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Review

Petition to replace current OGTT criteria for diagnosing prediabetes with the 1-hour post-load plasma glucose ≥ 155 mg/dl (8.6 mmol/L)

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ABSTRACT

Many individuals with prediabetes, as presently defined, will progress to diabetes (T2D) despite the considerable benefit of lifestyle modification. Therefore, it is paramount to screen individuals at increased risk with a more sensitive method capable of identifying prediabetes at an even earlier time point in the lengthy trajectory to T2D. This petition reviews findings demonstrating that the 1-hour (1-h) postload plasma glucose (PG) ≥ 155 mg/dl (8.6 mmol/L) in those with normal glucose tolerance (NGT) during an oral glucose tolerance test (OGTT) is highly predictive for detecting progression to T2D, micro- and macrovascular complications and mortality in individuals at increased risk. Furthermore, the STOP DIABETES Study documented effective interventions that reduce the future risk of T2D in those with NGT and a 1-h PG ≥ 155 mg/dl (8·6 mmol/L). The 1-h OGTT represents a valuable opportunity to extend the proven benefit of diabetes prevention to the sizeable and growing population of individuals at increased risk of progression to T2D. The substantial evidence provided in this petition strongly supports redefining current diagnostic criteria for prediabetes with the elevated 1-h PG level. The authors therefore advocate a 1-h OGTT to detect prediabetes and hence, thwart the global diabetes epidemic.
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Contents

1. Case report

A 36 year-old Asian female was referred after being diagnosed with gestational diabetes mellitus (GDM) for which she was treated with metformin. She gave birth to a 7 lbs. 10 oz. (4.83 kg) full term healthy infant after undergoing C-section due to breech position. She gained approximately 30 lbs. (13.6 kg) during the course of her pregnancy. Both her parents have prediabetes and her maternal grandfather has insulin–requiring diabetes. Her average weight approximates 165 lbs. (75 kg) and the maximum weight about 200 lbs. (90.9 kg). Several weeks after giving birth, the postpartum oral glucose tolerance test (OGTT) was consistent with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [FPG = 112 mg/dL (6.2 mmol/L) and 2-h = 194 mg/dL (10.8 mmol/L)]. She currently exercises 2–3 times weekly.

There is no clinical history of polycystic ovarian syndrome (PCOS). She denied frequent infections or polyuria. She had a retinal tear in her right eye and underwent laser therapy. There is no history of hypertension or hyperlipidemia. There is no known history of renal, liver or cardiovascular diseases. She has modified her diet and reduced consumption of simple carbohydrates but snacks on rice chips, chocolates and fruit. She does not smoke or drink.

On physical examination, her weight was 91 kg. (BMI was 32.4 kg/m^2). Blood Pressure was 122/78 mmHg, pulse was 83 beats per minute.

Laboratory Results: creatinine was 0.72 mg/dL (63.66 μmol/L); TSH was 0.57 mIU/mL, Free T was 1.1 ng/dL (14.16 pmol/L), LDL-cholesterol was 57 mg/dL (1.48 mmol/L), triglycerides were 60 mg/dL (0.68 mmol/L), cortisol was 11.8 ug/dL (325.68 nmol/L). HbA_{1c} was 5.5% (37 mmol/mol); Urine microalbumin/creatinine was 25 mg/g_{creat} (2.83 mg/$mmol_{creat}$).

75 g OGTT*			
	Fasting	1-h	2-h
Glucose [mg/dl (mmol/L)]	97 (5.4)	219 (12.2)	118 (6.6)
Insulin (uU/mL)	12.3	124.6	67.4

*ADA Standards of Medical Care, Diabetes Care 2017; 40 (Supplement 1): S14.

The HbA_{1c} and the OGTT were "technically normal" as the fasting and 2-h levels fell below current criteria for prediabetes or T2D (although the fasting glucose level was borderline elevated). The 1-hour glucose and insulin levels were elevated suggesting that she may be insulin resistant and therefore at an elevated risk for progression to T2D (although she was informed that there are currently no international standards for defining the 1-hour post-load PG level). She was advised that the greatest risk for progressing to T2D, which may occur many years subsequent to being diagnosed with GDM, was her elevated weight. She was counseled to lose weight with a BMI goal of 23 kg/m^2 (given her Asian ethnicity) and to engage in regular exercise, consult with a dietitian, and avoid excessive carbohydrates. A follow-up laboratory evaluation in 4–6 months with consideration of repeating a 1-hour OGTT was recommended. Furthermore, she was advised to perform capillary blood glucose monitoring fasting and 1–2 h post-prandial with specifically prescribed target goals.

2. Introduction

The International Diabetes Federation (IDF) estimates that globally 425 million individuals or 8.8% of the world's population (1 in 11 adults) have diabetes with 629 million adults, or 9.9%, expected to develop diabetes by 2045 [1]. In addition, 7.3% of the world's population, or 352 million individuals, have impaired glucose tolerance (IGT) and are considered at increased risk for developing diabetes with an expectation that this will increase to 532 million, or 8.3%, in 2045 [1].

This petition to modify current OGTT criteria for detecting prediabetes is based on considerable epidemiologic evidence in different populations demonstrating that an elevated 1-h PG can identify individuals with NGT at increased risk for T2D, micro- and macrovascular complications and mortality.

3. What are the inadequacies of current diagnostic criteria for prediabetes?

Despite the considerable benefit of lifestyle modification in thwarting the insidious progression to diabetes, many individuals with prediabetes as presently defined will progress even when initially responsive. Furthermore, the vast majority of individuals at risk of developing T2D are not promptly identified. Therefore, it is paramount to screen individuals at increased risk with a more sensitive method capable of identifying prediabetes at an even earlier time point before glucose levels progress than current diagnostic criteria for prediabetes permits.

3.1. *Discrepant diagnostic criteria*

Diagnostic techniques for identifying those at increased risk include glucose (fasting, OGTT) and/or HbA_{1c} measurements. Current diagnostic modalities can be discrepant as they may identify different populations depending on whether glucose or HbA_{1c} levels are employed [2–4]. Table 1 illustrates that there is currently no international consensus on the definition of prediabetes as the American Diabetes Association (ADA), World Health Organization (WHO) and the International Expert Committee (IEC) propose different criteria [5].

