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Original article

Elevated fasting glucose levels within normal range are associated with an increased risk of metabolic syndrome in older women

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ABSTRACT

Objective: The prevalence of cardiovascular disease (CVD) and metabolic syndrome (MetS) increases with increasing fasting plasma glucose (FPG) levels in an elderly population with pre-diabetes or diabetes. However, it remains unknown whether the relationship between elevated FPG and increased risks of MetS exists in older women with normoglycemia (FPG < 100 mg/dL). Therefore, the present study was conducted to fill the lack of information in that area.

Materials and methods: We included 6505 apparently healthy women, aged 65 years and older, with normoglycemia who participated in routine health checkups at health screening centers in Taiwan. Components of MetS (FPG, waist circumference (WC), high-density lipoprotein cholesterol (HDL-C), triglycerides, and systolic/diastolic blood pressure), body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), total cholesterol, and percentage body fat (PBF) were examined in all subjects.

Results: Subjects were sub-grouped by FPG levels (<90 mg/dL, 91–95 mg/dL and >95 mg/dL for group 1, group 2 and group 3, respectively). Subjects in group 2 and group 3 were 1.22-fold ($P = 0.017$) and 1.25-fold ($P = 0.007$) more likely to have MetS compared with those in group 1. Age, WC, BMI, PBF, systolic and diastolic blood pressure, total cholesterol, triglycerides, and HDL-C were significantly correlated with FPG, whereas HDL-C was negatively correlated with FPG. In a multivariate stepwise regression analysis, PBF, LDL-C, triglycerides, and age were significantly and independently associated with FPG.

Conclusion: Among older women, the risk of MetS was significantly associated with elevated FPG even for subjects with normal FPG. Lifestyle interventions for reducing PBF and controlling dyslipidemia could help reduce the risk of MetS in this population.

1. Introduction

Together, hypertension, hyperglycemia, dyslipidemia, and obesity contribute to an increased incidence of cardiovascular disease (CVD) and diabetes. As such, the World Health Organization (WHO) and National Cholesterol Education Program (NCEP) defined metabolic syndrome (MetS) as a separate entity in 1998 and 2001, respectively [1,2]. Through defining MetS as an independent entity, the WHO and NCEP aimed to better identify subjects at a high risk for CVD and diabetes and thus initiate preventive and interventional strategies at an earlier stage. Consequently, several studies have recently focused on MetS. Several other MetS definition had been proposed by the American Association of Clinical Endocrinologists (AACE) and international diabetes federation (IDF). However, the central concept of the definition was the same including central obesity, high blood pressure (BP), fasting plasma glucose (FPG) level and dyslipidemia. Therefore, a global consensus of the MetS definition had been held and the latest definition of MetS was proposed [3].

Due to the Westernized lifestyle of those in Taiwan, the incidence of type 2 diabetes (T2D) has increased dramatically [4]. Insulin resistance and impaired insulin secretion are important underlying causes of T2D, and both insulin sensitivity and secretion progressively decline with age [5]. Not surprisingly, the incidences of pre-diabetes and T2D increase concomitant with an elevation in FPG in older people [6]. T2D is a cardiovascular disease (CVD) equivalent and imparts

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a 2 to 3-fold increased risk for developing CVD [7]. This increased risk for CVD is established for those with well-documented diabetes and may also apply to those with pre-diabetes. Barzilay et al. reported that the prevalence of CVD increased with increasing glucose levels in an elderly population and that the prevalence of CVD is 77% and 68% in older men and women with pre-diabetes, respectively [8]. Notably, these studies typically divided their study cohorts into 3 groups: normoglycemic, pre-diabetic, and diabetic. Therefore, it remains controversial whether the relationship between elevated FPG and increased risks of CVD exists in subjects with normal glucose tolerance [9,10]. Several studies have shown that young or middle-aged adults with elevated FPG had a higher risk of developing diabetes [11,12]. However, aside from the risk of developing diabetes, the other components of MetS have not been investigated to date. In older subjects, the risk of MetS or T2D is expected to be higher than in younger populations. Therefore, the present study investigated whether increased FPG can increase the risk of MetS despite being within the normal range among a cohort of older women.

