Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 1487–1492
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Distribution and cardiovascular risk correlates of hemoglobin A_{1c} in nondiabetic younger adults: the Bogalusa Heart Study

Quoc Manh Nguyen, Sathanur R. Srinivasan, Ji-Hua Xu, Wei Chen, Gerald S. Berenson*

Tulane Center for Cardiovascular Health, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

Received 25 July 2007; accepted 9 April 2008

Abstract

Excess glycated hemoglobin (HbA_{1c}), an indicator of long-term glucose homeostasis, is recognized as a risk factor for cardiovascular (CV) disease and mortality even among persons without diabetes. However, information is scant regarding its distribution and correlates of CV risk in nondiabetic younger adults. This aspect was examined in a biracial (black-white) community-based sample of 1111 younger adults (mean age: 36.2 years; 71% white, 43% male) enrolled in the Bogalusa Heart Study. Blacks vs whites and women vs men had higher HbA_{1c} values ($P < .0001$). In bivariate analysis adjusted for age, race, sex, and smoking status, significant adverse trends were noted for body mass index, waist circumference, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), total cholesterol to HDL-C ratio, insulin, glucose, and homeostasis model assessment of insulin resistance across HbA_{1c} quartiles; trends were not significant for mean arterial blood pressure, triglycerides, C-reactive protein, adiponectin, and estimated glomerular filtration rate. In multivariate analysis, besides race and sex, total cholesterol to HDL-C ratio and waist circumference were independent correlates of HbA_{1c}. Furthermore, the prevalence of excess (top decile) HbA_{1c} was 1.6-fold ($P < .05$) higher among those with metabolic syndrome defined by the National Cholesterol Education Program Adult Treatment Panel III and 2.1-fold ($P < .01$) and 1.5-fold ($P < .05$) higher, respectively, among those with positive parental history of CV disease and type 2 diabetes mellitus. These findings underscore the potential value of HbA_{1c} in risk assessments of CV disease and type 2 diabetes mellitus in nondiabetic, apparently "healthy" younger adults.

1. Introduction

That elevated levels of blood glucose are associated with excess risk of cardiovascular (CV) disease even among persons without diabetes is well recognized [1]. Glycosylated hemoglobin A_{1c} (HbA_{1c}) is an indicator of the status of glucose homeostasis over the preceding 2 to 3 months. In addition, it reflects oxidative stress and protein glycation of tissues including the vasculature [2]. Compared with fasting glucose, it has less intraindividual variation and tracks well over time [3,4]. Furthermore, measurement of HbA_{1c} is simple to perform and inexpensive, and does not require overnight fasting. Therefore, HbA_{1c} is considered useful as a measure of dysglycemia and related risk in population studies [5].

Although normative distribution of HbA_{1c} and its correlates of CV risk have been described for pediatric [6], and middle- and older-aged groups [7], such data for the US nondiabetic black and white younger adults are scant. The present study examines this aspect as part of the Bogalusa Heart Study, a biracial (black-white) community-based investigation of the early natural history of CV disease [8].

2. Methods

2.1. Study population

Individuals (n = 1203) aged 24 to 43 years, residing in the biracial (65% white, 35% black) community of Bogalusa, LA, were examined in 2000 to 2001 as part of long-term cohort follow-up study. Diabetic individuals (n = 70) with fasting glucose levels greater than 125 mg/dL, with HbA_{1c} levels greater than or equal to 7%, or on medications for diabetes were excluded from the study. Individuals (n = 4) with C-reactive protein (CRP) levels greater than 10 mg/L

* Corresponding author. Tel.: +1 504 988 7179; fax: +1 504 988 7194.
E-mail address: berenson@tulane.edu (G.S. Berenson).

0026-0495/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2008.04.011

were also excluded to minimize the effect of any acute infection. These exclusions along with nonfasting status resulted in 1111 fasting individuals (mean age: 36.2 years; 71% white, 43% male) who had data on HbA_{1c} along with other variables of metabolic syndrome for the study. The Institutional Review Board of the Tulane University Health Sciences Center approved this study. All participants gave their informed consent.