The definitions of prediabetes have varying sensitivities and specificities that identify different although overlapping populations. Some individuals with T2D detected by the OGTT may no longer be classified as such when using HbA_{1c} criteria ($HbA_{1c} \geq 6.5\%$; 48 mmol/mol). Several medical conditions can affect the HbA_{1c} measurement including hematological disorders, renal failure, hypertriglyceridemia, age, and ethnic disparities [6]. Furthermore, progression rates to diabetes appear to differ by prediabetes definitions with a HbA_{1c} level between 6.0 and 6.4% (42–46 mmol/mol) possibly identifying individuals at lower risk than with other criteria [7]. Furthermore, longitudinal studies have shown that 50–60% of individuals with prediabetes based on current criteria did not progress to diabetes in about 10 years whereas 30–40% of those with diabetes had NGT at baseline [8].

Table 1 – Definitions of prediabetes [5].

	ADA	WHO	IEC
IFG (FPG)	100–125 mg/dl (5.6–6.9 mmol/L)	110–125 mg/dl (6.1–6.9 mmol/L)	
IGT (2-h PG) after 75 g OGTT	140–199 mg/dl (7.8–11.0 mmol/L)	140–199 mg/dl (7.8–11.0 mmol/L)	
HbA_{1c}	5.7–6.4% (39–46 mmol/mol)		6.0–6.4% (42–46 mmol/mol)

By employing current definitions of prediabetes, individuals at increased risk may inadvertently be diagnosed relatively late in the gradual progression to diabetes obviating the potential benefit of earlier intervention when β-cell function is more intact [9–11]. Therefore, diagnostic measures with greater sensitivity are needed to identify individuals at increased risk of developing T2D as β-cell function has consistently been found to be significantly reduced at glucose levels *below* established thresholds for IFG or IGT [12–14]. Prediabetes is also associated with increased risk for cardiovascular disease and other complications [15,16]. Therefore, implementation of lifestyle intervention *before* glucose levels achieve current critical thresholds for prediabetes should be considerably more effective in thwarting progression to diabetes, reducing complications, and improve health outcomes and quality of life [9–11]. This should provide benefit beyond that demonstrated in global diabetes prevention programs in those with IGT.

4. What is the background for recommending the 1-h post-load plasma glucose level for predicting progression to type 2 diabetes mellitus?

Large-scale population studies have consistently shown that the 1-h PG ≥ 155 mg/dl (8.6 mmol/L) during the OGTT may predict incident T2D and associated complications better than fasting plasma glucose (FPG) or 2-h PG levels. Studies investigating the 1-h PG studies are listed in Table 2 and have also recently been summarized (17, 18). Section 7 discusses the derivation of the 1-h PG level in greater detail.

5. Why was the 2-h post-load PG level for detecting prediabetes initially selected instead of the 1-h post-load PG?

In 1979, the National Diabetes Data Group (NDDG) recommended that an interim glucose level (1/2-h, 1-h, or 1 1/2-h) be measured to diagnose IGT defined by a 2-h value ≥ 140 mg/dl (7.8 mmol/L) but <200 mg/dl (11.1 mmol/L) [31]. Due to the impracticality of measuring interim levels, the NDDG recommended a modification whereby IGT could be diagnosed if fasting and 2-h glucose levels met prespecified threshold levels. Furthermore, as the 2-h OGTT level was found to be more reproducible and provided a more sensitive and specific indicator of diabetic status than the 1-h, the latter measurement was abandoned [32,33]. WHO and ADA criteria subsequently considered the 2-h PG as the only post-load value required. It should be noted that the criteria then did not require that the selection of the 1-h or 2-h PG be based on the presence of diabetes complications. This question was recently addressed by Paddock et al. who compared the 1- and 2-h PG concentrations for predicting diabetic retinopathy [33]. Prevalence and incidence of diabetic retinopathy, based on direct ophthalmoscopy, changed in a similar manner across the distributions of 1 h-PG and 2 h-PG concentrations. Receiver operating characteristics (ROC) analysis showed that 1 h-PG and 2 h-PG were similar in identifying prevalent and incident diabetic retinopathy. The authors recommended that the 1 h-PG should be considered as an alternative post-load glucose time point to identify those at elevated risk for diabetic retinopathy [34].

6. Is the 1-h post-load level preferable to HbA_{1c} and other post-load values such as shape of the glucose curve or the incremental area under the glucose concentration curve $\Delta_{(G0\text{-}120)}$?

The effectiveness of HbA_{1c} and the 1-h PG ≥ 155 mg/dl (8.6 mmol/L) were assessed for identifying dysglycemia in 212 subjects in a real-life clinical setting [35]. When comparing the accuracy of HbA_{1c} and an elevated 1-h PG with fasting and 2-h PG levels during the OGTT, the level of agreement was two-fold greater for the elevated 1-h PG than HbA_{1c} categories defined by the ADA (5.7–6.4%; 39–46 mmol/mol) and the IEC (6.0–6.4%; 42–46 mmol/mol) [35]. The 1-h PG ≥ 155 mg/dl (8.6 mmol/L) was therefore found to be superior for detecting high-risk individuals compared with HbA_{1c}. Furthermore, HbA_{1c} was a less precise correlate of insulin sensitivity and β-cell function than the 1-h PG and correlated poorly with the 2-h PG. Abdul-Ghani et al, in a study of 687 subjects free of T2D, demonstrated that although the HbA_{1c} alone is a significant predictor of future risk of T2D, its predictive power was weaker when compared with the 1-h PG. [36]. The area under the receiver operator characteristic (ROC) curve of HbA_{1c} was significantly lower than the 1-h PG (0.73 vs 0.84).

Alyass et al [20] evaluated the performance of fourteen OGTT glucose traits from the longitudinal Botnia and Malmö Preventive Project (MPP) cohorts such as post-load glucose at different time points (30, 60, 90 min along with FPG and 2-h PG), shape of the glucose curve and $AUCG_{0\text{-}120}$ in predicting T2D. Using this rigorous mathematical approach, the study demonstrated the 1-h PG as the most relevant OGTT-derived trait with which to classify middle-aged European adults at increased risk for incident T2D.

