Published in final edited form as:

Metabolism. 2014 June ; 63(6): 767–772. doi:10.1016/j.metabol.2014.03.002.

Glucoregulatory Function among African Americans and European Americans with Normal or Pre-diabetic Hemoglobin A1c Levels

Sotonte Ebenibo, MBBS, Chimaroke Edeoga, MBBS, Jim Wan, PhD, and Samuel Dagogo-Jack, MD

Division of Endocrinology, Diabetes and Metabolism and General Clinical Research Center, University of Tennessee Health Science Center, Memphis, TN

Abstract

Objective—A hemoglobin (Hb) A1c range of 5.7%-6.4% has been recommended for the diagnosis of prediabetes. To determine the significance of such “prediabetic” HbA1c levels, we compared glucoregulatory function in persons with HbA1c levels of 5.7%-6.4% and those with HbA1c < 5.7%.

Methods—We studied 280 nondiabetic adults (142 black, 138 white; mean ($\pm$ SD) age 44.2 $\pm$ 10.6 y). Each subject underwent clinical assessment, blood sampling for HbA1c measurement, and a 75-g oral glucose tolerance test at baseline. Additional assessments during subsequent outpatient visits included insulin sensitivity, using homeostasis model assessment (HOMA)-IR and the hyperinsulinemic euglycemic clamp; insulin secretion, using HOMA-B and frequently samples intravenous glucose tolerance test (FSIVGTT) and disposition index (DI); and measurement of fat mass, using DXA.

Results—Compared to subjects with HbA1c < 5.7%, persons with HbA1c levels of 5.7%-6.4% were older, and had higher body mass index (BMI) and insulin secretion but similar insulin sensitivity. When the two groups were matched in age and BMI, persons with HbA1c 5.7–6.4% were indistinguishable from those with HbA1c <5.7% with regard to all measures of glycemia glucoregulatory function.

Conclusions—Unlike glucose-defined prediabetes status, an HbA1c range of 5.7%- 6.4% does not reliably identify individuals with impaired insulin action or secretion, the classical defects underlying the pathophysiology of prediabetes. Thus, HbA1c cannot validly replace blood glucose

© 2014 Elsevier Inc. All rights reserved

Correspondence to: Samuel Dagogo-Jack, MD 920 Madison Avenue, Suite 300A University of Tennessee Health Science Center Memphis, TN 38163 Tel.: 901-448-5318 Fax: 901-448-5332 sdj@uthsc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure: The authors have no conflict of interest to disclose with regard to the content of this manuscript.

Authors' Individual Contributions Samuel Dagogo-Jack: study concept and design, writing of manuscript

Chimaroke Edeoga: data collection, review and revision of manuscript

Sotonte Ebenibo: data analysis, review and revision of manuscript

Jim Wan: statistical analysis, reviewed and revised of manuscript

measurement in the diagnosis of prediabetes. If utilized as a screening test due to convenience, aberrant HbA1c values should be corroborated with blood glucose measurement before therapeutic intervention.

Keywords

Prediabetes diagnosis; A1C; Race/Ethnicity; Insulin sensitivity; Insulin secretion

INTRODUCTION

Since 2009, several organizations have recommended the use of glycated hemoglobin (HbA1c) levels for the diagnosis of diabetes and prediabetes [1–3]. Currently, diabetes can be diagnosed if the HbA1c level is confirmed to be 6.5% or greater, and prediabetes (or “high risk for diabetes”) is diagnosed if the HbA1c falls within the range of 5.7–6.4% [4]. Traditionally, the diagnosis of diabetes has been based on measurement of fasting plasma glucose (FPG, > 126 mg/dl or 7.0 mmol/l) or the standard 75-gm oral glucose tolerance test (OGTT) (2-hr plasma glucose {2hrPG} > 200 mg/dl or 11.1 mmol/l) [5, 6]. Similarly, the traditional diagnosis of pre-diabetes has relied on measurement of FPG (impaired fasting glucose {IFG}, 100 – 125 mg/dl or 5.6–6.9 mmol/l) [6] or OGTT (impaired glucose tolerance {IGT}, 2hrPG 140–199 mg/dl or 7.8–11.0 mmol/dl) [7].

