1-h-PG value ≥155 mg/dL occurred in 16.7% of subjects with NGT, 57.7% and 73.4% of those with IFG and IGT, respectively (10). Similarly, in the population-based Botnia Study including 2442 white individuals, the prevalence of individuals with a 1-h-PG level ≥155 mg/dL was 15.8% among subjects with NGT, 34.3% among those with isolated IFG, 81.3% in the isolated IGT group, and 79.2% in the combined IFG + IGT group (11). In the Catanzaro Metabolic Risk Factors (CATAMERI) study comprising 3020 adult white individuals carrying at least one cardiovascular risk factor, the frequency of individuals with 1-h-PG ≥155 mg/dL ranged from 25.4% in the NGT group to 56.6% in the isolated IFG group, 77.6% in the isolated IGT group, 93.8% in the combined IFG + IGT group, and 98.8% among newly diagnosed T2DM subjects (20). These data suggest that a 1-h-PG ≥155 mg/dL may be an earlier biomarker of dysglycemia than IGT in the lengthy trajectory from prediabetes to T2DM. A higher frequency of individuals with 1-h-PG ≥155 mg/dL occurs also among subjects with prediabetes according to the HbA1c criteria (HbA1c: 5.7% to 6.4%). Indeed, in the CATAMERI study, a 1-h-PG value ≥155 mg/dL was observed in 71.0% of individuals having HbA1c-defined prediabetes, and in 40.9% of those with HbA1c level <5.7% (22). In the Israel Study of Glucose Intolerance, Obesity, and Hypertension (Israel GOH Study) including 853 individuals of mixed ethnic origin, the prevalence of 1-h-PG ≥155 mg/dL was 25.4% and 78.9% in the NGT and IGT groups, respectively (15). Moreover, in 236 individuals referred to the New York University Langone Diabetes and Endocrine Associates for T2DM screening, the proportion of individuals having 1-h-PG ≥155 mg/dL was 28.9% among those with NGT, 60.5% among those with IFG, 94.4% and 85.5% among those having IGT and IFG + IGT, respectively, and 90% in the T2DM group (24). In the Malmö Preventive Project (MPP), a prospective population-based cohort study, a 1-h-PG ≥155 mg/dL was reported in 33.2% of individuals with NGT (25).

Thus, the frequency of subjects with NGT-1h-high varies on the basis of the study design, ranging from 11% to 16% in population-based studies (10, 11, 19) to 25% to 42% in cohorts enriched for high-risk subjects (12, 15, 20–26). In addition, all these studies have consistently shown that the frequency of individuals with 1-h-PG ≥155 mg/dL increases as glucose tolerance deteriorates, with almost all subjects with combined IFG + IGT or newly diagnosed T2DM having 1-hour postload hyperglycemia (≥155 mg/dL).

1-h-PG as a predictor of T2DM development

A number of longitudinal studies in different ethnic groups have shown that subjects with NGT-1h-high are at increased risk of developing T2DM as compared with subjects with NGT with 1-h-PG <155 mg/dL (NGT-1h-low) (Table 2). In 2007, Abdul-Ghani *et al.* (28) have shown that 1-h-PG measure has a greater ability to predict future T2DM as determined by the area under the receiver operating characteristic (ROC) curve than fasting and 2-hour postload glucose concentration (2-h-PG). This observation was confirmed by the Botnia study showing that 1-h-PG had a greater predictive power for future T2DM (area under the ROC curve: 0.795), as compared with both fasting plasma glucose (area under the ROC curve: 0.672) and 2-h-PG (area under the ROC curve: 0.688) (11). Likewise, using

Table 2. Longitudinal Studies Evaluating the Association Between 1-h-PG and T2DM

Study Name	Population Characteristics	Follow-Up	Number of Subjects
San Antonio Heart Study (28)	Adult Mexican-American population	7–8 y	1551
Botnia Study (11)	Adult Scandinavian white population	7–8 y	2442
MPP (25)	Adult white men	39 y	4934
Korean Genome and Epidemiology Study (31)	Adult Koreans	12 y	5703
Southwestern Native American community study (32)	Southwestern Native Americans	12 y	2436
Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialties Centre (33)	Asian Indian adults	3.5 y	1356
Israel GOH Study (15)	Adult individuals of mixed ethnic origin	24 y	853
CATAMERI study (13)	Adult white individuals carrying at least one cardiovascular risk factor	5 y	392
Study of Latino Adolescents at Risk (SOLAR) study (26)	Latino children with obesity at high risk of T2DM	8 y	201
Japanese population study (29)	Japanese workers	4.5 y	1445
Dr. Mohan's Diabetes Specialties Centre (12)	Asian Indian adults at high risk of T2DM	12 y	1179
First Affiliated Hospital of Sun Yatsen University, Guangzhou (30)	Han Chinese adults	10 y	116

unique mathematical methods to assess the performance of 14 OGTT-derived indexes in future T2DM prediction in the Botnia and MPP studies, it has been shown that 1-h-PG outperformed fasting and 2-h-PG levels (14). Importantly, in the MPP study, 1-h-PG provided a better prognostic yield power than 2-h-PG, both if used alone and when added to a clinical prediction model including age, body mass index (BMI), blood pressure, fasting glucose, triglycerides, and family history of diabetes (34). These results were consistent with those of a historical cohort study conducted in Japanese workers in public school and in Han Chinese individuals (29, 30).

