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Original Article

Clinical Relevance of Serum Prolactin Levels to Inflammatory Reaction in Male Patients

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To clarify the relevance of prolactin (PRL) to clinical parameters in patients who visited our general medicine department, medical records of 353 patients in whom serum PRL levels were measured during the period from 2016 to 2018 were retrospectively reviewed. Data for 140 patients (M/F: 42/98) were analyzed after excluding patients lacking detailed records and patients taking dopaminergic agents. Median serum PRL levels were significantly lower in males than females: 6.5 ng/ml (IQR: 4.2-10.3) versus 8.1 ng/ml (5.9-12.9), respectively. Pain and general fatigue were the major symptoms at the first visit, and past histories of hypertension and dyslipidemia were frequent. Male patients with relatively high PRL levels (≥ 10 ng/ml) had significantly lower levels of serum albumin and significantly higher levels of serum LDH than those with low PRL (< 10 ng/ml). There were significant correlations of male PRL level with the erythrocyte sedimentation rate ($R = 0.62$), serum LDH level ($R = 0.39$) and serum albumin level ($R = -0.52$), while the level of serum CRP ($R = 0.33$) showed an insignificant but weak positive correlation with PRL level. Collectively, these results show that PRL levels had gender-specific relevance to various clinical factors, with PRL levels in males being significantly related to inflammatory status.

Key words: hormones, hyperprolactinemia, inflammation, pituitary, prolactin

Prolactin (PRL) is a polypeptide hormone that is phylogenetically well-conserved but elicits various species-dependent functions [1, 2]. PRL is related to the regulation of osmotic pressure in fish and amphibians, fat retention in reptiles and birds, and glucose-lipid metabolism, bone homeostasis and development of the mammary gland in mammals [3].

In humans, PRL secretion is regulated in an inhibitory manner by dopaminergic neurons that project from the hypothalamus to PRL-producing cells in the anterior pituitary gland [4]. Since dopaminergic actions are mainly mediated by dopaminergic D2 receptors (D2R), various agents that bind D2R can affect serum PRL levels [5]. In a clinical setting, hyperprolactinemia is considered in cases of galactorrhea, infertility and sexual dysfunction [5-7].

Other causes of hyperprolactinemia include PRL-producing pituitary adenomas (prolactinomas), hypothyroidism and chronic kidney disease [8, 9]. In addition, PRL receptors have been considered as therapeutic targets for some cancers (*e.g.*, prostate cancer and breast cancer) and autoimmune diseases (*e.g.*, rheumatoid arthritis and systemic lupus erythematosus) [10, 11]. It

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has also been shown that hyperprolactinemia in some patients is related to psychiatric conditions such as depression and anxiety [12, 13]. Given that several pathophysiological functions related to PRL have recently been uncovered, the clinical measurement of serum PRL levels could become more widely adopted.

In the present study, we retrospectively investigated the relevance of serum PRL levels to various clinical parameters in patients who visited a general medicine department with various symptoms at the first visits. It was of interest that there were significant correlations between serum PRL levels and inflammatory indexes, particularly in male patients. The present findings may expand the utility of PRL measurement in serum to a gender-specific inflammatory index.

Patients and Methods

Study design. We screened the medical records of 353 patients whose serum PRL levels were measured between January 2016 and December 2018 at the Department of General Medicine, Okayama University Hospital. Of those patients, 194 patients who did not have the required laboratory data and clinical information regarding self-rating depression scale (SDS) and frequency scale for symptoms of gastroesophageal reflux disease (FSSG) and 19 patients who were administered drugs that affect D2R were excluded. Among the 213 excluded cases, 128 cases were treated for hypothalamo- and pituitary-related disorders, and 103 of those 128 cases were examined in regular checkups for previously diagnosed pituitary tumors, while the other 25 cases had pituitary dysfunction from an autoimmune condition or unknown causes other than tumorous lesions. As a result, 140 patients were included in the present analysis. The decision to examine serum PRL levels was made by individual physicians for clinical purposes when hypothalamo- and/or pituitary-related symptoms were suspected. Patients with pituitary prolactinomas were not included in the present study. Data for other biochemical parameters were obtained within 1 week after measurement of PRL. Blood tests were performed in cases with adequate insurance coverage. Information on this retrospective study was disclosed on our hospital website and posted on a hospital wall, and a contact point was provided for participants who wished to opt-out. This study was approved by the Ethical Committee of Okayama University Hospital (No. 1902-005) and adhered to the Declaration of Helsinki.

