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Serum Levels of Testosterone in Patients with Polycythemia Vera

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Abstract

Despite its association with vascular events such as myocardial and cerebral infarction, polycythemia vera (PV) is characterized by low serum total cholesterol levels. Because several sex hormones are derived from cholesterol, statins may induce hypogodanism in male patients. Therefore, we assessed the relationship between serum total cholesterol and sex hormone levels according to gender. Medical records of 41 patients with erythrocytosis (hemoglobin concentrations: men >18.5 g/dL; women >16.5 g/dL) collected between August 2005 and December 2014 were reviewed for patient age, and gender, as well as clinical hematology, biochemistry, and endocrinology laboratory findings. Serum levels of testosterone were lower in men with PV than in patients with reactive erythrocytosis (RE) (PV: 385 ± 78 ng/mL versus RE: 529 ± 46 ng/mL). However, serum levels of testosterone in women with PV were comparable to those in patients in the non-erythrocytic group (PV: 20.5 ± 3.5 ng/mL versus non-erythrocytic group: 21.0 ± 4.3 ng/mL). Serum levels of testosterone were not related to serum levels of cholesterol. Therefore, we speculated that lower testosterone levels were not due to lower serum levels of cholesterol, a known adverse effect of statin. In conclusion, we report for the first time that serum levels of testosterone were lower in male PV patients than in those with RE; however, serum levels of testosterone in female patients with PV were not lower.

Keywords

Polycythemia Vera, *JAK2 V617F* Mutation, Hypocholesterolemia, Testosterone

1. Introduction

Because several sex hormones are derived from cholesterol, statins may induce hypogodanism such as erectile dysfunction in male patients through severe hypocholesterolemia [1] [2]. Although some types of statins have been shown to improve erectile dysfunction [3] [4], their effects were not due to sex hormone production. Be-

cause erectile dysfunction is often associated with endothelial dysfunction, statins may improve endothelial function by reducing serum cholesterol levels.

Moreover, statins also inhibit testosterone synthesis in animal experiments [5]. Statins significantly reduced luteinizing hormone (LH)-stimulated testosterone production in rat Leydig cells, suggesting two possible mechanisms by which statins might induce decreased testosterone levels. First, statins may reduce serum levels of testosterone due to hypocholesterolemia [1] [2]. Second, statins may inhibit testosterone synthesis [5].

However, we previously reported that serum levels of total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B were significantly lower in patients with polycythemia vera (PV) than in those with reactive erythrocytosis (RE) without the Janus Kinase 2 (*JAK*2) V167F gene mutation [6]. PV is classified as a myeloproliferative neoplasm and typically occurs in people 60 - 79 years of age. Thrombotic events such as myocardial infarction, cerebral infarction, and deep vein thrombosis are the main clinical complications of PV [7]. The *JAK*2 gene mutation has become an important criterion for the diagnosis of PV as the *JAK*2 V617F mutation is observed in approximately 95% of patients with PV [8]. However, other mutations involving *JAK*2 exon 12, the Von Hippel-Lindau Tumor Suppressor (*VHL*) gene, and hypoxia-inducible factor-2 are also associated with idiopathic erythrocytosis [9] [10].

Thus, we revisited the relationship between serum total cholesterol levels and sex hormones, especially testosterone, from the viewpoints of gender differences. We reported that serum levels of testosterone in male patients with PV were lower than those in patients with RE, while serum levels of testosterone in female patients with PV were almost equal to those in non-erythrocytic females, in spite of the presence of hypocholesterolemia in female patients with PV.

2. Patients and Methods

2.1. Patients

Tokyo Metropolitan Bokutoh Hospital is located in eastern Tokyo. We retrospectively reviewed the medical records of 34 patients at this hospital with erythrocytosis (hemoglobin [Hb]: men, >18.5 g/dL; women, >16.5 g/dL), collected between August 2005 and December 2014. The medical records were reviewed for patient age, gender, and laboratory test results. Patients taking medications such as statins for hypercholesterolemia were excluded from this study. Male and female patients were divided into PV and reactive erythrocytosis (RE) groups according to World Health Organization (WHO) classifications. The non-erythrocytic subjects included both medically healthy workers under 65 years of age and hypertensive patients without hyperlipidemia >65 years of age (N = 18). All subjects provided informed consent for their participation in the study, and the study design was approved by the ethics review board of our institution.

2.2. Methods

Venous blood was collected into evacuated tubes in order to measure the sex hormone profile (testosterone, free testosterone, estrogen, follicle-stimulating hormone [FSH], LH, and corticosteroids) during initial phlebotomy tests in our department. Serum samples were collected, frozen immediately, and stored at −80˚C until further analysis. The serum hormone profiles were measured by the BML company (Tokyo, Japan).

