Relatively low sex hormone-binding globulin concentration is a risk factor for hyperuricemia in middle-aged Japanese men

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Summary
Objective: Low testosterone and hyperuricemia are associated with metabolic syndrome (MetS). However, little is known about the nature of the relationships between serum testosterone and sex hormone-binding globulin (SHBG) concentrations, and hyperuricemia.

Methods: We evaluated the relationships between serum testosterone (calculated bioavailable testosterone [cbT], calculated free testosterone [cFT], SHBG, and total testosterone [TT]) and metabolic indices, including serum uric acid, in 363 Japanese males (mean age 51.1 ± 8.7 years) at routine health examinations.

Results: Participants with hyperuricemia (≥7.0 mg/dL) demonstrated lower adiponectin, cbT, cFT, SHBG, and TT, but a higher MetS prevalence and higher values of various MetS-related parameters than those without hyperuricemia (<7.0 mg/dL). Binary regression analysis revealed that less than 52 nmol/L SHBG, less than 5.0 μg/mL serum adiponectin, greater than or equal to 7.0 g/dL total protein, and greater than or equal to 1.0 mg/dL creatinine were statistically significant risk factors for hyperuricemia. Receiver operating characteristic analysis confirmed that less than 46.5 nmol/L (area under the curve [AUC] = 0.645) SHBG and less than 3.68 μg/mL (AUC = 0.691) adiponectin concentrations were significant risk factors for hyperuricemia.

Conclusions: We provide evidence that low SHBG provides an important marker for hyperuricemia in middle-aged Japanese men. This finding provides clinical evidence that low SHBG is closely associated with MetS, which is often accompanied with hyperuricemia.

KEYWORDS
Adiponectin, sex-hormone-binding globulin, testosterone, uric acid
1 | INTRODUCTION

Uric acid is a final product in purine metabolism, being produced in the liver and excreted mainly through the kidneys, but also via the intestine. Approximately two-thirds of uric acid is produced endogenously, and the remaining third is derived from purines abundant in the diet. Abnormalities in uric acid metabolism and its decreased excretion by the kidneys are the major causes of hyperuricemia and gout development. Hyperuricemia is a well-known comorbidity of metabolic syndrome (MetS).

Key factors explaining the relationship between MetS and hyperuricemia are thought to be ectopic fat accumulation and insulin resistance. Hyperinsulinemia caused by insulin resistance is thought to cause greater reabsorption of uric acid, as well as sodium, in the renal proximal tubule, via urate transporter. In addition, in obese patients with visceral fat accumulation, activation of the pentose phosphate pathway and lipogenesis in the liver is likely to be accompanied by an upregulation of de novo purine synthesis and uric acid production.

As serum uric acid concentration rises, the prevalence of MetS has been shown to increase. Furthermore, as the number of components of MetS increases, serum uric acid concentrations also increase. Indeed, visceral fat mass has been reported to show a positive correlation with serum uric acid levels and a negative correlation with uric acid clearance.

The relationship between testosterone and uric acid is complicated. A higher testosterone concentration is likely to lead to hyperuricemia, because the greater muscle mass caused by testosterone action is associated with the suppression of uric acid excretion, as shown mainly by testosterone replacement therapy in patients with female-to-male gender dysphoria. However, hyperuricemia is also associated with chronic inflammation and ectopic fat accumulation, which are considered to be mediated via lower testosterone levels.

Total testosterone (TT) is an index that combines free T (FT), albumin-bound T (25-65%), bioavailable T, and sex hormone-binding globulin (SHBG)-bound T (35-75%), which contains the majority of T. Men with MetS and type 2 diabetes mellitus (T2DM) were found to exhibit low testosterone levels. Also, low SHBG was reported to be a predictor of non-alcoholic fatty liver disease (NAFLD) in both men and women. Meta-analysis revealed that serum FT and TT levels were associated with MetS in men and that SHBG levels correlated with MetS in both men and women.