Analysis of clinical parameters. Information on the patients' initial symptoms and past histories was obtained from hospital medical records. Each patient had multiple manifestations and diagnosed diseases. We obtained information on all of them, and those common to two or more patients were analyzed. Age, body mass index (BMI), SDS and FSSG were also evaluated. Blood biochemical data included the following parameters: white blood cells, red blood cells, hemoglobin, hematocrit and platelets for blood cell counts; total bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γGTP), creatinine and estimated glomerular filtration rate (eGFR) for liver and renal functions; C-reactive protein (CRP), erythrocyte sedimentation rate in one hour (ESR), ferritin, immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), 50% hemolytic unit of complement (CH50) and fibrinogen for inflammatory markers; and hemoglobin A1c (HbA1c), total cholesterol, uric acid, adrenocorticotropic hormone (ACTH), cortisol, follicle-stimulating hormone (FSH), growth hormone (GH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), and ratio of TSH/FT4 and total testosterone for endocrine and metabolic markers. The levels of the above-mentioned factors were determined using an auto-analyzer system at the Central Laboratory of Okayama University Hospital. PRL levels were determined by a fluorescence enzyme immunoassay or chemiluminescence enzyme immunoassay using a commercially available kit (Tosoh Corporation, Tokyo). The accuracy and correlation of both assay systems were validated previously.

Statistical analysis. All statistical analyses were performed with EZR, version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [14]. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Continuous measurements were tested by the Mann-Whitney *U* test or Spearman's rank correlation coefficient, since the serum PRL levels did not follow a normal distribution in either gender ($p < 0.01$ by the Shapiro-Wilk normality test). All tests

were two-sided, and p values of less than 0.05 were considered to indicate statistical significance.

Results

Patients' characteristics and distribution of serum PRL levels. The 140 patients analyzed in the present study included 42 males (30%) and 98 females (70%). As shown in Fig. 1A, the mean age of males was 48.5 ± 18.4 years and that of females was 44.7 ± 19.4 years. As shown in the left panel of Fig. 1B, the serum PRL level in male patients was significantly lower than that in female patients. The median PRL level in male patients was 6.5 (interquartile range (IQR): 4.2-10.3) ng/ml and the median level in female patients was 8.1 (IQR: 5.9-12.9) ng/ml (Fig. 1B, *left*). We also stratified female patients according to their age at the time of examination in order to account for the potential effects of menopause, which in Japanese is considered to occur at around 50 years of age [15]. As shown in the middle panel of Fig. 1B, among patients aged < 50 years, the serum PRL level was significantly higher in females than males; however, no gender-dependent difference in serum PRL levels was observed in patients aged ≥ 50 years (Fig. 1B, *right*). As shown in Fig. 1C, the correlation between serum PRL levels and age was not significant in male patients ($R = 0.17$, $p = 0.30$). Also, in female patients, the correlation of serum PRL levels with age was not significant in either the group aged < 50 years ($R = 0.025$, $p = 0.85$) or the group aged ≥ 50 years ($R = 0.037$, $p = 0.83$) (Fig. 1D).