HbA1c is a minor hemoglobin variant that results from nonenzymatic amino-terminal glycosylation of the β -chain of the hemoglobin molecule [8]. The observation that HbA1c levels are correlated with average blood glucose levels over the preceding 3 months led to the use of HbA1c a “gold standard” measure of glycemic control in people with diabetes and a prognosticator of vascular complications of diabetes in landmark studies [8–11]. The advantages of HbA1c as a clinical test include its obvious role as a measure of chronic rather than acute glycemic burden, the lack of requirement for fasting specimens, preanalytical sample stability, and greater measurement precision, among others [1,12]. These advantages make the HbA1c test a valuable tool for monitoring glycemic control in established patients with diabetes. However, there is less experience with measurement of HbA1c in nondiabetic persons, and the utility of the test as a valid indicator of early dysglycemia is yet to be established. In the present study, we aimed to determine the metabolic significance of HbA1c-defined prediabetes status by comparing markers of glucoregulatory function in nondiabetic persons whose HbA1c levels fall either within or below the 5.7–6.4% for diagnosis of prediabetes.

RESEARCH DESIGN AND METHODS

Study Subjects

We studied 287 adult subjects (147 black and 140 white) who had no history or evidence of diabetes. Based on HbA1c levels at enrollment, the subjects were classified as normal (HbA1c <5.7%, N=189) or “prediabetic” (A1c 5.7 – 6.4%, N=98), based on the American Diabetes Association criteria [4]. The subjects are participants in the ongoing Pathobiology of Prediabetes in A Biracial Cohort (POP-ABC) study, a longitudinal study of incident dysglycemia among normoglycemic offspring of parents with type 2 diabetes. The design

and methods, and baseline characteristics, of the POP-ABC study have been published [13, 14]. In brief, eligibility criteria in POP-ABC included age 18–65 years, absence of a history or evidence of diabetes, self-reported non-Hispanic white (European American) or non-Hispanic black (African American) race/ethnicity status, having one or both biological parents with type 2 diabetes, and normal oral glucose tolerance test at baseline [13]. The POP-ABC study protocol was approved by the Institution Review Board of the University of Tennessee Health Science Center. All subjects gave written informed consent prior to the initiation of the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Participants were studied as outpatients at the University of Tennessee General Clinical Research Center. After medical history-taking, physical examination, and anthropometric measurements, fasting blood specimens were collected for chemical analyses, including HbA1c level, followed by OGTT during the initial visit. The body mass index (BMI) was calculated as the weight in kilogram divided by height in meter squared. Normal fasting glucose (<100 mg/dl or 5.6 mmol/l) was defined according to the 2003 revised American Diabetes Association criteria [6] and normal glucose tolerance was defined by the 1985 World Health Organization criterion (2-hr plasma glucose <7.8 mmol/l), based on a 75-gram OGTT [7]. The homeostasis model assessment (HOMA) method was used to calculate indices of insulin resistance (HOMA-IR) and β -cell function (HOMA-B) from fasting plasma glucose and insulin values [15]. A frequently-sampled intravenous glucose tolerance test (FSIVGTT) and hyperinsulinemic euglycemic clamp were performed during the second and third visits, respectively. The visits were scheduled approximately 8 weeks apart. For the FSIVGTT arterialized blood samples for glucose and insulin measurements were collected 30 min before and at 2, 3, 4, 5, 7, and 10 min following the intravenous glucose bolus (25 g) [13, 16]. The acute insulin secretory response to glucose (AIRg) was calculated as the mean incremental plasma insulin levels in specimens obtained at 3, 4, and 5 minutes during the FSIVGTT [16]. Total body fat, trunk fat and lean mass were measured by DXA during Visit 2. For the hyperinsulinemic euglycemic clamp [17], a primed, continuous intravenous insulin infusion (12.0 pmol/ $\text{kg}^{-1} \cdot \text{min}^{-1}$) was administered for 180 min with blood glucose concentration maintained at ~ 5.6 mmol/l (100 mg/dl) using a variable rate dextrose (20%) infusion. Arterialized blood sampling for glucose and insulin levels was performed every ten minutes. Insulin sensitivity (S_i) was estimated as the rate of maximal insulin-stimulated glucose disposal during the last 60 min of insulin infusion, normalized to estimated metabolic body size (EMBS). The latter was calculated as fat-free mass + 17.7 kg [16, 18]. The disposition index (DI) was calculated as the product of AIRg and S_i values.