7. How was the 1-h PG level during the OGTT that identifies individuals at risk for developing T2D derived and what is known about the 1-h level PG level corresponding with the 2-h PG level diagnostic of T2D?

Longitudinal studies summarized in Table 2 have robustly demonstrated that individuals with NGT having a 1-h PG value following the 75 g standard OGTT ≥ 155 mg/dl (≥8.6 mmol/L) are at increased risk to develop T2D [37].

The threshold of 155 mg/dl (8.6 mmol/L) was initially identified in 1611 participants without diabetes in the San Antonio Heart Study (SAHS) [19] where it was evident that the 1-h PG predicted risk of T2D in the subsequent 7–8 years with higher accuracy than in those with IGT [threshold 140 mg/dl (7.8 mmol/L)]. A predictive model based on the PG at 1-h during the OGTT and the presence or absence of the metabolic syndrome, independent of the 2-h PG concentration, performed equally well in stratifying subjects for future risk of T2D compared with the model that included the 2-h PG concentration. The ROC analysis was 0.84 for 1-h PG vs. 0.79 for IGT. When a cut point for continuous variables was used as threshold for predicting future T2D, 155 mg/dl (8.6 mmol/L)

Table 2 – Odds, hazard ratios and C-statistics for T2D prediction of 1 h-PG in cohort studies.

1st author and Year of publication	Study Cohort	N (sample size)	Follow-up (years)	1 h-PG Cut off (mg/dl)*	Findings			
					OR/HR T2D	Sensitivity T2D	Specificity T2D	C-statistic
Abdul-Ghani MA et al 2008 [19]	SAHS	1611 Mexican Americans	8	155	(a) without metabolic syndrome NGT1-h PG > 155 mg/dl vs. NGT1-h PG < 155 mg/dl HR [95%CI]: 3.4 [1.8–6.4] (b) with metabolic syndrome NGT1-h PG > 155 mg/dl vs. NGT1-h PG < 155 mg/dl HR [95%CI]: 15.2[7.8–29.3]	0.75	0.79	NA
Abdul-Ghani MA et al 2010 [21]	SAHS and BOTNIA	3450 Mexican Americans Finnish	7–8	150	FPG < 90 mg/dl and 1-h PG > 150 mg/dl OR [95%CI]: 7.1 [3.3–17] FPG 90–100 mg/dl and 1-h PG > 150 mg/dl OR [95%CI]: 11.3 [5.0–25.8] FPG > 100 mg/dl and 1-h PG > 150 mg/dl OR [95%CI]: 17.7 [7.5–41.9]	NA	NA	NA
Priya M et al 2013 [22]	Data from tertiary diabetes center	1179 NGT Indians	4.0	155	NGT1-h PG > 155 mg/dl vs. NGT1-h PG < 155 mg/dl proportion (n, %): 98 (19.5) vs. 50 (8.0) OR [95%CI]: 2.18 [1.23–3.89]	66.2	60.8	NA
Alyass A et al 2015 [20]	BOTNIA	2603 Finnish	4.94	160	OR [95%CI]: 8.0 [5.5–11.6]	0.75	0.73	AUC_{ROC} 0.83 (95% CI 0.80,0.77)
Alyass A et al 2015 [20]	MPP	2386 Swedish	23.5	151	OR [95%CI]: 3.8 [3.1–4.7]	0.62	0.70	AUC_{ROC} 0.74 (95% CI 0.72, 0.77)
Fiorentino VT et al 2015 [23]	CATAMERI and EUGENE2	392 Caucasians	5.2	155	NGT1-h PG > 155 mg/dl vs. NGT1-h PG < 155 mg/dl HR [95%CI]: 4.02 [1.06–15.26]	NA	NA	NA
Bergman et al. 2016 [24]	GOH	853 non diabetic multiethnic people	24	155	NGT1-h PG > 155 mg/dl vs. NGT1-h PG < 155 mg/dl OR [95%CI]: 4.35 [2.50–7.73]	55.6	77.2	AUC_{ROC} 0.736 (95% CI 0.699, 0.773)

Oka et al 2016 [25]	Historical cohort study.	1445 Japanese workers	4.5	#205	1-h PG Q4 vs. Q1: HR [95%CI]: 42.5 [5.7–315.2]) Compared with the first quartile, the hazard ratio for future diabetes in the fourth quartile of 1-h plasma glucose was 42.5 [95% CI 5.7–315.2 (P < 0.05)] and the hazard ratio in the fourth quartile of 2-h plasma glucose was 4.4 [95% CI 1.8–10.8 (P < 0.05)], after adjustments for covariates including FPG. Compared with the first quartile, the hazard ratio for future diabetes in the fourth quartile of 1-h plasma glucose was 42.5 [95% CI 5.7–315.2 (P < 0.05)] and the hazard ratio in the fourth quartile of 2-h plasma glucose was 4.4 [95% CI 1.8–10.8 (P < 0.05)], after adjustments for covariates including FPG.	NA	NA	AUC_{ROC} 0.88 (95%CI 0.84, 0.91)
Oh et al. 2017 [26]	KoGES	5703 NGT Koreans	12	144	NGT1-h PG > 144 mg/dl vs. NGT1-h PG < 144 mg/dl HR [95%CI]: 2.84 [2.34–3.45]	0.7	0.68	AUC_{ROC} 0.74 (95%CI NA)
Paddock et al. 2017 [27]	SWNA	1946 people from Arizona	12.8#	168	NGT1-h PG > 168 mg/dl vs. NGT1-h PG < 168 mg/dl HR [95%CI]: 1.71 [1.60–1.82]	Reported for different cutpoints	Reported for different cutpoints	AUC_{ROC} 0.672 (95%CI NA) at 5 Y AUC_{ROC} 0.728 (95%CI NA) at 25 y
Pareek M et al 2018 [28]	MPP	Population based cohort of 4867 Swedish men	12 and 39	155	NGT1-h PG > 155 mg/dl vs. NGT1-h < PG 155 mg/dl HR [95%CI]: 3.87 [2.16–6.93] after 12 y NGT1-h PG > 155 mg/dl vs. NGT1-h < PG 155 mg/dl HR [95%CI]: 2.93 [2.48–3.46] after 39 y	NA	NA	C-index 0.698 at 12 y

