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Original article

# Comparison of glycated hemoglobin with fasting plasma glucose in definition of glycemic component of the metabolic syndrome in an Iranian population

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ABSTRACT

*Aims:* The aim of this study was to compare the utility of glycated hemoglobin (GHb) versus the fasting plasma glucose (FPG) in definition of glycemic component of the metabolic syndrome (MetS) in a non-diabetic Iranian population.

*Methods:* A cross-sectional study of first-degree relatives (FDRs) of patients with type 2 diabetes was conducted from 2003 to 2005. A total of 2410 non-diabetic FDRs of consecutive patients with type 2 diabetes 30–60 years old were examined. All subjects underwent a standard 75 g 2-h oral glucose tolerance test and GHb measurement. Consensus criteria in 2009 were used to identify MetS. Glycemic component of MetS was defined as either FPG $\geq$ 100 mg/dl or GHb $\geq$ 5.7%. The mean (SD) age of participants was 43.6 (6.5) years.

*Results:* The prevalence of MetS was 33.5% (95% confidence interval (CI): 31.6, 35.4) based on FPG criterion alone and 28.6% (95% CI: 26.8, 30.4) based on GHb criterion alone. Use of combination of both criteria increased the prevalence of MetS (36.7%; 95% CI: 34.8, 38.6). There was 88.7% (95% CI: 87.5, 90.0) agreement between the GHb and FPG when either was used to define MetS ($\kappa$ coefficient = 0.737).

*Conclusions:* These data indicate that using GHb may be an acceptable surrogate of FPG to define glycemic component of MetS.



## 1. Introduction

Metabolic syndrome (MetS), a clustering of factors that occur together more often than by chance alone, is an important clinical and public health problem worldwide and poses a significant risk for cardiovascular disease and type 2 diabetes [1]. Several clinical definitions have been proposed by different organizations over the past 15 years [2,3]. In 2009, a unified definition of MetS was proposed by several organizations [1] and consists of three of the five components, including elevated waist circumference, elevated triglycerides and reduced high density lipoprotein cholesterol (HDL), elevated blood pressure and fasting glucose, in which insulin resistance plays a key pathogenic role. This new definition considers that abdominal obesity is not an obligatory component of MetS. In 2010, the American Diabetes Association (ADA) has recommended the use of the glycated hemoglobin (GHb) to diagnose pre-diabetes and diabetes [4]. These changes in the definition of raised plasma glucose have prompted a few authors to use of a GHb criterion instead of the FPG in the definition of MetS. While use of GHb instead of FPG in definition of MetS has been described in only four studies from United States [5], Europe [6,7] and Asia [8], comprehensive data for Middle East populations have not been reported.

The objective of this study, therefore, was to assess the use of GHb instead of FPG in definition of glycemic component of the MetS in a non-diabetic Iranian population.

Racial disparities in GHb values and MetS exist [9–12]. The reason for ethnic differences are not clear but can be ascribed to differences in rates of obesity, hypertension, glucose intolerance, and body fat distribution patterns. Therefore, at an ethnological level, the study contributes by characterizing the occurrence of MetS based on FPG and/or GHb criteria in a specific population from central Iran.

## 2. Subjects and methods

Our sample comprised 3176 (818 men and 2358 women) first-degree relatives (FDRs) for a consecutive sample of patients with type 2 diabetes attending clinics in Isfahan Endocrine and Metabolism Research Center affiliated to Isfahan University of

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Medical Sciences, Iran, between 2003 and 2005. Participants with diabetes mellitus ($n = 504$) were excluded because there is controversy whether the diagnosis of MetS convey additional meaning in individuals with diabetes who should already be aggressively treated due to high cardiovascular risk. Those with no GHb measured ($n = 262$) were also excluded from the study; 2410 (620 men and 1790 women) subjects were included in analysis of the utility of GHb and FPG in definition of glycemic component of the MetS. The study protocol was approved by the Institutional Review Board of Isfahan University of Medical Sciences, Iran, and an informed consent form was signed by each participant.

