Elevated Serum Mannose Levels as a Marker of Polycystic Ovary Syndrome

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Background: Recent reports have highlighted the role of monosaccharide biosynthesis in the pathogenesis of polycystic ovary syndrome (PCOS), suggesting that these processes may serve as a biomarker in PCOS. Mannose is the main monosaccharide for protein glycosylation in mammals; however, the correlation between mannose and PCOS remains largely unknown.

Materials and Methods: A total of 132 Chinese Han women were recruited at Shengjing Hospital of China Medical University. Mannose levels were measured in serum samples collected from 71 patients with PCOS (29 lean, 42 obese) and 61 control subjects (28 lean, 33 obese). Receiver operating characteristics (ROC) curves were prepared to compare the diagnostic performance of mannose and hormonal parameters, individually or in combination. Multivariate logistic regression analysis was used to assess whether serum mannose levels were associated with PCOS after adjusting for other co-variables.

Results: We showed that serum mannose levels were significantly increased in PCOS patients compared with control subjects regardless of obese status, and hyperandrogenic PCOS patients had higher serum mannose levels than normo-androgenic PCOS and control subjects. In addition, serum mannose levels were significantly correlated with serum androgen levels. Mannose had an area under the curve (AUC) of 73% at a cutoff value of 225.79 ng/mL with a sensitivity of 66.2% and specificity of 73.8% for predicting PCOS. There were no differences between mannose, total testosterone, free testosterone, or dehydroepiandrosterone sulfate in the reliability of predicting PCOS using the method outlined by Hanley and McNeil. Combining mannose and total testosterone resulted in a higher AUC of 83.3%, and had moderate sensitivity (78.9%) and specificity (77%) for predicting PCOS. The positive and negative predictive values were 80% and 75.8%, respectively. Multivariate logistic regression revealed that higher serum mannose levels were strongly associated with an increased risk of PCOS ($P = 0.016$; odds ratio, 5.623; 95% confidence interval, 1.371–23.070).

Conclusion: Taken together, substantially elevated serum mannose levels are significantly associated with PCOS, highlighting the importance of further research into the role of mannose in the pathogenesis of PCOS.

Keywords: mannose, monosaccharide, PCOS (polycystic ovary syndrome), serum, insulin resistance
INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder (1) and has significant and diverse reproductive and metabolic features, including obesity, insulin resistance, type 2 diabetes, and adverse cardiovascular risk profiles (2, 3). Monosaccharides are the simplest carbohydrates and serve as the main source of energy for metabolism (4). Recently, by RNA sequencing techniques, we found that monosaccharide biosynthesis is a novel pathway marker to distinguish between normal and PCOS follicles, but the relationship between monosaccharide and PCOS remains largely unknown (5).

Mannose is the predominant monosaccharide for protein glycosylation in mammals (6), a process which predominantly occurs in the liver (7). Notably, the importance of mannose in PCOS-related metabolic disorders has been increasingly recognized, for example, plasma mannose levels are significantly elevated in subjects with insulin resistance (7, 8). Mechanistically, the expression of mannose metabolism and utilization genes was markedly decreased in the livers of obese subjects with metabolic abnormalities (7, 8). In addition, studies have shown that elevated plasma mannose levels contribute to the development of several common chronic diseases, including type 2 diabetes and cardiovascular disease, rather than just being a predictive biomarker (9). Despite these advances in knowledge, the role of mannose in the pathogenesis of PCOS remains poorly understood. Thus, with the aim of elucidating the relationship between mannose levels and PCOS, the present study involved measuring and evaluating serum mannose levels from PCOS patients and control subjects.

MATERIALS AND METHODS

Ethical Statement

This study was conducted in accordance with ethical standards and the Helsinki Declaration of 1975.