2.2. General examination

Subjects were instructed to fast for 12 hours before the screening, with compliance ascertained by an interview on the day of examination. Standardized protocols were used by trained examiners. All measurements were made in replicate, and mean values were used. Height and weight were measured to calculate body mass index (BMI; weight in kilograms divided by the square of height in meters) as a measure of overall adiposity. Waist circumference was measured as an indicator of abdominal visceral fat. Blood pressure measurements were obtained on the right arm of the subjects in a relaxed, sitting position. Systolic and diastolic blood pressures were measured using a mercury sphygmomanometer. Blood pressure levels were reported as the mean of 6 replicate readings taken by each of 2 randomly assigned examiners. Mean arterial pressure (MAP), calculated as diastolic blood pressure plus one third of the pulse pressure, was used in the analysis.

2.3. Laboratory analyses

Cholesterol and triglycerides (TG) levels in the serum were assayed using enzymatic procedures on a Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures [9]. The laboratory is being monitored for the precision and accuracy of lipid measurements by the Lipid Standardization and Surveillance Program of the Centers for Disease Control and Prevention (Atlanta, GA). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Phadebas; Pharmacia Diagnostics, Piscataway, NJ); adiponectin levels were measured by radioimmunoassay (Linco Research, St Charles, MO). Glucose and creatinine levels were measured as part of a multiple chemistry profile (SMA20) with the multichannel Olympus Au-5000 analyzer (Olympus, Lake Success, NY). Plasma high-sensitivity CRP was measured by latex particle-enhanced immunoturbidimetric assay on a Hitachi 902 Automatic Analyzer; HbA_{1c} in whole blood was measured by turbidimetric immunoinhibition assay on a Hitachi 902 Automatic Analyzer (Tinaquant, Roche Diagnostics). Insulin resistance status was assessed as homeostasis model assessment of insulin resistance (HOMA-IR) according to the formula described previously [10]: [insulin (in microunits per milliliter) × glucose (in millimoles per liter)/22.5]. The estimated glomerular filtration rate (EGFR) was assessed by a reexpressed 4-variable Modification of Diet in Renal Disease study equation [11]: EGFR (in milliliters per minute per 1.73 m^2) = 175 × (serum creatinine in milligrams per deciliter)$^{-1.154}$ × age$^{-0.203}$ (× 0.742 if female) (× 1.21 if black). On the basis of 10% blind duplicate determinations of study sample, intraclass correlation coefficient of reliability was 0.98 for HbA_{1c}; thus, reported measurements reflected 98% of the (true) interindividual variability among this study cohort.

2.4. Statistical analysis

All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC). General linear models were used to examine race and sex differences in risk factor variables. All P values were 2-tailed and adjusted for covariates where appropriate. Wherever race-sex interaction was present, separate models were used by race or sex. The trends of CV risk factors by HbA_{1c} quartiles were examined by using multiple linear regression adjusted for age, race, sex, and smoking status (yes/no). Individuals were considered smokers if they reported current use of cigarettes or having stopped smoking within the past year.

Models assessing the independent relation between CV risk factor variables and HbA_{1c} were constructed using multiple linear regression. The independent variables included in these models were age, race, sex, smoking status, MAP, ratio of total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C), HOMA-IR, CRP, adiponectin, and EGFR, without (model 1) or with (model 2) waist circumference. The TC/HDL-C ratio was chosen as a measure of dyslipidemia because it is a marker of insulin resistance characteristic of metabolic syndrome [12]. Continuous variables were tested for normality using a Kolmogorov-Smirnov test. Values of HbA_{1c} and other continuous risk factor variables, except age, used in the analyses were log transformed to improve normality.

Relationship of metabolic syndrome to HbA_{1c} was examined by comparing the prevalence of individuals at top decile of HbA_{1c} by metabolic syndrome status (yes/no) using χ^2 tests. Likewise, association of excess (top decile) HbA_{1c} with parental history of CV disease (myocardial infarction, coronary artery bypass surgery, angioplasty, angina, and stroke) or type 2 diabetes mellitus was examined by using χ^2 test. Top decile of the distribution was arbitrarily chosen to denote excess HbA_{1c}. Metabolic syndrome risk factors and their cutoff values were used in this analysis as defined by the National Cholesterol Education Program Adult Treatment Panel III [13].

