Review of Methods for Detecting Glycemic Disorders

Short title: Detecting Glycemic Disorders

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Abbreviations

1,5- AG	1,5- anhydroglucitol
1-h PG	1-hour plasma glucose
2-h PG	2-hour plasma glucose
aROC	Area under the Receiver-Operating Characteristic curves
ADA	American Diabetes Association
ALT	Alanine Aminotransferase
BCAA	Branched-Chain Amino Acids
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DI	Disposition Index
DPP	Diabetes Prevention Program
FPG	Fasting Plasma Glucose
GA	Glycated Albumin
GCT	Glucose Challenge Test
GDM	Gestational Diabetes Mellitus
GV	Glycemic Variability
HOMA	Homeostasis Model Assessment
IDF	International Diabetes Federation
IEC	International Expert Committee
IFG	Impaired Fasting Glucose
IGT	Impaired glucose Tolerance
MARD	Mean Absolute Relative Difference
NDDG	National Diabetes Data Group
NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
PG	Plasma Glucose
ROC	Receiver-Operating Characteristic Curves
SMBG	Self-Monitoring of Blood Glucose
SI	Insulin Sensitivity
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

Highlights

- A 1-hour plasma glucose (1-h PG) threshold ≥155 mg/dl (8.6 mmol/L) during an oral glucose tolerance test (OGTT) may be a suitable biomarker for identifying normal glucose tolerant (NGT) individuals at risk for future type 2 diabetes (T2D).
- A one-hour, non-fasting, 50g Glucose Challenge Test (GCT) performed during a routine health care visit has potential for practical screening of glucose disorders.
- The shape of the glucose curve reflects the cumulative effect of insulin sensitivity and response on glucose concentrations with prospective studies warranted to evaluate its prognostic utility.
- The continuous glucose monitor (CGM) has facilitated insight into the pathophysiology of prediabetes and phenotypes of T2D and holds promise for detecting glycemic disorders.
- Metabolomic profiling including amino acids, lipids, carbohydrates and other metabolites may be useful for early diagnosis of glycemic disorders.
- Non-classical markers for assessing glycemic disorders including fructosamine, glycated albumin, and 1,5-anhydroglucitol that evaluate shorter periods of glucose exposure than HbA1c have potential use as adjunctive tools.

Abstract

Prediabetes (intermediate hyperglycemia) consists of two abnormalities, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) detected by a standardized 75-gram oral glucose tolerance test (OGTT). Individuals with isolated IGT or combined IFG and IGT have increased risk for developing type 2 diabetes (T2D) and cardiovascular disease (CVD). Diagnosing prediabetes early and accurately is critical in order to refer high-risk individuals for intensive lifestyle modification. However, there is currently no international consensus for diagnosing prediabetes with HbA1c or glucose measurements based upon American Diabetes Association (ADA) and the World Health Organization (WHO) criteria that identify different populations at risk for progressing to diabetes. Various caveats affecting the accuracy of interpreting the HbA1c including genetics complicate this further. This review describes established methods for detecting glucose disorders based upon glucose and HbA1c parameters as well as novel approaches including the 1-hour plasma glucose (1-h PG), glucose challenge test (GCT), shape of the glucose curve, genetics, continuous glucose monitoring (CGM), measures of insulin secretion and sensitivity, metabolomics, and ancillary tools such as fructosamine, glycated albumin (GA), 1,5- anhydroglucitol (1,5-AG). Of the approaches considered, the 1-h PG has considerable potential as a biomarker for detecting glucose disorders if confirmed by additional data including health economic analysis. Whether the 1-h OGTT is superior to genetics and omics in providing greater precision for individualized treatment requires further investigation. These methods will need to demonstrate substantially superiority to simpler tools for detecting glucose disorders to justify their cost and complexity.

Keywords: prediabetes, type 2 diabetes, HbA1c, glycemic variability, biomarkers, oral glucose tolerance test, continuous glucose monitoring, metabolomics, cardiovascular disease.

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1. Introduction

Prediabetes (intermediate hyperglycemia), a condition that can precede the development of type 2 diabetes (T2D) by many years, is defined by blood glucose levels that are higher than normal but below established threshold criteria defining diabetes. In 2017, an estimated 7.3% (352 million adults) of the global population had prediabetes, a figure expected to rise to 8.3% (587 million adults) by the year 2045 [1].

Prediabetes consists of two abnormalities, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), the latter detected by a standardized 75-gram oral glucose tolerance test (OGTT). Accurately diagnosing prediabetes is critical so that high-risk individuals can be referred for lifestyle intervention to prevent progression to T2D and associated complications. Glucose and HbA1c diagnostic criteria for prediabetes proposed by the American Diabetes Association (ADA) and the World Health Organization (WHO) differ in their sensitivities and specificities [2] identifying, therefore, different populations at risk for progressing to diabetes. Furthermore, as there are currently five distinct definitions for prediabetes, an international consensus would benefit the development of unambiguous and evidence-based criteria [3]. Differences in genetics and the glycation gap affecting the accuracy of HbA1c levels complicate this further [4, 5]. The risk of future T2D and cardiovascular disease (CVD) is continuous along the spectrum of 1- and 2-hour plasma glucose (1-h PG, 2-h PG) and HbA1c values. Although inevitably any cut-point will be arbitrary, the goal remains to identify with greater accuracy those at risk of developing T2D and CVD.

This review will consider established diagnostic methods based on glucose and HbA1c parameters as well as alternative approaches. These include the 1-h PG, the Glucose Challenge Test (GCT), the shape of the glucose curve, genetic testing, continuous glucose monitoring (CGM) with assessment of glycemic variability (GV), measurements of insulin secretion and insulin sensitivity, metabolomics and ancillary tools such as fructosamine, glycated albumin (GA), 1,5-anhydroglucitol (1,5-AG). While these approaches have broadened insight into the pathophysiology and mechanisms underlying glucose disorders, in many instances, their complexity and expense likely make their use impractical and thus remain research tools.

2. Diagnosing Type 2 Diabetes

T2D is a disorder of impaired glucose homeostasis with the diagnosis based upon three different measurements: fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG) after a 75-gram glucose load, and HbA1c. Each provides vital information about glucose metabolism and reflects different physiological mechanisms. The FPG reflects glucose homeostasis in the post-absorptive state while the 2-h PG primarily reflects disposal of an exogenous glucose load [6]. The HbA1c correlates strongly with overall glycemia as it reflects the average glucose over 2-3 months. The FPG strongly correlates with HbA1c in the non-diabetic range as elevations in the FPG concentration are present throughout the day. In contrast, post-prandial hyperglycemic excursions are transient, occurring 3-4 hours after each meal, while 2-h PG are more strongly associated with elevations in HbA1c with increasing overall glycemia. Therefore, it is not surprising that the HbA1c has a stronger correlation with the FPG than the 2-h PG [7-10].

2.1. Fasting Plasma Glucose and Diagnosis of T2D

Before 1997, diabetes was diagnosed based on a FPG concentration >140 mg/dl (7.8 mmol/L) which was arbitrarily determined to represent the upper limit of normal FPG. In 1997, the ADA Expert Committee [11] revised the criteria for diagnosing diabetes [12] reducing the FPG cut-point for diabetes from 140 mg/dl (7.8 mmol/L) to 126 mg/dl (7.0 mmol/L) and retained the 2-h PG cut-point >200 mg/dl (11.1 mmol/L). The revised FPG concentration threshold was based upon three different studies [11, 13, 14] which demonstrated that the risk of proliferative diabetic retinopathy increased significantly when the FPG exceeded 126 mg/dl (7.0 mmol/L) and the 2-h PG was >200 mg/dl(11.1 mmol/L). The ADA Expert Committee reasoned that if a complication of the disease was present at a FPG ≥126 mg/dl (7.0 mmol/L), then the disease, i.e. diabetes, must exist.

2.2. 2-hour Plasma Glucose and Microvascular Disease

Microvascular end-points (retinopathy and microalbuminuria) have been essential for defining glycemic thresholds and developing current diagnostic criteria. In a study of 960 Pima Indians, diabetic retinopathy (microaneurysms or hemorrhages) was largely confined to a 2-h PG level ≥ 240 mg/dl (13.33 mmol/L) rather than a 2-h PG level < 200 mg/dl (11.11 mmol/L). A previous investigation in this population identified found 252 mg/dl (14 mmol/L) optimal for diagnosing retinopathy [15].Threshold values of 2-h PG for retinopathy ranged from 194 mg/dl (10.8 mmol/L) [11] to 198 mg/dl (11 mmol/L) in Japanese [16], 218 mg/dl (12.1 mmol/L) in Egyptian [14] , and 236 mg/dl (13.1 mmol/L) in Australian populations [17]. Therefore, the current 2-h PG diagnostic threshold represents a reasonable compromise replicated in other studies [18, 19]. A more recent investigation of nine pooled studies in a multiethnic population of 21,334 participants from 5 countries with 2-h PG and diabetic-specific retinopathy demonstrated that a 2-h PG of 234 mg/dl (13.0 mmol/L) was optimal for identifying moderate or severe non-proliferative diabetic retinopathy [20]. It is worth mentioning that isolated retinopathy is also common in individuals without diabetes and, furthermore, the risk of diabetes-specific retinopathy varies with ethnicity [21].

The 2-h PG threshold value predictive of microalbuminuria and diabetic nephropathy has been investigated less extensively. The percentage of individuals in a Pima Indian population with nephropathy (protein to creatinine ratio ≥1.0 g:g) was 1.6% in the group with 2-h PG < 227 mg/dl (12.6 mmol/L) and 6.2% in those with higher levels while the 5-year incidence was 1.2% and 3.6%, respectively [13]. In the 2,182 participants of the Australian Diabetes Obesity and Lifestyle study, unlike retinopathy, the 2-h PG showed no evidence of a threshold effect [17].

Nevertheless, in the 3,644 adults enrolled in the 2005-2014 National Health and Nutrition Examination Survey (NHANES) with prediabetes based on HbA1c and FPG levels, the adjusted odds ratio (95% confidence interval) was 2.05 (95%CI 1.33-3.14) for albuminuria (albumin ⩾30 mg/g of creatinine) associated with a 2-h PG ≥ 200 mg/dl (11.1 mmol/L) [22]. The current diagnostic cut-point of 200 mg/dl (11.1 mmol/L) therefore represents a threshold beyond which the risks of retinopathy and, in general, microvascular diseases rise.

2.3. HbA1c and Diagnosis of T2D

Due to limitations in measuring the FPG and 2-h PG (Table 1), an International Expert Committee (IEC) in 2009 recommended HbA1c for diagnosing diabetes [23] which was endorsed by the ADA [24] (Table 1). The HbA1c measurement is standardized worldwide and quality assurance tests are in place [25]. Nonetheless, the use of HbA1c for diabetes diagnosis has certain limitations that raise concerns about its use as the sole method for diabetes diagnosis (Table 1).

HbA1c increases with age independent of glucose tolerance [26-31] and is affected by ethnicity [32-38] and genetic factors [39, 40]. Data from NHANES [27] have demonstrated that the relationship between HbA1c and plasma glucose concentrations (both fasting and 2-h PG) is shifted to the right in African Americans, compared to Mexican Americans and non-Hispanic white subjects, having an approximately 0.65% higher level than Caucasians [27] under comparable glucose conditions. Because of the narrow non-diabetic HbA1c range, the influence of ethnicity can significantly affect the classification of subjects.

Genetic makeup also affects the HbA1c level independent of PG concentration [39-41]. Thus, relying solely on the HbA1c to diagnose diabetes can result in approximately 650,000 missed

cases of diabetes in the US alone. These factors should therefore be taken into account when T2D is diagnosed based strictly upon HbA1c levels [42-44].

2.3.1. HbA1c Cut-Point to Diagnose T2D

Similar to glucose, the deterioration in glucose homeostasis in relation to HbA1c follows a continuum, presenting a challenge when determining the HbA1c cut-point for diagnosing diabetes. The IEC has set the HbA1c $\geq 6.5\%$ (48 mmol/mol) as the cut-point for the diagnosis of diabetes [23]. This decision was based on the DETECT-2 study [20] examining pooled data from 44,623 patients in 12 different studies which found that the incidence of proliferative diabetic retinopathy increased significantly at this threshold. However, this threshold has not been consistently found so caution should be exercised when using HbA1c alone as the diagnostic criteria for diabetes (31, 59-63, 64, 65).

2.3.2. Diabetes Diagnosis: HbA1c versus Glucose Criteria

The cut-point for the diagnosis of T2D with both HbA1c and glucose criteria is based upon the threshold for development of retinopathy. However, studies examining their concordance revealed significant disagreement. Glucose criteria, especially the 2-h PG, have greater sensitivity than HbA1c in diagnosing diabetes in the majority of cohorts [27, 28, 45-51] each diagnosing distinct patient populations.

In cross-sectional data from 5,395 nondiabetic participants in NHANES (2005-2010), the number of subjects diagnosed with diabetes by glucose criteria was more than double than those identified with HbA1c criteria (5.7% versus 2.23%) [45]. Thus, the sensitivity of HbA1c criteria (HbA1c >6.5%; 48 mmol/mol)) was only 41%, although it had 99% specificity in identifying subjects with diabetes diagnosed by glucose criteria. Other studies have similarly demonstrated

low sensitivity (20-40%) and high specificity of HbA1c criteria [28, 47-49, 51, 52]. The sensitivity of HbA1c in detecting patients with diabetes varies amongst ethnic groups [32, 36, 53, 54] being higher in Chinese [53], Asian Indian (75), and African populations [55] than in Caucasians. When viewed collectively, data suggest that a HbA1c <6.5% (48 mmol/mol) does not exclude the presence of diabetes. Thus, a HbA1c threshold of 6.5% (48 mmol/mol) for diagnosing diabetes may leave many undiagnosed (i.e. high false negative rate) and untreated despite having increased risk of microvascular complications according to glucose criteria.