Patients and Blood Samples

For blood sample collection, lean control patients (n = 28), lean patients with PCOS (n = 29), obese control patients (n = 33), and obese patients with PCOS (n = 42) were recruited at Shengjing Hospital of China Medical University. A female body mass index (BMI) ≥ 23 kg/m² was used as the diagnostic criterion for overweightness and obesity in Asians (10). For this study, obesity refers to both overweight and obese patients. PCOS was defined according to the Rotterdam criteria (11), and

| TABLE 1 | Description of the study participants categorized by BMI. |
|-----------|-----------------|-------|-----------------|-----------------|-------|-----------------|-------|
|           | Control         | PCOS  | P-value         | Control         | PCOS  | P-value         |
| N         | 33              | 42    | 0.206           | 28              | 29    | 0.099           |
| Age (year)| 32.52 ± 4.09    | 31.43 ± 3.28 | 0.111           | 32.00 ± 2.72    | 30.72 ± 3.01 | 0.133           |
| BMI (kg/m²)| 25.57 ± 2.37    | 26.36 ± 1.86 | 0.001           | 20.58 ± 1.41    | 21.19 ± 1.62 | 0.004           |
| Mannose (ng/mL)| 178.32 (142.37–276.02) | 280.77 (202.21–392.25) | 0.001 | 188.16 (141.37–224.51) | 245.36 (185.74–339.64) | 0.004 |
| Total testosterone (nM)| 1.42 (1.01–1.91) | 2.20 (1.84–2.61) | 0.001 | 1.47 (1.20–1.90) | 2.22 (1.80–2.79) | 0.001 |
| Free testosterone (nM)| 0.017 (0.014–0.024) | 0.026 (0.020–0.032) | 0.001 | 0.019 (0.012–0.023) | 0.030 (0.022–0.039) | 0.005 |
| SHBG (nM)| 52.69 (31.86–87.22) | 30.47 (20.68–50.43) | 0.001 | 60.70 (34.45–110.50) | 53.89 (31.48–80.22) | 0.615 |
| DHEAS (nM)| 3190.40 (1624.55–4403.42) | 4104.39 (3068.61–6063.29) | 0.001 | 2540.31 (1708.84–4403.06) | 5489.75 (3367.46–7874.31) | 0.001 |
| AMH (pmol/L)| 16.07 (10.60–38.27) | 60.01 (47.57–98.26) | 0.001 | 26.28 (19.14–43.64) | 62.83 (41.20–86.86) | 0.001 |
| FSH (IU/L)| 7.93 (4.19) | 6.11 ± 1.59 | 0.012 | 7.42 ± 2.40 | 6.88 ± 2.28 | 0.392 |
| LH (IU/L)| 4.03 (2.95–6.02) | 10.59 (6.99–14.17) | 0.001 | 5.10 (4.00–7.12) | 13.44 (9.46–21.99) | 0.001 |
| Estradiol (nM)| 0.16 ± 0.07 | 0.24 ± 0.13 | 0.003 | 0.21 ± 0.15 | 0.27 ± 0.16 | 0.139 |
| Prolactin (ng/mL)| 10.75 ± 3.92 | 11.03 ± 7.22 | 0.841 | 12.50 ± 4.25 | 11.53 ± 5.38 | 0.450 |
| TSH (mIU/mL)| 1.77 (1.47–2.82) | 1.96 (1.11–2.54) | 0.623 | 1.90 (1.25–2.88) | 2.10 (1.18–2.81) | 0.943 |
| FPG (mg/dL)| 5.10 ± 0.37 | 5.07 ± 0.38 | 0.778 | 5.00 ± 0.34 | 5.03 ± 0.37 | 0.802 |
| Fi (mIU/mL)| 12.50 (9.40–15.70) | 15.30 (11.38–19.55) | 0.046 | 12.86 (11.30–20.78) | 16.89 (11.30–25.30) | 0.565 |
| HOMA-IR| 3.15 ± 1.87 | 3.61 ± 1.56 | 0.243 | 2.09 ± 0.93 | 1.91 ± 0.86 | 0.439 |
| QUICKI| 0.33 ± 0.02 | 0.32 ± 0.02 | 0.120 | 0.35 ± 0.02 | 0.35 ± 0.02 | 0.458 |
| TC (mM)| 4.38 ± 0.77 | 4.86 ± 0.67 | 0.005 | 4.54 ± 0.61 | 4.57 ± 0.76 | 0.844 |
| LDL-C (mM)| 2.74 ± 0.82 | 3.02 ± 0.55 | 0.086 | 2.69 ± 0.56 | 2.65 ± 0.64 | 0.811 |
| HDL-C (mM)| 1.22 (1.08–1.43) | 1.11 (0.93–1.31) | 0.096 | 1.49 (1.30–1.77) | 1.30 (1.13–1.49) | 0.042 |
| Triglycerides (mM)| 1.27 (0.66–1.56) | 1.40 (1.00–2.13) | 0.123 | 0.87 (0.59–1.08) | 0.87 (0.54–1.54) | 0.376 |