Table 2 – (continued)

1st author and Year of publication	Study Cohort	N (sample size)	Follow-up (years)	1 h-PG Cut off (mg/dl)	Findings				
					OR/HR T2D	Sensitivity T2D	Specificity T2D	C-statistic	
Sai Prasanna et al 2017 [29]	Data from electronic health records	1356 Indians	5.6	153	NGT1-h > 153 mg/dl OR [95% CI]: 1.026 [1.019–1.033]	0.64	0.66	C-index 0.637 at 39 y	
Standberg TE et al 2011 [30]	Helsinki Businessmen	2756	37[#]	161	NGT1-h > 161 mg/dl and BMI < 30 kg/m^2 OR [95% CI]:4.71 [3.36–6.60] NGT1-h > 161 mg/dl and BMI ≥ 30 kg/m^2 OR [95% CI]:10.13 [6.46–18.59]	NA	NA	NA	

Abbreviations: Malmö Preventive Project, MMP; San Antonio Heart Study, SAHS; CATAnzaro Metabolic Risk factors, CATAMERI; European Network on Functional Genomics of T2D, EUGENE 2; Israel Study of Glucose Intolerance, Obesity and Hypertension, GOH; Korean Genome and Epidemiology Study, KoGES; Southwestern Native American, SWNA; Normal Glucose Tolerance, NGT.

Notes: NA: not available from the manuscript. Follow-up time is reported as mean otherwise # refers to median value.

C-statistics refers to the area under the receiver-operating characteristic curve (AUC_{ROC}) for 1 h plasma glucose for future diabetes.

* To convert mg/dl to mmol/L, divide by 18.

was determined to be the most accurate 1-h PG value with sensitivity 0.75 and specificity 0.79 to predict incident diabetes, while the 2-h PG value of 140 mg/dl (7.8 mmol/L) had a sensitivity 0.51 and specificity 0.92. In addition, another report of 1551 subjects without diabetes from the SAHS confirmed that 1-h PG was a good predictor for future T2D and had a greater area under the ROC curve compared with the 2-h PG concentration [38].

As another example, the 1-h value of 155 mg/dl (8.6 mmol/L) was identified as most predictive of T2D in mixed populations of Caucasians and Hispanics, while 161 mg/dl (8.94 mmol/L) was found to be optimal in the pan-European population of the Relationship between Insulin Sensitivity and Cardiovascular disease risk (RISC) study conducted in Finnish and Swedish populations [38]. In Asians, the threshold identified was lower. Nevertheless, 155 mg/dl (8.6 mmol/L) may represent a reasonable compromise in terms of sensitivity and specificity for predicting T2D and therefore, for screening and prevention in different ethnicities [38].

In the combined populations of the Botnia (N = 2603) and MPP (N = 2386) Studies, the 1-h PG was confirmed as the best predictor of incident T2D among 14 OGTT derived indices of risk over a follow-up period of 4.94 years and 23.5 years. Of the 75% of those who progressed to T2D in the entire Botnia cohort, 30% had a 1-h PG above the threshold at baseline. Of the 2386 participants in the MPP, 873 (37%) had a 1-h PG value equal to or greater than 151 mg/dl (8.4 mmol/L) at baseline and 33.3% developed T2D vs 11.8% of participants displaying a 1-h PG < 151 mg/dl. Sixty-two per cent of those progressing to T2D during a 23.5 year follow-up had a 1-h PG ≥ 151 mg/dl (8.4 mmol/L) at baseline [20].

In a larger sample from the MPP cohort (N = 4867), the cumulative T2D incidence density per 1000 person years was 2.2 after 12 years follow-up which increased to 8.8 after 39 years in those with NGT at baseline but having a 1-h PG ≥ 155 mg/dl (8.6 mmol/L) [20]. The cumulative incidence density was even higher in those with IGT with a 1–h PG above the threshold, i.e. 6.3 and 9.6 after 12 and 39 years follow-up, respectively. The presence of a 1-h PG ≥ 155 mg/dl (8.6 mmol/L) was associated with greater discriminative ability than when based on a 2-h PG at both 12 and 39 years follow-up. Noteworthy, the presence of an elevated 1-h PG together with IFG or IGT was associated with greater risk of T2D than IFG or IGT alone. Subjects with IGT at baseline but with a 1-h PG below the threshold constituted a minority but, importantly, very few progressed to T2D while all the individuals with IGT who progressed to diabetes were captured by a high 1-h PG.

The 1-h PG level corresponding with the 2-h level diagnostic of T2D (200 mg/dl; 11.1 mmol/L) was evaluated in 951 European patients with coronary artery disease in the EUROASPIRE IV Trial [39]. An algorithm was created based on HbA_{1c}, FPG, and 1-h PG limiting the need for a 2-h PG. A 2-h ≥ 200 mg/dl (11.1 mmol/L) was the reference for undiagnosed T2D. The yield of HbA_{1c}, FPG and 1-h PG were compared with the 2-h PG level. In ROC analysis, a 1-h PG ≥ 216 mg/dl (12.0 mmol/L) balanced sensitivity and specificity for detecting T2D (both = 82%; positive and negative predictive values 40% and 97%). A combination of FPG < 117 mg/dl

(6.5 mmol/L) and 1-h PG < 200 mg/dl (11.1 mmol/L) excluded 99% of T2D. A combination of FPG > 144 mg/dl (8.0 mmol/L) and 1-h > 270 mg/dl (15.0 mmol/L) identified 100% of those with undiagnosed with T2D. Further studies are required to confirm the 1-h PG level corresponding with the 2-h level diagnostic of T2D.