In clinical practice, obtaining simultaneous FPG and HbA1c measurements is convenient as diabetes screening is primarily performed using a single fasting blood sample. Given the partial overlap between HbA1c and FPG, measuring both will increase the likelihood of identifying diabetes [53, 54, 56]. The combination of HbA1c > 6.5% (48 mmol/mol) and/or FPG >126 mg/dl (7.0 mmol/L) identifies >85% of patients with T2D in Chinese (69) and Asian Indian (71) populations. Likewise, the combination of FPG and HbA1c has been shown to identify 80% of patients with diabetes [9] in a Korean population although the optimal cut-point for FPG and HbA1c in this study was 100 mg/dl (5.6 mmol/L) and 5.5% (37 mmol/mol), respectively.

Using the FPG and HbA1c alone for the diagnosis of diabetes will primarily miss subjects with isolated postprandial hyperglycemia. The risk of microvascular risk in this population, constituting approximately 20% of those with T2D, has not been examined. Moreover, the 2-h PG has a stronger association with the incidence of CVD, the major cause of death in T2D. NHANES (2005-2014) [22] demonstrated that 6.9% and 8.2% of individuals respectively diagnosed as having prediabetes and NGT with the FPG and HbA1c, had T2D with a 2-h PG >200 mg/dl (11.1 mmol/L). Those diagnosed with T2D by an isolated 2-h PG had significantly higher rates of hypertension, dyslipidemia (low HDL and high triglycerides), microalbuminuria

and elevated alanine aminotransferase (ALT). Thus, measuring a FPG and HbA1c alone without a 2-h PG will preclude identifying those at high risk for CVD [22, 57].

3. Diagnosing Prediabetes

3.1. Fasting Plasma Glucose and Prediabetes – IFG

The ADA Expert Committee introduced IFG (FPG=110-125 mg/dl [6.1 -6.9 mmol/L]) in 1997 (77) as a "prediabetes" condition overcoming limitations in diagnosing IGT (Table 1).The IFG designation was intended to identify individuals with IGT without an OGTT although subsequent studies demonstrated that it had a low sensitivity for this purpose. Furthermore, as IFG identifies a distinct population [58, 59], the threshold was reduced to 100 mg/dl (5.6 mmol/L) making its predictive value comparable to IGT [60].

IFG is pathophysiologically distinct from IGT [58, 61]. Isolated IFG may confer similar risk for conversion to T2D (~5 fold) as isolated IGT [59] although this is not uniformly agreed upon as will be seen below. The relative risk progressively increases with the FPG, steeply increasing within the IFG range [59]. However, it is not clear whether the increase in FPG confers risk for diabetes independently or if this is secondary to its strong correlation with the 1-h and 2-h PG level (81). When participants with IFG and NGT are matched for 1-h PG levels, the risk for T2D is similar indicating that the contribution of FPG is small and primarily due to the increase in the 1-h PG. Individuals with both IFG and IGT have double the risk of T2D compared to either isolated IFG or IGT [59, 62]. Finally, IFG does not confer an elevated risk of CVD [63] .

3.2. 2-Hour Plasma Glucose and Prediabetes- IGT

The National Diabetes Data Group created the term IGT in 1979 defined by a 2-h PG = 140-199 mg/dl (7.8-11.1 mmol/L) [12]. Individuals with IGT manifest elevated future risk of T2D with

the annual progression rate varying with ethnicity from 5-11%. However, IGT does not always progress to T2D, the lifelong future risk of T2D approximating 50%. Moreover, as IGT constitutes approximately 40% of all subjects progressing to T2D,individuals may progress to T2D in the absence of IGT. As already noted, individuals with both IFG and IGT have twice the risk of developing T2D and as discussed in greater detail below, unlike IFG, IGT is associated with elevated cardiovascular risk (84).

3.3. HbA1c and Diagnosis of Prediabetes

HbA1c was recommended for diagnosing prediabetes to address limitations associated with glucose measurements (Table 1). However, both cross-sectional and longitudinal studies comparing HbA1c with glucose criteria (i.e. IFG and/or IGT) demonstrated that the latter outperformed HbA1c and captured twice the number of subjects progressing to T2D. Similar to FPG, the future risk of T2D increases continuously with the HbA1c level with no threshold above which diabetes risk increases. Thus, determining the HbA1c range for prediabetes is challenging. The International Expert Committee (IEC) recommended [23] that an HbA1c = 6.0% - 6.4% (42-46 mmol/mol) identified high-risk individuals with prediabetes whereas this cut-point was later lowered by the ADA to 5.7% (39 mmol/mol) [24] with HbA1c=5.7-6.4% (39-46 mmol/mol), the current range for diagnosing prediabetes.

NHANES 2005-2006 [27] and 2011-2014 [64] demonstrated that the prevalence of prediabetes with HbA1c =5.7-6.4% (39-46 mmol/mol)) was significantly less than when diagnosed by an OGTT. Although the relative risk of progression to T2D is similar whether prediabetes is diagnosed by HbA1c or glucose criteria, the absolute number is higher when diagnosed with glucose criteria [65].

To understand the pitfalls of relying exclusively on HbA1c, it is important to note that β-cell failure is primarily responsible for deterioration of glucose tolerance. However, as HbA1c is insensitive for identifying individuals with early impairment in β-cell function, its isolated use will classify a large number of high-risk individuals as normal. This point is exemplified in a high-risk population of Mexican Americans in whom β-cell function in those with NGT and HbA1c < 5.7% was comparable to NGT subjects with HbA1c = 5.7–6.4% [66]. Notably, participants with IFG or IGT had a marked decrease in β-cell function independent of the HbA1c level. Therefore, utilizing an OGTT is preferable for identifying individuals with early β-cell dysfunction who are at increased future risk for T2D. Finally, although HbA1c alone is a weaker predictor of future risk for T2D compared with the 1-h PG (see below), it provides additive information when combined with established prediction models (88).

3.4. 1-hour Plasma Glucose

3.4.1. Early Biomarker of Dysglycemia

The 1-h PG during the 75-gram OGTT appears to be a useful early biomarker of dysglycemia [67, 68]. A cut-off of 155 mg/dl (8.6 mmol/L) was initially identified in the San Antonio Heart Study (SAHS) based on the greater predictive power of the 1-h PG for future T2D compared with fasting and 2-h PG determined by the aROC curve method [69]. Evaluation of fourteen OGTT glucose-derived indices in two longitudinal studies, the Botnia and the Malmö Prevention Project (MPP) cohorts, demonstrated that the 1-h PG was the best predictor for mid- and long-term incident T2D in middle-aged European adults with NGT [70]. Moreover, the 1-h PG in a German cohort had higher predictive power comparing the aROC curves for future T2D with FPG, 2-h PG, and HbA1c (aROC 0.70, 0.84, 0.79, and 0.73 for FPG, 1-h PG, 2-h PG, and HbA1c, respectively) [71]. These results were confirmed in different ethnic groups including

Mexican Americans, Japanese, Han Chinese, Korean, Southwestern Native American, and Asian Indian adults (Table 3) [72-76]. Notably, the Botnia Prospective Study cohort demonstrated that the 1-h PG outperformed fasting and 2-h PG levels in predicting progression to T2D either alone or in combination with six metabolic markers including glucose, mannose, a-hydroxybutyrate, α-tocopherol, bradykinin-hydroxyproline, and the unknown metabolite X-12063 [77]. The predictive power of the 1-h PG for T2D in various cohorts is summarized in Table 3 and Table 4 comparing the AUC of FPG, 1-h PG, and 2-h PG for predicting T2D. Several longitudinal studies have confirmed that those with NGT *and* a 1-h PG value $\geq$ 155 mg/dl ($\geq$8.6 mmol/L) were at increased risk for T2D [69, 78-83]. A meta-analysis of six prospective studies demonstrated the greater risk of progression [OR 4.33, 95% CI 3.40 to 5.51]) [67]. Moreover, individuals with IFG and/or IGT *and* a 1-h PG $\geq$ 155 mg/dl (8.6 mmol/L) have a 2-5fold greater future risk of T2D.

Studies exploring pathophysiological mechanisms have shown that individuals with NGT *and* a 1-h PG $\geq$ 155 mg/dl (8.6mmol/L) share several abnormalities observed in IGT including impaired insulin sensitivity, β-cell dysfunction, β-cell glucose sensitivity, and reduced insulin clearance [81, 84-94]. Another pathophysiologic defect linked to excessive excursions of 1-h PG in subjects with NGT is increased intestinal glucose absorption. T2D has been associated with increased intestinal glucose uptake [95-98] and accelerated absorption playing a role in excessive post-load glucose excursions [99-101]. The latter is dependent on gastric emptying and duodenal abundance of the glucose carrier sodium/glucose co-transporter 1 (SGLT-1) and glucose transporter 2 (GLUT-2) [99, 102, 103] both of which are increased in T2D [98]. In subjects undergoing upper endoscopy, duodenal expression of SGLT-1, but not GLUT-2, was increased significantly in those with NGT and 1-h PG $\geq$ 155 mg/dl (8.6 mmol/L) as well as IGT [100].

However, a positive relationship was not observed between duodenal SGLT-1 expression with fasting or 2-h PG levels suggesting that accelerated glucose absorption in determining early post-prandial hyperglycemia is related to increased expression of duodenal SGTL-1 [100]. These observations were subsequently confirmed by a study showing enhanced rate of oral glucose absorption, measured by labelled OGTT, in those with 1-h PG ≥ 155 mg/dl (8.6 mmol/L) but not the 2-h PG [101].

The frequency of subjects with NGT and elevated 1-h PG varies based on study design ranging from 11% to 16% in population-based studies, to 25% to 42% in cohorts enriched for high-risk subjects [67]. 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. These data suggest that a 1-h 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. Furthermore, as the progression from NGT to IGT follows a continuum, there is no absolute threshold value for determining risk. For example, in the RISC cohort, the 1-h PG of 155 mg/dl (8.6mmol/L) was the most practical capturing 22% of the population compared with other cut-off values. A threshold of 137 mg/dl (7.6mmol/L) corresponded to 38% of the population with NGT whereas a cut-off value of 114 mg/dl (6.32 mmol/L) would identify 66% of the population [83].

A health economic analysis is important to determine the acceptability of the 1-h PG in clinical practice. Although there is a need for a formal technical health assessment, simulation of benefits from the 1-h PG as a classification tool in the Finnish population demonstrated improved quality

of life, increased life expectancy and considerable cost savings. Alyass et al therefore concluded that the 1-h PG could have benefit in Finland as well as globally [70, 104].

3.4.2. Predictor of Complications and Adverse Outcomes

The 1-h PG is an independent risk factor for micro- and macrovascular complications as well as mortality [82, 105-108] possibly explained by its association with a pro-atherogenic risk profile [109] and several cardiovascular risk factors including thrombosis, endothelial dysfunction, oxidative stress, worse lipid profile, increased blood pressure, inflammatory markers, and uric acid (162). Furthermore, the 1-h PG correlates with increased arterial stiffness, carotid intima-media thickness, increased left ventricular mass and left ventricular diastolic dysfunction (162). The combination of an elevated 1-h PG *and* IGT resulted in higher risk for T2D, micro- and macrovascular risk as well as mortality suggesting that individuals at high-risk should be diagnosed *before* progressing to IGT (137,140).

3.4.3. Reproducibility

Briker et al studied the reproducibility of the 1-h PG ≥ 155 mg/dl (8.6 mmol/L) in 119 subjects with repeat OGTT in the Africans in America Study [110] and found it equivalent to fasting and 2-h PG levels. Additional reproducibility data from a larger cohort in well-designed trials would be of interest.

4. Genetic Testing and Risk Prediction of T2D

Attempts to predict T2D with genetic tests have thus far been unsuccessful. Prior to the genome-wide association studies (GWAS) era, three genetic variants in *KCNJ*, *PPARG* and *TCF7L2*

genes were associated with T2D risk. Sensitivity and specificity to predict T2D provided an aROC of 0.58 [111]. During the last decade, large-scale GWAS have identified more than 400 gene single nucleotide polymorphisms (SNPs) influencing T2D risk [112]. Most of these variants are widely shared within and between populations but have only a modest effect on individual predisposition in contrast to the alleles that drive rarer subtypes of diabetes. To an extent, combining these variants in a genetic score can predict an individual's risk of developing T2D [112, 113].

Nevertheless, there is a need to combine genetic and clinical information further to maximize risk prediction. In the most recent GWAS for T2D, the entire set of associated variants detected explained ~20% of the overall variation for disease risk in European populations [112]. Indeed, estimates of T2D heritability vary widely [114] around a median of 40%. Therefore, as genetics contribute to about half of the variation in risk for each individual, integration with accurate and robust measures of other contributing factors is required[115].

Initial studies in 2008 constructed restricted-to-significant polygenic scores (rsPSs), i.e. scores composed of 16-18 variants known at the time to be at the extreme of a statistical distribution and weighted to reflect their respective effect size on the hyperglycemic trait [116-118]. Their predictive performance did not outweigh clinical risk factors for T2D. The predictive ability of an 18 SNP rsPS was tested in 2377 participants of the Framingham Offspring Study during 28 years of follow-up. The aROC for incident diabetes, with the score adjusted for age and sex, was 0.58. A clinical model that included age, sex, family history, BMI, fasting glucose, systolic blood pressure, HDL cholesterol, and triglyceride levels demonstrated an aROC of 0.90. Combining

694 both did not enhance aROC and resulted in risk reclassification of less than 4%. Nevertheless,
695 those with rsPS >21 (~11% of the cohort) had 2.6 higher odds of developing T2D than did those
696 with rsPG ≤15 (~25% of the cohort)[116]. RsPS of 18 SNPs and a clinical score tested in 4097
697 participants from Scotland, demonstrated aROCs of 0.60 and 0.78, respectively, while combining
698 both resulted in a slight increase in the aROC to 0.80 [117].
699
700 Lyssenko et al. [118] examined a 16 SNP rsPS in 16000 Swedish and 2770 Finnish subjects
701 followed for a median of 23.5 years. The score adjusted for age and sex predicted T2D incidence
702 with an aROC of 0.62. A score system of clinical factors, namely age, sex, a family history of
703 diabetes, BMI, blood pressure, triglycerides, FPG, provided an aROC of 0.74. A combination of
704 rsPS and clinical factors produced an aROC of 0.75 with reclassification of 9% and 20% of
705 subjects from the Swedish and Finnish studies respectively, to a higher risk category.
706
707 Although larger GWAS have identified novel loci significantly associated with T2D,
708 improvements in genetic score performance have been more modest. An rsPS of 62 SNP in the
709 Framingham Offspring Study [119] produced an aROC for T2D prediction of 0.72 while the
710 aROC generated with scoring clinical variables was 0.90 and combining both produced an aROC
711 of 0.91. Similar outcomes were reported in the Coronary Artery Risk Development in Young
712 Adults [119].
713
714 More recently, Mahajan et al. [112] generated a global extended polygenic score (gePSs) that
715 included large numbers of significant subthreshold variants from T2D GWAS meta-analysis of
716 almost 460000 European individuals (effective sample size ~158000). An optimized gePS

comprising 171249 variants was constructed with 5639 cases and 112307 controls from the UK Biobank, which was then used to predict T2D case-control status in separate sets of 13480 cases and 311390 controls. The aROC was 0.73 after adjusting for age and sex.