3. Results

Mean levels of anthropometric, hemodynamic, and metabolic variables are presented in Table 1 by race and sex. There was no significant age difference among the race-sex groups. Blacks vs whites had higher BMI (women only),

Table 1
Characteristics of study cohort by race and sex

Variable (mean ± SD)	White men (n = 356)	Black men (n = 122)	White women (n = 434)	Black women (n = 199)
Age (y)	36.5 ± 4.4	36.5 ± 4.4	36.3 ± 4.4	35.4 ± 4.9
BMI (kg/m^2)	28.9 ±5.5	29.4 ± 7.3	28.0 ± 6.7	31.6 ± 8.7^{a}
Waist (cm)	98.7 ± 14.0^{x}	96.9 ± 17.9	86.4 ± 15.9	93.7 ± 18.6^{a}
MAP (mm Hg)	92.7 ± 8.7^{x}	100.5 ± 13.3^{a,x}	86.8 ± 8.8	92.7 ± 11.8^{a}
LDL-C (mg/dL)	130.0 ± 33.9	122.3 ± 40.6	124.3 ± 32.5^{a}	116.3 ± 31.2
HDL-C (mg/dL)	41.4 ± 11.8	49.9 ± 16.3^{a}	50.8 ± 12.7^{x}	51.9 ± 13.0
TG (mg/dL)	159.4 ± 118.4^{a,x}	125.7 ± 108.2^{x}	119.5 ± 68.7^{a}	87.5 ± 38.3
TC/HDL-C ratio	5.0 ± 1.5^{a,x}	4.1 ± 1.5^{x}	4.0 ± 1.2^{a}	3.7 ± 1.0
Insulin (μU/mL)	12.5 ± 9.2	12.1 ± 9.5	11.1 ± 7.4	14.4 ± 11.3^{a,x}
Glucose (mg/dL)	84.9 ± 10.3^{x}	83.6 ± 11.3	81.1 ± 8.7	82.7 ± 11.2
HOMA-IR	2.7 ± 2.3^{x}	2.6 ± 2.4	2.3 ± 1.8	3.3 ± 4.7^{a,x}
CRP (mg/L)	1.7 ± 1.9	2.1 ± 2.2	2.5 ± 2.3^{x}	2.5 ± 2.3
Adiponectin (μg/mL)	7.5 ± 3.5^{a}	6.9 ± 5.5	10.3 ± 4.6^{a,x}	8.2 ± 4.2^{x}
EGFR (mL/[min 1.73 m^2])	90.8 ± 15.3	96.7 ± 20.7	92.2 ± 21.3	108.2 ± 22.9^{a,x}

Race-sex difference (adjusted for age): the superscript *a* (for race) and *x* (for sex) denote higher ($P < .05$) value compared with other race or sex.

waist circumference (women only), MAP, HDL-C (men only), insulin (women only), HOMA-IR (women only), and EGFR (women only) and lower low-density lipoprotein cholesterol (LDL-C) (women only), TG, TC/HDL-C ratio, and adiponectin. Men vs women displayed higher waist circumference (whites only), MAP, TG, TC/HDL-C ratio, and glucose (whites only) and lower HDL-C (whites only), insulin (blacks only), CRP (whites only), adiponectin, and EGFR (blacks only). Furthermore, white men and black women had higher HOMA-IR than their counterparts.

Mean and selected percentiles of HbA_{1c} in the study cohort by race and sex are given in Table 2. Blacks vs whites and women vs men had significantly higher values.

Table 3 shows trends of CV risk factor variables (adjusted for age, race, sex, and smoking status) by quartiles of HbA_{1c}. Significant adverse trends were noted for BMI, waist, LDL-C, HDL-C, TC/HDL-C ratio, insulin, glucose, and HOMA-IR across HbA_{1c} quartiles. Trends were not significant for TG, MAP, CRP, adiponectin, and EGFR.

The independent multivariate relationship between HbA_{1c} and CV risk factor variables is presented in Table 4. Significant independent predictors of HbA_{1c} in both model 1 (without waist circumference) and model 2 (with waist circumference) were black race, female sex, and TC/HDL-C ratio. In addition, HOMA-IR entered as predictor variable in model 1. However, waist replaced HOMA-IR as an independent predictor in model 2. Overall, the identified predictor variables in model 1 and model 2 accounted for 5.7% and 6.3% of the variance in HbA_{1c}, respectively.