8. How does the 1-h PG compare with previous diagnostic criteria for predicting diabetes and complications?

A cut off value of 155 mg/dl (8.6 mmol/L) for the 1-h PG may identify a category of high-risk individuals comparable to IFG and IGT. A threshold value for IFG of 110 mg/dl (6.1 mmol/L) was chosen arbitrarily as it represented "near the level above which acute phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of developing micro- and macro vascular complications" [40]. Similarly, individuals with NGT having a 1-h PG above the threshold have impaired β-cell responsiveness to a glucose stimulus while being insulin resistant and, as such, are at increased risk of developing diabetes [23,40].

As to the diagnosis of overt diabetes, the diagnostic 2-h PG cut off value of 200 mg/dl (11.1 mmol/L) was justified "largely because at approximately that point in glucose distribution where the prevalence of the microvascular complications considered specific for hyperglycemia (i.e. retinopathy) started to increase dramatically" [40]. For example, the Whitehall survey found that retinopathy developed after 6–8 years follow-up in individuals with a 2-h PG at baseline ≥ 229 mg/dl (12.7 mmol/L) [41]. Studies in Pima Indians [42,43], Egyptians [44], and data from the NHANES III [40] demonstrated the robust association between high FPG and increased risk of retinopathy over time. Threshold values of FPG ranging from 123 (6.8 mmol/L) to 129 mg/dl (7.2 mmol/L) were predictive of increased risk. Therefore, the Committee agreed on a FPG value of 126 mg/dl (7.0 mmol/L) as reasonably equivalent to the 2-h PG diagnostic cut off in terms of enhanced risk for retinopathy [40].

Nonetheless, robust evidence demonstrates that high 1-h PG is also associated with increased risk of retinopathy. In the MPP, the adjusted hazard ratios for incident diabetic retinopathy during 39 years follow-up was significantly higher in NGT participants with 1-h PG ≥ 155 mg/dl (8.6 mmol/L) (HR 5.23, 95%CI 3.24–8.43; p < 0.001) and IGT with 1-h PG above the threshold (HR 4.67, 95%CI 1.75–12.48; p < 0.001). The risk of retinopathy was not increased in those with IGT having a 1-h PG below the threshold compared with NGT alone [28]. As noted earlier, in a longitudinal study of an American Indian community, the ability of 1-h PG and 2-h PG concentrations to predict retinopathy have been investigated with cross-sectional ($n = 2895$) and longitudinal ($n = 1703$) analyses of prevalence and incidence of diabetic retinopathy, respectively, based on direct ophthalmoscopy. ROC analysis showed that 1-h PG and 2-h PG do not have different predictive values for identifying cases. More importantly, the 1-h PG cut points of 230 (12.8 mmol/L) and 173 mg/dl (9.6 mmol/L) did not have different accuracies compared with the 2 h-PG cut points of 200 mg/dl (11.1 mmol/L) and 140 mg/l (7.8 mmol/L) [34].

The Finnish Diabetes Prevention Study follow-up analysis demonstrated that CVD incidence among those with IGT at baseline was associated with an updated mean HbA_{1c}, 1-h PG and 2-h PG, HR per 1 unit SD of 1.57 (95% CI 1.16 to 2.11), p = 0.0032, 1.51 (1.03 to 2.23), p = 0.036 and 1.60 (1.10 to 2.34), p = 0.014, respectively, but not with the updated mean FPG (p = 0.11) [45]. In analyses of the last value prior to the CVD event the same three glycemic measurements were associated with the CVD events, with HRs per 1 unit SD of 1.45 (1.06 to 1.98), p = 0.020, 1.55 (1.04 to 2.29), p = 0.030 and 2.19 (1.51 to 3.18), p, 0.0001, respectively, but only 2-h PG remained significant in pairwise comparisons. A limitation of this study was the relatively small number of patients (504) and CVD events (34 events during the prediabetic phase and 52 after T2D was diagnosed) implying relatively wide confidence intervals for the estimated HR. Larger studies in individuals at increased risk have demonstrated that the 1-h level is significantly more predictive of microvascular complications, cardiovascular disease and mortality than the 2-h PG level (see Section 11.0, Table 5 and supplemental data).

9. What is known about the epidemiology of the 1-h post-load glucose level ≥ 155 mg/dl?

Several observational studies in different ethnic groups have analysed the proportion of individuals with NGT (i.e, normal FPG and 2-h PG levels) having a 1-h PG level ≥ 155 mg/dl (8.6 mmol/L) across glucose tolerance categories (Table 3). The frequency of 1-h post-load PG level ≥ 155 mg/dl (8.6 mmol/L) in those with NGT varies based on the study design, ranging from 11 to 16% in population-based studies of obese youth to 25–42% in cohorts enriched with high-risk subjects. It is noteworthy that the frequency of individuals with 1-h PG level ≥ 155 mg/dl (8.6 mmol/L) increases as glucose tolerance deteriorates with 56.6% in individuals with isolated IFG, 77.6% in individuals with isolated IGT, and 93.8% in those with combined IFG + IGT, and 98.8% in subjects with newly diagnosed T2D [46]. Similar findings are shown in Table 4 for the Israel Study of Glucose Intolerance, Obesity and Hypertension (GOH) [24] demonstrating the incremental cohort distribution shift towards the high 1-h value as the severity of dysglycemia progresses. These data suggest that a 1-hour post-load PG level ≥ 155 mg/dl (8.6 mmol/L) may be an earlier biomarker of dysglycemia than IGT in the lengthy trajectory from prediabetes to T2D.

10. What is known regarding the pathophysiology of NGT with 1-h PG ≥ 155 mg/dl (8.6 mmol/L)?

The natural history of the progression from normal glucose homeostasis to the onset of T2D appears to be characterised by three different phases [53]. The first phase occurs when β-cell function compensates for the increased insulin demand owing to reduced insulin sensitivity. The second phase occurs when β-cell function is still maintained but the β-cell mass starts to decrease leading finally to the irre-

Table 3 – Proportion of subjects with NGT and a 1-h PG ≥ 155 mg/dl (8.6 mmol/L) in various studies.