Khera et al. [113] applied an analogous approach with a deeper gePS of almost 7 million variants that, after adjusting for age and sex, generated a similar aROC. Performance of gePS and risk estimates were also confirmed by the direct-to-consumer company 23andMe in their data set of 1,479,116 individuals. In individuals from the UK Biobank in the top 2.5-5.0% of the gePS distribution had a threefold increased risk of T2D and tenfold increase compared to those in the bottom 2.5% [112]. A different approach to estimate genetic risk of T2D based on patterns of genetic association across diabetes-related quantitate traits (glycemic measures, insulin secretion and insulin resistance) [120-122] demonstrated that T2D risk variants impact disease predisposition.

Although GWAS has provided insight into the potential of genetic risk profiling, its clinical applicability remains uncertain. While a potential role for common variant risk scores to predicting risk for T2D was suggested earlier, subsequent studies demonstrated their limited increase in performance over clinical models that can be generated from more readily accessible risk factors. The substantial polygenicity and small effect of most risk variants have major implications for precision medicine. Nonetheless, overcoming obstacles in translating genetics may yet hold significant promise for future strategies in the prevention of T2D [123].

5. The 50g Glucose Challenge Test (GCT)

Table 1 outlines the advantages and limitations of different screening tests. . The 50g glucose challenge test (GCT 1-h glucose), performed at any time without fasting, whereas the standardized 75g OGTT requires a 10-12 hour overnight fast. . Both tests are characterized by decreased reproducibility [124, 125]. The 50g glucose challenge test (GCT) could, however, provide optimal accuracy, precision and convenience for identifying dysglycemia.

5.1. The GCT in Screening for Gestational Diabetes Mellitus

The GCT has long been used in a two-step screening process for the diagnosis of GDM [126], and was the standard screening approach for GDM until 2010 when both the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [127] and the ADA [128], recommended one-step testing using a 75g OGTT alone.

The two-step approach involves a 50g GCT for initial screening during weeks 24-28 of gestation. A 50g glucose solution (without prior fasting) is ingested with a glucose determination performed 1-h later (GCT 1-h glucose). If the GCT 1-h glucose level is ≥130 mg/dl (7.2 mmol/L) or ≥ 140 mg/dl (7.8 mmol/L), a second test (either a 75g OGTT or 100g OGTT) is conducted to confirm the diagnosis of GDM. The two-step approach is endorsed by the American College of Obstetrics and Gynecology [129] and is widely used in clinical practice.

The stepwise screening approach with the GCT may reduce by over 50% the number of pregnant women requiring a follow-up OGTT [130]. Moreover, an elevated GCT 1-h has been associated with increased pregnancy and fetal complications [131]. In addition to its utility to detect GDM,

higher GCT 1-h glucose levels have also been associated with increased risk for long-term metabolic sequelae and CVD during and after the postpartum period [132-137], increasing along the continuum of GCT 1-h glucose values even within the non-diagnostic glucose range [132, 135, 138, 139].

These findings suggest that the GCT is a good predictor for future risk of T2D after pregnancy and could be useful for screening in the non-pregnant, high-risk population. The two-step GCT may maximize identifying high-risk individuals while limiting confirmatory testing.

5.2. The GCT in Non-Pregnant Individuals

Two studies have evaluated the GCT as a screening test for prediabetes or diabetes in the non-pregnant population [140, 141]. The Screening for Impaired Glucose Tolerance (SIGT) study was conducted in 1573 subjects not known to have diabetes. Participants were evaluated with measurements of HbA1c, random plasma and capillary glucose, a 75g OGTT (FPG and 1- and 2-h PG [1-h and 2-h OGTT] levels). Using the OGTT as the diagnostic standard, 4.6% of SIGT participants were found to have undiagnosed diabetes and 18.7% had "high-risk" prediabetes [using WHO criteria; FPG 110-125 mg/dl (6.1-6.9 mmol/L) and/or 2-h OGTT glucose 140-199 mg/dl (7.8-11.1 mmol/L), without diabetes]. The GCT 1-h glucose performed better than HbA1c in detecting either dysglycemia ("high-risk" prediabetes or diabetes; ROC: 0.82, GCT 1-h glucose vs 0.71, HbA1c, $p<0.001$) or diabetes (ROC: 0.90, GCT 1-h glucose vs 0.82, HbA1c, $p=0.018$), and similarly to FPG (ROC 0.83 dysglycemia; ROC 0.93 diabetes). Of note, the 1-h OGTT glucose had ROCs of 0.88 for dysglycemia and 0.93 for diabetes – performing better than both the GCT 1-h glucose and the FPG. A GCT 1-h glucose cutoff of 160 mg/dl (8.9 mmol/L)

had a sensitivity of 82% and specificity of 81% for identifying diabetes and a sensitivity of 53% and specificity of 87% for identifying dysglycemia. A lower cut-off of 140 mg/dl (7.8 mmol/L) provided improved sensitivities of 92% and 77% for diabetes and dysglycemia, respectively, but reduced specificities of 63% and 72%, respectively.

A subsequent study evaluated the GCT to screen for dysglycemia in the U.S. Veterans population [141]. Subjects recruited from VA primary care clinics underwent testing procedures similar to the SIGT study without measurement of 1-h OGTT glucose levels [140]. Among the 1535 Veterans enrolled, 9.8% had previously undiagnosed diabetes and 21.6% found to have "high-risk" prediabetes by the OGTT, higher than in the SIGT study, reflecting greater average age, BMI, and prevalence of African-Americans. The GCT 1-h glucose accurately predicted both diabetes and dysglycemia with ROCs of 0.85 and 0.76, respectively, and performed better than the HbA1c (0.67 and 0.63; both $p<0.05$ compared to the GCT). A GCT 1-h glucose threshold >140 mg/dl (7.8 mmol/L) had 87% sensitivity and 61% specificity for identifying diabetes. A higher cutoff of 160 mg/dl (8.9 mmol/L) had lower sensitivity of 76% but a higher specificity of 79%.

In summary, the GCT was an accurate screening test for diabetes as well as dysglycemia in two distinct cohorts. Moreover, differences in age, sex, race, BMI, and other risk factors did not alter the performance of the GCT in either study [140, 141]. Whether the GCT 1-h glucose would predict future development of diabetes similar to the 1-h OGTT [142, 143] has not been studied.

5.3. Cost Effectiveness

In both the SIGT [140] and VA screening studies [141], the GCT was found to be cost-effective. In the SIGT study, a GCT 1-h glucose threshold >140 mg/dl (7.8 mmol/L) would identify 40% of the at-risk population requiring a follow-up OGTT for confirmatory diagnosis [140]. Among these individuals, 45% had either diabetes or prediabetes, which represented only 18% of the initial screening cohort; this approach, therefore, allowed targeted diagnostic testing in a subset of the at-risk population [140]., The cost of this stepwise approach was lower than standard screening recommendations and was deemed to be cost-effective [140, 141]. From a healthcare system perspective, GCT-based screening was projected to be cost-saving over 3 years compared to no screening, particularly in higher-risk individuals with greater age or BMI [144].

The 50g GCT may provide an alternative approach to screening as it can be conducted any time of the day without fasting, requires one hour during a routine health care visit and appears to be cost-effective, it. The 50g GCT is convenient and accurate – important features for improving screening and detection rates of prediabetes and diabetes.

6. The Shape of the Glucose Curve

The desire to improve diabetes risk stratification has spurred a newfound interest in identifying reliable and accurate alternatives to standard FPG, 2-h PG, and HbA1c thresholds. Although established thresholds are highly specific for diabetes, up to 30% of high-risk individuals may have values within the normal range. Furthermore, the predictive ability for diabetes risk may vary with age, race, ethnicity, and the incidence of diabetes in the population [55, 59, 145, 146]. The OGTT values are discrete, ordered determinations from an underlying, continuous process to assess an individual's glucose regulation. Therefore, the glucose curve shape is an attractive candidate biomarker since it is obtained during a standard OGTT and can reflect an individual's metabolic information, a predictor for screening dysglycemia, abnormal IR, and secretory state [147-150]. Differences in the shape of the glucose curve have been documented since the 1950s, coinciding with the concurrent use of the OGTT for the characterization of hyperglycemia [151]. However, it is only recently that investigators considered using the glucose curve characteristics as a diagnostic and predictive tool. When applying novel methods, the entire curve is used as the basic unit of information instead of OGTT measurements at specific time points.

6.1. Definition of glucose curve shape

The shape of the glucose curve is defined by the pattern of rising and falling glucose concentrations after a fixed oral glucose load. While some authors have described the glucose curve shape after a prolonged 3-hour OGTT [148], the conventional definition is to describe the curve shape after a standard 75gram 2-h OGTT [147, 149, 150]. The curve is obtained by either plotting glucose concentrations for at least 4 pre-specified time points (Figure 1A) or by using 3 or more glucose concentrations for latent mixed class trajectory modeling [152] (Figure 1B).

6.2. Monophasic vs. Biphasic Shape

In 2003, Tschritter *et al.* developed a simple index to classify the shape of the glucose curve into 2 distinct shapes: a monophasic or biphasic curve [149]. Subsequent studies have conformed to this definition with minimal variation. The monophasic curve is characterized by a gradual increase in glucose with a single peak and then falling, and the biphasic curve by a gradual rise in glucose to a peak, a gradual fall in glucose to a nadir and subsequent rise in glucose concentrations [149]. A third "unclassified" curve is sometimes described as a continuous rise in glucose without a definite peak, its diagnostic utility unclear as it is often omitted with greater attention given to the differences between monophasic and biphasic curve shapes [147-150].

The rationale for the binary classification lies within its simplicity, ease of use, and association with pathological features of diabetes. Defining the curves as monophasic vs. biphasic shapes do not require sophisticated mathematical modeling or equations and provide diagnostic and phenotypic insight into the individual's glucose and insulin metabolic profile [147-150]. The monophasic compared to the biphasic curve has been associated with lower SI and decreased pancreatic β-cell function, measures that were validated against the hyperinsulinemia euglycemic clamp as well as mathematical equations from the OGTT [153-156]. A longitudinal model simulating progression to diabetes in a hypothetical subject [157] provided additional biological insight into the dynamic nature of the glucose curve shape [157]. This model showed that both β-cell failure and increasing IR were associated with a monophasic curve, a delay in the time to peak glucose and a rising glucose peak [157]. The model and clinical analysis agreed that the probability of a biphasic curve was low with progressive hyperglycemia with the shape of the curve not related to race, ethnicity or age.

Arguably, the most significant advantage of the curve shape is to improve early risk stratification in individuals with normal fasting and 2-h PG concentrations who might benefit from early intervention. Several studies in children, adults, and pregnant women have examined the predictive ability of the monophasic curve shape for prediabetes and diabetes [158-161]. Compared to the biphasic curve, the monophasic curve was a better predictor of prediabetes and diabetes in healthy adults after 3 years and in individuals at high-risk for both type 1 diabetes (T1D) and T2D after 8 years [158-160]. The curve shape has assessed the pathophysiologic evolution of diabetes. Arslanian *et al*. evaluated the predictive capabilities of the shape of the curve for determining disease progression and treatment response in a randomized controlled trial of metformin, metformin + rosiglitazone and metformin + lifestyle, in youths with T2D [162]. In this study, the monophasic curve shape was associated with the highest treatment failure rates and the need for additional insulin therapy after an average of 2 years [162].

However, not all studies have demonstrated improved diagnostic utility in using the simple binary shape classification [157, 163]. The monophasic shape is ubiquitous occurring in both high and low-risk individuals with NGT. Overall, a significant limitation of the binary shape classification is that the discriminatory ability of the monophasic curve for diabetes is linked to its collinearity with overall glycemia, and the curve shape by itself does not account for the relative magnitude of the glucose excursions [70]. Therefore, the monophasic curve shape had poor reproducibility and low diagnostic sensitivity evaluated over time and failed to capture the biological heterogeneity in glucose curves or account for variabilities in measurement [158, 164]. High false positive rates were observed in overweight and obese children and in post-menopausal women for prediabetes across different racial and ethnic groups [157, 163-165]. Heterogeneity in the glucose curve shape was observed across the spectrum of glucose tolerance

[155]. Furthermore, up to 20% of individuals did not fit into the binary monophasic vs. biphasic classification and the implication of having a monophasic curve during a 2-h test but a biphasic curve after a 3-h test are unknown [148].

6.3. Modeling of the Glucose Curve

Alternative approaches for delineating the heterogeneity of the glucose response curves have been developed. Modeling techniques are used to create shape indices that account for the complexity and biologic variability of glucose curve shapes with the premise that compound shapes have the lowest total glucose excursions and the highest β-cell function relative to SI [70, 160, 161, 166]. For example, Alyass *et al.* investigated the performance of 14 OGTT glucose curve traits in T2D prediction and found that the highest predictive power was related to shapes that had the most significant total area under the glucose curve and the highest absolute concentration at the 1-h time point [167]. Curve fitting with functional principal component analysis was also used in women during the first trimester of pregnancy to forecast the development of GDM later in pregnancy [161]. This technique extracted common temporal characteristics of a set of curves and was superior to simple binary shape classification for predicting GDM. However, the statistical expertise that is required for curve fitting and principal component analysis limits its clinical use.