Fig. 1 illustrates the relationship between prevalence of excess HbA_{1c} (top decile) and status (yes/no) of metabolic syndrome, and parental histories of CV disease and type 2 diabetes mellitus in the study cohort. Prevalence of excess HbA_{1c} was 1.6-fold higher among those with metabolic syndrome ($P < .05$), 2.1-fold ($P < .001$) higher among those with positive parental history of CV disease, and 1.5-fold ($P < .05$) higher among those with parental type 2 diabetes mellitus.

Table 2
Mean and percentile distribution of HbA_{1c} in young adults by race and sex

	Mean ± SD * (%)	Selected percentiles						
		5th	10th	25th	50th	75th	90th	95th
White men	5.7 ± 0.4	5.1	5.3	5.5	5.7	6.0	6.2	6.3
Black men	5.8 ± 0.4	5.0	5.2	5.6	5.8	6.0	6.2	6.3
White women	5.8 ± 0.3	5.2	5.4	5.6	5.8	6.0	6.2	6.3
Black women	5.9 ± 0.4	5.4	5.5	5.7	5.9	6.1	6.5	6.7
Total sample	5.8 ± 0.4	5.2	5.3	5.6	5.8	6.0	6.2	6.4

* $P < .0001$ for comparison of blacks vs whites and men vs women, adjusted for age and race (or sex).

4. Discussion

This community-based study provides normative distribution of HbA_{1c} by race and sex in nondiabetic black and white younger adults, and demonstrates that excess HbA_{1c} relates to metabolic syndrome trait and positive parental histories of CV disease and type 2 diabetes mellitus. It is noteworthy that these observations are based on an apparently "healthy" cohort, free of selection bias.

The observed race (blacks > whites) difference in HbA_{1c} levels in the study cohort is in agreement with an earlier report [6]. The excess in HbA_{1c} in blacks vs whites, although modest and within reference range, may reflect their adverse profile of parameters related to glucose homeostasis such as insulin sensitivity, secretion, and clearance in childhood and adulthood, and higher prevalence of type 2 diabetes mellitus [14-17]. The black-white difference in HbA_{1c} noted in this study was independent of measures of body fatness and insulin resistance, known correlates of HbA_{1c} [6,7,18]. Whether genetic or other factors related to HbA_{1c} metabolism could account for this racial divergence is not known. With respect to sex difference, previous studies have found no difference [6,7,19]; however, women vs men displayed higher HbA_{1c} in the current study, independent of measures

Table 3
Trends of CV risk factor variables by HbA_{1c} level in young adults

Variable (mean ± SD)	Quartile of HbA_{1c} (range, %)				
	1 (4.5-5.5), n = 273	2 (5.6-5.7), n = 288	3 (5.8-5.9), n = 273	4 (6.0-6.9), n = 277	*P* for trend*
BMI (kg/m^2)	27.9 ± 6.3	28.9 ± 6.9	28.9 ± 6.4	30.6 ± 7.8	.0002
Waist (cm)	90.4 ± 16.2	92.4 ± 17.0	93.4 ± 16.7	94.9 ± 17.7	.0001
MAP (mm Hg)	91.1 ± 10.9	90.8 ± 10.6	91.1 ± 10.3	92.1 ± 11.4	.380
LDL-C (mg/dL)	123.2 ± 35.3	122.9 ± 32.6	126.7 ± 34.6	125.5 ± 33.5	.020
HDL-C (mg/dL)	49.1 ± 14.5	48.4 ± 14.2	46.5 ± 12.9	47.5 ± 12.8	.0003
TG (mg/dL)	129.9 ± 96.8	129.1 ± 87.5	131.0 ± 101.4	118.8 ± 82.6	.524
TC/HDL-C ratio	4.2 ± 1.5	4.2 ± 1.4	4.4 ± 1.4	4.3 ± 1.3	.0002
Insulin (μU/mL)	11.7 ± 9.9	12.0 ± 8.7	12.0 ± 8.3	14.1 ± 16.9	.013
Glucose (mg/dL)	82.6 ± 10.3	82.7 ± 8.9	81.4 ± 9.5	84.9 ± 11.4	.011
HOMA-IR	2.5 ± 2.6	2.5 ± 2.0	2.5 ± 1.9	3.1 ± 4.0	.006
CRP (mg/L)	2.1 ± 2.1	2.2 ± 2.2	2.3 ± 2.3	2.2 ± 2.3	.924
Adiponectin (μg/mL)	8.9 ± 5.2	9.0 ± 4.6	8.4 ± 4.2	8.4 ± 3.8	.283
EGFR (mL/[min $1.73m^2$])	91.9 ± 18.3	94.6 ± 21.8	96.9 ± 20.1	97.2 ± 22.4	.088