BMi, body mass index; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; FPG, fasting plasma glucose; Fi, fasting serum insulin; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin-sensitivity check index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Mean ± standard deviation or median (interquartile range) are shown. The Mann–Whitney U test was used for non-normal distribution data and Student’s t test was used for normal distribution data.
the exclusion criteria are described in our previous publication (12). Briefly, these included: < 3 years since menarche; tobacco smoking; hormonal medication; pregnancy; lactation; medications (insulin-sensitizing drugs, oral contraceptives, antiandrogens, statins, aspirin, nicotinic acid, corticosteroids, and gonadotropin-releasing hormone agonists and antagonists) taken within the preceding 6 months; endocrine abnormalities such as diabetes mellitus, hyperprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumor, Cushing's syndrome; and a history of any known neoplastic, infectious, or inflammatory diseases. Characteristics of the subjects are provided in Table 1 and Supplementary Table 1.

To study the relationship between mannose and androgens, the study population of PCOS patients was further subdivided into a normo-androgenic and hyperandrogenic group based on serum androgen levels. Biochemical hyperandrogenism was diagnosed when serum androgen levels were as follows: total testosterone > 2.524 nmol/L, free testosterone > 0.043 nmol/L, and dehydroepiandrosterone sulfate (DHEAS) > 7649.24 nmol/L, all of which represent the 95th percentile of basal serum androgens in the control group of 61 healthy Chinese women without hirsutism or a family history of PCOS. Characteristics of the subjects in the subgroups are provided in Table 2.

### Measurement of Mannose

Serum mannose concentrations were determined by a competitive enzyme immunoassay (OKEH02595; Aviva Systems Biology, San Diego, CA, USA). Prior to the measurements, each serum sample was diluted in a 1:5 ratio with assay buffer. The assay was performed according to the manufacturer's instructions. In our experiment, the inter-assay coefficient of variation (CV) was 6.1% and the intra-assay CV was 9.6%.

### Table 2: Blood samples were collected in the morning after an overnight fast, between the 3rd and 5th days of spontaneous menses or progesterin-withdrawal bleeding. Blood samples were analyzed for lipids, along with insulin and glucose levels, by semi-automated enzymatic methods, whereas luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone, prolactin, and thyroid-stimulating hormone (TSH) were assayed using a chemiluminescence analyzer.

This study was designed to investigate the Chinese Han population, which is the main ethnic group in China, comprising 92% of the total population. The study was approved by the Institutional Review Board at China Medical University on 28th February 2015 (reference number 2015PS108K). Written informed consent was obtained from all study participants.
range of the assay was 1.56–100 ng/mL. The antibody used was specific for human mannose and does not significantly cross-react with other relevant proteins.

**Measurement of Sex Hormone-Binding Globulin (SHBG), Free Testosterone, and DHEAS**

Serum concentrations of SHBG (Human SHBG ELISA Kit; RayBiotech, Norcross, GA, USA); free testosterone (CSB-E05096h, Cusabio Biotech, Wuhan, China); and DHEAS (CSB-E05105h, Cusabio Biotech, Wuhan, China) were measured using commercial enzyme-linked immunosorbent assay kits following the manufacturer’s protocol. The assay sensitivity limits for detecting SHBG, free testosterone, and DHEAS were described by the manufacturer as 1.2 pmol/L, 3.75 pg/mL, and 10 ng/mL, respectively. The intra-assay CVs were 10, 15, and 15%; and the inter-assay CVs were 12, 15, and 15%, respectively. Concentrations were determined by comparing the optical densities (450 nm) of samples with the standard curve.