The patients' initial symptoms and their past histories are shown in Fig. 2. The most frequent symptom was pain (26.3%, 42 of 160 symptoms), including somatic pain (20.6%, 33/160) and headache (6.9%, 11/160), followed by general fatigue (23.1%, 37/160),

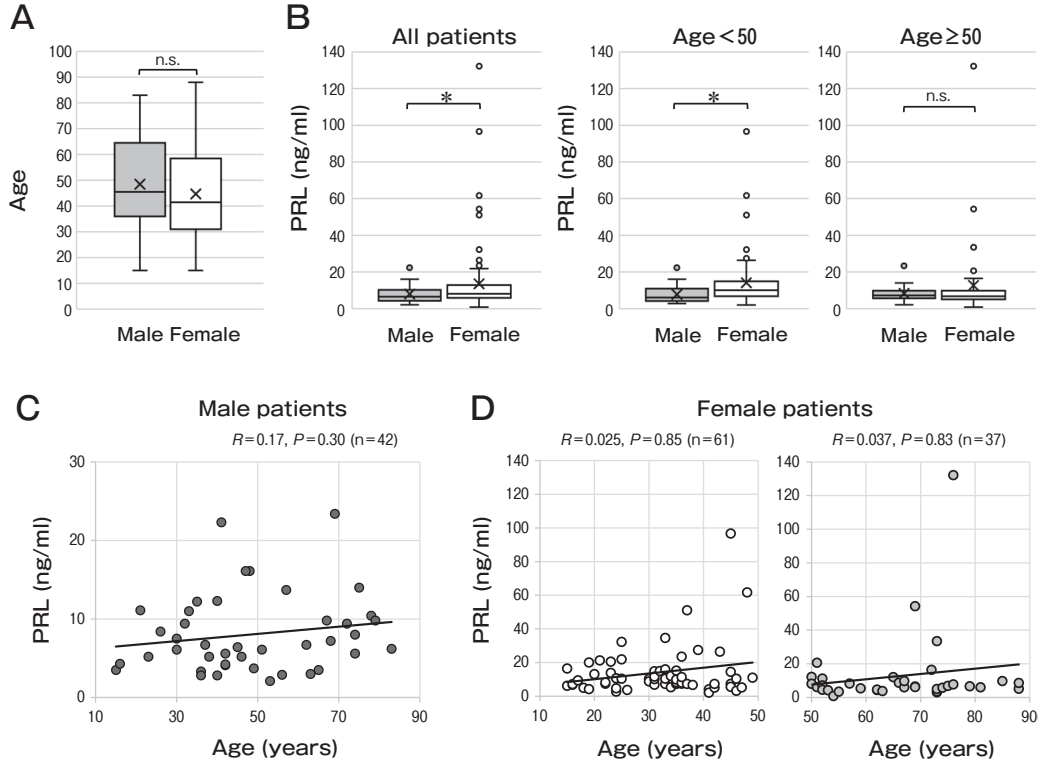

Fig. 1 Age- and gender-dependent distributions of serum PRL levels. The age-dependent distribution (A) and serum PRL levels (B) are shown for each gender. In each panel, the upper horizontal line of the box is the 75th percentile, the lower horizontal line of the box is the 25th percentile, the horizontal bar within the box is the median, the upper horizontal bar outside the box is the maximum value within 1.5 times the interquartile range, and the lower horizontal bar outside the box is the minimum value within 1.5 times the interquartile range. Interrelationships between age and serum PRL levels in male (C) and female (D) patients are shown. *$p < 0.05$, statistically significant difference between the indicated groups (B) and correlations between indicated factors (C and D). n.s., not significant; PRL, prolactin.

