

Using Glycosylated Hemoglobin to Define the Metabolic Syndrome in United States Adults

KWOK LEUNG ONG, MPHIL¹
ANNETTE W.K. TSO, MD^{1,2}
KAREN S.L. LAM, MD^{1,2}

STACEY S. CHERNY, PHD^{3,4}
PAK CHUNG SHAM, MD^{3,4,5}
BERNARD M.Y. CHEUNG, PHD^{1,2}

OBJECTIVE — To compare the use of GHb and fasting plasma glucose (FPG) to define the metabolic syndrome (MetS).

RESEARCH DESIGN AND METHODS — Data from the U.S. National Health and Nutrition Examination Survey 1999–2006 were used. MetS was defined using the consensus criteria in 2009. Raised blood glucose was defined as either FPG ≥ 100 mg/dl (5.6 mmol/l) or GHb $\geq 5.7\%$.

RESULTS — In 2003–2006, there was 91.3% agreement between GHb and FPG when either was used to define MetS. The agreement was good irrespective of age, sex, race/ethnicity, BMI, and diabetes status ($\geq 87.4\%$). Similar results were found in 1999–2002. Among subjects without diabetes, only the use of GHb alone, but not FPG, resulted in significant association with cardiovascular diseases (odds ratio 1.45, $P = 0.005$).

CONCLUSIONS — Using GHb instead of FPG to define MetS is feasible. It also identifies individuals with increased cardiovascular risk.

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The metabolic syndrome (MetS) describes the clustering of closely related cardiovascular risk factors (1). The definition of MetS, proposed in 2001 by the National Cholesterol Education Program (NCEP) Expert Panel (2), was later modified in accordance with the revised definition of impaired fasting glucose from the American Diabetes Association (ADA) in 2004 (1,3). Recently, a unified definition of MetS was proposed jointly by several organizations in 2009 (4), while ADA proposed the use of GHb in the definition of diabetes and the category of increased diabetes risk (which also includes impaired fasting glucose and impaired glucose tolerance) in 2010 (5). Therefore, we investigated whether GHb can be used instead of fast-

ing plasma glucose (FPG) in identifying individuals with MetS.

RESEARCH DESIGN AND METHODS

Data from the cross-sectional U.S. National Health and Nutrition Examination Survey (NHANES) 2003–2006 were used in initial analysis (6). For confirmation, we used the cross-sectional data from NHANES 1999–2002. All participants gave informed consent, and the study received approval from the Centers for Disease Control and Prevention Institutional Review Board.

MetS was defined using the consensus criteria in 2009 (4). Under this definition, a person has MetS if he or she meets three or more of the following criteria: 1) central obesity, defined using

ethnic-specific cut points of waist circumference, 2) triglycerides ≥ 150 mg/dl (1.7 mmol/l), 3) HDL cholesterol < 40 mg/dl (1.0 mmol/l) in men and < 50 mg/dl (1.3 mmol/l) in women, 4) blood pressure $\geq 130/85$ mmHg or on antihypertensive medication, or 5) raised blood glucose, defined as FPG ≥ 100 mg/dl (5.6 mmol/l) or on antidiabetic medication. For non-Hispanic whites and blacks, and people of other races and mixed races, the cut points for waist circumference were ≥ 94 cm in men and ≥ 80 cm in women. For Mexican Americans and other Hispanics, the cut points were ≥ 90 cm in men and ≥ 80 cm in women. In a separate analysis, MetS was defined using the NCEP criteria, which were the same as the consensus criteria in 2009 (4), except that central obesity was defined as waist circumference ≥ 102 cm in men and ≥ 88 cm in women (1,3). The uses of GHb $\geq 5.7\%$ or FPG ≥ 100 mg/dl in the definition of the glycemic component of MetS were compared. Agreement between two definitions was defined as the percentage of participants who were classified the same under both definitions (7,8).

The laboratory methods have been described in detail elsewhere (6,8–11). Data on GHb and FPG were adjusted so that measurements across survey periods could be combined (6). History of cardiovascular diseases was obtained from self-reported questionnaires. Statistical analysis was performed using the complex samples function of SPSS version 15.0 (SPSS, Chicago, IL). Fasting sampling weights were used in all analyses to adjust for oversampling and nonresponse bias and to approximate the distribution to the U.S. population in the year 2000.