* Adjusted for age, race, sex, and smoking (yes/no).

of body fatness and insulin resistance. The reason(s) for the discrepancy between studies is not clear.

Besides race and sex, TC/HDL-C ratio and waist circumference, measures related to metabolic syndrome [12,20], were independent correlates of HbA_{1c} in this study cohort. Although insulin resistance/hyperinsulinemia is pathologically linked to dysglycemia, the observed increases in HbA_{1c} appear to be mediated primarily through excess body fatness because HOMA-IR was no longer significant when waist circumference was introduced in the multivariate regression model. Because obesity is commonly linked to insulin resistance and the compensatory hyperinsulinemia [21], it may as well play a role as an initiating factor in the development of dysglycemia. This is consistent with our earlier observations showing a temporal association between the degree of baseline adiposity and the incidence of hyperinsulinemia in children, adolescents, and younger adults alike, independent of baseline insulin level [22], and childhood obesity rather than insulin resistance as a powerful predictor for developing metabolic syndrome in young adulthood [23].

Table 4
Predictors of HbA_{1c} in young adults

Predictors	Standardized coefficient	
	Model 1	Model 2
Race (black > white)	0.16 §	0.16 §
Sex (female > male)	0.14 ‡	0.16 §
TC/HDL-C ratio	0.11 †	0.10 †
HOMA-IR	0.11 †	
Waist		0.11 *
Model R^2 (%)	5.8	6.3

Model 1: age, race, sex, smoking (yes/no), MAP, TC/HDL-C ratio, HOMA-IR, CRP, adiponectin, and EGFR.
Model 2: model 1 + waist.
* $P < .05$.
† $P < .01$.
‡ $P < .001$.
§ $P < .0001$.

In studies including the present one, the predictor variables associated with higher HbA_{1c} accounted for only 3% to 7% of its variance among persons without diabetes [6,7]. Although not examined in the present study, hematologic factors, known correlates of HbA_{1c} metabolism [24], were found to contribute little to its variance in healthy population [7]. Whether genetic factors may be involved in the physiological differences in HbA_{1c} metabolism among persons without diabetes is not known.

Based on the association between HbA_{1c} and metabolic syndrome in nondiabetic first-degree relatives of persons with type 2 diabetes mellitus, excess HbA_{1c} has been proposed as a surrogate for the syndrome [18]. In the current study, prevalence of excess (top decile) HbA_{1c} was significantly associated with metabolic syndrome and with positive parental history of CV disease and type 2 diabetes mellitus. Because metabolic syndrome, CV disease, and type 2 diabetes mellitus all have a strong genetic and familial

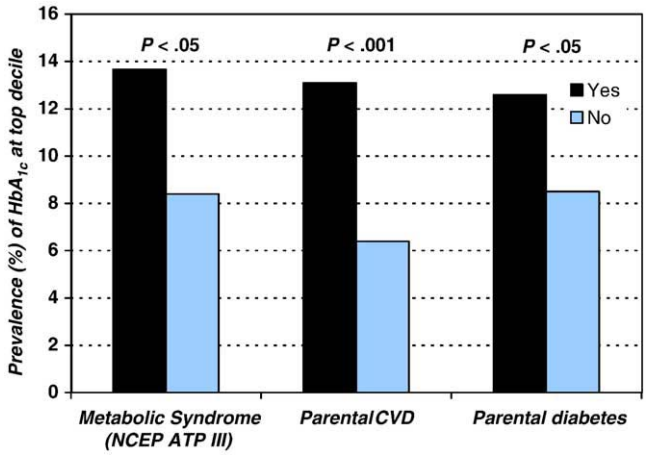

Fig. 1. Prevalence of excess HbA_{1c} (top decile) by status (yes/no) of metabolic syndrome and by parental histories of CV disease and type 2 diabetes mellitus in younger adults. The Bogalusa Heart Study.