Recently, latent class trajectory analysis, another robust statistical tool often used in extensive epidemiological analyses of growth, showed promise for diagnosing and predicting diabetes and its complications (Figure 1B) [152, 168-170]. Latent class analysis was designed to capture subtle differences in metabolic phenotype over time with the additional advantage of providing probabilities for a class assignment. Four main glucose curve classes (Class 1-4) were consistently observed that differed from each other in pathophysiological characteristics such as

glucose excursions and declining insulin sensitivity and secretion with time [152, 170]. Class 1 was associated with the lowest diabetes risk and Class 4 with highest rates of diabetes progression and hyperglycemia at the 2-h time point. Class 3 is notable because it is characterized by high 30-minute post glucose, despite normal fasting and 2-h glucose, and was associated with a ~4-fold increased risk for diabetes and higher all-cause mortality rate over an approximate 12 year period [169].

The advantages of using the latent class analysis technique as an epidemiologic and potentially clinical tool include its ability to discern the certainty for latent class classification, its high reproducibility and the added value of documenting changes over time in a non-arbitrary manner. Further, although this modeling is most robust when utilizing five glucose time-points, reliable results can still be achieved with only three glucose time-points [171]. The integrated glucose response classifier model is available online for public use at https://steno.shinyapps.io/grc2h/. However, the application of this sophisticated model and its potential for changing screening and diagnostic paradigms remains to be determined.

The shape of the glucose curve is a dynamic biomarker reflecting the cumulative effect of insulin sensitivity and response on glucose concentrations. A more complex shape is associated with a lower risk for diabetes, but using the monophasic vs. biphasic binary classification has relatively low sensitivity. Modeling patterns of change in shape over time could be a robust clinical or epidemiologic metabolic tool but would require conducting OGTTs with at least 4 glucose measurements and may increase the economic and personal patient burden associated with blood collection procedures and analysis that may limit its widespread clinical applicability. Prospective studies are warranted to evaluate the prognostic utility of OGTT-derived shape

indices or latent-class model derived sub-groups as promising tools for identifying high-risk subgroups and improve diabetes screening and risk stratification.

7. Continuous Glucose Monitoring and Glycemic Variability

Novel Continuous Glucose Monitoring (CGM) devices [172-175] are increasingly replacing conventional self-monitoring of blood glucose (SMBG) [176, 177] with the principal advantages of capturing glucose fluctuations referred to as short-term glycemic variability (GV) and for detecting silent hyper- and hypoglycemic episodes [174, 178-180]. Therefore, CGM is a powerful tool to improve assessment of glucose homeostasis during insulin therapy [172, 173, 181]. Extending its use to prediabetes may help identify different phenotypes of early dysglycemia (IFG and IGT).

7.1. Insights from Continuous Glucose Monitoring Technology

7.1.1. The evolution of 24-h glucose profiles from normal glucose tolerance to advanced glycemic disorders

7.1.1.1. Nondiabetic Individuals

In 153 nondiabetic individuals (HbA1c< 5.7% [39 mmol/mol]) aged 7-80 years [182] wearing the Dexcom G6 system for approximately 10 days on an ambulatory basis, Shah et al established that the average 24-h glucose was 99 ± 7 mg/dl (5.5 +/- 0.39 mmol/L) and the within-individual coefficient of variation (% CV) for glucose was 17 ± 3%. In this study, glucose values below 54 mg/dl (3.0 mmol/L) and above 180 mg/dl (10 mmol/L) were uncommon with the median time spent above 140 mg/dl (7.8 mmol/L) or below 70 mg/dl (3.9 mmol/L) being 30 or 15 minutes per day, respectively. Postprandial glucose excursions were not quantified and information on other

subtle glycemic disorders such as the presence or absence of the dawn phenomenon were not provided [183].

7.1.2. Key stages from prediabetes to overt T2D

7.1.2.1.The dawn phenomenon

The dawn phenomenon corresponds to a rise in PG > 20 mg/dl (1.11 mmol/L) during the end of the nocturnal period in the absence of nutritional intake (fasting state). This is mainly due to the circadian variation in hepatic glucose production which starts to increase in the evening, reaches a peak towards the end of the overnight period before declining during the daytime until its late afternoon nadir [184]. Its main consequences include elevation of the early morning fasting blood glucose with or without an abnormally elevated and delayed post-breakfast glucose excursion referred to as the "extended dawn phenomenon" [184]. The latter is postulated to be due to an extended period of hepatic glucose production not encountered in non-diabetic subjects [185] complemented by intestinal hydrolysis of carbohydrates following breakfast. In those with normal metabolism, hepatic glucose overproduction is prevented by an increase in endogenous insulin and a decrease in glucagon secretion. The dawn phenomenon is evident when HbA1c levels range from 5.7 to 6.4% (39-46 mmol/mol), when postprandial glucose excursions and basal glucose exposure (nocturnal and interprandial glucose concentrations) remain within the normal range [186]. These observations suggest that the dawn phenomenon represents an early expression of dysglycemia (prediabetes) in the natural history of T2D[187]. Detection of the dawn phenomenon necessitates the use of CGM to demonstrate the magnitude of the difference between the nocturnal glucose nadir and the pre-breakfast glucose value.

7.1.2.2. Post-meal hyperglycemia

When the HbA1c level exceeds 6.5% (46 mmol/mol), excess postprandial glucose elevations (average 2-h postprandial $\geq$ 140 mg/dl [7.8 mmol/L]) are observed which usually remain isolated as long as HbA1c does not exceed 7.0% (53 mmol/mol) [186]. Post-meal hyperglycemia resulting from the extended dawn phenomenon is frequently combined with the dawn phenomenon representing the state of prediabetes that precedes overt T2D. The complete characterization (phenotyping) of this stage can also be best revealed by conducting CGM in those with HbA1c levels between 6.5 and 6.9% (48- 52 mmol/mol) (Figures 2)[187].

7.1.2.3. Basal hyperglycemia

When the HbA1c is 7% to 8% (53- 64 mmol/mol), postprandial and basal (fasting and interprandial) glucose contribute equally to overall hyperglycemia [188] whereas with a HbA1c level > 8% (64 mmol/mol), the basal component increases linearly while the postprandial contribution remains relatively constant approximating one percentage point of HbA1c [189]. Therefore, basal glucose becomes the major contributor to overall hyperglycemia in advanced T2D (Figure 2).

7.2. Glycemic Variability for Detecting Prediabetes

The continuum of deteriorating glucose homeostasis is also associated with a progressive increase in within-day GV expressed by % CV for glucose. The median % CV in non-insulin treated individuals with HbA1c levels ranging from 6.4 to 7.0% (46 to 53 mmol/mol) and 7.1 to 8.6% (54 to 70 mmol/mol), are 18.6% and 23.7%, respectively, compared to a median % CV of = 27.8% in insulin-treated T2D [190]. In contrast, the % CV in non-diabetic subjects is approximately 17%, but fails to distinguish the early stages of dysglycemia. Although GV increases from NGT to prediabetes, IFG and IGT [191], it is debated whether GV reflects the

continuum from prediabetes to diabetes [191, 192]. Nevertheless, CGM appears to be valuable for unraveling the early changes in overall glucose homeostasis in the natural history of the disease.

8. 7.3. Classifying Dysglycemic States

In a study [193] involving 800 healthy subjects and individuals with prediabetes, CGM was regarded as a key technology for assessing the variability of postprandial glycemic responses while at the same time useful for improving diet quality and preventing T2D and its complications. Postprandial glucose excursions can be accurately predicted by integrating glucose responses into a machine-learning algorithm that takes into account several clinically scalable biomarkers such as blood parameters, bioanthropometrics, physical activity and microbiota. This study supports incorporating personalized precision nutrition to prevent prediabetes and its potential conversion to overt diabetes [194]. Therefore, the CGM could represent a key reference for implementing such strategies in the future based on detecting different phenotypic glycemic patterns in their early stages and beyond.

7.4.Strengths and Weaknesses

The main advantage of CGM resides in the ability to determine interstitial glucose values at frequent intervals thereby capturing infinite details of daily glucose homeostasis. However, CGM systems have shortcomings. The glucose oxidase embedded in the biosensor oxidizes each molecule of glucose with the electric current generated by the chemical reaction being proportional to the glucose concentration in the interstitial fluid [195]. The slope of the linear relationship between these two parameters corresponds to the biosensor sensitivity, the assessment of which requires calibration of the device by aligning the interstitial glucose with a

reference glucose value [196, 197]. However, these two values usually differ by approximately 10-20 mg/dl (0.55-1.11 mmol/L) [196-198], a difference that becomes crucial when glucose concentrations are in the near-normal range [197, 198] encountered in the prediabetes state. Another potential source of error is the lag time approximating 10 to 15 minutes, especially when measurements are made during periods of sudden and rapid changes in circulating glucose [199].

In conclusion, an inexact relationship exists between glucose concentrations and interstitial values recorded by CMG devices [199]. Consequently, CGM has not been approved for detecting glucose intolerant states although this may become a reality in the future. Nonetheless, CGM represents an important development to better understand the pathophysiology of prediabetes, differentiate the different phenotypes of T2D in addition to aiding the clinician to better manage each individual based on the different degrees and patterns of dysglycemia.

8. Insulin Resistance and Insulin Secretion

IR and deterioration of β-cell function are fundamental to the initial development and progression of impaired glucose regulation [200]. Alterations in these principal homeostatic mechanisms are among the best predictors of the risk for T2D with several techniques developed for *in vivo* assessment.

8.1. Insulin Sensitivity (SI)

8.1.1. Clamp technique

The euglycemic insulin clamp technique remains the gold standard for measurement of insulin action *in vivo* [201]. The technique is accurate and, because it is based on the achievement of a

steady-state condition, it can be combined with other methodologies (e.g., mathematical modeling, tracer infusion, indirect calorimetry, arteriovenous catheterization) allowing comprehensive evaluation of insulin action on glucose, lipids, and protein metabolism at the whole body as well as tissue levels [202]. Collaborative efforts, such as the RISC (Relationship between Insulin Sensitivity and Cardiovascular Disease) Study, have pooled euglycemic clamp studies in 13 European countries to establish a prospective, observational study as well as determine to what extent SI and β-cell function (estimated by mathematical modelling of an OGTT (see below), could account for progression or regression of glucose intolerance. After adjustment for family history of diabetes, age, waist-to-hip ratio, fasting and post-load glucose levels, IR was an independent predictor of progression from NGT to IGT [203]. Insulin resistance determined by the euglycemic clamp was found to be a major risk factor for the development of T2D in Pima Indians [204].

8.1.2. Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)

Unlike the glucose clamp, which depends on steady-state conditions, the minimal model approach uses dynamic data obtained with rapid intravenous injection of glucose. This is usually applied in assessing SI during a FSIVGTT [205] or its more modern insulin-modified version. Simplified, short sampling protocols have been developed to facilitate studying larger numbers of subjects. The FSIVGTT can allow the estimation of other parameters of interest, e.g. glucose effectiveness (Sg), i.e. the capacity of glucose to enhance its own cellular uptake and to suppress endogenous glucose production and acute insulin response (AIR). The FSIVGTT was performed in 1,230 Hispanic-Americans and African-Americans in the Insulin Resistance Atherosclerosis Study (IRAS) Family Study [206]. After adjustment for confounding factors, SI was inversely

associated with development of T2D (OR 0.53, 95% CI 0.39-0.73; $p < 0.001$). In the IRAS Study, Sg was an independent risk factor for future diabetes in individuals with family history of diabetes with similar results demonstrated independent of age, sex, race/ethnicity, glucose tolerance, and adiposity [206]. Using the same technique, the development of T2D was found to be preceded and predicted by defects in both insulin-dependent and insulin-independent glucose uptake [207] Moreover, these defects were detected more than a decade before the diagnosis of T2D when subjects were normoglycemic

8.1.3. Oral Glucose Tolerance Test (OGTT)

Though accurate, the clamp technique and the FSIVGTT are labor intensive and, therefore, difficult for use in the clinical setting or in large epidemiological studies. Alternatively, surrogate measures of insulin secretion and SI have been derived from more commonly used diagnostic procedures. From this perspective, the OGTT, the most frequently used method to assess glucose tolerance, can offer a simple and more physiologic approach. Surrogate markers of insulin action can be derived by concomitant plasma glucose, insulin and C-peptide measurements. The SI index-Matsuda [ISI (Matsuda)] reflects a composite estimate of hepatic and muscle SI [208].The Insulin Sensitivity Index (ISI) is defined as the ratio between PG clearance rate and mean plasma insulin concentration [209]. These indexes correlate well with direct estimates of SI obtained from glucose clamp studies. In a prospective study combining various cohorts [210], the ISI index was best at predicting onset of T2D compared with other surrogate indexes derived from dynamic tests, including the Stumvoll index [211], also derived from OGTT data.

While all prior indexes are empirical, the OGTT-based IS (oral glucose insulin sensitivity [OGIS]) index is based on a glucose-insulin model [212]. The OGIS correlates well with the

clamp and in a Japanese study reported the most sensitive index for assessment among individuals with pre-hypertension/prediabetes [213].

8.1.4. Simple Indexes of Insulin Action

HOMA was proposed by Matthews *et al*. [214] and remains the most widely used surrogate measure of insulin action and β-cell function in clinical and epidemiologic studies. Based on a structural model of the physiological feedback loop between the liver and the β-cell in the fasting state, HOMA-IR provides an estimate of SI derived from FPG and insulin concentrations. Recently, the HOMA model was expanded and improved equations (HOMA2) were provided to compute HOMA2-IR as well as HOMA2-beta for β-cell function [215]. HOMA-IR is simple, inexpensive and correlates well with SI determined by the euglycemic insulin clamp [216] or the minimal model derived from the FSIVGTT [217].

The ability of the HOMA model to predict the development of T2D has been evaluated in cross-sectional and cohort studies. Cross-sectional studies have shown strong associations between HOMA-IR and HOMA-B and the prevalence of IGT and T2D in Japanese [218], Mexican-American and non-Hispanic white subjects [219]. HOMA-IR was a strong and independent predictor of incident IGT in Japanese Americans over a 10-year follow-up [220] as well as the 10-year diabetes incidence in the Italian Bruneck Study [221]. In a study of combined prospective data involving 3,574 participants including non-Hispanic white, African-American, Hispanic American, and Mexican subjects followed between 5–8 years, HOMA-IR provided an even more consistent predictor of T2D compared with other IR indexes [210].