**Statistical Analyses**

All statistical analyses were conducted using the Statistical Packages for Social Sciences, version 22 (IBM Corp., Armonk, NY). A two independent proportions power analysis, conducted by an independent statistician via Power Analysis and Sample Size, version 11.0 (NCSS, LLC., Kaysville, Utah, USA) was used to estimate sample size. Normality of distribution of the continuous variables was assessed using the Kolmogorov–Smirnov test. Non-normally distributed variables were logarithmically transformed (log_{10}) before statistical analysis. Comparisons between PCOS patients and controls were performed using the independent-sample t test and Mann–Whitney U test for normally and non-normally distributed variables, respectively. Furthermore, the one-way analysis of variance (ANOVA) with Tukey or Dunnett’s post-hoc test (two-sided) was conducted for multi-group comparisons. The Pearson correlation coefficient was used to test the relationship between two quantitative variables. Multivariate logistic regression analysis was used to assess the strength of the association of serum mannose and PCOS. Receiver operating characteristics (ROC) curves were prepared to compare the diagnostic performance of mannose and hormonal parameters, either individually or in combination. The area under the ROC curve (AUC) with 95% confidence interval (CI), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the diagnosis of PCOS were calculated. The Youden index was calculated to determine the optimal cutoff point. Descriptive results of study participants are expressed as means ± standard error (SE) or median (interquartile range). Bonferroni tests were performed to adjust for multiple testing. All tests were two-sided, and a P value of < 0.05 was considered to convey statistically significant differences.

**RESULTS**

**PCOS Patients Exhibit High Serum Mannose Levels**

To systematically study the relationship between serum mannose levels and PCOS in the context of BMI, the study population of control subjects and PCOS patients was divided into obese and non-obese subgroups. As shown in **Figure 1** and **Table 1**, serum mannose levels were significantly higher in PCOS patients than in control subjects, regardless of obese status. Accordingly, serum mannose levels were greater in PCOS patients than in control subjects when the non-obese and obese subgroups were combined (**Figure 1** and **Supplementary Table 1**).

**Serum Mannose Levels Showed a Positive Relationship and Similar Diagnostic Performance to Androgens in PCOS**

As stated, serum mannose levels were markedly elevated in PCOS patients. Therefore, using ROC curves, we compared the performance of mannose levels with androgens as diagnostic indicators of PCOS. As shown in **Figure 2A** and **Table 2**, serum mannose levels were higher in normo-androgenic PCOS patients than in control subjects. In addition, mannose levels were also elevated in the hyperandrogenic PCOS patients compared to normo-androgenic PCOS patients. Correlation analyses were used to examine the relationship between serum mannose levels and the major androgens. Notably, serum mannose levels were correlated with total testosterone and DHEAS levels, and exhibited a stronger association with free testosterone (**Figure 2B**). The diagnostic performance of mannose was evaluated using ROC curves and compared with total testosterone, free testosterone, and DHEAS. As shown in **Figures 2C,G**, mannose had an AUC of 73% at a cutoff value of 225.79 ng/mL with a sensitivity of 66.2% and specificity of
FIGURE 2 | Correlation and ROC analysis between serum mannose and androgens. (A) Differences in serum mannose levels in control subjects, normo-androgenic PCOS patients, and hyperandrogenic PCOS patients. (B) Correlation between serum total testosterone and free testosterone, and DHEAS and mannose levels, respectively. Both parameters were log-transformed for the plot. (C–G) Diagnostic potential of serum mannose, total testosterone, free testosterone, and DHEAS estimated using ROC analysis. ROC curve analysis of the individual androgens, and combining the individual androgens with mannose, respectively. AUC, cutoff value, sensitivity, and specificity are indicated. Bar graphs show the mean ± standard error (SE). **P < 0.01 vs. control. PCOS, polycystic ovary syndrome; DHEAS, dehydroepiandrosterone sulfate; ROC, receiver operating characteristic; AUC, the area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