component, a positive parental history is recognized as a surrogate indicator of risk in the offspring [25-27]. Furthermore, metabolic syndrome is a strong predictor of CV disease and type 2 diabetes mellitus [28,29]. Taken together, it appears that excess HbA_{1c} within reference range may be a biomarker of risk for developing these conditions.

In this study, HbA_{1c} was not associated with the inflammation-related markers CRP and adiponectin either in bivariate or multivariate analysis. Earlier studies conducted mainly in middle-aged and older adults having type 2 diabetes mellitus and other CV comorbidities showed an association between HbA_{1c} and CRP [30,31]. It should be mentioned, however, that in one study levels increased with HbA_{1c} only among persons with diabetes having HbA_{1c} level greater than 9% [32]; in another study of persons without diabetes, this relationship disappeared after adjustment for body fatness [30]. With respect to adiponectin, no previous data are available for comparison. It is likely that the lack of association of HbA_{1c} with CRP and adiponectin in this study cohort may be due to their younger age and nondiabetic status.

As limitations, this study lacks direct measurements of postchallenge glucose and in vivo insulin action and secretion used in clinical and etiologic studies. Instead, we used well-established simple surrogate measures that are applicable to population studies. Reported parental medical histories were not verified in this study cohort. However, nonsystematic misclassification of self-reported histories would most likely result in an underestimation of the true differences between the groups. Furthermore, because of lack of dietary intake data, this study did not address the known role of diet, in particular calcium, magnesium, and glycemic index of carbohydrates, in the regulation of glucose homeostasis and related risk of obesity, CV disease, and type 2 diabetes mellitus [33-38]. Finally, this study is cross-sectional and observational in nature and cannot address the issue of causality or pathophysiological mechanisms.

In summary, excess HbA_{1c} within reference range is adversely associated with metabolic syndrome and parental histories of CV disease and type 2 diabetes mellitus in nondiabetic, apparently healthy younger adults. These findings underscore the potential value of HbA_{1c} in risk assessments of CV disease and type 2 diabetes mellitus in younger adults. Additional population-based studies are obviously needed to develop consensus regarding cutoff points to define risk status in this age group.

Acknowledgment

The Bogalusa Heart Study is a joint effort of many investigators and staff members, whose contributions are gratefully acknowledged. We are especially grateful to the study participants.

Supported by grants AG16592 from the National Institute on Aging and 0555168B from the American Heart Association.

References

[1] Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233-40.

[2] Brownlee M. Glycation and diabetic complications. Diabetes 1994;43: 836-41.

[3] Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care 2002;25:275-8.

[4] Meigs JB, Nathan DM, Cupples LA, Wilson PW, Singer DE. Tracking of glycated hemoglobin in the original cohort of the Framingham Heart Study. J Clin Epidemiol 1996;49:411-7.

[5] Meigs JB, Nathan DM, D'Agostino Sr RB, Wilson PW. Fasting and post-challenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care 2002;25:1845-50.

[6] Saaddine JB, Fagot-Campagna A, Rolka D, Narayan KM, Geiss L, Eberhardt M, et al. Distribution of HbA(1c) levels for children and young adults in the U.S.: Third National Health and Nutrition Examination Survey. Diabetes Care 2002;25:1326-30.

[7] Simon D, Senan C, Garnier P, Saint-Paul M, Papoz L. Epidemiological features of glycated haemoglobin A1c distribution in a healthy population. The Telecom Study. Diabetologia 1989;32:864-9.

[8] The Bogalusa Heart Study 20th Anniversary Symposium. Am J Med Sci 1995;310(Suppl 1):S1-S138.

[9] Srinivasan SR, Berenson GS. Serum lipoproteins in children and methods for study. In: Lewis LA, editor. Handbook of electrophoresis. Boca Raton (Fla): CRC Press; 1983. p. 185-204.

[10] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

[11] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247-54.