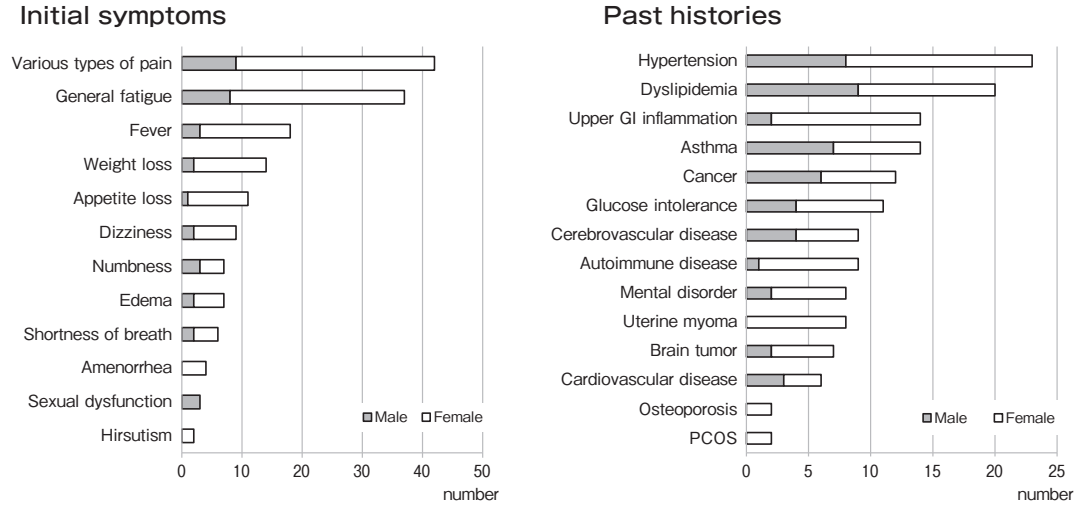

Fig. 2 Patients' main initial symptoms and past histories. The left panel shows patients' main initial symptoms (total of 160 symptoms in 140 patients) and the right panel shows past histories (145 past histories for 140 patients). Grey bars and white bars indicate the data for male and female patients, respectively. GI, gastrointestinal; PCOS, polycystic ovary syndrome.

fever (11.3%, 18/160) and weight loss (8.8%, 14/160). These symptoms were predominant in female patients, with female ratios of 78.8% for various types of pain, 78.4% for general fatigue, 83.3% for fever and 85.7% for weight loss (Fig. 2, *left*). The manifestations directly related to hyperprolactinemia included sexual dysfunction (1.9%, 3/160) in males and amenorrhea (2.5%, 4/160) and hirsutism (1.3%, 2/160) in females (Fig. 2, *left*). The most frequent past histories were hypertension (15.9%, 23 of 145 histories) and dyslipidemia (13.8%, 20/145) followed by upper gastrointestinal (GI) inflammation (9.7%, 14/145) and asthma (9.7%, 14/145) (Fig. 2, *right*). The female ratios were relatively high for upper GI inflammation (85.7%, 12/14) and hypertension (65.2%, 15/23). In addition, past histories possibly related to hyperprolactinemia included mental disorders (5.5%, 8/145), brain tumors (4.8%, 7/145) and, in female cases, polycystic ovary syndrome (PCOS; 2.1%, 2/97) (Fig. 2, *right*). Regarding the mental condition of the patients, the serum PRL level did not show a significant correlation with SDS in either of the gender groups (male: $R=0.030$, $p=0.85$; female: $R=-0.056$, $p=0.58$) (Table 1).

Relevance of serum PRL levels to inflammatory parameters. The patients were divided into 2 groups according to whether their serum PRL levels were higher or lower than 10 ng/ml (Fig. 3). A comparison of the groups with relatively high (≥10 ng/ml) and low (<10 ng/ml) serum PRL levels showed that the patients with high PRL levels had higher levels of ESR regardless of gender, though the difference was not significant (Fig. 3A). The group of male patients with relatively high PRL levels had a significantly lower level of serum albumin (Fig. 3B) but higher levels of LDH (Fig. 3C), whereas these trends were not found in female patients (Fig. 3A-C). Of note, as shown in Fig. 4, significant correlations were observed between the serum PRL level and ESR ($R=0.62$, $^{**}p<0.01$; Fig. 4A) and between the serum levels of LDH ($R=0.39$, $^{*}p<0.05$; Fig. 4B) and albumin ($R=-0.52$, $^{*}p<0.01$; Fig. 4C). The serum PRL level also showed a weak positive correlation with CRP ($R=0.33$, $p=0.076$) in male patients (Fig. 4D). The male patients for whom results are shown in Fig. 4 included 2 patients with hypothalamo- and pituitary-related diseases in their past history (Fig. 2, *right*). One patient had undergone curative surgery for acromegaly without medication or hormone replacement therapy (HRT) and the other patient had been treated with HRT for hypopituitarism after surgery for craniopharyngioma. Even when these 2 patients were excluded from the analysis, the significant relations remained between the serum PRL level and inflammatory markers in male patients (Fig. 4). The statistics after exclusion of these 2 cases were as follows: ESR: $R=0.65$, $^{**}p<0.01$; albumin: $R=-0.53$, $^{**}p<0.01$; LDH: $R=0.35$, $^{*}p<0.05$; and CRP: $R=0.30$, $p=0.12$. On the other hand, in