Previously, TT was found to be the optimum serum testosterone parameter for use as an index of MetS in middle-aged Japanese men. Other research showed that hyperinsulinemia reduced SHBG, the largest fraction of TT, resulting in a decreased TT concentration. Low concentrations of bioactive serum testosterone were also correlated with MetS in men. Because TT measurements would include the reductions in both bioactive T and SHBG associated with MetS, it was considered that TT would provide the most sensitive indicator of MetS.

Although both low serum endogenous testosterone and hyperuricemia are associated with MetS, the nature of the relationship between these parameters has not been established. To date, a single report has indicated that gonadal dysfunction defined by low TT was negatively correlated with hyperuricemia in T2DM, and there have been no specific studies of the relationship between hyperuricemia and SHBG.

Hence, the current study examined the hypothesis that hyperuricemia is associated with various serum testosterone indicators, including SHBG, in healthy males.

2 | MATERIALS AND METHODS

2.1 | Participants

The first 684 participants that visited for a medical check were recruited at the Department of Preventive Medicine Iizuka Hospital. Excluded subjects included 163 women and 60 men taking drugs for diabetes mellitus and/or hyperlipidemia. The subjects taking antihypertensive medications were not excluded, because they were only considered to be hypertensive, even if their blood pressure was normal on the day of the medical check. All serum hormones targeted in this study were measured in 365 of the remaining 461 male subjects. None of these 365 participants were taking drugs for hyperuricemia. Two subjects lacked body measurement data and were also excluded. The remaining 363 asymptomatic male participants with a mean age of 51.1 ± 8.7 years (mean ± standard deviation [SD]) were analysed. The protocol of this study was approved by the Institutional Review Boards of Iizuka Hospital and Fukuoka University Hospital and complied with the principles of the Declaration of Helsinki.

2.2 | Anthropometric and serum measurements and calculations

Collected anthropometric data included body weight and height used to calculate body mass index (BMI) and waist circumference. Blood pressure (BP) was also measured.

Blood samples were collected from fasted participants in the morning and assayed to determine the index related to glucose metabolism (fasting blood glucose [FBG], fasting immunoreactive insulin [F-IRI], and glycohemoglobin [HbA1c]) and lipid profiles (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], serum triglycerides [TGs], and total cholesterol [TC]). The homeostasis model assessment of insulin resistance (HOMA-R) was calculated as [F-IRI [μU/mL] × FBG [mmol/L]]/22.523 and was used as an index of insulin sensitivity. Beta cell function (HOMA-β) was calculated as [F-IRI [μU/mL] × 20]/[FBG [mmol/L] − 3.5]23 and was used as a functional index of insulin secretion. Blood samples were also used to measure serum T concentrations in its various forms: calculated bioavailable testosterone (cFT), calculated free testosterone (cFT), SHBG, and TT.
The diagnosis of MetS in men followed international (International Diabetes Federation [IDF], 2009 version) and domestic (Japanese) criteria. For MetS diagnosis using IDF criteria, three or more of the following five items were required: (a) waist circumference greater than or equal to 90 cm, (b) serum TG greater than or equal to 150 mg/dL, (c) HDL-C less than 40 mg/dL, (d) serum FBG greater than or equal to 100 mg/dL, and (e) systolic and/or diastolic BP (SBP/DBP) greater than or equal to 130/85 mmHg. The diagnosis of MetS using Japanese criteria required a waist circumference of greater than or equal to 85 cm and two or more of the following three items: (a) serum TG greater than or equal to 150 mg/dL and/or HDL-C less than 40 mg/dL, (b) FBG greater than or equal to 110 mg/dL, and (c) SBP and/or DBP greater than or equal to 130/85 mmHg.

3 | RESULTS

The clinical characteristics of all 363 participants and comparisons of the values for participants with hyperuricemia (serum uric acid ≥ 7.0 mg/dL) (N = 74, 20.4%) and without hyperuricemia (serum uric acid < 7.0 mg/dL) (N = 289, 79.6%) are shown in Table 1. The mean serum uric acid concentration of the cohort was 5.97 ± 1.21 mg/dL. MetS was diagnosed in 96 (26.4%) and 85 (23.4%) men using the IDF and Japanese criteria, respectively.