RESULTS — After excluding pregnant women and subjects with missing data in BMI, GHb, and the five components of MetS, there were 3,551 and 3,412 participants aged ≥ 20 years in NHANES 1999–2002 and 2003–2006, respectively, who had fasted for 8–24 h.

As shown in Table 1, in NHANES 2003–2006, the use of GHb alone resulted in a lower percentage of people meeting the glycemic criteria of MetS

From the ¹Department of Medicine, University of Hong Kong, Hong Kong, China; the ²Research Centre of Heart, Brain, Hormone and Healthy Aging, University of Hong Kong, Hong Kong, China; the ³Department of Psychiatry, University of Hong Kong, Hong Kong, China; the ⁴State Key Laboratory of Brain and Cognitive Sciences, University of Hong Kong, Hong Kong, China; and the ⁵Genome Research Centre, University of Hong Kong, Hong Kong, China.

Co-corresponding authors: Annette W.K. Tso, awtkto@hku.hk and Bernard M.Y. Cheung, mycheung@hku.hk. Received 30 January 2010 and accepted 12 May 2010. Published ahead of print at <http://care.diabetesjournals.org> on 26 May 2010. DOI: 10.2337/dc10-0190

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Table 1—Prevalence of MetS based on the consensus criteria in 2009 and its glycemic component, using different definitions for raised blood glucose, in NHANES 2003–2006

	MetS			Raised blood glucose		
	(1) FPG ≥ 100 mg/dl, GHb $\geq 5.7\%$, or on medication	(2) FPG ≥ 100 mg/dl or on medication	(3) GHb $\geq 5.7\%$ or on medication	(1) FPG ≥ 100 mg/dl, GHb $\geq 5.7\%$, or on medication	(2) FPG ≥ 100 mg/dl or on medication	(3) GHb $\geq 5.7\%$ or on medication
Overall	41.1 \pm 1.2	38.8 \pm 1.3	34.8 \pm 0.9*	43.2 \pm 1.7†	36.4 \pm 1.7	24.9 \pm 0.9‡
Age (years)						
20–39	23.1 \pm 1.5	21.8 \pm 1.6	18.4 \pm 1.3	22.9 \pm 1.4	19.2 \pm 1.5	9.2 \pm 0.8‡
40–59	45.2 \pm 1.7	43.3 \pm 1.8	38.2 \pm 1.5*	47.3 \pm 2.6	40.3 \pm 2.5	25.9 \pm 1.6‡
≥ 60	64.3 \pm 2.2	59.7 \pm 2.1	56.3 \pm 2.1	70.1 \pm 2.0‡	58.6 \pm 2.0	49.4 \pm 2.1†
Sex						
Male	43.1 \pm 1.3	41.5 \pm 1.4	35.4 \pm 1.2‡	48.8 \pm 2.0*	42.9 \pm 2.1	24.8 \pm 1.1‡
Female	39.2 \pm 1.9	36.1 \pm 1.9	34.2 \pm 1.7	37.7 \pm 1.9†	30.0 \pm 1.7	24.9 \pm 1.3*
Race/ethnicity						
Non-Hispanic white	42.0 \pm 1.7	40.1 \pm 1.8	35.0 \pm 1.3*	41.8 \pm 2.3	36.1 \pm 2.2	22.0 \pm 1.2‡
Non-Hispanic black	39.8 \pm 1.5*	35.2 \pm 1.5	35.3 \pm 1.5	49.0 \pm 2.1‡	35.0 \pm 1.9	38.3 \pm 1.8
Mexican American	41.0 \pm 2.3	38.0 \pm 2.3	35.4 \pm 1.7	45.2 \pm 3.1	36.9 \pm 3.4	29.0 \pm 2.1*
Other	36.0 \pm 3.3	33.0 \pm 3.2	31.7 \pm 3.8	45.7 \pm 3.2	39.9 \pm 3.4	29.0 \pm 3.8*
BMI (kg/m ²)						
<25.0	12.7 \pm 1.1	11.5 \pm 1.0	10.1 \pm 1.0	26.2 \pm 2.1*	20.6 \pm 1.9	12.9 \pm 1.3‡
25.0–29.9	44.1 \pm 2.6	41.9 \pm 2.6	36.3 \pm 1.9	44.3 \pm 2.3	38.5 \pm 2.4	23.3 \pm 1.3‡
≥ 30.0	66.3 \pm 1.1*	62.7 \pm 1.4	57.6 \pm 1.6*	58.8 \pm 1.5‡	49.8 \pm 1.8	38.2 \pm 1.5‡
Diabetes						
No	36.3 \pm 1.3	33.8 \pm 1.4	29.5 \pm 1.0†	37.1 \pm 1.8†	29.8 \pm 1.8	17.2 \pm 0.7‡
Yes	86.3 \pm 2.2	86.0 \pm 2.2	85.1 \pm 2.3	100.0 \pm 0.0	98.9 \pm 0.6	96.7 \pm 1.2
Agreement between definitions (2) and (3)	91.3 \pm 0.7	94.0 \pm 0.8	91.0 \pm 1.1	90.6 \pm 0.7	98.5 \pm 0.7	95.7 \pm 1.6