Assays—Plasma glucose was measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA) and plasma insulin by a chemiluminescent assay using commercial kits (Immulite, Siemens Ltd., Llanberis, Gwynedd, UK). An ion-exchange high-performance liquid chromatography method (Bio-Rad, Hercules, CA) was used to measure HbA1c. The within-run and between-run coefficients of variation for the HbA1c assay were 0.82% and 0.51%, respectively.

Statistical analyses—Data are expressed as means $\pm$ SD, unless SEM is specified. Comparisons between normal HbA1c and prediabetic HbA1c groups and across other defined groups were analyzed using unpaired t tests, linear regression and ANOVA for continuous variables and chi-squared test for nominal variables. Statistical analyses were run on an IBM StatView program (SAS Institute Inc., Cary, NC). $P < 0.05$ was accepted as significant.

RESULTS

Table 1 shows demographic characteristics and glycemic and adiposity measures in black and white subjects stratified by HbA1c status. Compared to persons with HbA1c $< 5.7\%$, individuals in the HbA1c 5.7–6.4% group were older and tended to have higher BMI and FPG. However, total body and trunk fat mass did not differ significantly by HbA1c status in black or white subjects (Table 1).

In the fasting state, there were no significant differences in plasma insulin levels, insulin sensitivity (HOMA-IR), or insulin secretion (HOMA-B) between individuals with “prediabetic” HbA1c and those with HbA1c $< 5.7\%$ (Table 1). Following oral glucose challenge (OGTT), the 2hrPG and glucose area-under-the-curve (AUC) values were similar in persons with HbA1c $< 5.7\%$ and those with HbA1c 5.7–6.4% (Table 1). Plasma glucose levels were similar in both groups during FSIVGTT (Fig. 1A), but subjects with HbA1c 5.7–6.4% showed greater insulin excursions than did those with HbA1c $< 5.7\%$ (Fig. 1B). Both the AIRg and insulin AUC during FSIVGTT were significantly higher among subjects with HbA1c 5.7–6.4%, compared to those with HbA1c $< 5.7\%$ (Table 1). Insulin sensitivity, assessed by the hyperinsulinemic euglycemic clamp, was not significantly different between two HbA1c groups (Fig. 1C, Table 1). The DI, which integrates insulin sensitivity and secretion, was greater in white but not black subjects in the “prediabetic” HbA1c group (Fig. 1D). Within each HbA1c group, African Americans had higher values for AIRg, insulin-AUC and DI than did European Americans (Table 1).

As already noted (Table 1), the subjects with “prediabetic” HbA1c were significantly older and had nominally higher values for all measures of adiposity compared to those whose HbA1c was lower than 5.7%. To account for possible confounding effects of age and adiposity on our findings, we compared the various glucoregulatory measures in a subset of 196 subjects matched in the following variables: gender, age (within 2 years), BMI (within 2 kg/m²), total fat mass (within 2 kg), and trunk fat (within 1 kg) (Table 2). When the two groups were matched in age, BMI, total body fat and trunk fat mass, persons with “prediabetic” HbA1c levels and those with HbA1c $< 5.7\%$ had nearly identical values for FPG, 2hPG, glucose AUC, fasting insulin, insulin sensitivity (by HOMA-IR and clamp), and insulin secretion (HOMA-B and DI).

DISCUSSION

We found in the present study that nondiabetic African Americans and European Americans with an HbA1c range of 5.7–6.4% were not more insulin resistant than their counterparts whose HbA1c levels were $< 5.7\%$, nor did they show any evidence of impaired insulin

secretion. Furthermore, individuals in the two HbA1c strata who were matched in age, gender and adiposity were indistinguishable with regard to glycemia and all measures of glucoregulatory function. Evidence of insulin resistance and loss of first-phase or early insulin secretion are the hallmarks of evolving type 2 diabetes [16]. The same two key defects also characterize the pathophysiology of prediabetes [19–21]. When prediabetic subjects are identified using conventional plasma glucose criteria (IFG, IGT), studies have consistently demonstrated evidence of insulin resistance and insulin secretory defects in such subjects, compared to persons with normal glucose regulation [16, 20–23].