Significantly higher albumin, alanine aminotransferase (ALT) activity, aspartate aminotransferase (AST) activity, BMI, creatinine, DBP, FBG, F-IRI, gamma-glutamyl transferase (γGTP), HOMA-R, HOMA-β, SBP, serum total protein, TG, waist circumference, and number of individuals with MetS were found in the [uric acid] greater than or equal to 7.0 mg/dL group than in the [uric acid] less than 7.0 mg/dL group. In contrast, lower adiponectin, cFT, HDL-C, serum TT, and SHBG were found in the [uric acid] greater than or equal to 7.0 mg/dL group compared with the [uric acid] less than 7.0 mg/dL group. There was no difference in the serum concentration of 25-(OH)VD3 between the two groups.

The clinical data with and without MetS, defined with IDF criteria, are shown in Table 2. As expected, participants with MetS had significantly higher BP (SBP and/or DBP), BMI, γ-GTP, serum ALT and AST, TG, waist circumference, and uric acid than those without MetS. Furthermore, as previously reported, participants with MetS had significantly lower serum adiponectin, cBT, cFT, SHBG, and TT concentrations than those without MetS.

The relationships between the various serum testosterone values, uric acid concentration, and metabolic indices are shown in Table 3. Uric acid concentration and all of the testosterone values showed weak inverse correlations with BMI, SBP, and waist circumference. Serum SHBG, TT, and uric acid concentrations showed inverse correlations with adiponectin and TG. In addition, HOMA-β, HOMA-R, and insulin showed inverse correlations with all of the testosterone values, but not with uric acid.

To identify the predictors of hyperuricemia, binary regression analysis was carried out and ORs were calculated (Table 4). An FBG concentration of greater than or equal to 110 mg/dL and a TG concentration of greater than or equal to 150 mg/dL were used as cut-off values to diagnose MetS. A BMI greater than or equal to 25 kg/m² was the cut-off value recommended by the Japan Society for the Study of Obesity. In Japan, HOMA-R greater than or equal to 1.6 and HOMA-β greater than or equal to 60 are generally used as cut-off values for the diagnosis of MetS, median serum concentrations of less than 8.0 mg/dL cFT, less than 52 nmol/L SHBG, and less than 5.0 ng/mL TT were generally used as cut-off values for the diagnosis of insulin resistance and insulin secretion, respectively. Because no cut-off levels for cFT, SHBG, and TT have been published for the diagnosis of MetS, median serum concentrations of less than 8.0 ng/dL cFT, less than 52 nmol/L SHBG, and less than 5.0 ng/mL TT were tentatively selected for use in logistic regression analyses. Similarly, because no cut-off values for serum adiponectin, albumin, ALT, ASL, γGTP, and total protein were available for the diagnosis of MetS, median serum values of less than 5.0 μg/mL adiponectin and greater than or equal to 4.3 g/dL albumin, 35 IU/L ALT, 30 IU/L ASL, 70 IU/L γGTP, and
7.0 g/dL total protein were tentatively selected for logistic regression analyses. Unadjusted binary regression analyses revealed that adiponectin, albumin, BMI, creatinine, F-IRI, HOMA-β, HOMA-R, SBP, SHBG, TG, total protein, TT, and MetS (IDF criteria) were statistically significant markers of hyperuricemia, and after adjustment, adiponectin ($P = .002$), creatinine ($P < .001$), SHBG ($P = .007$), and total protein ($P = 0.047$) remained statistically significant (Table 4).
Lastly, ROC curve analysis was used to calculate the cut-off values for these predictors. As shown in Table 5, less than 46.5 nmol/L SHBG was a significant predictor of hyperuricemia (AUC = 0.645, P < .001), together with less than 3.68 μg/mL (AUC = 0.691, P < .001) adiponectin, greater than or equal to 1.0 mg/dL (AUC = 0.700, P < .001) serum creatinine, and greater than or equal to 7.2 g/dL (AUC = 0.617, P = 0.002) total protein.