Study name	Mean age	Gender (% Women)	Proportion of individuals with NGT and 1-hour post-load plasma glucose ≥ 155 mg/dl (%)
San Antonio Heart Study (N = 1611)[19]	NA	NA	16.7
Botnia Study (N = 2442)[44]	46 ± 0.3	54	15.8
Chiba Foundation for Health Promotion & Disease Prevention (N = 4970)[47]	38.8 ± 9.4	41	10.8
CATAMERI study (N = 3020)[48]	48 ± 13	53	25.4
Section of Endocrinology, University of Florence (N = 1062)[49]	NA	NA	24.0
GENFIEV (N = 926)[50]	NA	NA	39.0
The Israel GOH Study (N = 853)[24]	48.1 ± 6.8	48	25.4
Dr. Mohan's Diabetes Specialties Centre (N = 1179)[22]	NA	NA	42.5
The New York University Langone Diabetes and Endocrine Associates (N = 236)[12]	55.7 ± 12.8	69	28.9
Malmö Preventive Project (N = 4867)[28]	48	0	33.2
SOLAR study (N = 233)[51]	11.1 ± 1.7	43	35.2
Endocrinology and Diabetology Unit, Bambino Gesu' Children's Hospital (N = 1038)[52]	11.3 ± 2.8	NA	11.0

Abbreviations: Malmö Preventive Project, MMP; San Antonio Heart Study, SAHS; CATAnzaro Metabolic Risk factors, CATAMERI; Genetic, Physiopathology And Evolution Of Type 2 Diabetes, GENFIEV; Israel Study of Glucose Intolerance, Obesity and Hypertension, GOH; Study of Latino Adolescents at Risk of Type 2 Diabetes, SOLAR.

Table 4 – Number of individuals in each glycemic category according to high vs. low 1-h PG in Israel GOH Study [24]

	1-h PG	
	<155 mg/dl n (%)	≥155 mg/dl n (%)
NGT	667 (81.9)	147 (18.1)
IFG	455 (59.9)	305 (40.1)
IGT	36 (35.0)	67 (65.0)
IFG + IGT	47 (16.7)	234 (83.3)
T2D	8 (4.1)	185 (95.9)

versible impairment of β-cell responsiveness. This leads to the third phase where β-cells can no longer maintain glucose homeostasis and diabetes develops. The entire process requires more than a decade when fasting and 2-h PG levels may remain in the normal range even in the absence of IGT. There are individuals who develop T2D during a decade, having normal FPG and 2-h PG at the baseline observation. There is a continuum of risk for developing type 2 diabetes across the spectrum of 2-h PG. As 2-h PG values increase, there is a decline in β-cell glucose sensitivity (i.e., a measure of the dependence of the insulin response to a glucose stimulus) although total insulin secretion may be maintained [54].

The RISC study [38] found that there was a progressive and significant decline in insulin sensitivity and β-cell glucose sensitivity (i.e., representing the dependence of insulin secretion on absolute glucose concentration at any time point during the OGTT) progressing from NGT with normal 1-h PG to NGT with high 1-h PG, and to individuals with IGT while basal and total insulin secretion significantly increased. No differences were found in β-cell rate sensitivity (i.e., representing the dependence of insulin secretion on the rate of change of glucose concentration) and the potentiation factor between NGT with high 1-h PG and IGT. This suggests that NGT with a high 1-h PG represents a risk for T2D which may or may not be related to IGT with reduced β-cell glucose sensitivity as the phenotypic signature and pathogenetic cause.

Longitudinal studies also describe individuals with IGT and high 1-h PG. In particular, the MPP [28] demonstrated that the hazard ratio of developing diabetes is higher in NGT with high 1-h PG (HR 3.87; 95%CI 2.16–6.93) and in those with IGT with high 1-h PG (HR 9.0; 95%CI 3.83–21.16) in contrast to individuals with IGT having a normal 1-h PG after 12 years of follow-up (Table 2). After 39 years of follow-up, individuals with NGT and IGT with high 1-h PG had similarly higher HR (2.93, 95%CI 2.48–3.46 vs. 2.76, 95%CI 1.87–4.06), while it was lower in the IGT group with normal 1-h PG (HR 1.17, 95%CI 0.43–3.15) (Table 2). There were a minority of individuals who had IGT and a normal 1-h PG, few progressing to diabetes consistent with findings from the Israel GOH study [24].

Therefore, it can be concluded that individuals with NGT and a high 1-h PG have reduced β-cell glucose sensitivity but still maintain NGT due to residual β-cell mass and

preserved second phase insulin secretion. The subsequent loss of second phase insulin secretion results in IGT and gradually overt T2D.

11. Is the 1-h post-load glucose levels ≥ 155 mg/dl (8.6 mmol/L) associated with cardiovascular risk factors, organ damage and adverse outcomes (e.g. mortality)?

NGT individuals with an elevated 1-h PG have been found to be at increased risk of having an unfavourable cardiometabolic risk profile and cardiovascular organ damage. Furthermore, studies in cells, animals, and humans suggest that an elevated 1-h glucose level is a sufficient stimulus for increasing several cardiovascular risk factors, such as inflammation, thrombosis, and endothelial dysfunction, with oxidative stress generation as the possible pathogenetic factor [55]. These findings are summarized in Table 5.

Several longitudinal studies have evaluated the impact of 1-h PG on cardiovascular adverse events, and all-cause mortality. In the Helsinki Businessmen Study comprising 2756 healthy men without diabetes followed for 44 years, a strong association between 1-h PG levels and cardiovascular mortality was observed ($P < 0.001$). Individuals with BMI < 30 kg/m^2 and 1-h PG concentration > 161 mg/dl (8.9 mmol/L) exhibited a 1.33-fold increase (95% CI, 1.12–1.57; $P < 0.001$) in all-cause mortality, compared with those having a BMI < 25 kg/m^2 and 1-h PG ≤ 161 mg/dl (8.9 mmol/L) after adjusting for age and smoking [30]. In the population-based Erfurt Male Cohort Study (ERFORT), 1125 men aged 40 to 59 without diabetes years were followed for 30 years [70]. Individuals with a 1-h PG concentration > 200 mg/dl (11.1 mmol/L) exhibited a 1.49-fold increased risk for death (95% CI, 1.17–1.88) compared with men having 1-h PG levels ≤ 200 mg/dl (11.1 mmol/L) after adjusting for age, smoking, BMI, education, hypertension, total cholesterol and triglycerides [70].