Table 1 Correlations between serum PRL levels and clinical parameters

	Male			Female		
Comparison				with PRL		
	number	*R*	*P* values	number	*R*	*P* values
Patients' profile						
Age	42	0.17	0.30	61 (<50 years)	0.03	0.85
				37 (≥50 years)	0.04	0.83
BMI	42	−0.050	0.76	98	−0.17	0.10
SDS	42	0.030	0.85	98	−0.056	0.58
FSSG	42	0.021	0.90	94	−0.049	0.64
Blood cell count						
White blood cell	36	0.18	0.29	91	−0.082	0.44
Red blood cell	36	−0.12	0.48	91	−0.018	0.87
Hemoglobin	36	−0.22	0.20	91	0.038	0.72
Hematocrit	36	−0.16	0.35	91	0.059	0.58
Platelet	36	−0.21	0.22	91	0.14	0.18
Liver and renal function						
Total bilirubin	33	−0.047	0.80	87	0.040	0.72
Total protein	25	−0.31	0.13	64	−0.077	0.55
Albumin	34	−0.52	0.0015**	88	−0.11	0.33
AST	35	0.17	0.33	90	−0.068	0.53
ALT	35	−0.045	0.80	90	−0.040	0.71
ALP	35	0.058	0.74	88	−0.15	0.17
LDH	35	0.39	0.021*	88	−0.074	0.49
γGTP	33	0.053	0.77	84	−0.004	0.97
Creatinine	35	0.014	0.94	91	0.036	0.74
eGFR	35	−0.059	0.74	91	0.039	0.71
Inflammatory markers						
CRP	29	0.33	0.076	83	−0.12	0.27
ESR	17	0.62	0.0074**	45	0.12	0.42
Ferritin	12	0.21	0.51	33	0.12	0.50
IgG	10	−0.037	0.92	38	0.025	0.88
IgA	10	0.35	0.33	33	0.040	0.83
IgM	10	−0.10	0.79	33	−0.013	0.94
CH50	8	0.64	0.09	31	−0.13	0.47
Fibrinogen	7	−0.56	0.19	24	−0.12	0.59
Endocrine and metabolic markers						
HbA1c	24	0.16	0.46	67	−0.19	0.13
Total cholesterol	31	−0.056	0.76	76	−0.16	0.16
Uric acid	35	−0.089	0.61	87	−0.024	0.83
ACTH	33	0.19	0.29	72	−0.0069	0.95
Cortisol	33	0.21	0.25	74	0.11	0.37
FSH	38	0.16	0.32	51 (<50 years)	−0.2	0.17
				35 (≥50 years)	−0.17	0.32
GH	36	−0.057	0.74	73	0.32	0.0062**
TSH	36	0.40	0.015*	90	0.12	0.28
FT4	36	−0.34	0.044*	84	−0.060	0.59
TSH/FT4	36	0.45	0.0063**	84	0.14	0.21
Total teststerone	25	0.079	0.71	37	−0.036	0.83

**$P<0.01$ and *$P<0.05$, statistically significant between the indicated factors.

ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CH50, 50% hemolytic unit of complement; CRP, C-reactive protein; eGFR, creatinine and estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate in one hour; FSH, follicle-stimulating hormone; FSSG, frequency scale for the symptoms of gastroesophageal reflux disease; FT4, free thyroxine; γGTP, γ-glutamyl transpeptidase; GH, growth hormone; HbA1c, hemoglobin A1c; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; PRL, prolactin; SDS, self-rating depression scale; TSH, thyroid-stimulating hormone; Parentheses indicate patients' age.