In an analysis performed on 5703 Koreans with NGT enrolled from the Korean Genome and Epidemiology Study, the area under the ROC curve for incident T2DM was higher for 1-h-PG (0.74) than for fasting (0.61) or 2-h-PG (0.63) (31). Consistent with these reports, a study carried out in a Southwestern Native American community in Arizona has shown that 1-h-PG is as effective as 2-h-PG for predicting T2DM (32). In a cohort of 1356 Asian Indian adults recruited at a tertiary diabetes center in Chennai, South India, the area under the ROC curve for incident T2DM was higher for 1-h-PG (0.716) than for fasting (0.593) or 2-h-PG (0.618). The cutoff for 1-h-PG level for predicting future T2DM identified in this study was 153 mg/dL, with 64% sensitivity and 66% specificity (33).

Additionally, in the Israel GOH Study, individuals with NGT-1h-high have been found to exhibit an increased risk to develop T2DM during a 24-year follow-up (OR = 4.35, 95% CI = 2.50 to 7.73) after adjusting for sex, age, smoking, BMI, blood pressure, fasting blood glucose, and insulin (15). Similar results were observed in a retrospective study carried out in Asian Indians (12). Moreover, in an analysis of longitudinal data from the CATAMERI study, it has been shown that individuals with NGT-1h-high had a higher risk of future T2DM than subjects with NGT-1h-low or isolated IFG. Indeed, in a Cox proportional-hazard regression analysis, the risk of future T2DM for individuals with NGT-1h-high was 4.02 (95% CI = 1.06 to 15.26), whereas for subjects with isolated IFG, the risk was 1.91 (95% CI = 0.44 to 8.29) (13). Similarly, in the MPP study, adjusted hazard ratio (HR) for future T2DM was significantly greater in individuals with NGT-1h-high (25). Indeed, in the multivariable Cox proportional-hazard regression analyses adjusted for age, BMI, fasting glucose, triglycerides, and family history of diabetes, the risk of T2DM for individuals with NGT-1h-high was 4.29 (95% CI = 2.42 to 7.60) at 12-year follow-up and 2.91 (95% CI = 2.47 to 3.42) at 39-year follow-up (25).

We performed a meta-analysis using a random-effects model of the prospective studies carried out in adults (11, 13, 15, 25, 28, 33) to calculate the OR to develop T2DM of individuals with NGT-1h-high, IGT alone, or a combination with 1-h-PG ≥155 mg/dL as compared with the NGT-1h-low group (the reference category) (Figs. 1–3). The OR for the development of T2DM was 4.33 (95% CI = 3.40 to 5.51) for subjects with NGT-1h-high and 6.20 (95% CI = 3.07 to 12.50) for individuals with IGT alone (Figs. 1 and 2). An even increased risk to develop T2DM was observed in subjects with IGT and 1-hour PG ≥155 mg/dL (10.73, 95% CI = 7.66 to 15.02) (Fig. 3). Taken together, these results suggest that a 1-h-PG value ≥155 mg/dL during an OGTT may be a valuable prediction tool for identifying a unique and large previously unappreciated subgroup of NGT individuals at risk for future T2DM, which could benefit from preventative measures. Additionally, a 1-h-PG value ≥155 mg/dL may recognize among subjects with IGT those having an even greater risk to develop T2DM.

Pathophysiological abnormalities associated with NGT-1h-high condition

Conceptually, 1-hour postload hyperglycemia may arise from defective β-cell function, impaired insulin action, accelerated gastric emptying, and increased glucose absorption in the proximal intestine (Fig. 4).

An analysis performed on nondiabetic offspring of patients with T2DM participating in the European Network on Functional Genomics of Type 2 Diabetes study demonstrated that individuals with NGT-1h-high had a reduced insulin sensitivity, evaluated by the hyperinsulinemic euglycemic clamp, compared with individuals with NGT-1h-low (35). In addition, individuals with NGT-1h-high had lower acute insulin response during an intravenous glucose tolerance test, lower insulin secretion assessed by OGTT-derived indexes, and lower β-cell function measured by the so-called disposition index (insulin sensitivity × insulin secretion) as

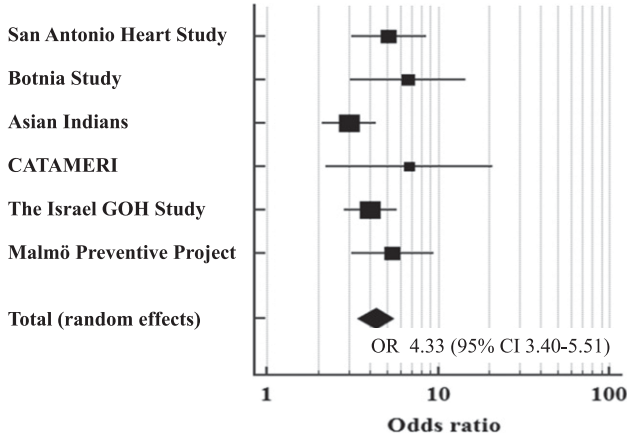

Figure 1. Meta-analysis of prospective studies evaluating the association between subjects with NGT-1h-high and the risk to develop T2DM during the follow-up.