#### 4 | DISCUSSION

In the present study, it was found that relatively low concentrations of adiponectin and SHBG are predictors of hyperuricemia, defined as a serum uric acid concentration greater than or equal to 7.0 mg/dL, using binary logistic regression analysis. ROC analysis established 3.68 μg/mL serum adiponectin and 46.5 nmol/L SHBG as cut-off values for the prediction of greater than or equal to 7.0 mg/dL uric acid, with AUC values of 0.691 and 0.645, respectively. These results also suggest a close association between serum uric acid levels and MetS, considering the reported beneficial effects of adiponectin and SHBG on obesity or MetS, respectively. This is the first study to establish relationships between measures of testosterone status, especially SHBG, and hyperuricemia. Although the measurement of adiponectin and SHBG for the prediction of hyperuricemia is not as practical as uric acid measurements, these values may help provide a comprehensive understanding of the pathophysiology of MetS.

The precise mechanism underlying the inverse relationship between SHBG and hyperuricemia is unclear. Hepatic SHBG production may be downregulated by insulin, consistent with effects observed in cultured HepG2 cells. Intracellular uric acid stimulates hepatic gluconeogenesis by inactivating adenosine monophosphate protein kinase (AMPK) and activating adenosine monophosphate dehydrogenase (AMPD), and hyperuricemia has been reported to cause insulin resistance by reducing endothelial nitric oxide (NO) synthase activity. Thus, hyperuricemia may result in hyperinsulinemia, leading to a reduction in SHBG production in the liver. Although the relationship between uric acid and insulin resistance was not so strong in this study, the above hypothesis may be supported by a significant positive correlation between serum uric acid and SHBG levels.
Table 3

| Association between various testosterone values, uric acid, and metabolic markers |
|---------------------------------------------|
| **BMI, kg/m²** | **TT** | **SHBG** | **cFT** | **cbT** | **Uric acid** |
| Waist, cm | -.337*** | -.269*** | -.147** | -.137** | .236*** |
| SBP, mmHg | -.375*** | -.272*** | -.177*** | -.169*** | .233*** |
| DBP, mmHg | -.231*** | -.156** | -.179*** | -.148** | .141*** |
| Triglycerides, mg/dL | -.269*** | -.266*** | -.053 | -.046 | .223*** |
| HDL-C, mg/dL | .106 | .147** | -.042 | -.050 | .070 |
| LDL-C, mg/dL | .015 | .023 | .018 | .022 | .056 |
| adiponectin, µg/mL | .221*** | .190*** | .080 | .059 | -.233*** |
| FBG, mg/dL | -.217*** | -.153** | -.110 | -.152*** | .046 |
| Insulin, µU/mL | -.340*** | -.271*** | -.167*** | -.153*** | .105*** |
| HbA1c, % | -.078 | .069 | -.145*** | -.152** | .004 |
| HOMA-ΔR | -.329*** | -.256** | -.167*** | -.151*** | .084 |
| HOMA-β | -.274*** | -.231*** | -.126*** | -.122*** | .094 |

Note. Correlation coefficient was determined using Pearson product-moment correlation method (parametric). *P < .05 was considered to be significant.

Abbreviations: BMI, body mass index; cbT, calculated bioavailable testosterone; cFT, calculated free testosterone; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycohemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-β, homeostasis model assessment for β cell function; HOMA-R, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; TT, total testosterone.

* P < .05.
** P < .01.
*** P < .001.

Acid and F-IRI concentrations and a negative correlation between SHBG and F-IRI (Table 3).

Such functional interaction between uric acid and SHBG may be mediated through AMPK signalling. As mentioned above, uric acid inactivates AMPK. However, SHBG production is upregulated by adiponectin-AMPK signalling in HepG2 cells32, 33 and downregulated by inflammatory cytokines (tumour necrosis factor α and interleukin-1β).33 So, hyperuricemia-induced AMPK inactivation in liver may result in the reduction of SHBG production.