The Quantitative insulin sensitivity check index (QUICKI) is an empirically derived mathematical transformation of fasting blood glucose and plasma insulin concentrations [222]. Though QUICKI is based on a completely different rationale than HOMA, the two indexes are related and have been suggested as simple, inexpensive, and minimally invasive surrogates for measurements of SI that can be used in large epidemiological studies [223].

8.2. Insulin Secretion

Insulin secretion is tightly regulated through an integrated process encompassing finely tuned feedback between the β-cell, PG levels and other nutrients, SI, incretin hormones, neuropeptides, and neuronal control. Disruption of this network and the reduction of β-cell mass are responsible for abnormal insulin secretion in T2D. These abnormalities develop over an extended period starting long before diabetes is diagnosed [224-227] most likely reflecting a predisposing genetic background [228]. Early alterations in insulin secretion tend to be qualitative rather than quantitative. Plasma insulin concentrations after an oral glucose load in predisposed subjects may not differ from those obtained in individuals without predisposition but when adjusted for prevalent plasma glucose levels and SI, a clear impairment of β-cell function becomes apparent [229, 230]. In predisposed individuals, even among those with NGT, β-cell function worsens with an increase in the 2-h PG levels [229, 230]. Several approaches for assessing insulin secretion have been proposed defining β-cell function trajectory in the transition from NGT to overt diabetes.

8.2.1. Dynamic tests

The magnitude and kinetics of insulin secretion after a glucose challenge can be determined during a hyperglycemic clamp [201], through minimal model analysis of the response to rapid intravenous injection of glucose [205] or during an OGTT. With the hyperglycemic clamp, PG concentrations are rapidly increased above baseline (usually $\geq$ 125 mg/dl [6.9mmol/L]) and glycemic levels maintained for variable periods allowing evaluation of first-and second-phase insulin secretion. An estimation of the first-phase insulin secretion (AIR) is also provided by the FSIVGTT. In the IRAS Study, after adjustment for confounding factors, AIR was inversely associated with development of T2D (OR 0.22, 95% CI 0.14-0.34 per SD; both $p < 0.001$) [206]. In addition, Osei and coworkers [231] showed that first-degree relatives of African-American patients with T2D who progressed to either IGT and/or T2D had decreased mean acute first-phase insulin secretion before diagnosis. Data from the OGTT can be used to calculate the Insulinogenic Index, i.e. the ratio between the increment in plasma glucose and insulin concentrations 30 min after glucose ingestion. Among 319 subjects in whom an OGTT was performed, the insulinogenic index adjusted for severity of IR was significantly worse in subjects with IGT and combined IFG/IGT than subjects with IFG [61] , suggesting that subjects with IGT and IFG may have different metabolic characteristics and different rates of progression to T2D. These data strongly point to the loss of first-phase insulin secretion as a very early feature of β-cell dysfunction. First-phase insulin secretion plays an important role in priming the liver to suppress endogenous glucose production in response to glucose or nutrient ingestion [232, 233] and it has been identified as an independent predictor for the development of IGT [234] and T2D [235, 236].

All of the methods described have several limitations that preclude their routine clinical use as diabetes risk predictors. These include the complexity of the tests and the need to integrate different control components that may affect the response of the β-cell to changes in glucose levels (e.g., the action of incretins). Nevertheless, these measures are important research tools further enhanced with mathematical models to describe the complex functions of dynamic insulin secretion [237, 238]. Of relevance, mathematical modeling allows assessment of parameters such as glucose sensitivity (i.e. the ability of the β-cell to respond incrementally with an increase in glucose concentration), rate sensitivity (i.e. the response to the rate of change in glucose levels), and the potentiation factor (i.e. the augmentation of β-cell response). These parameters have a significant advantage and =are derived from the PG and C-peptide response to an OGTT as well as a standard mixed meal, allowing assessment of β-cell function under physiologic conditions. In the RISC Study, glucose sensitivity was an independent predictor for progression from NGT to IGT. In particular, logistic regression revealed that baseline and follow-up changes in β-cell glucose sensitivity and SI, rather than the classical clinical predictors (adiposity, familial diabetes and glucose levels), were the key independent predictors of progression accounting for >50% of the progression from normal to IGT [239].

8.2.2. Simple Indexes of β-cell Function

Different indexes based on fasting plasma insulin in relation to fasting blood glucose have been proposed as proxies of β-cell function. Among these, the HOMA-B index [214] and its more recent revision HOMA2-B [215] are the best known and most commonly used. However, while

HOMA-IR is considered a reliable index of SI, more controversy exists with respect to the accuracy of HOMA-B as an assessment of pancreatic β-cell function[237]. Nonetheless, the index has been used in epidemiologic studies such as the Women's Health Initiative Observational Study including 82,069 postmenopausal women showing that low HOMA-B was independently and consistently associated (OR 0.57, 95% CI 0.51–0.63) with increased diabetes risk after adjustment for confounding risk factors [240]. The main limitation of HOMA-B resides in its non-comprehensive dynamic response after ingestion of a glucose challenge or a standard meal. Further highlighting the utility of a simple index of β-cell function, Abdul-Ghani et. al. [217] demonstrated that the insulin secretion/insulin resistance index derived from the OGTT provides a superior method for predicting future development of T2D compared with the diagnosis of IGT based on the 2-h PG concentration.

8.2.3. Disposition Index

When jointly evaluated in the Women's Health Initiative Observational Study, the relationship of HOMA-IR and HOMA-B with diabetes risk appeared to be not only independent but also additive implying a strong relationship between insulin secretion and SI. This relationship was initially introduced by Kahn and co-workers [241] and a disposition index (DI, i.e., the product of SI and insulin secretory response) has been used as a composite parameter for quantification of glucose disposition *in vivo*. DI has been shown to predict conversion to diabetes [242] and reflects alterations of early glucose intolerance in Japanese individuals with prediabetes [243].

8.3. Parameters of insulin action/secretion and 1-hour OGTT

As described earlier, the 1-h PG <155 mg/dl (8.6 mmol/L) has been proposed as a potential diagnostic parameter for identification of individuals at a high-risk of developing diabetes [68]. The Genetic Physiopathology and Evolution (GENFIEV) Study, involving >1000 individuals at risk of diabetes, found that NGT subjects with a 1-h PG >155 mg/dl (8.6 mmol/L)were more insulin-resistant (HOMA-IR 2.68±1.93 vs. 2.14±1.22 mmol/L x µU/ml; $p<0.001$),had worse insulin secretion (Insulinogenic Index: 0.052±0.030 vs. 0.092±0.17; $p<0.001$), and β-cell performance (Disposition Index: 0.026±0.025 vs. 0.055±0.097; $p<0.0001$) compared to those with 1-h PG ≤155 mg/dl (8.6 mmol/L) [85]. A reduction in first-phase insulin secretion (1381±865 *vs*. 1721±1384 [pmol · m^{-2} BSA] · [mmol·l^{-1}·min^{-1}]$^{-1}$; $p<0.005$) and lower β-cell sensitivity were confirmed in NGT with 1-h PG >155 mg/dl (8.6 mmol/L) compared with NGT with 1-h PG ≤155 mg/dl (8.6 mmol/L). Of interest, NGT individuals with 1-h >155 mg/dl (8.6 mmol/L) had a similar degree of SI as individuals with IGT though the latter had worse insulin secretion. This observation is in keeping with the concept that β-cell failure, rather than IR, accounts for the progressive deterioration of glucose homeostasis.

Marini *et al*. [84] also found that NGT subjects with 1-h >155 mg/dl (8.6mmol/L) had an impairment of SI similar to individuals with IGT. They also reported that subjects with 1-h PG >155 mg/dl (8.6mmol/L), compared with NGT with 1-h PG ≤155 mg/dl (8.6mmol/L), had lower AIR during intravenous glucose tolerance test (IVGTT) whereas no difference was apparent in insulin secretion assessed by OGTT-derived indexes. Because of this apparent discrepancy, they proposed that these individuals may retain a substantial incretin effect or, alternatively, a lower sensitivity of the β-cell may already be present. Other smaller studies confirmed that 1-h PG

>155 mg/dl (8.6mmol/L) is associated with alterations in β-cell function and SI [86, 244]. These results lend further support to previous observations that impaired β-cell function is an early defect in those at risk of developing T2D. In both the San Antonio Metabolism [229] and the RISC [87] Studies, β-cell function was found to be already drastically impaired in NGT subjects with the highest 2-h PG values. Nonetheless, in the RISC Study, NGT individuals with 1-h PG >161 mg/dl (8.9 mmol/L) had greater IR, reduced β-cell glucose sensitivity, and reduced β-cell rate sensitivity [87],features confirmed across ethnic groups. Thus, in Chinese subjects with NGT subjects and 1-h PG ≥ 200 mg/dl (11.1 mmol/L), several metabolic abnormalities were identified which seemed to be associated more with the impairment of early insulin release than IR determined by HOMA [245].

In summary, though a standardized cut-off may still need to be identified, available evidence strongly supports the role of impaired β-cell function that can be aggravated by concomitant IR as a feature in NGT subjects with elevated 1-h PG levels. This provides support for the pathophysiologic plausibility of the 1-h PG for early identification of individuals at risk of developing T2D.

9. Metabolomics

Metabolomics is a promising tool for screening and diagnosis of T2D. Novel high-throughput analytic chemistry methods enable the measurement of a large number of molecules comprising the human metabolome. Mass spectrometry (MS) and nuclear magnetic resonance (NMR) perform comprehensive metabolic profiling [246]. Gas chromatography (GC), isotope dilution ultrahigh-performance liquid chromatography (LC) coupled to tandem mass spectrometry (MS/MS) assays [247], as well as high-throughput NMR metabolomics can be used for absolute

quantification [248]. Metabolomic profiling can be either non-targeted, by performing a comprehensive analysis of all measurable molecular components in a given biological sample, or targeted, by measuring a pre-selected metabolite panel [246]. Overall, metabolomic technologies have made it possible to assess a large number of substrates representing different metabolic pathways.

9.1. Metabolites for diagnosing prediabetes and diabetes

Several metabolites including amino acids, lipids and carbohydrates have potential as biomarkers for T2D [249, 250].

9.1.1. Amino Acids

Several amino acids were consistently associated with the risk of developing T2D [249] with extensive evidence demonstrating the association of BCAAs with obesity, IR and T2D [249].

Metabolomic analysis in a subset of individuals in the Framingham Heart Study demonstrated that increased levels of BCAAs and aromatic amino acids (AAA) were associated with future T2D [251]. Elevated levels of plasma BCAAs, including valine, leucine, and isoleucine, were associated with IR and found to predict the onset of T2D [251]. The association of BCAAs with incident diabetes and underlying metabolic abnormalities is generally stronger in Caucasian and Hispanic populations [252].

The relationship between BCAA, IR and T2D is rather complex illustrated by a Mendelian randomization study suggesting that IR may drive circulating BCAAs levels [253]. However, despite BCAAs being highly correlated with BMI, insulin levels, HOMA-IR and T2D, these were only modestly associated with IFG or combined IFG and IGT, and not with IGT [247]. This suggested that different metabolites could pinpoint diverse metabolic imbalances within the same

clinical condition. Furthermore, in the TwinsUK study, the branched-chain keto-acid metabolite, 3-methyl-2-oxovalerate was the strongest predictive biomarker for IFG after glucose in addition to being moderately heritable [250]. In the Insulin Resistance Atherosclerosis Study (IRAS), participants without diabetes with higher plasma BCAAs had lower insulin sensitivity, insulin clearance rate and higher fasting insulin concentrations. The addition of BCAAs to models that included traditional risk factors for T2D resulted in a trend to improve incident T2D–predictive capacity: metabolic syndrome (aROC without BCAA 0.62 vs with BCAA 0.66), IFG (aROC without BCAA 0.72 vs with BCAA 0.74), and BMI (aROC without BCAA 0.68 vs with BCAA 0.69), although these differences were not statistically significant [252].

9.1.2. Lipid metabolites

Free fatty acids and triglycerides have been associated with the risk of prediabetes and T2D. Saturated fatty acids, including myristic (C14:0), palmitic (C16:0), stearic (C18:0) are increased in both IFG and diabetes [254, 255]. Oleic acid (monounsaturated omega-9 acid), arachidonic and linoleic acids (polyunsaturated omega-6 acids) are also higher in individuals with IFG and diabetes [254, 255]. In a nested case-cohort study, the EPIC-InterAct, a fatty acid pattern score with high relative concentrations of linoleic acid (C18:2n-6), stearic acid (C18:0), odd-chain saturated fatty acids, very-long-chain saturated fatty acid (>20 carbons), and low relative concentrations of linolenic acid (18:3n-6), palmitic acid, and long-chain monounsaturated fatty acids, was associated with a reduced risk of developing T2D [256]. Plasma triacylglycerols with lower carbon number and double-bond content have been associated with an increased risk of T2D whereas those with higher carbon number and double bonds were associated with decreased risk [257, 258]. Furthermore, triglycerides with odd-chain fatty acids were also inversely associated with T2D after adjusting for total triglycerides [259].

Acylcarnitines, produced in the mitochondria by the enzyme carnitine o-acetyltransferase, have also been associated with higher risk of prediabetes and T2D [260, 261]. In the Nutrition and Health of Aging Population in China (NHAPC) Study, a panel of acylcarnitines, especially long-chain acylcarnitines, was significantly associated with risk of developing T2D and was able to improve the predictive ability for incident diabetes beyond conventional risk factors including BMI and fasting glucose [262]. The addition of selected acylcarnitines to a model including conventional risk factors improved the aROC for incident T2D from 0.73 to 0.89.