The Israel GOH Study followed 1945 individuals without diabetes for 33 years at baseline [71]. Plasma glucose levels were determined 1-h after a 100 gr oral glucose load and the association of the 1-h PG with all-cause mortality was assessed. Individuals with NGT having baseline 1-h PG levels ≥ 155 mg/dl (8.6 mmol/L) exhibited a 1.32-fold increased risk for death (95% CI, 1.12–1.56) compared with NGT individuals having a 1-h PG < 155 mg/dl (8.6 mmol/L) after adjusting for gender, age, smoking and BMI, FPG, and blood pressure. In the MPP, after 39 years follow-up, NGT individuals with 1-h PG ≥ 155 mg/dl (8.6 mmol/L) exhibited a 1.24-fold increased risk for incident myocardial infarction and fatal ischemic heart disease (95% CI, 1.10–1.39) and a 1.29-fold increased risk for mortality (95% CI, 1.19–1.39) compared with NGT individuals with 1-h PG levels < 155 mg/dl (8.6 mmol/L) after adjusting for age, BMI, impaired fasting glucose, triglycerides, and family history of diabetes (28). Furthermore, in the MPP, higher levels of 1-h PG levels, but not fasting or 2-h PG levels, were found to be an independent predictor of cardiovascular death (HR 1.09, 95% CI:1.01–1.17, $p = 0.02$) and all-cause mortality (HR 1.10, 95% CI:1.05–1.16, $p < 0.0001$). The addition of the 1-h PG parameter to clinical risk factors significantly improved their capability to predict cardiovascular death and all-cause mortality [28].

Furthermore, in a cohort of 39,573 subjects without diabetes participating in the Chicago Heart Association Detection Project in Industry, higher levels of glucose concentrations measured 1-h after a 50 gr oral glucose load were found to be associated with a greater risk of stroke and coronary artery disease, and increased cardiovascular and total mortality during a follow-up of 22 years in both men and women. This was independent of several cardiovascular risk factors including age, BMI, race, smoking habit, and blood pressure [73]. These observations are consistent with results of the Honolulu Heart Program comprising 6394 Japanese-American men without diabetes followed for 12 years that demonstrated glucose concentrations 1-h after a 50 gr glucose challenge were positively associated with fatal and nonfatal coronary artery disease [74].

As an overall, the evidence presented supports the 1-h PG ≥ 155 mg/dl (8.6 mmol/L) as a suitable glycemic parameter capable of detecting individuals at risk of cardiovascular organ damage and adverse outcomes (see supplementary data).

Table 5 – Association of 1-h post-load glucose levels ≥ 155 mg/dl (8.6 mmol/L) with cardiovascular risk factors, organ damage and adverse outcomes.*

- Association with cardiovascular risk factors
  - Insulin resistance [16,38]
  - Obesity [56,57]
  - Pro-atherogenic lipid profile [58]
  - Increased uric acid [59]
  - Increased liver enzymes [56]
  - Increased viscosity [60]
  - Reduced Vitamin D [61]
  - Increase in pro-inflammatory markers [62]
  - Reduction in molecules with anti-inflammatory properties [62,63]
- Subclinical target organ damage:
  - Subclinical atherosclerosis [64,65]
  - Vascular stiffness [47,66]
  - Left ventricular hypertrophy [67]
  - Impaired diastolic function [68]
  - Decline in kidney function [69]
  - Fatty liver [56]
- Capability of predicting progression to:
  - Macrovascular Complications [28,73,74]
  - All cause-mortality [28,30,67,70–74]

* Modified from reference [17].

12. Should the 1-h PG replace the 2-h PG for classifying prediabetes or should it be based on both 1-h PG and 2-h PG levels?

There is no evidence that combining the 1-h PG level ≥ 155 mg/dl (8.6 mmol/L) with either FPG or the 2-h PG level adds to its predictive capacity [75]. In the Botnia Prospective Study, the combination of the 1-h and 2-h PG levels was *not* superior to the 1-h level for improving the early prediction of T2D [75].

The sensitivity, specificity, and net predictive values for the 1-h and 2-h values were derived from the MPP and Israel GOH Study [18]. The sensitivity was considerably greater for the 1-h PG levels although somewhat less specific when contrasted with the 2-h PG values in both studies. However, the sensitivity and specificity relationships were more optimal in both cohorts for the 1-h PG level. Furthermore, the negative predictive values for the 1-h levels were substantially greater than their respective 2-h positive predictive values.

Measurement of the 1-h PG level alone would increase the likelihood of identifying a larger group at increased risk. Individuals in both the MPP and Israel GOH Study having *both* a 1-hour level ≥ 155 mg/dl (8.6 mmol/L) *and* IGT had the greatest risk for microvascular disease, diabetes, and mortality possibly related to the increased duration of exposure to hyperglycemia as IGT may occur subsequent to the elevation in the 1-h level [18]. Hence, the 2-h measurement in conjunction with the 1-h PG may identify individuals at particularly increased risk for progression to T2D and complications.

The scatter-plot in the Supplementary Data depicts the association between the 1-h PG and 2-h PG in the MPP. Venn diagrams in the Supplementary Data demonstrate the relationship between the 1-h PG, IFG and IGT for the MPP [28], CATAMERI Study [48] and Israel GOH Study [18,24].

13. What is the evidence that intervention in individuals with a 1-h PG ≥ 155 mg/dl (8.6 mmol/L) is effective?

The STOP DIABETES Study [76] was a retrospective observational study of 422 individuals at increased risk of T2D with well-established risk factors in a community practice in southern California. Participants had an OGTT and were risk stratified based on the presence and severity of insulin resistance, impaired β-cell function, and glycemia (i.e., 1-h PG ≥ 155 mg/dl (8·6 mmol/L).