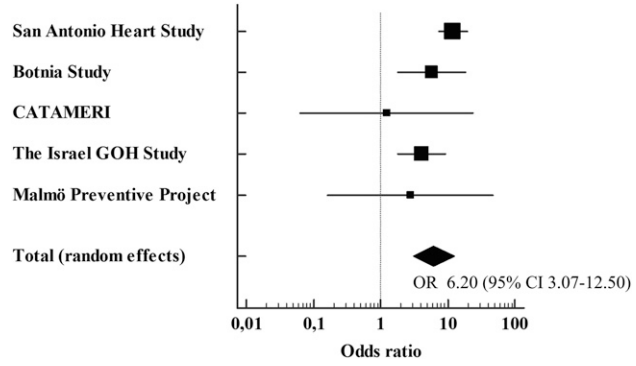

Figure 2. Meta-analysis of prospective studies evaluating the risk to develop T2DM in subjects with IGT.

compared with individuals with NGT-1h-low (35). Notably, no difference in insulin sensitivity and β-cell function was observed between individuals with NGT-1h-high and individuals with IGT (35). A study carried out in a Southwestern Native American community in Arizona has shown that 1-h-PG levels were more closely associated ($r = -0.384$) with acute insulin release, assessed by intravenous glucose tolerance test, than 2-h-PG ($r = -0.281$), whereas the latter glycemic parameter was more closely associated ($r = -0.408$) with insulin sensitivity, evaluated by the hyperinsulinemic euglycemic clamp, than 1-h-PG ($r = -0.340$) (32).

Additionally, a study conducted in youth subjects who were overweight/with obesity aged 10 to 20 years recruited at the Children's Hospital of Pittsburgh reported that youths with 1-h-PG ≥155 mg/dL had lower insulin sensitivity and impaired β-cell function than those with 1-h-PG <155 mg/dL (36). Moreover, Latino children with obesity and 1-h-PG ≥155 mg/dL exhibited impaired β-cell function as compared with those with 1-h-PG <155 mg/dL (26). Similarly, a study performed on 244 children and adolescents who were overweight/with obesity recruited at the Pediatric Endocrinology Clinic of the University of Chieti, Italy, described that NGT subjects with 1-h-PG ≥132.5 mg/dL had lower

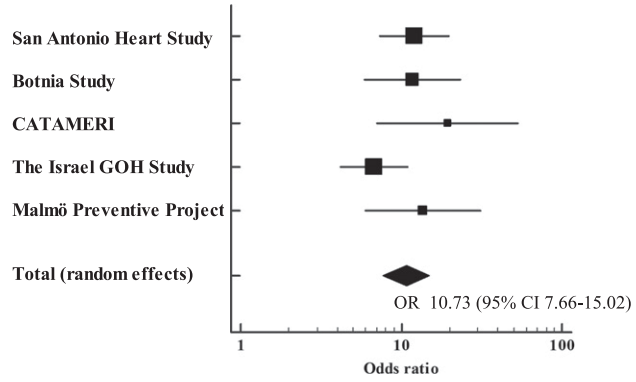

Figure 3. Meta-analysis of prospective studies evaluating the risk to develop T2DM in subjects with IGT and 1-hour postload glucose levels ≥155 mg/dL.

insulin sensitivity and β-cell function (37). Several other studies have confirmed the association between 1-hour postload hyperglycemia and both insulin sensitivity reduction and β-cell function impairment in different ethnic populations, including individuals referred to the New York University Langone Diabetes and Endocrine Associates, a cohort of Chinese individuals, and white adults (23, 24, 38, 39).

Insulin clearance plays a role in insulin metabolism, and impaired insulin clearance predicts T2DM development (40–43). It has been shown that individuals with NGT-1h-high had a reduction in insulin clearance as compared with individuals with NGT-1h-low, similarly to individuals with IGT (44). Additionally, the reduced insulin clearance observed in individuals with NGT-1h-high and IGT was associated with higher fasting and 2-hour postload plasma insulin levels as compared with individuals with NGT-1h-low (44). Sustained hyperinsulinemia after a meal due to impaired insulin clearance may have metabolic effects inducing hypoglycemia during the late postprandial period as suggested by the evidence that individuals with IGT have hypoglycemic episodes in the late postprandial period (45).