Different groups of phospholipids have been associated with distinct associations with the risk of prediabetes and T2D [259, 263, 264]. Two plasma lipid profiles were associated with T2D after 3.8 years median follow-up in the PREDIMED trial. A profile including lysophospholipids, phosphatidylcholine-plasmalogens, sphingomyelins, and cholesterol esters was associated with lower risk of T2D while another comprising phosphatidylethanolamines, triglycerides and diacylglycerols was associated with higher risk [259]. A composite of all lipid scores significantly improved prediction of T2D beyond conventional risk factors although the effect size was small (aROC 0.84 vs 0.83).

9.1.3. Carbohydrate metabolites

Other carbohydrate metabolites than glucose are altered in prediabetes and T2D including mannose, fructose, and inositol [250, 258, 265-268].

In two independent cohort studies, mannose was associated with incident T2D after adjusting for confounding factors including HbA1c and glucose [269]. Using a machine learning approach, mannose was a robust metabolic marker to predict progression to T2D comparable to the 1-h PG in the Botnia Prospective Study [77]. Using the optimal cutoff, mannose had a sensitivity of

0.60, a specificity of 0.72 and an aROC of 0.70 for incident T2D. Mannose, alone or in combination with other metabolites, also improved predictive performance when combined with the 1-h PG [77].

9.2. Overview of metabolomics for diagnosing glycemic disorders

Metabolomics is not currently an established resource in routine clinical practice for diagnosing glycemic disorders. The strongest evidence for the potential of individual metabolomics to diagnose prediabetes and diabetes comes from a meta-analysis [249]. Due to the considerable heterogeneity of reported lipid and carbohydrate metabolites, only studies examining the prospective association between several amino acids and T2D were included. There was an approximate 35% higher risk of T2D for isoleucine, leucine, valine or tyrosine and 26% for phenylalanine with an inverse association of glycine and glutamine observed [249].

A metabolomics profile combining amino acids, lipids, carbohydrates and other metabolites holds promise as a more effective screening tool for the early diagnoses of glycemic disorders compared to isolated metabolites [270-272]. Fasting metabolomics, as an alternative to OGTT for detecting IGT, identified a novel metabolite-based test in nondiabetic subjects participating in the Relationship between Insulin Sensitivity and Cardiovascular Disease Study (RISC Study; 11.7% IGT) and the Diabetes Mellitus and Vascular Health Initiative (DMVhi) cohort in the DEXLIFE project (11.8% IGT) [271]. The addition of this metabolite panel to fasting glucose improved the aROC curve for predicting IGT prediction from 0.70 to 0.82 in the RISC Study and from 0.77 to 0.83 in the DMVhi [271].

However, despite the considerable potential for metabolomics to define new biomarkers of disease, only a few studies have reported sensitivity, specificity data or aROC curves thereby

limiting translation into the clinical setting. Overall, metabolomics panels have low added predictive value for T2D compared to prediction models using traditional risk factors (i.e., BMI, metabolic syndrome, IFG), illustrated by modest increases in aROCs [77, 247, 249, 252, 273]. Metabolomics, therefore, are not currently cost-effective and have limited value to assess risk for or diagnose glycemic disorders.

10. Fructosamine, Glycated Albumin, and 1,5-Anhydroglucitol

Non-classical methods for assessing glycemic control include markers that evaluate shorter periods of glucose exposure than HbA1c. These markers allow a more detailed understanding of alterations in glycemic control, have potential use as screening or diagnostic tools for diabetes and other glycemic disorders and provide additional information in assessing glycemic control in specific populations (e.g. pediatrics or pregnancy). This section will review fructosamine, glycated albumin, and 1,5-anhydroglucitol as alternative or added markers for detecting glycemic disorders.

10.1. Fructosamine

Glycation is a spontaneous non-enzymatic reaction, the product of the reaction of carbohydrate moieties with the amino groups of proteins, DNA, and lipids, resulting in impaired biomolecules. The glycation process is highly accelerated in diabetes and is associated with complications. Serum fructosamine is a glycoprotein that results from the covalent attachment between a sugar (such as glucose or fructose) to total serum proteins mostly, but not exclusively, albumin. This will form an aldimine, a product of the Schiff reaction, which thereafter forms ketoamines (proteins that contain fructosyl-lysine or fructosyl-(N-terminal) aminoacids). The term fructosamine therefore reflects the linkage of ketoamines resulting in the glycation of serum

proteins. The ketoamine can thereafter be converted to advanced glycation end products (AGEs) contributing to organ damage.

In contrast to intracellular hemoglobin, plasma proteins are more susceptible of being glycated reflecting GV more accurately [274]. Because glycated proteins have a more rapid turnover than HbA1c, which is dependent on erythrocyte turnover taking about 120 days, they are therefore not affected by erythrocyte or hemoglobin characteristics providing relevant information on blood glucose levels over the previous 2-4 weeks. Hence, they are short-term markers increasing in states of high glucose concentrations [275, 276]. The reference range for fructosamine is 200-285 umol/L, which reflects the contribution of glycated albumin as well as all glycated proteins, each with a different half-life and level of glycation. This biomarker can also be detected in saliva being significantly higher in T2D and having a positive correlation with fasting, postprandial plasma glucose, and HbA1c levels [277] . Because its measurement does not require fasting, the use of fructosamine is convenient and cost-effective [278]. Furthermore, fructosamine may be a valuable indicator to assess risk for T2D independent of baseline fasting glucose and HbA1c measurements in individuals without diabetes [279, 280]. Fructosamine can be affected by clinical conditions associated with altered protein metabolism or protein loss as in the nephrotic syndrome as well as diminished protein synthesis (hepatic disease, cirrhosis), thyroid disease and malnutrition [281, 282].

Even though HbA1c is relevant for diagnosing and managing diabetes, several studies reinforce its limitation in subjects affected by microvascular and macrovascular complications in which short-term markers may play an important role [283]. The Atherosclerosis Risk in Communities

(ARIC) study demonstrated that fructosamine was associated with risk of diabetes and those with the highest levels had greater risk for retinopathy and albuminuria [284, 285]. In chronic kidney disease (CKD), fructosamine increased with the progression of diabetic nephropathy, although it is not clear if this was linked to early microangiopathic events [286]. On the other hand, Jung et al. [287] suggested that the biomarker does not perform well in older adults with severe CKD. Further studies are needed to confirm the effectiveness of fructosamine as a marker of microvascular complications.

Fructosamine performs better than HbA1c when monitoring glucose control during short-term exercise [288] and appears to be more reliable when assessing patients requiring tighter glucose control as in GDM and with increased post-prandial glucose excursions [289, 290]. A short-term marker of glycemia is needed in GDM because HbA1c measurements are not reliable as glucose and iron concentrations decrease while erythrocyte turnover increases [290, 291]. Fructosamine is a preferred alternative because it can be obtained from a single random blood sample and does not require an OGTT [292]. However, fructosamine was insensitive for identifying GDM in early pregnancy [293] . Therefore, fructosamine may be a good biomarker to predict neonatal outcomes and maternal glycemia but additional studies are needed to establish suitable reference ranges [293-297].

In summary, fructosamine may provide a more precise estimation of GV and short-term therapeutic efficacy than HbA1c and implemented in circumstances when HbA1c may not be accurate.

10.2. Glycated Albumin

Albumin constitutes about 60% of total blood protein content, present in concentrations of 35-50 g/L, and has independent relevance as a glycemic marker. Glycation of albumin in the presence of hyperglycemia leads to structural alterations through spontaneous non-enzymatic Maillard reactions [298, 299]. Further oxidation of these Amadori products can produce AGEs, thought to be pathologic, as glycated albumin (GA) bound to AGE receptors (RAGEs) have considerable immunogenic properties [299, 300] .

Due to the shorter half-life of albumin than hemoglobin, GA measurements are representative of a far shorter prior period of exposure to circulating glucose than HbA1c approximating 2-3 weeks, similar to fructosamine [282] . Furthermore, albumin is approximately 10 times more sensitive to glycation than hemoglobin [301].

As GA is not affected by the same limitations as hemoglobin, it may be an acceptable alternative biomarker of glycemic control when HbA1c is unreliable as in CKD, particularly during hemodialysis [302]. It also seems to be a better predictor of cardiovascular complications and risk of hospitalization or death in these patients when HbA1c is especially unreliable in the presence of anemia or erythropoietin administration [303, 304].

Similar to fructosamine, the use of GA is limited in pathological conditions affecting albumin metabolism including nephrotic syndrome, hyperthyroidism, glucocorticoid or iron therapy, malnutrition, and advanced liver disease [282, 305-307]. Another possible confounding factor is the interference of BMI with GA measurements [307]. While GA may underestimate glycemic

control in overweight/obese individuals, the discrepancy seems to attenuate progressively with progression of prediabetes or BMI above 30 kg/m^2 [308, 309]. The negative correlation of GA with obesity is possibly related to the contribution of obesity-associated chronic inflammation in accelerating albumin catabolism [283].

GA may have a role in the diagnosis of diabetes and prediabetes. While GA may detect undiagnosed diabetes, it was not superior to HbA1c in population studies [277]. Nevertheless, cut-off values have been established to diagnose diabetes mainly in Asian populations but recently in Caucasian and Afro-American populations as well [310-312]. However, GA was not considered to have adequate sensitivity to detect prediabetes and predict T2D [313].

Combining GA and fasting glucose has been proposed to possess adequate sensitivity and specificity to detect diabetes and prediabetes [314]. Furthermore, GA may be a better glycemic marker than HbA1c to monitor women with GDM [315]. The earlier window of estimating glycemic control with GA may be especially valuable for monitoring lifestyle or pharmacological interventions to control diabetes [316] . The shorter half-life of albumin suggests that changes in glucose levels can be confirmed in four weeks by monitoring GA as opposed to waiting 12 weeks with HbA1c, thereby allowing for earlier therapeutic adjustments [316, 317].

GA has also been proposed as a marker of inflammation and has additional value to HbA1c regarding assessment of β-cell secretory dysfunction, postprandial glucose excursions, unstable fluctuating glycemia, hypoglycemic episodes as well as predicting outcomes in GDM [289, 308,

317-321]. GA was shown to be associated particularly with perinatal complications in newborn babies of mothers with GDM performing better than HbA1c as well as predicting birthweight and large-for-date infants [322].

Novel implications for GA in the pathological processes related to diabetes have been recently proposed [323]. This highlighted the role of albumin as a carrier protein involved in the crosstalk between organs related to overall control of insulin sensitivity. Indeed, circulating GA derived from hyperglycemia seems to further impair intracellular insulin signaling in skeletal muscle and adipose tissue [324, 325]. Studies have not been particularly productive seeking genetic determinants of GA [326].

GA plays a role as an atherogenic factor in the development of complications. GA leads to the irreversible potentiation of atherogenic, thrombogenic and inflammatory responses, exacerbating cardiovascular risk, abolition of the anti-inflammatory effect of HDL-cholesterol, and the antioxidant effect of circulating albumin itself [327-329]. In addition, glycation was shown to render albumin cytotoxic for several cerebral and vascular cell types and also less effective in preventing the aggregation of β-amyloid fibers suspected of contributing to the progression of Alzheimer's disease [330]. Of note, GA/HbA1c but not GA or HbA1c alone correlates with risk of Alzheimer's disease [331].

In summary, GA is not only an alternative marker of glycemic control when HbA1c is unreliable but also appears to be an independent risk factor for diabetes complications and further impairment of SI.

10.3. 1,5- anhydroglucitol

1,5- anhydroglucitol (1,5-AG) is a non-traditional glycemic biomarker based on a non-glycation mechanism in different research and clinical endeavors mainly related to glycemic disorders. 1,5-1,5-AG is a glucidic molecule, ubiquitous in many different food sources, is in a relatively stable concentration based on food intake, intestinal absorption, glomerular filtration and tubular reabsorption [332]. The tubular reabsorption of 1,5-AG, through co-transporter SGLT4, is competitive with glucose [333]. In situations where the glucose concentration exceeds the renal threshold approximating 180 mg/dl (10 mmol/L), glucose glomerular excretion is increased as is its tubular reabsorption. In this situation, 1,5-AG usually filtered in the glomeruli is not reabsorbed in the tubules, increasing its urinary excretion and decreasing plasma concentration. In contrast with other biomarkers, including HbA1c, fructosamine and GA that increase directly with hyperglycemia, the plasma concentration of 1,5-AG decreases.

Earlier studies demonstrated that the plasma concentration of 1,5-AG could be a marker of previous (1-2 weeks) exposure to hyperglycemia above the glucose renal threshold, reflecting post-prandial hyperglycemic peaks [334, 335]. Automated and quantitative 1,5-AG measurements can be performed using commercially available biochemical assay kits[336-338]. FDA approved this marker for monitoring intermediate-term glycemic control in those with diabetes and post-prandial hyperglycemia [339].

In the ARIC study, the reference range for healthy individuals was 2.5 to 28.7 ug/mL [312]. 4.9% of previously considered healthy individuals had a 1,5-AG concentration <10 ug/mL, the

cut-off for defining exposure to hyperglycemia, potentially representing a subset of the population with higher post-prandial glycemic peaks. Published reference values in various populations, while showing differences in the healthy reference range, do not alter 10 μg/mL as the threshold for exposure to hyperglycemia [340]. Demographic differences in 1,5-AG concentrations may be due to non-glycemic causes such as dietary or other determinants including rate of glucose digestion, enteric uptake and possibly genetic variants conditioning these factors [340, 341].

1,5-AG was measured in studies of individuals with NGT, isolated IFG and/or IGT and diabetes. The combination of FPG and 1,5-AG was shown to exclude the diagnosis of diabetes when the FPG was <100 mg/dl (5.6 mmol/L) and 1,5-AG > 15.9 μg/mL. Diabetes was diagnosed by either a FPG ≥ 126 mg/dl (7.0 mmol/L) or serum 1,5-AG level ≤ 15.9 μg/mL with an OGTT performed if neither of these criteria were met. Using the aforementioned criteria, the sensitivity, specificity, PPV, and NPV for the combination of FPG and 1,5-AG were 78.7%, 72.3%, 72.0%, and 78.9%, respectively. When combining FPG and 1,5-AG employing a single sample, an OGTT could be avoided in 75.8% of cases representing a more efficient process for screening and diagnosing diabetes [342].