2. Materials and methods

2.1. Study population

The data were collected from the MJ Health Screening Centers' database in Taiwan from 1999 to 2008. MJ Health Screening Centers are privately-owned clinics located throughout Taiwan that provide regular health examinations to their members. All study participants were kept anonymous, and informed consent was obtained from all participants. Data were provided by MJ Health Screening Center for research purposes only, and the study protocol was approved by the institutional review board of MJ Health Screening Center and Tri-Service General Hospital.

We randomly selected 25,609 women who were aged 65 years and older and visited the MJ Health Screening Centers in Taiwan for routine health checkups. 12,763 subjects with a history of diabetes, hypertension, hyperlipidemia, and cardiovascular disease and those taking medications for these diseases or medications known to affect components of MetS were excluded from our analysis. Additional 5942 subjects with fasting glucose levels >100 mg/dL and 426 subjects with fasting glucose levels <80 mg/dL were excluded. A total of 6505 women were eligible for analysis.

Because there is a positive correlation between age and FPG [6,13], we expected that grouping subjects according to FPG alone might result in age stratification. This would distort the statistical analyses, because the incidence of MetS in a given group could be attributable to age rather than FPG itself. To address this problem, we grouped participants first by age and then by FPG. The age range of subjects in this study was 65 to 89 years. As a result, 25 age groups were generated. Within each age group, subjects were divided into 3 sub-groups based on FPG (low, intermediate, and high FPG). Finally, all FPG sub-groups across the age groups were pooled together to form a new larger group. Thus, the 6505 subjects were divided into 3 groups of approximately equal number. Group 1 contained 25 groups of subjects with the lowest FPG compared with others within the same age group. Group 2 and group 3 were formed in the same way and included subjects with intermediate and high FPG, respectively.

2.2. Anthropometric measurements and general data

Members of the senior nursing staff used a questionnaire first to obtain the subjects' medical history, including any current medications. A thorough history taking and complete physical examinations were performed by physicians. Body weight and height were measured by an auto-anthropometer, Nakamura KN-5000A (Nakamura, Tokyo, Japan). Body weight was measured to the nearest 0.1 kg while the subjects were barefoot and wearing light indoor clothing. Body height was recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference (WC) was measured at the midway point between the inferior margin of the last rib and the crest of the ilium in a horizontal plane and was recorded to the nearest 0.1 cm. BP was measured twice on the right arm with the subject in a sitting position after 5 min of rest using a computerized auto-mercury-sphygmomanometer, Citizen CH-5000 (Citizen, Tokyo, Japan). The 2 measurements were taken at 10 min intervals. The mean of these two readings was used in the analysis. Percentage body fat (PBF) was evaluated using a body composition analyzer, TANITA (Nakamura, Tokyo, Japan), which uses a patented 'foot-to-foot' pressure contact electrode bioelectrical impedance analysis technique [14]. PBF, as calculated by TANITA, is a highly researched proprietary formula combining impedance and weight measurements with height, gender, and age information.

2.3. Laboratory measurements

After a 10-hour fast, subjects' blood samples were drawn from the antecubital vein for biochemical analysis. Plasma was separated from blood within 1 h, stored at −70 °C, and analyzed for FPG and lipid profiles. FPG was detected using the glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Springs Instruments, Yellow Springs, OH). Total cholesterol (TC) and triglycerides were measured using the dry multilayer analytical slide method in a Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentrations were analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation.

2.4. Definition of metabolic syndrome

The latest harmonized criteria of MetS in 2009 [3] with some modification were used: WC cutoff of ≥80 cm for women was applied for Taiwanese [15], an elevated triglyceride level (≥150 mg/dL), a reduced HDL-C level (<50 mg/dL for women), elevated BP (≥130 mm Hg systolic BP or ≥85 mm Hg diastolic BP), and an elevated FPG concentration (≥100 mg/dL). All subjects were normoglycemic; therefore, subjects had to have at least 3 of the other 4 criteria to be diagnosed with MetS.

2.5. Statistical analysis

The data are presented as means ± standard deviation unless indicated otherwise. Glucose concentration was recorded as an integer; therefore, numerous subjects had the same glucose concentrations and were categorized within the same tertile. As such, the numbers within the tertiles varied slightly. A one-way ANOVA using the Bonferroni test as a post-hoc test was applied to determine differences in continuous variables between the tertile groups. The age and triglyceride level were not normally distributed and were therefore logarithmically transformed before analysis. Logistic regression analysis was used to calculate odds ratios (ORs) for an increased risk of MetS or abnormal MetS components between the 3 groups. Correlations between FPG and each metabolic risk factor were evaluated using Pearson correlations. Multivariate stepwise regression analysis was further applied to identify which of the significant MetS components were independent risk factors for FPG. WC, BMI, systolic BP, TC, and HDL-C were excluded from the final model. A two-sided P-value < 0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics 18.0 software (SPSS Inc., Chicago, IL).