In the present study, HOMA-IR (a measure of insulin resistance derived from fasting plasma glucose and insulin levels), was not significantly greater in persons with “prediabetic” HbA1c levels compared with those whose HbA1c levels were <5.7%. The findings were similar for hyperinsulinemic euglycemic clamp, a more robust assessment of insulin sensitivity. Interestingly, African Americans and European Americans in our study had comparable values for both measures of insulin sensitivity, whereas data from the general population often show greater insulin resistance in African Americans compared to European Americans [24]. As our study participants are all offspring of parents with type 2 diabetes, our findings suggest that a similar genetic (parental) risk for diabetes probably attenuates ethnic disparities in insulin sensitivity.

Basal insulin secretion, assessed using HOMA-B (a measure derived from fasting plasma glucose and insulin levels), was not impaired in persons with “prediabetic” HbA1c levels compared to those with lower HbA1c levels. Remarkably, the acute insulin secretory response to iv glucose (AIRg) and the insulin-AUC were actually more robust in the group with “prediabetic” HbA1c levels than those with lower HbA1c levels (Table 1). The DI, which integrates insulin sensitivity and secretion, was greater in white but not black subjects in the “prediabetic” HbA1c group (Fig. 1D). Both measures of dynamic insulin secretion as well as the DI were also noted to be greater in African Americans than European Americans (Table 1, Fig. 1D), perhaps due to decreased insulin clearance in African Americans [25, 26]. Overall, our study shows that persons identified as having “prediabetes” based on HbA1c values of 5.7–6.4% show no evidence of defective insulin action or secretion, compared with persons of lower or “normal” HbA1c status.

Thus, HbA1c levels in the range of 5.7– 6.4% do not portend the presence of the glucoregulatory impairments that have been classically associated prediabetes and are predictive of future diabetes risk [16, 20–23]. The failure of HbA1c levels in the range of 5.7– 6.4% to identify individuals with significant glucoregulatory impairments similar to those demonstrable in persons with IFG or IGT supports the notion that nonglycemic factors contribute to the variance of HbA1c [27–33]. Such factors include genetic determinants, inter-individual variations in erythrocyte survival and membrane permeability, age, race/ethnicity, glycation and deglycation reactions and age, among others [27–33].

The strengths of our study include the relatively large biracial sample that enabled us to demonstrate the consistency of our findings in African Americans and European Americans. We also used robust measures for assessing insulin sensitivity (hyperinsulinemic euglycemic clamp) and insulin secretion (FSIVTT). However, one weakness is that behavioral factors

that could alter insulin sensitivity (such as dietary habits and physical activity) were not controlled in our study subjects. It is doubtful, though, that nonrandom variability in behavioral factors led to systematic and selective alterations in insulin sensitivity among subjects with HbA1c 5.7-6.4% compared to those at lower HbA1c levels. Also, as the HbA1c reflects glycemic burden over 2–3 months, another weakness of our study is that glycemia was not assessed by continuous glucose monitoring or multiple measurements integrated over time. However, that weakness would be more germane to the use of HbA1c for monitoring diabetes control, and less so to its use for the primary diagnosis of prediabetes and diabetes. Moreover, in the A1c-Derived Average Glucose (ADAG) study (34), where ~2,700 blood glucose readings were obtained from each subject over 3 months and correlated with HbA1c levels, the variability in blood glucose among individuals with HbA1c levels of 5.7– 6.4% was considerable (~80 mg/dl to ~200 mg/dl).

Given the lack of strong pathophysiological congruence of the HbA1c tests in classifying individuals with prediabetes, and the possible influence of nonglycemic factors on the variance of HbA1c, a diagnosis of prediabetes based on direct glucose measurement would be more prudent. If the HbA1c test is utilized as the screening tool for reason of convenience, aberrant values need to be corroborated with actual blood glucose measurement before therapeutic interventions [33, 35].

Acknowledgments

The POP-ABC study was supported by Grants R01 DK067269, R01 DK067269-04S1 and MO1 RR00211 from the National Institutes of Health, Grant 7-07-MN-13 from the American Diabetes Association, and State of Tennessee Clinical Research Center fund (UTHSC CRC E070166010). We are indebted to the participants who volunteered for this study.