[12] Jeppesen J, Facchini FS, Reaven GM. Individuals with high total cholesterol/HDL cholesterol ratio are insulin resistant. J Intern Med 1998;243:293-8.

[13] Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

[14] Haffner S, Howard R, Mayer B, Bergman RN, Savage PJ, Rewers M, et al. Insulin sensitivity and acute insulin responses in African Americans, non-Hispanic whites and Hispanics and NIDDM: the Insulin Resistance and Atherosclerosis Study. Diabetes 1997;46:63-9.

[15] Arslanian SA. Metabolic differences between Caucasian and African-American children and the relationship to type 2 diabetes mellitus. J Pediatr Endocrinol Metab 2002;15(suppl 1):509-17.

[16] Jiang X, Srinivasan SR, Radhakrishnamurthy B, et al. Racial (black-white) differences in insulin secretion and clearance in adolescents: the Bogalusa Heart Study. Pediatrics 1996;97:357-60.

[17] Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. JAMA 2000;283:2253-9.

[18] Osei K, Rhinesmith S, Gaillard T, Schuster D. Is glycosylated hemoglobin A1c a surrogate for metabolic syndrome in nondiabetic, first-degree relatives of African-American patients with type 2 diabetes? J Clin Endocrinol Metab 2003;88:4596-601.

[19] Forrest RD, Jackson CA, Yudkin JS. Glucose tolerance and glycohaemoglobin: a population study of male-to-female ratios. Diabet Med 1987;4:322-4.

[20] Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.

[21] Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000; 106:473-81.
[22] Srinivasan SR, Myers L, Berenson GS. Temporal association between obesity and hyperinsulinemia in children, adolescents, and young adults: the Bogalusa Heart Study. Metabolism 1999;48:928-34.
[23] Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. Diabetes 2002;51:204-9.
[24] Smith RJ, Koenig RJ, Binnerts A, Soeldner JS, Aoki TT. Regulation of hemoglobin AIc formation in human erythrocytes in vitro. Effects of physiologic factors other than glucose. J Clin Invest 1982;69: 1164-8.
[25] Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. Am J Epidemiol 1981;113:144-56.
[26] Barrett-Connor E, Khaw K. Family history of heart attack as an independent predictor of death due to cardiovascular disease. Circulation 1984;69:1065-9.
[27] Chen W, Srinivasan SR, Elkasabany A, Berenson GS. The association of cardiovascular risk factor clustering related to insulin resistance syndrome (syndrome X) between young parents and their offspring: the Bogalusa Heart Study. Atherosclerosis 1999;145:197-205.
[28] Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. Diabetes Care 2003;26:3153-9.
[29] Wilson PWF, D'Agostino RB, Parise H, Suillivan L, Beigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066-72.
[30] Gustavsson CG, Agardh CD. Markers of inflammation in patients with coronary artery disease are also associated with glycosylated haemoglobin A1c within the normal range. Eur Heart J 2004;25: 2120-4.
[31] Wu T, Dorn JP, Donahue RP, Sempos CT, Trevisan M. Associations of serum C-reactive protein with fasting insulin, glucose, and glycosylated hemoglobin: the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol 2002;155:65-71.
[32] King DE, Mainous AG, Buchanan TA, Pearson WS. C-reactive protein and glycemic control in adults with diabetes. Diabetes Care 2003;26: 1535-9.
[33] Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287: 2414-23.
[34] Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE, et al. Magnesium intake and risk of type 2 diabetes in men and women. Diabetes Care 2004;27:134-40.
[35] Barbagallo M, Dominguez LJ, Galioto A, Ferlisi A, Cani C, Malfa L, et al. Role of magnesium in insulin action, diabetes and cardiometabolic syndrome X. Mol Aspects Med 2003;24:39-52.
[36] Rosolová H, Mayer Jr O, Reaven GM. Insulin-mediated glucose disposal is decreased in normal subjects with relatively low plasma magnesium concentrations. Metabolism 2000;49:418-20.
[37] Jacqmain M, Doucet E, Després JP, Bouchard C, Tremblay A. Calcium intake, body composition, and lipoprotein-lipid concentrations in adults. Am J Clin Nutr 2003;77:1448-52.
[38] Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care 2006;29:650-6.