A similar study in Asian Indians demonstrated that levels of 1,5-AG were progressively lower as glucose intolerance progressed from normal to IGT to T2D [343]. Individuals without diabetes and low levels of 1,5-AG (<10μg/mL) were at higher risk for developing diabetes. There was also an association of low 1,5-AG with known risk factors for hyperglycemia [344]. The results of screening with 1,5-AG may differ depending on whether post-prandial hyperglycemia or IFG

is dominant [342]. In T2D, levels were lower in those with higher post-prandial glucose values [343].

Prolonged exposure to hyperglycemia, measured by glycated biomarkers, leads to micro- and macrovascular disease and is associated with greater morbidity and earlier mortality. Glycemic excursions, which may be an independent factor for CVD, may not be reflected with HbA1c [345]. However, 1,5-AG as a marker of short-term GV, has been associated with risk for CVD [346]. In the ARIC study, a 1,5-AG threshold of 6 µg/mL, as opposed to concentrations > 10 µg/mL, i.e., in the non-diabetic range, significantly increased the risk of coronary heart disease, heart failure, stroke and death [347]. In another study, low levels of 1,5-AG were associated with microvascular events (new or worsening nephropathy or retinopathy) when Hazard Ratios significantly increased with 1,5-AG values <10 µg/mL but there was no association with macrovascular outcomes (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) [348]. This contrasts with another study in which low 1,5-AG levels were independently associated with long-term cardiac mortality in an acute care setting even in patients with HbA1c <7% (53 mmol/mol) [349].

1,5-AG levels do not appear to be influenced by mild or moderate renal dysfunction supporting its role as a reliable glycemic marker in T2D with CKD [333]. Most studies with 1,5-AG have been performed in diabetic populations[350] and as a marker to demonstrate the efficacy of drugs prescribed in T2D except for SGLT2 inhibitors [351, 352]. 1,5-AG cannot be used in the latter class since they promote glucose excretion and falsely reduce 1,5-AG levels. It should also be noted that whereas fructosamine and GA have similar aROC values as HbA1c (0.83-0.87),

1,5-AG is lower (0.70) [353]. The aROC for HbA1c, however, was found to be lower (0.78) in conditions in which HbA1c is reportedly unreliable such as with hemodialysis [354], in which GA may be complementary [355].

In conclusion, the clinical management of glycemic disorders is predicated on glucose control and targeting other risk factors for preventing complications. Translating a continuous biochemical variable into a marker that categorizes different glycemic states into various risk groups could better inform decisions for selecting optimal therapies. The non-classical biomarkers, fructosamine, GA and 1,5-AG, have adjunctive roles for glycemic assessment.

11. Conclusions

Figure 3 provides an overview of methods for detecting glycemic disorders considered in this review. Several constitute important research tools and provide pathophysiologic and mechanistic insight while not feasible for clinical consideration. More sensitive, practical and precise biomarkers are therefore required capable of predicting progression to dysglycemic states at the earliest time point when the β-cell is still relatively functional and more likely responsive to lifestyle modification. As FPG and HbA1c either alone or in combination may underdiagnose a considerable number of high-risk individuals, the 2-h OGTT, rarely used in clinical practice, remains the current gold standard for screening. Therefore, to improve upon current diagnostic modalities, an alternative approach to the 2-h OGTT with greater practicality, simplicity and cost-effectiveness is required.

Combining biomarkers, including metabolites, may provide better precision for predicting dysglycemia but would add considerable complexity and expense especially given the enormity of the population at risk and therefore is not practical from a clinical perspective. Genetics, while encouraging, has not evolved to a point where it can provide useful information in routine practice. The GCT two-step screening may hold promise particularly given the ability to screen without regard to fasting is important. However, a second stage confirmatory OGTT is required for those failing the 50-gram screening which may therefore limit its widespread use. Furthermore, the 1-h OGTT appears to be more sensitive to predict risk for T2D although a comparative study would be worthwhile considering.

Latent class analysis, development of CGM technology and measurements of IR and insulin secretion have also been essential in furthering understanding the pathophysiology of dysglycemic disorders. Although these modalities offer refined approaches to diagnosing and characterizing glucose disorders, their complexity and expense make their general use impractical beyond basic assessment of clinical and glycemic parameters. Other tools such as fructosamine, GA and 1,5-AG are also informative and may be adjunctive or confirmatory to glucose or HbA1c for detecting dysglycemia.

Of the approaches considered in this review, the 1-h PG appears to be the most promising given its greater sensitivity than FPG, HbA1c and the 2-h PG for detecting individuals at high-risk for T2D. It furthermore appears to be superior to clinical risk factors and metabolomics with a 1-h OGTT being more practical and cost-effective than the other methods described making it more clinically acceptable. While data from the Finnish Diabetes Prevention Program support the cost-

effectiveness of the 1-h PG [70], a formal health economics evaluation would be important. Finally, although a 1-h PG could replace the 2-h OGTT and HbA1c for detecting high-risk individuals with prediabetes, a 2-h OGTT may still be necessary to diagnose T2D. A recent meta-analysis suggests that the 1-h PG at a higher threshold than for detecting prediabetes could serve this purpose [356]. A 1-h OGTT could eventually both detect prediabetes and diagnose T2D in high-risk populations.

Therefore, the 1-h PG has considerable potential as a biomarker for detecting glucose disorders if confirmed by additional data including health economic analysis. Whether the 1-h OGTT is superior to genetics and omics in providing greater precision for individualized treatment requires further investigation. These methods will need to demonstrate substantial superiority to simpler tools for detecting glucose disorders to justify their cost and complexity.

Figure Legends

Figure 1: Classification of glucose curve shape. (A) Simple analysis of curve shape: monophasic (red), biphasic (green) and unclassified (purple) and (B) Latent mixed class trajectory modeling of curve shape: Class 1 (green), Class 2 (blue), Class 3 (orange), Class 4 (red) (adapted from [152].

Figure 2: Illustration of the continuum in the deterioration of glucose homeostasis throughout the natural history of T2D.

HbA1c =5.7 - 6.4% (39-46 mmol/mol): dawn phenomenon

HbA1c =6.5 - 6.9% (48-52 mmol/mol): dawn phenomenon plus postprandial hyperglycemia

HbA1c ≥ 7% (53 mmol/mol): progressive increment of basal hyperglycemia.

The respective contributions of postprandial and basal hyperglycemia can be depicted as follows: postprandial > basal when HbA1c = 7.0 -7.4% (53-57 mmol/mol), equal when HbA1c = 7.5 - 7.9% (58-63 mmol/mol) and basal >postprandial when HbA1c ≥ 8.0% (64 mmol/mol). Total hyperglycemia is determined by the sum of the black (AUCbasal) and shaded areas (AUCpostprandial).

Figure 3. Overview of Methods for Detecting Glycemic Disorders

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Contributors

MB conceptualized and contributed to the organization, writing and editing of the review article. All authors contributed to the organization, writing and/or editing of the review article.

Declaration of Interest

We declare no competing interests.

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Table 1: Current screening tests for prediabetes/diabetes – advantages and limitations

Screening test	Advantages	Limitations
Fasting Plasma Glucose (FPG)	Can be performed as a single blood draw.	Requires overnight fast. Less sensitive than the OGTT.
Oral Glucose Tolerance Test (OGTT)	Includes assessment of both fasting plasma glucose and the 2-hour glucose after the oral glucose load. Allows assessment of the glucose response after an oral glucose challenge. Identifies more individuals with dysglycemia than the FPG or HbA1c.	Requires overnight fast. Associated nausea in a subset of individuals after ingestion of 75g glucose load. Two-hour test duration. Sensitive to day-to-day differences due to diet and/or physical activity. Can vary according to time of day of testing. Reproducibility is not as good as the FPG or HbA1c.
HbA1c	Reflects integrated glucose levels over preceding 3 months. Convenient. Does not require fasting. Can be performed as a single blood draw. High reproducibility (precision). Less day-to-day perturbations during stress and illness. Standardized worldwide. Quality assurance in place.	Less sensitive than the FPG and OGTT. Interpretation and accuracy can be affected by presence of hemoglobin variants (i.e., sickle cell trait), chronic renal failure, iron deficiency anemia, differences in red blood cell lifespan, and differences with age and race. May be high or low relative to underlying average glucose levels (accuracy – HbA1c "mismatches" as a reflection of average glucose levels).
Random Plasma Glucose (RPG)	Convenient. Does not require fasting. Can be performed as a single blood draw. Often included in "metabolic profile" panels Very specific when elevated.	Levels which (a) should be followed by confirmatory diagnostic tests, or (b) indicate a low likelihood of dysglycemia, have not been established.

Table 2: Conditions Affecting HbA1c

1) Children and young adults
2) Pregnancy
3) New onset T1D and any other short duration hyperglycemia
4) Renal failure
5) HIV infection
6) Hemoglobinopathies
7) Anemia
8) Iron deficiency
9) Conditions that alter RBC lifespan, e.g. erythropoietin therapy, splenomegaly, splenectomy, rheumatoid arthritis, antiviral therapy.
10) Genetics

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1742 **Table 3. The Predictive Power of 1-h PG for T2D in Various Cohorts**

Publication	Cohort	N	Follow-up (years)	1 h-PG cut-off (mg/dl)	Proportion of population above threshold	Area under the ROC curve	Sensitivity T2D	Specificity T2D	Positive Predictive Values
Abdul-Ghani MA et al. 2007	San Antonio Diabetes Prediction Model (SADPM)*	2616	7-8	155 (≥8.6 mmol/L)	NA	0.84	75%	79%	NA
Abdul-Ghani MA et al. 2008	San Antonio Heart Study*	1610	7-8	155 (≥8.6 mmol/L)	16.6% of NGT	NA	NA	NA	NA
Abdul-Ghani MA et al. 2009	Botnia Study*	2442	7-8	155 (≥8.6 mmol/L)	15.8% of NGT	0.795	NA	NA	NA
Priya M et al. 2013	Diabetes Specialties Centre in Chennai, India*	1179	13	155 (≥8.6 mmol/L)	42.5% of NGT	0.689	66%	61%	19.5%
Alyass A et al. 2015	Botnia Study**	2603	4.94	160 (≥8.9 mmol/L)	30% of total population	0.80	75%	73%	15%
Alyass A et al. 2015	Malmo Preventive Project**	2386	23.5	151 (≥8.4 mmol/L)	37% of total population	0.70	62%	70%	33%
Fiorentino VT et al. 2015	CATAMERI and EUGENE2*	392	5.2	155 (≥8.6 mmol/L)	19% of NGT	0.78§	87%§	64%§	26%§
Bergman M et al. 2016	The Israel GOH Study*	853	24	155 (≥8.6 mmol/L)	22% of NGT	0.736	55%	77%	NA
Oka R et al 2016	Japanese Workers*	1445	4.5	163 (≥9.0 mmol/L)	25% of total population	0.88	NA	NA	NA
Oh TJ et al. 2017	Korean Genome and Epidemiology Study (KoGES)*	5703	12	144 (≥8.0 mmol/L)	43% of total population	0.74	70%	68%	NA
Paddock et al. 2017	Southwestern Native American (SWNA)*	1946	12.8	168 (≥7.2 mmol/L)	NA	0.728	56%	79%	NA
Sai Prasanna	Tertiary diabetes	1356	3.5	153	NA	0.716	64%	66%	NA

et al. 2017	centre at Chennai, India*			(≥8.5 mmol/L)						
Pareek M et al. 2018	Malmö Preventive Project***	4867 Swedish men	12	155 (≥8.6 mmol/L)	32% of NGT	0.698	NA	NA	NA	
Pareek M et al. 2018	Malmö Preventive Project***	4867 Swedish men	39	155 (≥8.6 mmol/L)	32% of NGT	0.637	NA	NA	NA	
Manco M et al. 2019	Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC)*	797	3	155 (≥8.6 mmol/L)	22% of NGT	0.67	NA	NA	NA	
Saunajoki A.E. et al. 2020	Oulu45 population-based cohort study*	654	12	160 (≥8.9 mmol/L)	34%	0.81	NA	NA	NA	

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1744 *Definition of T2D based on FPG ≥126 mg/dl (7.0 mmol/L) and/or 2-h post-load ≥200 mg/dl (11.1
1745 mmol/L).

1746 **Botnia participants with incident T2D were diagnosed using patient records, follow-up FPG ≥126
1747 mg/dl (7.0 mmol/L), 2-h post-load ≥200 mg/dl (≥11.1 mmol/l) or HbA1c ≥6.5% (48 mmol/mol), while
1748 Malmö Preventive Project participants with incident T2D were diagnosed using patient records or follow-
1749 up FPG >126 mg/dL (7.0 mmol/L).

1750 ***Definition of T2D based on International Classification of Diseases (ICD) according to the relevant
1751 ICD-8 to ICD-10 codes.

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Table 4. Predictive Power of FPG, 1-h PG, and 2-h PG for T2D

Publication	Study Cohort	FPG	1-h PG	2-h PG
		Area under the ROC curve	Area under the ROC curve	Area under the ROC curve
Abdul-Ghani MA et al. 2007	San Antonio Diabetes Prediction Model (SADPM)*	0.75	0.84	0.79
Abdul-Ghani MA et al. 2009	Botnia Study*	0.672	0.795	0.688
Priya M et al. 2013	Diabetes Specialties Centre in Chennai, India*	0.622	0.689	0.608
Alyass A et al. 2015	Botnia Study**	0.65	0.80	0.71
Alyass A et al. 2015	Malmo Preventive Project**	0.65	0.70	0.61
Fiorentino VT et al. 2015	CATAMERI and EUGENE2*	0.73§	0.78§	0.73§
Bergman M et al. 2016	The Israel GOH Study*	NA	0.736	0.707
Oka R et al. 2016	Japanese Workers*	0.79	0.88	0.79
Oh TJ et al. 2017	Korean Genome and Epidemiology Study (KoGES)*	0.61	0.74	0.63
Paddock et al. 2017	Southwestern Native American (SWNA)*	NA	0.728	0.706
Sai Prasanna et al. 2017	Tertiary diabetes centre at Chennai, India*	0.593	0.716	0.618
Pareek M et al. 2018	Malmo Preventive Project***	NA	0.698	0.553
Pareek M et al. 2018	Malmo Preventive Project***	NA	0.637	0.511
Manco M et al. 2019	Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC)*	0.71	0.67	0.65
Saunajoki A.E. et al. 2020	Oulu45 population-based cohort study*	0.71	0.81	0.72

*Definition of type 2 diabetes based on fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/L) and/or 2-h post-load ≥200 mg/dl (11.1 mmol/L).