2.3. Statistical Analyses

We compared the differences between the PV and reactive erythrocytosis groups, or non-erythrocytosis groups by Wilcoxon's analysis. Data were expressed as group means ± standard errors of the mean or medians with interquartile ranges. All statistical calculations were performed using JMP version 8.0 (SAS Institute, Inc., Cary, NC), and significance was defined as $p < 0.05$.

The correlations between serum levels of cholesterol and sex hormones were assessed by linear regression analysis. For the linear regression analysis results, significance was defined as $p < 0.0001$.

3. Results

3.1. Sex Hormone Levels in Male Patients with PV

Of 41 patients with erythrocytosis, 21 were diagnosed with PV. The other 13 patients with erythrocytosis tested

negative for the *JAK2 V617F* mutation and were thus not diagnosed with PV (reactive erythrocytosis, RE). The patients with RE were all male (N = 13), and seven male patients were diagnosed with PV. We compared the clinical profiles, hematology, biochemistry (cholesterol and albumin), and sex hormone findings among male patients with PV (N = 7), non-PV erythrocytosis (N = 13) and non-erythrocytosis (N = 11), as shown in **Table 1**. Male patients with PV had significantly lower body mass index (BMI) than did those with RE. Serum cholesterol levels in patients with PV were lower than those with RE and those in the non-erythrocytic group. Among sex hormones, serum testosterone and estradiol levels were significantly lower in patients with PV than in patients with RE, as shown in **Table 1**.

There was no correlation between serum levels of cholesterol and sex hormones (testosterone: $r^2 = 0.08197$, $p = 0.1250$ and estradiol: $r^2 = 0.08952$, $p = 0.1082$).

3.2. Sex Hormones in Female Patients with PV

Among the female patients in this study, 11 had PV, and none had RE. Therefore, we compared the clinical, hematology, cholesterol, and sex hormone profiles between the PV (N = 14) and non-erythrocytosis (N = 7) groups. There were no differences in BMI or sex hormone levels between the PV and non-erythrocytosis groups, although serum cholesterol levels in patients with PV were significantly lower than those in patients with non-erythrocytosis (**Table 2**).

Table 1. Clinical profiles, hematology, serum cholesterol and sex hormone levels in male patients with erythrocytosis.

	Polycythemia vera N = 7	**Reactive erythrocytosis N = 13**	**Non-erythrocytosis N = 11**
Clinical profile			
Age	60 (4)	64 (3)	67 (2)
Height (cm)	168 (3)	164 (3)	161 (2)
Weight (kg)	61 (4)	67 (4)	60 (3)
Body mass index	21 (1)*	25 (1)	23 (1)
Hematology			
Red blood cells ($\times 10^4/\mu L$)	717 (36)*#	586 (12)	449 (14)
Hemoglobin (g/dL)	19.5 (0.4)#	19.7 (0.3)#	14.2 (0.3)
Hematocrit (%)	59.3 (1.3)#	57.6 (1.1)#	42.5 (0.9)
Mean Corpuscular volume (fL)	83.8 (3.5)*#	98.4 (1.5)	94.8 (2.1)
Platelet ($\times 10^4/\mu L$)	36.7 (7.1)*#	16.5 (0.8)	20.4 (1.2)
White blood cells (/μL)	17,257(4491)*#	6,408(309)	5,727(415)
Biochemistry			
Total cholesterol (mg/dL)	163 (12)#	186 (8)	190 (9)
Serum albumin (g/dL)	4.5 (0.1)	4.4 (0.1)	4.3 (0.1)
Sex hormone profile			
LH (mIU/mL)	5.9 (1.7)	7.2 (0.8)	6.9 (1.4)
FSH (mIU/mL)	16.7 (4.5)	9.1 (1.0)	14.1 (3.6)
Testosterone (ng/mL)	385 (78)*	529 (46)	570 (55)
Free testosterone (pg/mL)	8.0 (2.0)	8.5 (0.8)	7.5 (1.0)
Estradiol (pg/mL)	17.1 (4.1)*#	28.5 (2.5)	28.4 (3.0)
Cortisol (μg/dL)	13.5 (3.7)	12.0 (1.1)	13.1 (1.0)

Data are shown as means (standard errors). *: $p < 0.05$ vs. reactive erythrocytosis; #: $p < 0.05$ vs. non-polycythemic subjects; Reference value for sex hormones in men; Luteinizing hormone: 0.8 - 5.7 mIU/mL; Follicle-stimulating hormone: 2.0 - 8.3 mIU/mL Testosterone: 229 - 1,039 ng/dL; Free testosterone: 50 - 59 yrs: 6.9 - 18.4, 60 - 69 yrs: 5.4 - 16.7, 70 - 79 yrs: 4.5 - 18.8; Estradiol: 19 - 51 pg/mL; Cortisol: 4.5 - 21.1 μg/dL.