The regulatory relationship between uric acid and SHBG regarding hepatic fat accumulation may be mutually conflicting or compensatory. Uric acid induces hepatocyte endoplasmic reticulum stress, and then, as a result of the cleavage of sterol regulatory element-binding protein and its nuclear translocation, triglyceride is stimulated to accumulate in hepatocytes. From such ectopic fat accumulation in the liver, adiponectin secretion may be reduced and inflammatory cytokine secretion from adipose tissue increased. Indeed, in this study, serum uric acid concentration had a positive correlation with serum levels of TG and waist circumference and a negative correlation with serum adiponectin, as already reported in other studies.35, 36 As serum SHBG decreases, liver fat mass has been clinically reported to be increased. Conversely, it has been shown that serum SHBG concentrations were higher in individuals with lower levels of intrahepatic fat mass.38, 39 Recently, SHBG overexpression was found to protect against the progression of fatty liver disease induced by a high-fructose diet in mice, and exogenous SHBG inhibited lipogenesis by the reduction of PPAR expression through the extracellular signal-regulated kinase-1/2 mitogen-activated protein kinase pathway in HepG2 cells.40

From a dietary perspective, serum uric acid levels and the prevalence of gout both rise in proportion to the level of consumption of fructose or sucrose.41, 42 Interestingly, SHBG production by HepG2 cells was dose dependently reduced by supplementation of fructose or glucose in the medium, supporting a reciprocal association between SHBG and serum uric acid levels based on diet.

Interestingly, SHBG had a larger OR for its relationship with hyperuricemia than any of the other testosterone-related measurements, whereas TT was reported to be the most reliable marker of MetS.20 Serum testosterone and hyperuricemia thus have both positive and negative relationships, and SHBG not bound to testosterone seems to have the highest OR for hyperuricemia.

Binary logistic regression analysis revealed that relatively high concentrations of serum creatinine and total protein were also risk factors for [uric acid] greater than or equal to 7.0 mg/dL. These findings are compatible with the phenomenon observed in individuals that have hyperuricemia associated with a large muscle mass.44 In addition, the relationship between high serum creatinine and hyperuricemia may reflect chronic kidney disease due to hyperuricemia.45

Several limitations should be considered in this study. First, definitive conclusions regarding pathogenesis on the basis of the identified association between hyperuricemia and SHBG are not possible in this cross-sectional study. Second, this study was limited to middle-aged male participants. The relation between hyperuricemia and testosterone may be gender-specific, so the relation between hyperuricemia...
and testosterone status may be different in women. Most types of antihypertensive drugs are thought to be neutral regarding serum uric acid levels, but past work showed that thiazide slightly increased uric acid levels and losartan potassium, an angiotensin II receptor antagonist, reduced uric acid levels to about 0.7 mg/dL. A third limitation was that the current study had no information about the types/names of antihypertensive drugs. Fourth, information on alcohol use was not obtained from all 363 participants. However, for the 274 participants that provided alcohol habit information (226 drinking and 48 non-drinking participants), no significant difference was found for serum uric acid levels in drinking compared with non-drinking participants, suggesting that there was little impact of alcohol in this study (data not shown). Lastly, the present study did not investigate the influence of inherited genetic variants on hyperuricemia and the identified relationships. Recently, 23.9% of the variance in serum uric acid was reported to be explained by common, genome-wide, single nucleotide variants, which may have influenced the results of the present study.

In summary, approximately 20% of middle-aged asymptomatic Japanese men were found to have hyperuricemia during medical examination. All of the various testosterone indicators, including SHBG, showed negative correlations with serum uric acid. Therefore, building upon our previous findings that serum low TT concentration was a predictor for MetS, we provide evidence that low SHBG provides a reliable marker of hyperuricemia and was closely correlated with MetS. A reduction in SHBG may be the result of inflammation.