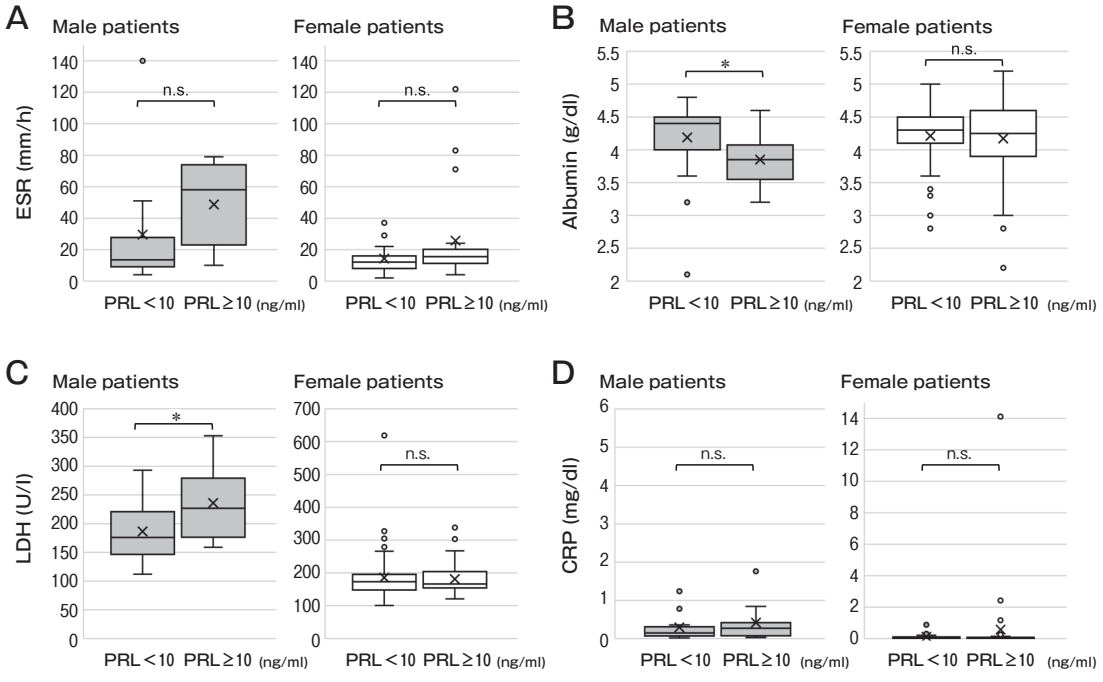

Fig. 3 Trends of inflammatory marker levels in relation to serum PRL levels. The patients were divided into two groups according to their serum PRL levels (≥10 ng/ml and <10 ng/ml). (**A**) ESR and serum concentrations of (**B**) albumin, (**C**) LDH, and (**D**) CRP in the patients are shown for each gender. An explanation of each panel is given in the legend of Fig. 2. $^{*}p<0.05$, statistically significant difference between the indicated factors. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate in one hour; LDH, lactate dehydrogenase; n.s., not significant; PRL, prolactin.

female patients, serum PRL levels had no significant relevance to the levels of ESR ($R=0.12$, $p=0.42$), albumin ($R=-0.11$, $p=0.33$), LDH ($R=-0.074$, $p=0.49$) or CRP ($R=-0.12$, $p=0.27$) (Table 1).

Interrelationships between serum PRL levels and other laboratory data. The PRL levels showed significant correlations with thyroid functions, including TSH ($R=0.40$, $^{*}p<0.05$), FT4 ($R=-0.34$, $^{*}p<0.05$) and the TSH/FT4 ratio ($R=0.45$, $^{**}p<0.01$), in male patients but not in female patients (Table 1). There were no significant correlations between male PRL levels and laboratory markers involved in the changes of ESR levels [16, 17], including age, BMI, hemoglobin, renal functions as determined by creatinine and eGFR, immunoglobulins including IgG, IgA and IgM, and fibrinogen, as shown in Table 1. Considering that menopause could affect serum FSH levels in female patients, female patients were analyzed by stratifying them into two age groups of <50 and ≥50 years for the correlation analysis between FSH and PRL. No significant correlation was found in either age group (age <50 years: $R=-0.20$, $p=0.17$; age ≥50 years: $R=-0.17$, $p=0.32$) (Table 1). In addition, the serum PRL level was positively correlated with the serum GH level ($R=0.32$, $^{**}p<0.01$) only in female patients (Table 1).