POP-ABC Research Group: Current: Samuel Dagogo-Jack, MD (Principal Investigator), Ann Ammons, BS, John Crisler, Chimaroke Edeoga, MBBS, MPH, Sotonte Ebenibo, MBBS, MPH, Ebenezer Nyenwe, MD, Jim Wan, PhD.

Past members: Emmanuel Chapp-Jumbo, MBBS (2009-2011), Ruben Cuervo, MD (2006-2007), Nonso Egbuonu, MBBS (2007-2010), Nicoleta Ionica, MD (2007-2008), Dorota Malinowski, MD (2007-2008).

Consultant: Steven Haffner, MD; Data and Safety Officer: Murray Heimberg, MD, PhD

Role of Funding Sources: The funding sources (National Institutes of Health, American Diabetes Association, and the State of Tennessee) had no role in the design and execution of the POP-ABC study, or analysis and publication of the data obtained from the study.

List of Abbreviations

2hrPG	2 hour plasma glucose
AIRg	acute insulin response to intravenous glucose
ANOVA	analysis of variance
AUC	area-under-the-curve
BMI	body mass index)
DI	disposition index
DXA	dual-energy x-ray absorptiometry

EMBS	estimated metabolic body size
FPG	fasting plasma glucose
FSIVGTT	frequently sampled intravenous glucose tolerance test
HbA1c	hemoglobin A1c
HOMA-B	homeostasis model assessment of beta-cell function
HOMA-IR	homeostasis model assessment of insulin resistance
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
OGTT	oral glucose tolerance test
POP-ABC	Pathobiology of Prediabetes in A Biracial Cohort
Si	insulin sensitivity

REFERENCES

1. The International Expert Committee. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. *Diabetes Care*. 2009; 32:1327–34. [PubMed: 19502545]
2. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2010; 33(Suppl.1):S62–S69. [PubMed: 20042775]
3. Canadian Diabetes Association. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Can J Diabetes*. 2013; 37(Suppl. 1):S8–S12. [PubMed: 24070969]
4. American Diabetes Association. Standards of Medical Care in Diabetes- 2014. *Diabetes Care*. 2014; 37(Suppl.1):S14–S16. [PubMed: 24357209]
5. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1997; 20:1183–97. [PubMed: 9203460]
6. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 2003; 26:3160–7. [PubMed: 14578255]
7. World Health Organization. Diagnosis and Classification of Diabetes Mellitus. World Health Organization; Geneva: 1999. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1.
8. Bunn HF, Gabbay KH, Gallop PM. The glycosylation of hemoglobin: relevance to diabetes mellitus. *Science*. 1978; 200:21–7. [PubMed: 635569]
9. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993; 329:977–86. [PubMed: 8366922]
10. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; 352:837–53. [PubMed: 9742976]
11. Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med*. 2004; 141:413–420. [PubMed: 15381514]
12. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan DM, National Academy of Clinical Biochemistry; Evidence-Based Laboratory Medicine Committee of the American Association for Clinical Chemistry. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care*. 2011; 34:e61–e99. doi: 10.2337/dc11-9998. [PubMed: 21617108]