Increased glucose absorption in the proximal intestine may be a major determinant of the initial increase of glycemia during an OGTT (46). The absorption of glucose is mediated by the sodium/glucose cotransporter 1 (SGLT-1), which transports the monosaccharide from the intestinal lumen into the enterocytes (47). We have recently demonstrated that duodenal SGLT-1 expression was significantly higher in individuals with NGT-1h-high, as well as in subjects with IGT and T2DM, in comparison with subjects NGT-1h-low (48). Moreover, we observed that duodenal SGLT-1 expression was positively correlated with 1-h-PG but not with fasting or 2-h-PG levels (48), suggesting that increased duodenal levels of SGLT-1 are associated with early postload plasma glucose excursions. Several studies have shown that consumption of a diet rich in glucose or fructose may lead to an increased intestinal SGLT-1 expression (49–51). Remarkably, individuals with NGT-1h-high have been found to exhibit higher dietary intake of oligosaccharides and fructose as compared with individuals with NGT-1h-low (52), providing a conceivable explanation for the increased SGLT-1 abundance observed in individuals with NGT-1h-high.

Association of NGT-1h-high condition with hepatic steatosis

The liver is known to play a pivotal role in maintaining glucose homeostasis, and nonalcoholic fatty liver disease (NAFLD) is widely recognized to be involved in the pathogenesis of T2DM (53–55).

In a study performed on 1000 subjects, individuals with NGT-1h-high displayed higher levels of the liver

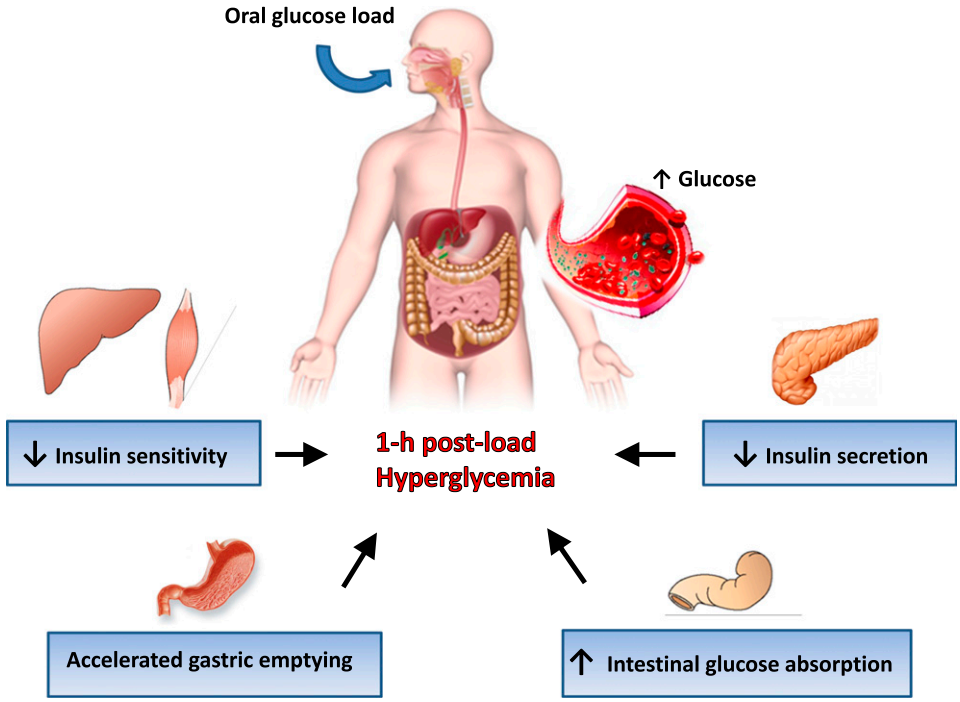

Figure 4. Pathophysiologic mechanisms underlying 1-hour postload hyperglycemia. Rapid excursion of plasma glucose concentrations after an oral glucose load may be caused by several abnormalities, including impaired β-cell function, reduced insulin sensitivity, accelerated gastric emptying, and/or increased glucose absorption in the proximal intestine.

damage biomarkers aspartate aminotransferase, alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT) in comparison with individuals with NGT-1h-low independently of several confounding factors (56). Furthermore, a study in which the presence of NAFLD was assessed in 700 subjects has shown that individuals with NGT-1h-high had a 1.7-fold increased risk of having NAFLD in comparison with subjects with NGT-1h-low; an even increased risk was observed in subjects with IGT (2.3-fold), but not in the isolated IFG group (1.1-fold) (57). Remarkably, individuals with NGT-1h-high and, even more evidently, subjects with IGT displayed elevated levels of several NAFLD biomarkers such as ALT, GGT, and high-sensitivity C-reactive protein and lower concentrations of IGF-1, whose hepatic synthesis has been found to be decreased in conditions of hepatic insulin resistance (57–59). Accordingly, hepatic insulin resistance, assessed by the liver insulin resistance index, was increased in subjects with NGT-1h-high as well as in individuals with IGT (57).