### 2.1. Procedures

Details of the recruitment, anthropometric measurements and laboratory methods have been described in detail elsewhere [13,14]. In summary, the FDRs of patients with type 2 diabetes included siblings or children and reported to clinics in the morning after an overnight fast. Height and weight were measured with subjects in light clothes and without shoes using standard apparatus. Waist was measured midway between the lower rib margin and the iliac-crest at the end of a gentle expiration. Hip circumference was measured over the greater trochanters directly over the underwear. Body mass index (BMI) (weight/height$^2$ [kg/m$^2$]) is recognized as the measure of overall obesity. Resting blood pressure (BP) was measured after subjects had been seated for 10 min by using a mercury sphygmomanometer and appropriately sized cuffs, using standard techniques. Those participants with plasma glucose (PG) $\geq$200 mg/dl were considered as diabetic. If fasting plasma glucose (FPG) was $\geq$126 and $<$200 mg/dl, a second FPG was measured on another day. If the second FPG was also $\geq$126 mg/dl, participants were considered as diabetic. Subjects with FPG $<$ 126 mg/dl underwent a standard oral glucose tolerance test [OGTT (75 g glucose 2-h)] according to the ADA criteria [4]. Venous blood was sampled 0, 30, 60, and 120 min after oral glucose administration. Plasma glucose $\geq$200 mg/dl at 2 h in OGTT were also considered diabetic.

Glycated hemoglobin (GHb) (measured by ion-exchange chromatography), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol (measured using standardized procedures), and low-density lipoprotein (LDL) cholesterol (calculated by the Friedewald equation [15]: LDL = (total cholesterol − HDL − triglyceride)/5, for total triglycerides less than 400 mg/dl) were assessed.

Cases of MetS were identified according to the consensus criteria released in 2009 [1], which was the same as the third report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [12]. It was considered present when at least three of the following characteristics were observed: central obesity, defined using ethnic-specific cut points of waist (waist circumference $\geq$102 cm in men and $\geq$88 cm in women); triglycerides $\geq$ 150 mg/dl; HDL $<$ 40 mg/dl in men and $<$50 mg/dl in women; blood pressure (BP) $\geq$130/85 mmHg or on antihypertensive medication, or raised plasma glucose, defined as FPG $\geq$ 100 mg/dl. We compared the use of GHb $\geq$ 5.7% versus the FPG $\geq$ 100 mg/dl in the definition of the glycemic component of MetS. With the use of GHb in definition of glycemic component of the MetS, we follow the ADA recommendations that established a cut-off point of $\geq$5.7% [16]. Agreement between two definitions was the percentage of individuals who were classified the same under both definitions.

### 2.2. Statistical analysis

Statistical methods used included the Student's $t$-test; chi squared test, analysis of variance or Kruskal–Walis tests for normally or non-normally distributed continuous variables respectively and general linear model. Age-, gender-adjusted means were calculated and compared using general linear models with Bonferroni correction for multiple comparisons. The $\kappa$ statistic was calculated as a measure of agreement between the two definitions of the MetS using the FPG and/or GHb, respectively. Analyses were performed using SPSS version 13 for Windows (SPSS Inc., Chicago, IL, USA). All tests for statistical

**Table 1**
Age and age-, gender-adjusted mean and proportion characteristics of non-diabetic first-degree relatives of patients with type 2 diabetes by diagnosis of metabolic syndrome according to fasting plasma glucose, glycated hemoglobin or both.