13. Dagogo-Jack S, Edeoga C, Nyenwe E, et al. Pathobiology of prediabetes in a biracial cohort (POP-ABC): design and methods. *Ethn Dis.* 2011; 21:33–9. [PubMed: 21462727]
14. Dagogo-Jack S, Edeoga E, Ebenibo S, et al. Pathobiology of prediabetes in a biracial cohort (POP-ABC): Baseline characteristics of enrolled subjects. *J Clin Endocrinol Metab.* 2013; 98:120–128. [PubMed: 23118422]
15. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985; 28:412–9. [PubMed: 3899825]
16. Weyer C, Bogardus C, Mott DM, et al. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest.* 1999; 104:787–94. [PubMed: 10491414]
17. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol.* 1979; 237:E214–E223. [PubMed: 382871]
18. Gerich JE. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity. *Endocr Rev.* 1998; 19:491–503. [PubMed: 9715377]
19. Beck-Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states. Sequence of events leading to non-insulin-dependent diabetes mellitus. *J Clin Invest.* 1994; 94:1714–21. [PubMed: 7962519]
20. Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care.* 2000; 24:89–94. [PubMed: 11194248]
21. Bock G, Dalla Man C, Campioni M, et al. Pathogenesis of pre-diabetes: mechanisms of fasting and postprandial hyperglycemia in people with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes.* 2006; 55:3536–49. [PubMed: 17130502]
22. Dagogo-Jack S, Askari H, Tykodi G. Glucoregulatory Physiology in Subjects with Low-Normal, High-Normal, or Impaired Fasting Glucose. *J Clin Endocrinol Metab.* 2009; 94:2031–6. [PubMed: 19276238]
23. Kanat M, Mari A, Norton L, et al. Distinct β -cell defects in impaired fasting glucose and impaired glucose tolerance. *Diabetes.* 2012; 61:447–53. [PubMed: 22275086]
24. Chiu KC, Chuang LM, Yoon C. Comparison of measured and estimated indices of insulin sensitivity and beta cell function: impact of ethnicity on insulin sensitivity and beta cell function in glucose-tolerant and normotensive subjects. *J Clin Endocrinol Metab.* 2001; 86:1620–5. [PubMed: 11297594]
25. Osei K, Schuster DP. Ethnic differences in secretion, sensitivity, and hepatic extraction of insulin in black and white Americans. *Diabet Med.* 1994; 11:755–62. [PubMed: 7851069]
26. Harris MI, Cowie CC, Gu K, et al. Higher fasting insulin but lower fasting C-peptide levels in African Americans in the US population. *Diabetes Metab Res Rev.* 2002; 18:149–55. [PubMed: 11994907]
27. Gould BJ, Davie SJ, Yudkin JS. Investigation of the mechanism underlying the variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. *Clin Chim Acta.* 1997; 260:49–64. [PubMed: 9101100]
28. Snieder H, Sawtell PA, Ross L, et al. HbA(1c) levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. *Diabetes.* 2001; 50:2858–63. [PubMed: 11723071]
29. Khera PK, Joiner CH, Carruthers A, et al. Evidence for interindividual heterogeneity in the glucose gradient across the human red blood cell membrane and its relationship to hemoglobin glycation. *Diabetes.* 2008; 57:2445–52. [PubMed: 18591386]
30. Cohen RM, Franco RS, Khera PK, et al. Red cell lifespan heterogeneity in hematologically normal people sufficient to alter the apparent HbA1c. *Blood.* 2008; 112:4284–91. [PubMed: 18694998]
31. Chapp-Jumbo E, Edeoga C, Wan J, et al. Ethnic disparity in hemoglobin A1c levels among normoglycemic offspring of parents with type 2 diabetes. *Endocr Pract.* 2012; 18:356–62. [PubMed: 22138077]

32. Cohen RM, Snieder H, Lindsell CJ, et al. Evidence for independent heritability of the glycation gap (glycosylation gap) fraction of HbA1c in non-diabetic twins. *Diabetes Care*. 2006; 29:1739–43. [PubMed: 16873773]
33. Dagogo-Jack S. Pitfalls in the use of HbA1c as a diagnostic test: the ethnic conundrum. *Nat Rev Endocrinol*. 2010; 6:589–93. [PubMed: 20680035]
34. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008; 31:1473–8. [PubMed: 18540046]
35. Kilpatrick ES, Maylor PW, Keevil BG. Biological variation of glycated hemoglobin: implications for diabetes screening and monitoring. *Diabetes Care*. 1998; 21:261–4. [PubMed: 9539993]

Fig. 1.

Comparison of plasma glucose (Panel A) and insulin (Panel B) levels during frequently sampled intravenous glucose tolerance test, and insulin sensitivity (Panel C) and disposition index (Panel D), in subjects with normal (<5.7%) or prediabetic (5.7-6.4%) HbA1c values. The plasma insulin area-under-the-curve (Panel B) was significantly greater in subjects with HbA1c 5.7– 6.4% than those with HbA1c <5.7% (P=0.001). *P=0.0002 versus white subjects with HbA1c <5.7%.