**TABLE 4** Predictors for hyperuricemia determined by the binary logistic regression analysis

| Variables          | Before Adjustment OR (95%CI) | P values | After Adjustment OR (95%CI) | P Values |
|--------------------|-------------------------------|----------|-----------------------------|----------|
| BMI ≥ 25 kg/m²     | 2.61 (1.54-4.41)              | <.001    | 1.81 (0.98-3.31)            | .056     |
| SBP ≥ 135 mmHg     | 2.11 (1.26-3.54)              | .005     | 1.77 (0.99-3.15)            | .054     |
| TT < 5.0 ng/mL     | 2.25 (1.30-3.90)              | .004     | Not applicable              |          |
| SHBG < 52 nmol/L   | 2.63 (1.46-4.74)              | .001     | 2.44 (1.27-4.68)            | .007     |
| cFT < 8.0 ng/dL    | 1.27 (0.75-2.15)              | .372     | Not applicable              |          |
| Adiponectin < 5.0 μg/mL | 3.41 (1.82-6.37) | <.001   | 2.96 (1.50-5.86)            | .002     |
| FBG ≥ 110 mg/dL    | 1.88 (0.98-3.61)              | .058     | Not applicable              |          |
| Insulin ≥ 10.4 μU/mL | 2.48 (1.29-4.79)         | .007     | Not applicable              |          |
| HOMA-R ≥ 1.6      | 2.04 (1.22-3.42)              | .007     | Not applicable              |          |
| HOMA-β ≥ 60        | 2.01 (1.20-3.37)              | .008     | Not applicable              |          |
| Total protein ≥ 7.0 g/dL | 2.06 (1.15-3.68)         | .015     | 1.93 (1.01-3.70)            | .047     |
| Albumin ≥ 4.3 g/dL | 2.03 (1.16-3.56)              | .014     | Not applicable              |          |
| AST ≥ 30 IU/L     | 1.72 (0.90-3.28)              | .101     | Not applicable              |          |
| ALT ≥ 35 IU/L     | 1.15 (0.63-2.10)              | .642     | 0.53 (0.26-1.08)            | .082     |
| γGTP ≥ 70 IU/L    | 1.66 (0.89-3.06)              | .109     | Not applicable              |          |
| S-Creatinine ≥ 1.0 mg/dL | 4.20 (2.31-7.65)     | <.001   | 4.45 (2.25-8.77)            | <.001    |
| Triglycerides ≥ 150 mg/dL | 2.21 (1.30-3.76)    | .003     | 1.77 (0.97-3.24)            | .064     |
| MetS (IDF)        | 2.30 (1.34-3.95)              | .002     | Not applicable              |          |
| MetS (JPN)        | 2.11 (1.21-3.68)              | .191     | Not applicable              |          |

Note. Chi-square value was 0.782 for Hosmer-Lemeshow test (P = .999).

**TABLE 5** Cut-off values of predictors and AUC for hyperuricemia determined by ROC curve analysis

| Predictors   | Cut-Off Values | AUC (95%CI) | P values |
|--------------|----------------|-------------|----------|
| SHBG         | 46.5 nmol/L    | 0.645 (0.577-0.712) | <.001    |
| Adiponectin  | 3.68 μg/mL     | 0.691 (0.625-0.756) | <.001    |
| Total protein| 7.2 g/dL       | 0.617 (0.546-0.689) | .002     |
| S-Creatinine | 1.0 mg/dL      | 0.700 (0.633-0.767) | <.001    |

Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristics; SHBG, sex hormone-binding globulin.
associated with hyperuricemia and from the ectopic fat accumulation associated with MetS. Therefore, SHBG may provide a valuable clinical marker for hyperuricemia.

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CONFLICT OF INTEREST
The authors declare no conflict of interest relevant to this manuscript.

AUTHOR CONTRIBUTIONS
The manuscript draft. Yuko Akehi contributed to the statistics. Hiromi Yano contributed to sample collection at lizuka Hospital. Nobuya Hamanoue, Ryoko Motonaga, Tomoko Tanaka, Chikayo Iwaya, Makito Tanabe, and Takashi Nomiyama were responsible for critically reading and reviewing the manuscript and discussion. Toshihiko Yanase organized the research, planned the analysis, and revised the manuscript as corresponding author.

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