Glycemic response was defined as normal if the participant had NGT according to the ADA criteria and a 1-h PG < 155 mg/dl (8·6 mmol/L). Moderate impairment in glucose tolerance was defined by the presence of NGT and 1-h PG ≥ 155 mg/dl (8·6 mmol/L), or IFG or IGT, or both, and 1-h PG < 155 mg/dl (8·6 mmol/L). A severe abnormality in glucose tolerance was defined by IFG or IGT, or both, and 1-h PG ≥ 155 mg/dl (than 8·6 mmol/L).

Metformin (850 mg/day), pioglitazone (15 mg/day), and lifestyle therapy were prescribed for those at intermediate-risk. Metformin, pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonist (based on insurance coverage), and lifestyle therapy were prescribed for those at high-risk. 200 (47%) individuals (76 high-risk and 124 intermediate-risk) declining pharmacotherapy received only lifestyle intervention which was not as intensive as in the Diabetes Prevention Program (DPP) [77] but consistent with the prevailing standard of care within the community. Participants were followed-up every 6 months and OGTTs were repeated at 6 months and subsequently every 2 years or sooner. The primary outcome, based on ADA criteria, was incidence of T2D from 2009 to 16.

Approximately 25% of participants had NGT with 1-h PG ≥ 155 mg/dl (8·6 mmol/L). The annual incidence of T2D in these individuals was higher than in those with IFG or IGT, or both (4·8% vs 3·8%). The incidence of T2D was equally reduced in these two groups by treatment with metformin and pioglitazone (to 1·7% and 1·9%, respectively) and metformin, pioglitazone, and GLP-1 receptor agonist (to 0% and 0·7%). The annual incidence of T2D in those receiving only lifestyle therapy was 4.1%. NGT was restored in 39% receiving lifestyle therapy only, 52% receiving metformin and pioglitazone and 77% receiving metformin, pioglitazone and GLP-1 receptor agonist.

The STOP Diabetes study identified a subgroup of individuals with NGT and a 1-h PG ≥ 155 mg/dl (8·6 mmol/L) who should be considered as having prediabetes and documented that effective interventions reduced their risk of progression to T2D.

14. Conclusions: Current OGTT criteria for prediabetes should be redefined with a 1-h post-load PG level

As current approaches for diagnosing prediabetes are suboptimal, we propose that the 1-h post-load PG level during the 75-g oral glucose tolerance test serve as a novel tool to detect prediabetes earlier than current screening criteria. Considerable evidence presented suggests that a 1-h PG ≥ 155 mg/dl (8.6 mmol/L) identifies individuals with reduced β-cell function in individuals with NGT. Identifying the earliest time point on the prediabetic continuum is critical to avoid the progressive and insidious deterioration in β-cell function. Rising glucose levels within the "normal range" occur considerably late in the evolution to diabetes [53] presenting an important opportunity for earlier diagnosis, treatment and possible reversal. An elevated 1-h PG level, not measured with current diagnostic standards, may provide an opportunity for the early identification of a large population at increased risk. When the 1-h PG level is elevated, lifestyle intervention may have the greatest benefit for preserving or reversing β-cell function and to prevent further progression to prediabetes and diabetes.

The 1-h PG level is more predictive of those likely to progress than the HbA_{1c} or 2-h PG values. An elevated 1-h post-load glucose level was a better predictor of T2D than isolated 2-h post-load levels in various populations. In addition, epidemiologic studies have consistently shown that a 1-h PG ≥ 155 mg/dl (8.6 mmol/L) predicted an increased risk for microvascular disease, myocardial infarction, fatal ischemic heart disease and mortality when the 2-h level was <140 mg/dl (7.8 mmol/L).

Furthermore, an important association has been demonstrated with a 1-h post-load PG level measurement in middle age and future Medicare charges [78]. Participants were classified based on 1-h postload PG levels < 120 (6.7 mmol/L), 120–199 (6.7–11.1 mmol/L), or ≥ 200 mg/dl (11.1 mmol/L). The main finding was that postload PG in middle age was positively associated with age-, race-and education-adjusted CVD-related, diabetes-related, and total Medicare charges in older age for both women and men. Individuals with low PG levels had reduced health care costs in older age and could reduce the risk of diabetes, CVD, other diabetes-related

chronic complications, mortality, as well as potentially decreasing subsequent Medicare expenditures. Preventive measures are vital to reduce disease burden and disability and to decrease future health care costs associated with the increasing prevalence of diabetes in an aging population. The authors concluded that "public health efforts need to include comprehensive national strategies and resources for primary prevention of diabetes including screening for high blood glucose levels from early life on, with the goal to end the diabetes epidemic and reduce health care" [78].

The observations presented in this petition lay the foundation for advancing epidemiology and global public health beyond the significant achievements in diabetes prevention stemming from the DPP [77] completed many years ago. The co-signatories to this petition, listed below, feel that the current findings present a valuable opportunity to extend the proven benefit of diabetes prevention to the sizeable and growing population of individuals at increased risk by identifying an earlier time point in the lengthy trajectory to diabetes with a 1-h PG determination. Hence, we advocate changing to a 1-h OGTT to screen for prediabetes and a 2-h OGTT and/or a HbA_{1c} measurement to diagnose T2D. Whereas we recognize the considerable challenges inherent in implementing this recommendation, there is the considerable upside potential for thwarting the enormous global diabetes epidemic. Therefore, we believe that the substantial evidence base provided in this petition strongly supports redefining current screening and diagnostic recommendations for prediabetes with the 1-h PG level.

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Contributions

MB conceptualized the petition, interpreted the data, drafted the manuscript, and reviewed the manuscript for important intellectual content. MM and GS drafted the manuscript, provided new data, interpreted the data and reviewed the manuscript for important intellectual content. RJ drafted the manuscript, interpreted the data and reviewed the manuscript for important intellectual content. RD, MP, AC interpreted the data, provided new data and reviewed the manuscript for important intellectual content. AC assisted in conceptualizing the petition and reviewed the manuscript for important intellectual content. MAG interpreted the data and reviewed the manuscript for important intellectual content. MB, JLM, PMN, MHO, IR, JR, SDP, and LG reviewed the manuscript for important intellectual content.

All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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Conflicts of interest

The authors declare that there is no conflict of interests regarding this petition.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2018.09.017.

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