Association of NGT-1h-high condition with cardiovascular risk factors

Numerous studies have reported that subjects with NGT-1h-high displayed an unfavorable cardiometabolic profile similarly to individuals with IGT (13, 56, 57, 60, 61).

Among individuals with NGT, those having 1-h-PG ≥155 mg/dL have been found to have higher BMI and abdominal obesity (13, 56, 57, 60, 61). In addition, it has been reported that individuals with NGT-1h-high exhibited an atherogenic lipid pattern similar to that observed in subjects with IGT and T2DM, with reduced concentrations of high-density lipoprotein (HDL) and increased levels of triglycerides and non-HDL cholesterol (61). Circulating levels of apoliprotein-B, which represent the total number of proatherogenic lipoprotein, as well as apoliprotein-B/apoliprotein-A ratio, have been found to be elevated in subjects with NGT-1h-high (61). Additionally, individuals with NGT-1h-high had, in comparison with subjects with NGT-1h-low, higher levels of uric acid (21, 62), which is considered an independent risk factor for the development of cardiovascular disease and T2DM, and a marker of chronic inflammation (63–68).

Accordingly, subjects with NGT-1h-high displayed an inflammatory profile that was intermediate between the one observed in individuals with NGT-1h-low and one of the individuals with IGT, with an unpaired balance between proinflammatory and anti-inflammatory factors, as demonstrated by higher levels of several inflammatory markers, including high-sensitivity C-reactive protein, C3 complement, erythrocyte sedimentation rate, fibrinogen, white blood cell count, and decreased concentrations of molecules with anti-inflammatory properties such as IGF-1 (21, 60).

There is evidence that IGF-1 is not only a stimulator of cell growth, but also a molecule with anti-inflammatory and antiatherogenic effects (59, 69–71). Low plasma IGF-1 concentrations have been reported to be involved in the pathogenesis of T2DM and cardiovascular organ damage (71–76). In a study carried out on 1126 individuals, lower

IGF-1 concentrations have been detected in subjects with NGT-1h-high, as well as in individuals with IGT and T2DM, in comparison with subjects with NGT-1h-low (77).

Another molecule with metabolic and anti-inflammatory effects that has been reported to be negatively associated with 1-hour postload glucose levels is 25-hydroxyvitamin D [25(OH)D]. Lower 25(OH)D levels represent not only a marker of osteomineral disorders, but also a risk factor for metabolic and cardiovascular diseases (78–81). In a study performed on 300 hypertensive never-treated individuals, subjects with NGT-1h-high showed reduced concentrations of 25(OH)D compared with subjects with NGT-1h-low and similar to those of the IGT group (82).

In a study performed on 1723 white adults, it has been observed that blood viscosity, a known cardiovascular risk factor, was increased in individuals with NGT-1h-high as well as in subjects with IFG and/or IGT, in comparison with individuals with NGT-1h-low, and 1-hour postchallenge glucose levels were positively associated with blood viscosity independently of the major cardiovascular risk factors (83). Furthermore, individuals with NGT-1h-high have been found to exhibit cardiac autonomic imbalance during an OGTT characterized by a sympathetic activation and a parasympathetic reduction as compared with individuals with NGT 1h-low (84). This observation may be clinically relevant because cardiac autonomic imbalance plays an important role in cardiac arrhythmogenesis.

Overall these data demonstrating the link between 1-hour postload hyperglycemia and several cardiovascular risk factors support the idea that hyperglycemia at 1 hour during an OGTT may be a useful marker to identify a subgroup of individuals with NGT at increased risk not only for T2DM, but also for cardiovascular disease.

Association of NGT-1h-high condition with cardiovascular organ damage

A number of studies have shown that individuals with NGT with 1-hour postload hyperglycemia are at increased risk of having cardiovascular organ damage.

It has been observed that individuals with NGT-1h-high displayed a significant increase in carotid intima–media thickness (cIMT), a well-established index of early atherosclerosis (85), in comparison with subjects with NGT-1h-low, which was comparable to that observed in individuals with IGT (86, 87).

Another surrogate marker of early vascular damage is arterial stiffness (88). By analyzing hemodynamic data of 584 hypertensive white individuals subjected to measurement of the arterial stiffness index pulse wave velocity and its central hemodynamic correlates, it has been found that subjects with NGT-1h-high exhibited significantly higher parameters of arterial stiffness and aortic hemodynamic as compared with individuals with NGT-1h-low (89). Similar results were observed in a study performed on normotensive Japanese subjects with NGT (19).

Additionally, in a cross-sectional study performed on 767 never-treated hypertensive subjects, individuals with NGT-1h-high showed an increased left ventricular mass that was comparable to that of individuals with either IGT or T2DM (90). Notably, the prevalence of left ventricular hypertrophy, a well-recognized predictor of cardiovascular events, was significantly higher in individuals with NGT-1h-high, as well as in subjects with IGT and T2DM, in comparison with individuals with NGT-1h-low (90). Moreover, subjects with NGT-1h-high as well as those with IGT or T2DM exhibited an impaired diastolic function as demonstrated by higher left atrium dimensions, isovolumetric relaxation time, and lower E wave to A wave ratio value in comparison with subjects with NGT-1h-low (91).