Table 2. Clinical profiles, hematology, serum cholesterol, and sex hormone levels in female patients with erythrocytosis.

	Polycythemia vera N = 14	Non-erythrocytosis N = 7
Clinical profile		
Age	70 (2)	74 (2)
Height (cm)	151 (8)	154 (5)
Weight (kg)	54 (3)	50 (2)
Body mass index	23 (1)	21 (1)
Hematology		
Red blood cells ($\times 10^4/\mu L$)	726 (21)#	410 (14)
Hemoglobin (g/dL)	18.2 (0.5)#	13.0 (13.6)
Hematocrit (%)	57.4 (1.0)#	39.0 (0.9)
Mean Corpuscular volume (fL)	80 (3)#	95 (2)
Platelet ($\times 10^4/\mu L$)	47.0 (4.8)#	21.0 (2.1)
White blood cells (/μL)	15,350 (1,858)#	5443 (56)
Biochemistry		
Total cholesterol (mg/dL)	159 (5)#	193 (10)
Serum albumin (g/dL)	4.1 (0.1)	4.3 (0.1)
Sex hormone profile		
LH (mIU/mL)	19.4 (1.4)	19.1 (2.7)
FSH (mIU/mL)	51.1 (5.9)	46.7 (6.2)
Testosterone (ng/mL)	20.5 (3.5)	21.0 (4.3)
Free testosterone (pg/mL)	16.4(6.0)	8.8 (2.2)
Estradiol (pg/mL)	12.3 (0.7)	15.1 (2.7)
Cortisol (μg/dL)		

Data are shown as means (standard errors). #: $p < 0.05$ vs. non-polycythemic subjects; Reference values for sex hormones in women; Luteinizing hormone after menopause: 5.7 - 64.3 mIU/mL; Follicle-stimulating hormone after menopause: <157.8 mIU/mL; Testosterone: 33.0 - 126 ng/dL; Estradiol after menopause: <39 pg/mL; Cortisol: 4.5 - 21.1 μg/dL.

4. Discussion

4.1. Serum Levels of Cholesterol and Sex Hormones in Patients with PV

There are two possible mechanisms by which statins might induce lower testosterone levels. First, statins may reduce serum testosterone levels via hypocholesterolemia [1] [2]. Serum levels of cholesterol in the male patients were lower than those in patients with RE and the non-erythrocytic group in this study, as shown in **Table 1**. However, lower cholesterol levels were not related to lower hormone (testosterone and estradiol) levels. In addition, serum levels of testosterone in female patients with PV were the same as those in the non-erythrocytic group, although the serum levels of cholesterol in female patients with PV were lower than those in the non-erythrocytic group. These data suggested that lower cholesterol levels were not related to lower testosterone levels. Second, lower LS levels may inhibit testosterone synthesis [5]. However, serum levels of LH and FSH in the male patients with PV in this study were not lower than those in the RE and non-erythrocytic groups. Therefore, it was likely that there was no LH-stimulated testosterone production in male patients with PV. Thus, our hypothesis that hypocholesterolemia might induce lower testosterone levels was mistaken.

4.2. Serum Levels of Testosterone Might Be Down-Regulated by Negative Feedback

Testosterone itself stimulates erythropoietin production and increases hematocrit [11]. Polycythemia is a known adverse effect of testosterone treatment for hypogonadism [12]. Moreover, in the chronic mountain sickness, serum testosterone levels increase with high hematocrit [13] [14]. Therefore, one possibility that serum testosterone may be down-regulated by negative feedback system in the male patients with PV, while erythropoietin

production is down-regulated by negative feedback system in the patients with PV [8]. We previously reported that serum levels of granulocyte-colony stimulating factor (G-CSF) in the patients with PV were lower than those in patients with with RE [15]. We speculate serum levels of testosterone may be down-regulated as same as erythropoietin and G-CSF. However, we do not understand the mechanism by which serum levels of estradiol in the male patients with PV were also lower than those in patients with RE. There is a rare case report showing the relationship between estrogen and polycythemia [16]. Estrogen is usually produced from testosterone during the aromatase activation. Aromatase inhibitors may increase testosterone, resulting from erythrocytosis. In our study, lower serum levels of testosterone in the male patients with PV affected lower serum levels of estrogen, in spite of the presence of aromatase.

Typical therapy for elderly patients with PV includes the use of hydroxyurea, which may induce hypogonadism [17]. However, while no patients in our study had hypogonadism, we should be aware of the potential for hypogonadism in male patients with PV after administration of hydroxyurea.

5. Conclusion

To our knowledge, this is the first study to report that serum levels of testosterone are lower in male PV patients than in those with RE.

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