| Characteristic | No MetS using either FPG or GHb | MetS using FPG only | MetS using GHb only | MetS using both FPG or GHb |
|---|---|---|---|---|
| Number (%) | 1526 (63.3) | 808 (33.5) | 690 (28.6) | 885 (36.7) |
| Age (yr.) | 42.2 (0.17) | 44.4 (0.23) | 44.4 (0.25) | 44.5 (0.22)*** |
| Height (cm) | 159.2 (0.15) | 159.7 (0.20) | 160.0 (0.22) | 159.7 (0.19)* |
| Weight (kg) | 70.1 (0.29) | 79.4 (0.39) | 80.1 (0.42) | 79.1 (0.38)*** |
| Waist circumference (cm) | 85.6 (0.22) | 94.4 (0.29) | 94.9 (0.32) | 94.2 (0.28)*** |
| Hip circumference (cm) | 105.4 (0.22) | 111.4 (0.30) | 111.6 (0.33) | 111.2 (0.29)*** |
| Waist-to-hip ratio | 0.81 (0.001) | 0.85 (0.002) | 0.85 (0.002) | 0.85 (0.002)*** |
| Body mass index (kg/m$^2$) | 27.7 (0.10) | 31.2 (0.14) | 31.3 (0.15) | 31.0 (0.13)*** |
| Fasting plasma glucose (mg/dl) | 93.2 (0.29) | 100.3 (0.40)***[a] | 96.9 (0.43) | 99.3 (0.38)*** |
| Plasma glucose 30 min (mg/dl) | 137.7 (0.82) | 151.6 (1.12)**[a] | 147.1 (1.22) | 150.0 (1.08)*** |
| Plasma glucose 60 min (mg/dl) | 137.7 (1.05) | 161.2 (1.44) | 157.5 (1.55) | 159.7 (1.38)*** |
| Plasma glucose 120 min (mg/dl) | 111.5 (0.83) | 123.5 (1.13) | 121.4 (1.22) | 123.1 (1.08)*** |
| Glycated hemoglobin (%) | 4.9 (0.02) | 5.2 (0.03) | 5.4 (0.03)***[b] | 5.3 (0.03)*** |
| Cholesterol (mg/dl) | 195.5 (1.00) | 204.7 (1.35) | 203.4 (1.46) | 203.8 (1.29)*** |
| LDL (mg/dl) | 121.1 (0.89) | 122.0 (1.21) | 120.9 (1.32) | 121.5 (1.16) |
| HDL (mg/dl) | 48.7 (0.28) | 40.8 (0.38) | 40.0 (0.41) | 41.0 (0.36)*** |
| Triglyceride (mg/dl) | 132.4 (2.72) | 220.1 (3.67) | 223.5 (4.00) | 216.7 (3.51)*** |
| Systolic BP (mm Hg) | 110.6 (0.41) | 122.6 (0.56) | 123.7 (0.60) | 121.9 (0.53)*** |
| Diastolic BP (mm Hg) | 71.3 (0.31) | 80.2 (0.41) | 81.4 (0.45) | 80.0 (0.40)*** |
| Obesity (BMI $\geq$ 30), no. (%) | 352 (23.5) | 467 (58.1) | 408 (59.7) | 492 (56.0)*** |
| Women, no. (%) | 1123 (73.7) | 621 (76.9) | 527 (76.4) | 667 (75.4) |

Age-, gender adjusted means were calculated using general linear models with Bonferroni correction for multiple comparisons. Data are express as mean (SE) or number (%). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ comparison across all four groups. [a]***$P < 0.001$, [a]**$P < 0.01$ the difference in the mean of the variables compared FPG-alone group with GHb-alone. [b]***$P < 0.001$. The difference in the mean of the variables compared GHb-alone group with FPG-alone. IGT: impaired glucose tolerance, LDL: low density lipoprotein cholesterol, and HDL: high density lipoprotein cholesterol.

significance were two-tailed, confidence intervals (CI) were set at 95% and $P < 0.05$ was considered significant.