Impaired kidney function is another widely recognized independent predictor of cardiovascular adverse events (92, 93). In a study performed on 1003 white individuals, subjects with NGT-1h-high exhibited decreased estimated glomerular filtrate rate levels as compared with individuals with NGT-1h-low (94). Accordingly, individuals with NGT-1h-high had a higher risk of having chronic kidney disease in comparison with subjects with NGT-1h-low even after adjustment for multiple confounding factors (94).

Association of NGT-1h-high condition with adverse outcomes

Given the association between 1-hour postload hyperglycemia in NGT subjects and T2DM risk and cardiovascular organ damage, it is reasonable to hypothesize that individuals with higher levels of 1-h-PG may have an increased risk of adverse outcomes. A few longitudinal studies evaluating the impact of 1-h-PG on cardiovascular adverse events and all-cause mortality have been published so far (Table 3). In the Helsinki Businessmen Study, 2756 healthy men were followed for 44 years, and a strong association between 1-h-PG levels and cardiovascular and all-cause mortality was observed ($P < 0.001$) (95). In the population-based Erfurt Male Cohort Study, 1135 men without diabetes aged 40 to 59 years were followed for 30 years. Individuals with 1-h-PG >200 mg/dL exhibited a 1.49-fold increased risk for death (95% CI = 1.17 to 1.88) as compared with men with 1-h-PG ≤200 mg/dL after adjusting for age, smoking, BMI, education, hypertension, total cholesterol, and triglycerides levels (96). In The Israel GOH Study, 1945 individuals were followed for 33 years and association of 1-h-PG with all-cause mortality was assessed. Subjects with NGT-1h-high exhibited a 1.32-fold increased risk for death (95% CI = 1.12 to 1.56) as compared with individuals with NGT-1h-low after adjusting for

Table 3. Longitudinal Studies Evaluating the Association Between 1-h-PG and Adverse Outcomes

Study Name	Population Characteristics	Follow-Up	Number of Subjects	Adverse Outcomes Associated With 1-h Postload Hyperglycemia at Baseline
Helsinki Businessmen Study (95)	Business executive men	44 y	2756	Cardiovascular and all-cause mortality
Erfurt Male Cohort Study (96)	white men	30 y	1135	All-cause mortality
Israel GOH Study (97)	Adult individuals of mixed ethnic origin	33 y	1945	All-cause mortality
MPP (25, 98)	Adult white men	39 y	4934	Myocardial infarction, fatal ischemic heart disease, cardiovascular and all-cause mortality
Chicago Heart Association Detection Project (99)	American industrial workers	22 y	26,753	Stroke and coronary artery disease, cardiovascular and total mortality
Honolulu Heart Program (100)	Japanese American men	12 y	6394	Fatal and nonfatal coronary artery disease

sex, age, smoking, BMI, fasting plasma glucose, and blood pressure (97). In the MMP study, after a 39-year follow-up, individuals with NGT-1h-high exhibited a 1.24-fold increased risk for incident myocardial infarction and fatal ischemic heart disease (95% CI = 1.10 to 1.39) and a higher total mortality (HR = 1.29; 95% CI = 1.19 to 1.39) as compared with individuals with NGT-1h-low after adjusting for age, BMI, fasting glucose, triglycerides, and family history of diabetes (25). Furthermore, in the MPP study, higher levels of 1-h-PG, but not fasting or 2-h-PG, were found to be an independent predictor of cardiovascular death (HR = 1.09, 95% CI = 1.01 to 1.17, $P = 0.02$) and all-cause mortality (HR = 1.10, 95% CI = 1.05 to 1.16, $P < 0.0001$) (98).

In the cohort of 26,753 subjects without diabetes from the Chicago Heart Association Detection Project in Industry, higher levels of 1-h-PG were associated with a greater risk of stroke and coronary artery disease and an increased cardiovascular and total mortality during a follow-up of 22 years in both men and women independently of several cardiovascular risk factors, including age, BMI, smoking habit, and blood pressure (99).

These observations are consistent with positive findings in 6394 Japanese-American men without diabetes of the Honolulu Heart Program followed for 12 years (100). In this study, 1-h-PG levels were positively associated with fatal and nonfatal coronary artery disease. Notably, men in the fourth quintile of 1-h-PG (157 to 189 mg/dL) had a twofold increased age-adjusted risk of fatal coronary artery disease in comparison with the lowest quintile ($P < 0.05$). Relative risk increased to threefold in individuals of the top quintile and remained statistically significant after further adjustment for BMI, total cholesterol, hypertension, left ventricular hypertrophy, and hematocrit ($P < 0.001$) (100).