3. Results

In total, 6505 women between the ages of 65 and 89 years with normal FPG (<100 mg/dL) were enrolled in this study. The mean age of the study population was 69.4 ± 4.2 years. The subjects were divided into tertiles according to FPG levels. Group 1 had the lowest FPG, and group 3 had the highest. Characteristics of the study subjects in each group are presented in Table 1. WC, BMI, PBF, diastolic BP, TC, and LDL-C were significantly higher in groups 2 and 3 than in group 1. HDL-C levels were significantly higher in group 1 than in the other 2 groups.

Table 2 shows the prevalence and ORs of MetS and abnormal MetS components in the 3 groups. Among all study subjects, 17.0% (1103) met the criteria for MetS. Group 3 had significantly higher ORs for abnormal WC, triglycerides, HDL-C, and BP than did group 1. Subjects in group 2 and group 3 had a 1.22-fold (P = 0.017) and 1.25-fold (P = 0.007) higher likelihood of having MetS compared with those in group 1, respectively.

Age, WC, BMI, PBF, systolic and diastolic BP, TC, triglycerides, and HDL-C were significantly correlated with FPG, whereas HDL-C was negatively correlated with FPG (Table 3). To evaluate which of these 10 factors had an independent relationship with FPG, we used a multivariate stepwise regression analysis (Table 4). PBF, LDL-C, triglycerides, and age were significantly and independently associated with FPG. Notably, neither BMI nor WC was independently associated with FPG in the final stepwise regression model.

4. Discussion

In the current study, we tried to demonstrate the relationship between FPG within normal limit and MetS itself and components. The results showed that groups 2 and 3 had 1.22- and 1.25-times higher risks of MetS than group 1, respectively. This suggests that the risk of MetS increases with increasing FPG even within the normal range in older women. Our study is the first to investigate these relationships in this specific age group with the unique grouping method and provides new information for understanding the role of FPG in the development of MetS.

Some studies in older non-diabetic individuals have indicated that high FPG levels are significantly associated with an increased risk of developing CVD [9,10,16–19]. However, most of these studies were conducted in subjects who were classified as having pre-diabetes or normoglycemia [16,17,19]. Only the Guangzhou Biobank Cohort Study [15] analyzed the relationships between risk factors of CVD and FPG in subjects with normoglycemia. The results indicated that CVD risk factors consistently increased with increasing FPG even in the normoglycemic range. However, there remain differences between the Guangzhou Biobank Cohort Study and the current study. First, the Guangzhou Biobank Cohort Study enrolled subjects who were using medication for hypertension and dyslipidemia at the time of the study. These drugs could have interfered with the evaluation of the relationship between FPG and MetS components. In our study, subjects using such medications were excluded. Although our more stringent exclusion criteria may have provided more accurate information, we expect that we underestimated the extent of the relationships. Another limitation of the Guangzhou Biobank Cohort Study was that they did not adjust for a potential age effect on MetS components. This is crucial, since age is positively correlated with increased FPG [6,13]. If the effect of age was not removed from the analysis, it would be difficult to determine whether the results were attributable to age or FPG itself. In our study, we used a special classification method to control the effect of age on the results. Although not totally novel, our unique methods should provide more accurate and important information regarding the relationship between FPG and MetS. The J-shaped CVD risk curve of FPG has been observed in various studies [20,21]. However, this phenomenon is not present in the current study. Based on our exclusion criteria, the extreme end of the disease was not included. For example, there will be little chances to have newly diagnosed diabetes with severe complications. Moreover, this is a cross-sectional study that the J-shaped CVD risk curve would be much harder to be demonstrated.

Previous analyses have established that WC is an independent determinant of PFG among a normoglycemic older population [18].

Table 1
Biochemical and anthropometric parameters of study subjects.