## 3. Results

The characteristics of the study participants by MetS are shown in Table 1. In age-, gender-adjusted comparisons of variables, those who had MetS using all three approaches (the two criteria used individually, and combined) were older and had higher age-adjusted mean weight, height, BMI, waist circumference, waist-hip ratio, and hip circumference, FPG, PG at 30, 60 and 120 min, triglyceride, cholesterol and had lower mean HDL. As expected, those who had MetS using FPG-alone criterion had higher FPG ($P < 0.001$) and plasma glucose at 30 min ($P < 0.01$) than those with MetS using GHb-alone criterion. Those who had MetS using GHb-alone criterion had higher GHb than in those with MetS using FPG-alone criterion ($P < 0.001$). The mean (SD) age of participants was 43.6 (6.5) years and 74.3% were women. The age, gender-adjusted mean (SD) GHb was 5.2% (0.8) for those with MetS using FPG criterion only and 5.4% (0.9.) for those with MetS using GHb criterion only ($P < 0.001$).

Of the 2410 participants (620 men and 1790 women), 808 had MetS using FPG criterion only and 690 had MetS using GHb criterion only and 855 had MetS using both FPG or GHb criteria. Overall prevalence of MetS using FPG criterion was 33.5% (95% CI: 31.6, 35.4) (30.2% in men and 34.7% in women). The prevalence of MetS using GHb criterion was significantly lower (28.6%; 95% CI: 26.8, 30.4) (26.3% in men and 29.4% in women) than that found using the FPG criterion ($P < 0.001$). Using combination of the two criteria increased the prevalence of MetS (36.7%; 95% CI: 34.8, 38.6 (35.2% in men and 37.3% in women). The agreement level between using FPG alone and GHb alone was 88.7% (95% CI: 87.5, 90.0) ($\kappa$ coefficient = 0.737). Under FPG-alone criterion but not the GHb criterion, 8.1% of participants had the MetS, and 3.2% of participants had MetS under the GHb criterion but not the FPG criterion. The agreement level between using FPG alone and combine GHb and FPG was 96.8% (95% CI: 96.0, 97.5) ($\kappa$ coefficient = 0.930). The agreement level between using GHb alone and combine GHb and FPG was 91.9% (95% CI: 90.8, 93.0) ($\kappa$ coefficient = 0.817).

Prevalence of MetS using all three approaches (the two criteria used individually, and combined) was higher in women than men, but its difference was not statistically significant, except using FPG criterion only ($P < 0.05$). The prevalence of MetS increased with age with the use of either or both criteria (data not shown).

## 4. Discussion

In this cross-sectional study of non-diabetic FDRs of patients with type 2 diabetes, prevalence of MetS using GHb alone was significantly lower than that obtained when FPG criterion was used, although good agreement (88.7%) was evident when either criterion was used to define glycemic component of the MetS.

To the best of our knowledge, there are only four studies which investigate the usefulness of GHb in definition of glycemic component of the MetS and present study add valuable information to the existing literature. In a study by Ong et al. [5], in the US National Health and Nutrition Examination survey data, the agreement between the GHb and FPG criteria when either was used to define MetS in non-diabetic subjects was 90.6%. Kim et al. [8] in a large cross-sectional study of non-diabetic Korean population reported that the agreement between the GHb and FPG criteria was 90.2%. Succurro et al. [6] reported that in 774 non-diabetic, Italian subjects, a 90.9% agreement existed between the use of GHb and the FPG for diagnosis of the MetS. Another study from Spain [7] also found good agreement between MetS and use of GHb and FPG criteria ($\kappa$ coefficient = 0.80). Our findings support the conclusion made by other studies [5–8] that a good agreement existed between the use of GHb and the FPG for diagnosis of the MetS and elevated GHb level of $\geq$5.7% can be consider as an acceptable surrogate marker for glycemic component in definition of MetS.