Association between 1-h-PG ≥155 mg/dL and a worse cardiometabolic profile in HbA1c-defined glycemic categories

In 2010, the ADA has proposed HbA1c as a diagnostic test for diabetes and prediabetes conditions in addition to fasting and 2-hour plasma glucose levels during an OGTT. According to ADA criteria, a level of HbA1c ≥ 6.5% is diagnostic of diabetes, whereas a value of HbA1c ranging from 5.7% to 6.4% identifies individuals at increased risk for future T2DM (8, 9). In a study performed in 687 white individuals free from T2DM at baseline and followed for a median follow-up of 3.5 years (101), it has been reported that, although HbA1c is a significant predictor of the future risk of T2DM, its predictive power is weaker compared with 1-h-PG level as demonstrated by the fact that the area under the ROC curve of HbA1c in predicting future T2DM (0.73) was significantly lower than that of 1-h-PG (0.84) (101). In line with this observation, 1-h-PG levels have been found to be more strongly correlated with 2-h-PG, insulin resistance, and β-cell dysfunction than HbA1c value in a cross-sectional analysis performed on 212 high-risk individuals recruited at the New York University Langone Diabetes and Endocrine Associates (102). Interestingly, the combined elevation of HbA1c and 1-h-PG levels has been shown to improve the predictive power for incident T2DM with subjects having HbA1c-defined prediabetes and 1-h-PG ≥155 mg/dL exhibiting a 40-fold increased risk to develop T2DM (101).

In a study carried out in 1495 individuals stratified according to HbA1c diagnostic thresholds for prediabetes and 1-h-PG levels (22), it was found that individuals having 1-h-PG ≥155 mg/dL exhibited a worse cardiometabolic profile characterized by higher visceral adiposity, triglycerides, and uric acid, and lower HDL cholesterol, insulin sensitivity, and β-cell function in comparison with subjects with 1-h-PG <155 mg/dL both in the group with HbA1c < 5.7% and in the group with prediabetes (HbA1c: 5.7% to 6.4%) (22). Interestingly, individuals with 1-h-PG ≥155 mg/dL having or not having prediabetes defined according to HbA1c-based criteria displayed, in comparison with their counterpart with 1-h-PG <155 mg/dL, greater levels of cIMT, pulse pressure, and myocardium workload estimated as the rate pressure product calculated

as heart rate × systolic blood pressure (22). Additionally, the ability of 1-h-PG levels to identify subjects with early carotid atherosclerosis (cIMT >0.90 mm) or with elevated vascular stiffness (pulse pressure >60 mm Hg) as assessed by the area under the ROC curve was higher (0.705 and 0.678, respectively) than that of fasting glucose (0.624 and 0.632, respectively), 2-h-PG (0.671 and 0.670), and HbA1c levels (0.677 and 0.581), and the addition of 1-h-PG ≥155 mg/dL to the prediabetes HbA1c values significantly improved the ability to detect elevated pulse pressure or vascular atherosclerosis (22).

Furthermore, in a study performed on 1108 white individuals, it has been demonstrated that the addition of 1-h-PG ≥155 mg/dL to the HbA1c diagnostic thresholds for prediabetes may identify subjects with an increased risk of having hepatic steatosis and an unfavorable metabolic profile characterized by higher values of biomarkers of hepatic injury, including aspartate aminotransferase, ALT and GGT, triglycerides, uric acid, inflammatory biomarkers, and insulin resistance, assessed by the HOMA-IR and liver insulin resistance index and lower levels of HDL and IGF-1 (103).

Taken together, these data demonstrate that 1-h-PG ≥155 mg/dL is associated with a worse cardiometabolic profile within HbA1c-defined glycemic categories, and the addition of 1-h-PG levels to HbA1c values increases the predictive power to identify individuals at higher risk of T2DM and the ability to detect subclinical organ damage.

Discussion

T2DM with its continuously growing diffusion represents a major public health problem, and early identification of high-risk individuals is essential to reduce its increasing prevalence (1). Longitudinal studies have reported that ~30% to 40% of individuals who develop T2DM were NGT at baseline (104, 105), suggesting that the exclusive measurement of fasting and 2-h-PG levels is not sufficient to recognize all individuals harboring an increased risk of future T2DM. As described in this review, several prospective studies have provided evidence that a plasma glucose value at 1 hour ≥155 mg/dL during an OGTT may capture, among individuals with NGT, those at elevated risk of developing T2DM (11, 13, 15, 25, 28, 33). Accordingly, several reports have shown that individuals with NGT-1h-high share with those having IGT several metabolic abnormalities, including impaired insulin sensitivity, β-cell dysfunction, reduced insulin clearance, and increased glucose intestinal absorption, which are known to be involved in the pathogenesis of T2DM (23–26, 35–39, 44, 48). These data coupled with the evidence that the prevalence of 1-h-PG values ≥155 mg/dL increases as glucose tolerance deteriorates, with almost all subjects with IGT or newly diagnosed T2DM having 1-hour postload hyperglycemia (≥155 mg/dL) (10, 11, 15, 22, 24), support the idea that a 1-h-PG value ≥155 mg/dL is an earlier biomarker of dysglycemia than IGT in the lengthy trajectory from prediabetes to T2DM. Moreover, a large body of studies have demonstrated that a 1-h-PG value ≥155 mg/dL in individuals with NGT is not only associated with an increased risk of future T2DM, but is also able to identify those with a worse cardiovascular phenotype characterized with a cluster of lipid, inflammatory and blood viscosity abnormalities, and subclinical organ damage such as NAFLD, carotid atherosclerosis, kidney dysfunction, and left ventricular hypertrophy (56, 57, 60–62, 83, 86, 89–91, 94). As a consequence, an increased risk of cardiovascular mortality and morbidity has been observed in individuals with NGT with 1-hour postload hyperglycemia (25, 95–100).