Table 1

Characteristics of 280 Study Subjects by Race and Hemoglobin A1c Status

	European American			African American		
	HbA1c<5.7%	HbA1c 5.7-6.4%	P value	HbA1c<5.7%	HbA1c 5.7-6.4%	P value
N(F/M)	94(58/36)	44(27/17)	0.9696	79(61/18)	63(45/18)	0.43
Age	45.7±9.92	51.1±9.12	0.0053	40.2±10.7	46.5±8.9	0.0004
BMI	28.2±6.34	29.9±7.68	0.0275	30.4±7.00	31.9±6.76	0.16
Total Fat(kg)	28.2 ±12.5	31.7±14.5	0.3789	29.9 ±14.1	33.6±14.0	0.54
Trunk Fat(kg)	14.1 ±6.64	16.17±7.80	0.9538	14.15±7.61	16.61±7.48	0.78
HbA1c(%)	5.29 ±0.33	5.83±0.14	0.0019	5.28 ±0.35	5.95±0.19	0.0029
FPG(mg/dl)	91.1±6.73	93.7±6.97	0.0337	88.9±7.56	91.6±6.39	0.13
2hrPG(mg/dl)	124±24.1	124±22.0	0.6305	121 ±29.0	126±29.4	0.30
OGTT-AUC	11959 ±168	12011±104	0.3492	11938±113	11979±96	0.13
F.Ins (pmol/l)	45.2 ±39.9	58.0 ±41.0	0.2455	45.2 ±37.7	48.3±36.3	0.87
HOMA-IR	178 ±1.62	2.34±1.68	0.2324	1.78±1.59	1.92±1.52	0.84
HOMA-B	88.9 ±80.1	104.5±74.6	0.3839	91.3±65.3	91.7 ±62.3	0.90
AI _{Rg} ×10 ² (pmol/l)	3.58±2.34	3.89±2.57	0.007	5.95±4.48	6.55 ±5.23	<0.0001
IVGTT Glu-AUC	2072 ±263	2063±206	0.1230	2010±308	2007±262	0.29
IVGTT Ins-AUC	523±305	598±365	0.0155	847±556	927 ±696	0.0011
Insulin sensitivity*	64.8±20.6	63.9±14.5	0.7193	62.7 ±21.8	65.3±24.9	0.78
DI×10 ³	21.3±14.9	25.2±16.8	0.0002	38.9±35.7	37.9±30.9	0.06

*
μmol/kgEMBS.min⁻¹

Table 2

Characteristics of 196 Matched Subjects by Hemoglobin A1c Status

	HbA1c <5.7%	HbA1c 5.7-6.4%	P value
N (M/F)	98 (72/26)	98 (72/26)	>0.5
Black/White	47/51	64/34	0.01
Age (Years)	47.0 ± 9.6	48.1 ± 9.2	0.44
BMI (kg/m ²)	31.1 ± 6.7	31.2 ± 7.1	0.91
Total Fat Mass (kg)	32.46 ± 13.9	32.75 ± 14.1	0.89
Trunk Fat Mass (kg)	16.03 ± 7.34	16.35 ± 7.54	0.77
HbA1c (%)	5.26 ± 0.39	5.91 ± 0.19	<0.0001
FPG (mg/dl)	91.1 ± 7.72	92.3 ± 6.61	0.23
2hrPG (mg/dl)	127 ± 26.9	126 ± 26.9	0.74
OGTT-Glucose AUC	11,957 ± 180.1	11,989 ± 99.1	0.12
F. Insulin (pmol/l)	46.5 ± 32.9	50.9 ± 50.8	0.48
HOMA-IR	2.00 ± 1.74	2.05 ± 1.58	0.84
HOMA-B	94.1 ± 70.4	95.4 ± 66.8	0.90
AI _{Rg} × 10 ² (pmol/l)	4.83 ± 4.10	5.82 ± 5.42	0.17
FSIVGTT Glucose-AUC	2010 ± 278	2019 ± 254	0.82
IVGTT Insulin-AUC	758.6 ± 879.2	834.4 ± 704.3	0.53
Insulin Sensitivity	59.6 ± 21.9	64.7 ± 21.2	0.18
DI × 10 ³	30.2 ± 30.3	33.5 ± 28.6	0.52

* $\mu\text{mol/kgEMBS.min}^{-1}$