**Botnia participants with incident type 2 diabetes were diagnosed using patient records, follow-up FPG ≥126 mg/dl (7.0 mmol/L), 2-h post-load ≥200 mg/dl (≥11.1 mmol/L) or HbA1c ≥6.5% (48 mmol/mol), while MPP participants with incident type 2 diabetes were diagnosed using patient records or follow-up FPG >126 mg/dl (7.0 mmol/L).

***Definition of T2D based on International Classification of Diseases (ICD) according to the relevant ICD-8 to ICD-10 codes.

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Figure 1

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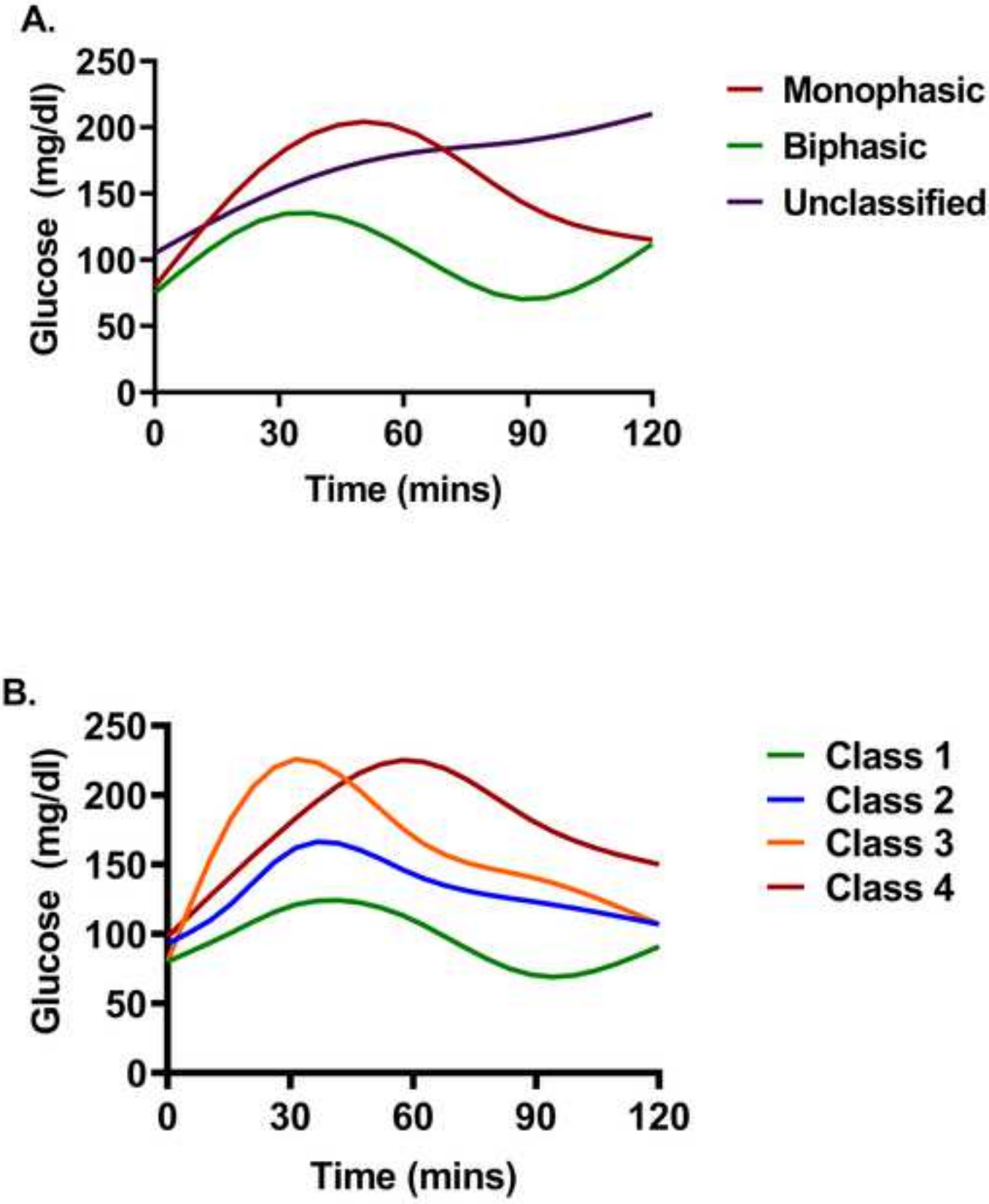


Figure 2

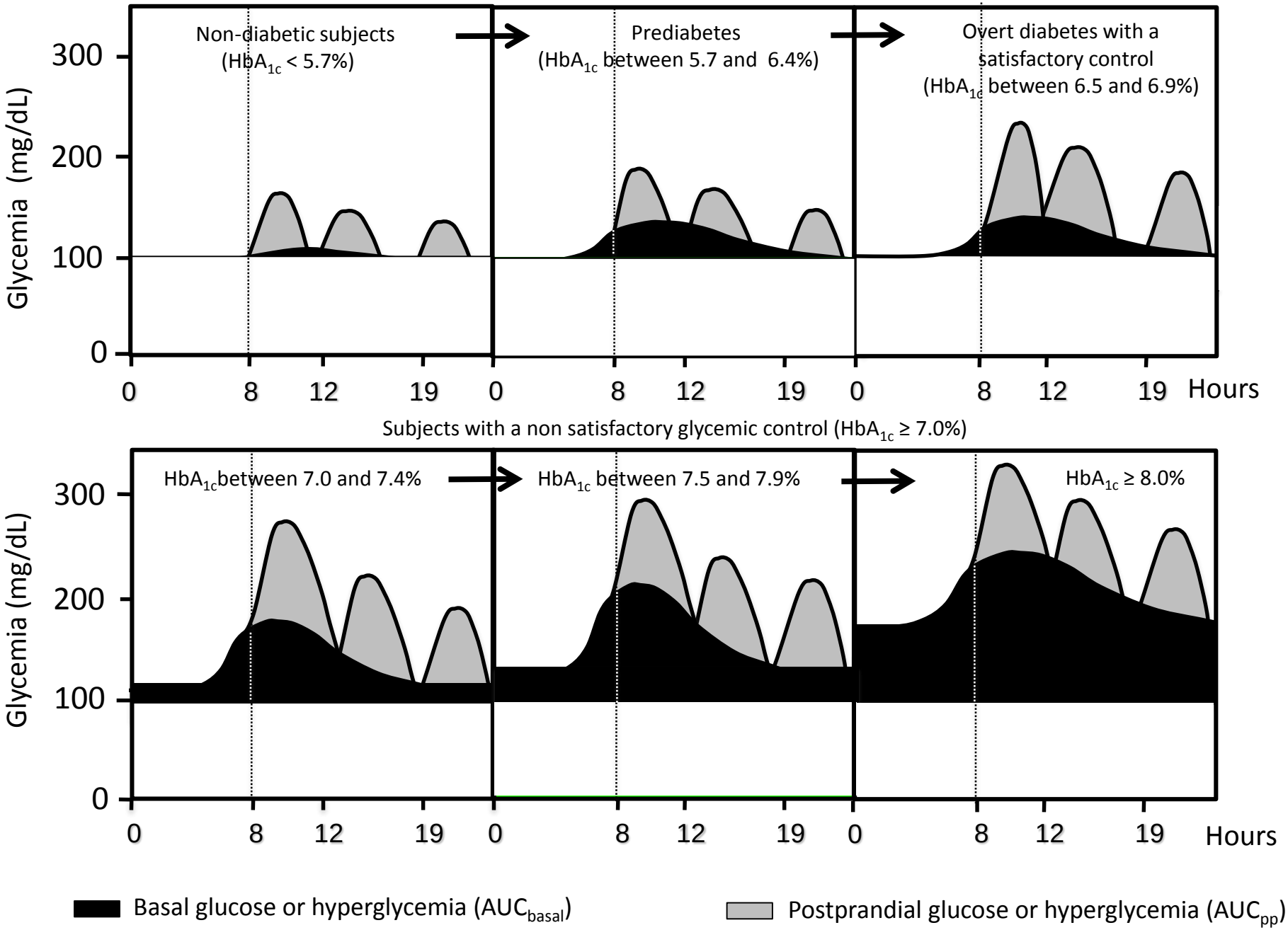
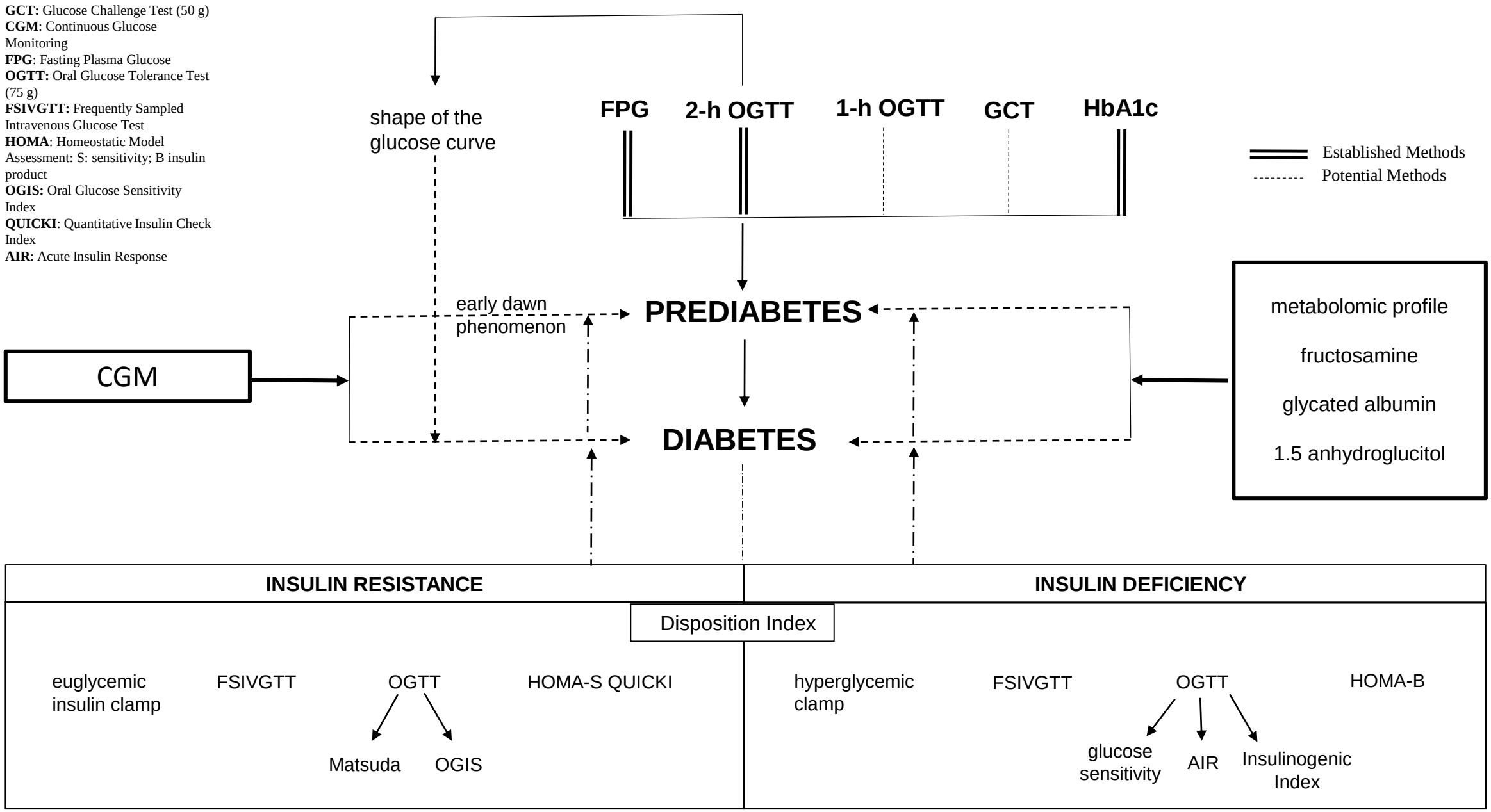

Non-diabetic subjects
(HbA1c < 5.7%)
Prediabetes
(HbA1c between 5.7 and 6.4%)
Overt diabetes with a satisfactory control
(HbA1c between 6.5 and 6.9%)
Glycemia (mg/dL)
300
200
100
0
0
8
12
19
Hours
Subjects with a non satisfactory glycemic control (HbA1c ≥ 7.0%)
HbA1cbetween 7.0 and 7.4%
HbA1c between 7.5 and 7.9%
HbA1c ≥ 8.0%
Basal glucose or hyperglycemia (AUCbasal)
Postprandial glucose or hyperglycemia (AUCpp)

Figure 3


GCT: Glucose Challenge Test (50 g)
CGM: Continuous Glucose Monitoring
FPG: Fasting Plasma Glucose
OGTT: Oral Glucose Tolerance Test (75 g)
FSIVGTT: Frequently Sampled Intravenous Glucose Test
HOMA: Homeostatic Model Assessment: S: sensitivity; B insulin product
OGIS: Oral Glucose Sensitivity Index
QUICKI: Quantitative Insulin Check Index
AIR: Acute Insulin Response
shape of the glucose curve
FPG
2-h OGTT
1-h OGTT
GCT
HbA1c
Established Methods
Potential Methods
early dawn phenomenon
PREDIABETES
DIABETES
CGM
metabolomic profile
fructosamine
glycated albumin
1.5 anhydroglucitol
INSULIN RESISTANCE
INSULIN DEFICIENCY
Disposition Index
euglycemic insulin clamp
FSIVGTT
OGTT
Matsuda
OGIS
HOMA-S QUICKI
hyperglycemic clamp
FSIVGTT
OGTT
glucose sensitivity
AIR
Insulinogenic Index
HOMA-B