Importantly, a value of 1-h-PG ≥155 mg/dL has been found to identity individuals with a worse cardiovascular risk profile and an increased risk to develop T2DM not only among those with NGT, but also among individuals with different HbA1c-defined glycemic categories. Indeed, it has been reported that individuals with or without HbA1c-defined prediabetes having 1-h-PG ≥155 mg/dL display a higher risk to develop T2DM and an unfavorable cardiometabolic risk burden as compared with the counterpart with 1-h-PG <155 mg/dL (22, 101, 103). Notably, it should be noted that among individuals classified as having a low cardiometabolic risk on the basis of HbA1c criterion (HbA1c < 5.7%), a considerable proportion of subjects (~41%) have 1-hour postload hyperglycemia and an unfavorable cardiometabolic risk profile (22), suggesting that a value of 1-h-PG ≥155 mg/dL may recognize a sizable subgroup of high-risk individuals that would be otherwise missed by employing HbA1c-based criteria alone.

In conclusion, even if the current ADA criteria do not recommend the measurement of 1-h-PG levels for identifying high-risk individuals (9), overall the available evidence indicates that employing the 1-h-PG criterion in addition to IFG/IGT definition and the recently established HbA1c diagnostic thresholds for prediabetes may be helpful to identify a new category of individuals at increased risk of T2DM and cardiovascular disease. Recently, Jagannathan *et al.* (106) and Bergman *et al.* (107) have also reviewed the literature regarding the association between increased levels of 1-h-PG and future T2DM and have proposed 1-h-PG as a unique early biomarker of dysglycemia, recommending the replacement of 2-hour OGTT with 1-hour OGTT, which is more acceptable in a clinical setting. Accordingly, after having comprehensively analyzed the current available evidence regarding epidemiology, pathophysiology, and the predictive ability of 1-hour postload hyperglycemia on

adverse clinical outcomes as described in the present review, we believe that a value of 1-h-PG ≥155 mg/dL is a valuable and early indicator of several alterations of glucose homeostasis, and therefore measurement of 1-h-PG levels should be recommended as a screening test for diagnosis of prediabetes. Because the 1-h-PG parameter is relatively easily obtained from an OGTT, its determination would maximize the information gained from a single test, making it a useful indicator of future risk of both T2DM and cardiovascular disease in individuals who would be otherwise missed by employing the ADA criteria alone. The proposed cut point for 1-h-PG identifies a considerable proportion of subjects at high risk among individuals with NGT, and its use could lead to more widespread preventive efforts and to a reduced economic burden due to prevention of both T2DM and its cardiovascular complications. The results of the reported studies highlight the potential benefit of targeting individuals with NGT with a 1-h-PG level ≥155 mg/dL and provide a robust rationale for revising the currently ADA-recommended screening criteria for glucose disorders. Because several studies have consistently demonstrated that lifestyle and/or pharmacological approaches may prevent T2DM and cardiovascular events in high-risk individuals (2–6), we believe that intervention trials in subjects with 1-h-PG ≥155 mg/dL are not necessary for redefining current screening and diagnostic recommendations with 1-h-PG levels. Indeed, a large amount of evidence indicates that 1-hour postload hyperglycemia is a dysglycemic condition associated with an increased risk of future T2DM (11, 13, 15, 25, 28, 33, 101, 107), and as such, it may benefit from preventive measures aimed to counteract T2DM onset. Notably, given the worse cardiometabolic profile and the increased risk of cardiovascular disease associated with 1-hour postload hyperglycemia, lifestyle modification and/or pharmaceutical treatments for the other cardiovascular risk factors such as obesity, hypertension, and hyperlipidemia may be helpful to prevent clinical adverse outcomes in subjects with 1-h-PG ≥155 mg/dL. Furthermore, considering that increased levels of 1-h-PG are an early biomarker of glucose homeostasis disorders (106, 107), employing 1-h-PG-level criterion may give the opportunity to identify and target intervention programs in an earlier stage of prediabetes, thus leading to a more suitable reduction of the risk of future T2DM and adverse cardiovascular events.

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