All data are weighted to the U.S. population and are expressed as % \pm SEM. Diabetes was defined as GHb $\geq 6.5\%$, FPG ≥ 126 mg/dl, or on antidiabetic medication. $n = 3,412$. * $P < 0.05$, † $P < 0.01$, and ‡ $P < 0.001$ compared with the use of FPG ≥ 100 mg/dl or on medication.

compared with the use of FPG alone, with 74.9% agreement between these two definitions. The use of GHb alone also resulted in a lower prevalence of MetS compared with the use of FPG alone (Table 1). The use of both GHb and FPG resulted in an insignificant increase in the prevalence compared with the use of FPG alone (41.1 vs. 38.8%, $P = 0.200$). There was 91.3% agreement between the use of GHb alone and the use of FPG alone. The agreement was good irrespective of age, sex, race/ethnicity, and BMI. The same trends were found in NHANES 1999–2002 or when the NCEP definition was used (see supplementary Tables A1 and A2, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc09-0190/DC1>).

Because there is controversy whether the diagnosis of MetS conveys additional meaning in subjects with diabetes who should already be aggressively treated due to high cardiovascular risk, a subgroup without diabetes (non-DM) was also examined. Similar to the overall cohort, in the non-DM group, the use of GHb alone resulted in lower prevalence of MetS compared with FPG alone, with 90.6% agreement (Table 1). Importantly, in this non-DM subgroup, only the use of GHb alone, but not FPG, resulted in significant association with cardiovascular diseases (odds ratio 1.45, $P = 0.005$) when the consensus criteria in 2009 was used to define MetS (supplementary Table A3).

CONCLUSIONS— The controversy regarding the definition of MetS has been addressed recently in a joint scientific statement (4). GHb reflects the average blood glucose level over several months, and its measurement does not require a fasting blood sample. In this study, we demonstrated that there was good agreement between GHb and FPG in identifying individuals with MetS, despite only a moderate agreement ($\sim 75\%$) between GHb and FPG in defining raised blood glucose. The components of MetS are inter-correlated; therefore, a certain degree of inaccuracy or fluctuation in one component is tolerated and does not result in misclassification. The agreement between GHb and FPG in the definition of MetS is good in different subgroups. We can therefore confidently conclude that using GHb instead of FPG to define MetS is feasible. This is true at least for Americans, based on the most up-to-date data on a nationally representative sample of Americans, and was confirmed using historical

data. It remains to be seen if our conclusions are also applicable to Asians, among whom the prevalence of raised blood glucose is likely to be different.

The current cut point of GHb identifies a slightly smaller group of people as having MetS. However, it also identifies subjects at high risk for cardiovascular diseases, even in those without diabetes, when the consensus criteria in 2009 are used to define MetS. Whether GHb results in better risk stratification needs to be investigated in large prospective studies.

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