Similar to US National Health and Nutrition Examination survey data [5] and Kim et al. study [8] we found that the use of the GHb criterion alone resulted in a lower prevalence of MetS compared with the use of the FPG criterion alone. The combine use of FPG and GHb criteria increased the prevalence of MetS. These results are contradictory to findings of two other studies [6,7] in European populations that showed the use of the GHb criterion alone resulted in a higher prevalence of MetS compared with the use of the FPG criterion alone. The discrepancies between these studies could be attributed to differences in ethnicity, age, and gender distribution of study populations and/or study methodology. The finding of lower prevalence of MetS using the GHb criterion is in line with the findings of our previous study [17] and others [18], which show that the incidence of pre-diabetes and diabetes using GHb values was lower than that yield by use of the FPG values.

Even though FPG and GHb criteria had good agreement in our study, GHb is superior in clinical practice because it is a simple test and does not need fasting state. The reason that the GHb criterion is inferior to the FPG criterion for defining MetS is because, the existence of hemoglobin or red cell abnormalities can increase the variability of GHb values. This variability may contribute to its inferior definition of MetS when compared with the FPG criterion. In addition, FPG and GHb may reflect different aspects of glucose metabolism. While GHb can reflect a variety of factors in glucose metabolism FPG levels largely depend upon insulin resistance and hepatic glucose production [19].

Our study sample was addressed to individuals at increased risk of MetS, cardiovascular disease and type 2 diabetes, because they had FDRs with the disease and it might be explained by the differences in levels of other risk factors. This group of individuals will only increase further over time as the prevalence of diabetes and MetS is expected to increase worldwide. Different studies have found that the incidence and prevalence of MetS, cardiovascular disease and type 2 diabetes is greater in those persons who have a family history of the disease [20–26].

Another finding that requires further elaboration is the non-significant higher prevalence of MetS in women by all of the criteria. This may be due to chance or higher prevalence of obesity or lower physical activity in women. The prevalence of obesity and abdominal obesity was found to be higher among women than men, and the difference was more evident in abdominal obesity. This may be due to genetic predisposition of Iranian women, lower smoking rates, high fertility rates, high illiteracy rates, high caloric intake or differences in epigenetic programming of Iranian women. The increased MetS in women could possibly be associated with parity, since childbearing has been suggested to be an important contributor to the development of obesity [27–30]. Other study suggest that weight gain by women in pregnancy leads to retaining weight [30], which would operate physiologically to lead to greater maternal obesity in addition to any influences of the parental role. In our study, however, we could not investigate the relationship between MetS and childbearing, since data on parity were not available. These results may also be explained by differences in physical activity. Iranian women may have less physical activity than men because of limited outdoor activities due to specific climatic and/or social conditions.

The strengths of the present study include the sample consisting of both men and women of a wide age range from an Iranian population, simultaneous assessment of FPG and plasma

glucose during a standard OGTT and GHb, and information on cardio-metabolic risk factors. More importantly, the present study is the first study in high-risk non-diabetic individuals to examine the use of the GHb criterion to define MetS in Middle East. This study also had some limitations. Most notably, the cross-sectional nature of our study did not provide insight into the time course of the development of MetS; therefore, no conclusions regarding the cause-effect relation or pathophysiological mechanisms can be made. In addition, the present findings were derived only from a specific population from central Iran, and the results could vary as a function of ethnic group. Previous studies have shown that racial disparities in GHb values and MetS exist [9–12]. Whether our findings could be extrapolated to non-diabetic subjects who are not genetically predisposed to diabetes or other racial and ethnic populations remains to be elucidated.

In conclusion, these data provides further evidence that using GHb and FPG criteria classify more or less the same groups of individuals as having MetS and GHb may be an acceptable surrogate of FPG to define glycemic component of MetS in FDRs of patients with type 2 diabetes. Further cohort studies are needed to better understand the role of GHb in definition of glycemic component of the MetS.

## Conflict of interest

None.

## Authors contributions

Janghorbani M conceived and designed the study, analyzed the data and wrote the manuscript, Amini M, recruited samples and contributed to discussion and revision of the manuscript and obtained funding for the Isfahan Diabetes Prevention Study.

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