Characteristics	Total	Group 1	Group 2	Group 3
Number of subjects	6505	2168	2168	2169
Age (years)	69.5 ± 4.2	69.5 ± 4.2	69.5 ± 4.2	69.5 ± 4.2
WC (cm)	77.3 ± 8.3	76.6 ± 8.3	77.3 ± 8.4[a]	77.9 ± 8.0[a]
BMI (kg/m^2)	23.4 ± 3.3	23.1 ± 3.2	23.4 ± 3.4[a]	23.6 ± 3.2[a]
BFM (%)	30.3 ± 6.7	29.7 ± 6.7	30.4 ± 6.8[a]	30.9 ± 6.4[a]
Systolic BP (mm Hg)	134 ± 20	132 ± 19	133 ± 20	136 ± 20[a,b]
Diastolic BP (mm Hg)	74 ± 11	73 ± 11	73 ± 11[a]	75 ± 11[a,b]
FPG (mg/dL)	93 ± 5	87 ± 3	94 ± 1[a]	98 ± 1[a,b]
Total cholesterol (mg/dL)	210 ± 38	207 ± 38	211 ± 37[a]	213 ± 38[a]
Triglycerides (mg/dL)	120 ± 68	118 ± 74	118 ± 61	123 ± 66[a,b]
HDL-C (mg/dL)	61 ± 16	62 ± 17	61 ± 16[a]	61 ± 16[a]
LDL-C (mg/dL)	125 ± 33	122 ± 33	127 ± 34[a]	128 ± 33[a]

Data are shown as mean ± standard deviation.
BMI = body mass index, BFM = body fat mass, BP = blood pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol.
[a] P < 0.05 versus group 1.
[b] P < 0.05 versus group 2.

Table 2
Prevalence and odds ratios (95% CI) for each component of metabolic syndrome among groups classified by fasting plasma glucose level.

	Prevalence (%) ORs (95% CI)		
	Group 1	Group 2	Group 3
Metabolic syndrome	15.2	17.9	18.2
	1 (Ref)	1.22 (1.04–1.43)[a]	1.25 (1.06–1.46)[b]
WC ≧ 80 cm	33.5	36.7	39.0
	1 (Ref)	1.15 (1.01–1.30)[a]	1.27 (1.12–1.43)[b]
TG ≧ 150 mg/dL	21.2	22.1	24.3
	1 (Ref)	1.05 (0.91–1.22)	1.19 (1.03–1.37)[a]
HDL-C < 50 mg/dL	23.3	25.2	25.9
	1 (Ref)	1.11 (0.96–1.27)	1.15 (1.00–1.32)[a]
SBP ≧ 130 mm Hg or	54.9	57.2	64.6
DBP ≧ 85 mm Hg	1 (Ref)	1.10 (0.97–1.24)	1.49 (1.32–1.69)[b]

CI, confidence interval; ORs, odds ratios; Ref, reference; WC, waist circumference; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a] P < 0.05.
[b] P < 0.01.

Table 3
Pearson correlation coefficients (r) of fasting plasma glucose with other metabolic parameters.

Parameters	r	P value
Age (year)[a]	0.036	0.002
WC (cm)	0.062	<0.001
BMI (kg/m^2)	0.066	<0.001
PBF (%)	0.079	<0.001
Systolic BP (mm Hg)	0.062	<0.001
Diastolic BP (mm Hg)	0.077	<0.001
Total cholesterol (mg/dL)	0.060	<0.001
Triglycerides (mg/dL)[a]	0.074	<0.001
HDL-C (mg/dL)	−0.044	<0.001
LDL-C (mg/dL)	0.070	<0.001

WC, waist circumference; BMI, body mass index; PBF, percentage body fat; BP, blood pressure; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol.
[a] Data were log-transformed for the analysis.

Table 4
Multivariate stepwise regression analysis for fasting plasma glucose as the dependent variable.

Independent variables	B[a] (95% CI)	P value
Age (year)[b]	7.281 (2.725–11.838)	0.002
PBF (%)	0.037 (0.018–0.055)	<0.001
Triglycerides (mg/dL)[b]	1.162 (0.556–1.767)	<0.001
LDL-C (mg/dL)	0.008 (0.004–0.011)	<0.001

Variables entered in the model for stepwise regression analyses: age, waist circumference, body mass index, PBF, systolic BP, diastolic BP, total cholesterol, triglycerides, HDL-C, LDL-C.
PBF, percentage body fat; BP, blood pressure; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.
[a] B values indicate regression coefficients in the equation.
[b] Data were log-transformed for the analysis.