73.8% for predicting PCOS. The PPV and NPV were 74.6% and 65.2%, respectively. There were no differences between mannose, total testosterone, free testosterone, and DHEAS in the reliability of predicting PCOS using the method outlined by Hanley and McNeil (13). However, when mannose and total testosterone levels were combined, there was a higher AUC of 83.3%, with moderate sensitivity (78.9%) and specificity (77%) for predicting PCOS (Figures 2D,G). The PPV and NPV were 80% and 75.8%, respectively. The combination of mannose and free testosterone resulted in an AUC of 77.9%, with moderate diagnostic sensitivity (80.3%) and poor diagnostic specificity (63.9%) for PCOS (Figures 2E,G). Combining mannose and DHEAS resulted in an AUC of 77.7%, with moderate diagnostic sensitivity (76.1%) and poor diagnostic specificity (67.2%) for predicting PCOS (Figures 2F,G). Notably, multivariate logistic regression revealed that elevated serum mannose levels were strongly associated with a high risk of PCOS (P = 0.016; odds ratio, 5.623; 95% confidence interval, 1.371–23.070; Table 3).

DISCUSSION

In this study, we reported for the first time that serum mannose levels are significantly increased in PCOS patients, and that hyperandrogenic PCOS patients had higher serum mannose levels compared to normo-androgenic PCOS patients and control subjects. In addition, serum mannose levels were
significantly correlated with serum androgen levels. These observations suggest a link between mannose and androgen metabolism. Notably, one previous report highlighted the function of the mannose receptor (ManR, Mrc1) in androgen metabolism, suggesting that the half-life for LH clearance was a function of the mannose receptor (ManR, Mrc1) in androgen metabolism. Notably, one previous report highlighted the observations suggest a link between mannose and androgen disorders. Apart from androgens, it is well-known the disease (PCOS, such as serum androgens, AMH, FSH, LH, fasting serum insulin (FI), and BMI were used as variables in a multivariate logistic regression model. It is important to note that, similar to total testosterone, serum mannose can be considered as an independent predictive factor for PCOS.

Although there is an inadequate understanding of the etiology of PCOS, insulin resistance is a relatively common feature of the disease (18) and the pathophysiology of PCOS involves alterations in insulin action in a variety of target tissues (19). Recent reports have identified mannose as having one of the strongest positive associations with insulin resistance among plasma metabolites (7–9). In agreement with these findings, we observed that elevated serum mannose levels are accompanied by increased FI levels in the PCOS patients in the obese subgroup. Interestingly, Dahan et al. reported that FI can be considered as a simple and accurate surrogate predictor of insulin resistance in PCOS patients and control subjects (20). Taken together, these studies suggest that mannose-related insulin resistance may have a role in the pathogenesis of PCOS, especially in obese PCOS patients.

The results of the present study reveal differences in serum mannose levels between control subjects and PCOS patients; however, it remains unclear whether mannose contributes directly to the pathogenesis of PCOS or are just biomarkers of this process. Together with our previous study (5), the present results highlight the importance of further investigation into the role of mannose in the biological mechanisms underlying the pathogenesis of PCOS.

**DATA AVAILABILITY STATEMENT**

The datasets generated for this study are available on request to the corresponding author.

**ETHICS STATEMENT**

All subjects signed a written informed consent before participating in the study which abides by the Declaration of Helsinki and was approved by the Ethical Review Board at China Medical University.

**AUTHOR CONTRIBUTIONS**

DL and XW conceived and designed the study. DF, BS, DL, FB, JJ, MS, and XS performed data acquisition and interpretation. DL and XW conceived and designed the study. DF, BS, DL, FB, JJ, MS, and XS performed data acquisition and interpretation. DL, XW, BS, and DF wrote the paper. All authors approved the final manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2019.00711/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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