However, the present data demonstrated that adiposity, as indicated by PBF, is more strongly associated with FPG than is BMI or WC in older Taiwanese women. There are several possible explanations for this observation. First, skeletal muscle mass decreases and body fat increases with age. For the same BMI or WC, older adults generally have more fat and less muscle mass than young adults [22]. Moreover, older women have significantly greater amounts of total body fat than do older men at an equivalent BMI [22]. Second, aging is associated with height loss, so BMI in older people may be overestimated and may not represent true adiposity [23]. Third, Gallagher et al. [24] found that PBF in older women was significantly associated with insulin resistance and glucose intolerance independently of WC and BMI. Therefore, it is not surprising that PBF, rather than WC or BMI, was independently correlated with FPG in the present study.

Our results showed that FPG has a positive correlation with LDL-C within the normal range. We cannot conclude that FPG has direct effect in LDL-C. However, decreasing LDL-C particle size and increasing LDL-C concentration were seen in subjects from insulin sensitivity to T2D [25]. Lipoprotein(a) (Lp(a)) which is an important cardiovascular risk factor had been proposed [26,27]. Oxidized Lp(a) may be more potent in atherosclerotic pathophysiology than native Lp(a). Increased blood glucose concentrations can induce oxidative modification of lipoproteins. Therefore, Saely et al. [26] found that the CVD predictive value of Lp(a) was more strong in nondiabetic patients than in patients with T2D. Lp(a) and FPG were significantly and positively correlated with oxidized Lp(a) independently after adjustment [26]. Kotani et al. [26] further demonstrated that increased FPG may enhance the oxidization of Lp(a) even at normal glucose levels. The correlation between hypertriglyceridemia and insulin resistance (IR) has been discussed extensively [28,29]. The United Kingdom Prospective Diabetes Study showed that TG was approximately 60 mg/dL higher in those who had progressed from IR into new-onset T2D than in age-matched non-T2D population [30]. In the DECODE study, positive relationship was shown between FPG and TG when FPG is in normal range [31]. Our study has similar finding and implies that FPG even in normal range progresses with IR.

Elevated FPG is mainly a result of hepatic glucose production that occurs in the setting of impaired insulin secretion and hepatic insulin insensitivity [32]. Both insulin sensitivity and secretion progressively decline with age [5]. Indeed, age was independently associated with increased PFG in the current study. The relationship between PFG and dyslipidemia can also be explained by insulin resistance-related deranged lipoprotein metabolism, including increased secretion of triglyceride-rich lipoprotein [33,34], enhanced production of LDL-C, and enhanced clearance of HDL-C by the kidney [35]. The current study showed that HDL-C was significantly associated with FPG by Pearson correlation analysis. This significant association, however, disappeared after multiple regression analysis, suggesting that HDL-C might be linked with PFG via other factors, such as age or adiposity. Future studies are needed to test this hypothesis.

Until now, there has been a paucity of evidence to suggest that lowering PFG from the high end of normal to the low end or middle range of normal would be beneficial among older women. The present study provided an opportunity for the medical community to reconsider the role of the normoglycemic range. It also suggests that improving adiposity could help reduce FPG and CVD risk in an older population.

However, we must note that the study included only older women. Thus, extrapolating these findings to other age groups, especially those below 65 years, should be done with caution, as there might be different relationships between FPG and MetS in younger adults. Similarly, the results of this study might be different in men, since sex can also influence CVD risk [36,37]. Next, all of the subjects included in this study were among the Chinese Han population in Taiwan. The role of FPG in MetS might be different in other ethnic groups. Moreover, our study population may not represent the general population, not only because of the strict exclusion criteria but also because the subjects in health checkup center may belong to higher social economic status. Finally, this cross-sectional study had less power compared to a longitudinal study. Future studies employing a follow-up design might be helpful to confirm the present findings.

In conclusion, advanced age, increased body fat, hypertriglyceridemia, and hyper-LDL cholesterolemia were independent determinants of FPG in older women with normoglycemia. The risk of CVD was significantly associated with elevated FPG, even when FPG remained within the normal range.

Learning points

- Among older women, the risk of MetS was significantly associated with elevated FPG even for subjects with normal FPG. Lifestyle interventions for reducing PBF and controlling dyslipidemia could help reduce the risk of MetS in this population.

Conflict of interests

There were no conflict of interest by all authors in the current study.

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