Discussion

In the present study, we found that PRL levels had gender-specific relevance to various clinical factors. In general, the PRL levels were lower in males than in females, and pain and general fatigue were frequent manifestations of all the patients. Past histories of hypertension and dyslipidemia were also frequent. Of interest, the serum PRL level in male patients was positively correlated with inflammatory indicators, including ESR and serum levels of LDH and CRP, but was negatively correlated with the serum level of albumin, suggesting that PRL is functionally involved in various inflammatory reactions like a cytokine. On the other hand, female PRL levels were not correlated with such an inflammatory status.

In recent pathophysiological research on PRL, much attention has been paid to inflammation, especially

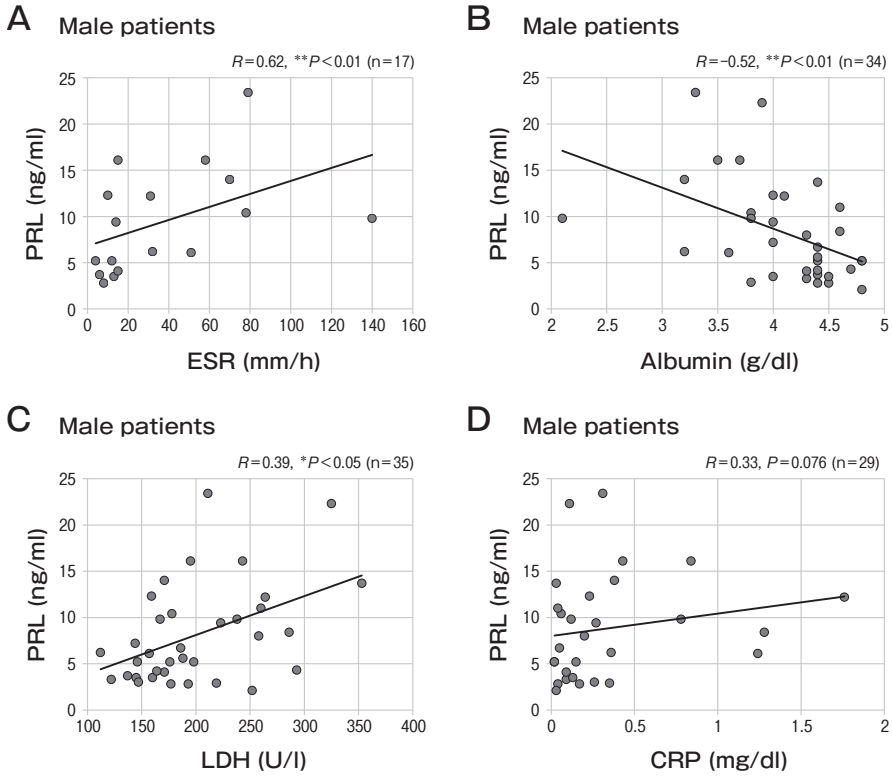

Fig. 4 Interrelationships between serum PRL levels and main inflammatory markers in male patients. Correlations of serum PRL level with (**A**) ESR and serum levels of (**B**) LDH, (**C**) albumin and (**D**) CRP are shown. $^{**}p<0.01$ and $^{*}p<0.05$, statistically significant difference between the indicated factors. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate in one hour; LDH, lactate dehydrogenase; n.s., not significant; PRL, prolactin.

inflammation in autoimmune diseases [18]. A meta-analysis conducted by Wu *et al.* revealed that the circulating PRL level in patients with rheumatoid arthritis was significantly higher than that in control patients [19], and the parameters for patients with higher circulating PRL levels were Asian race, age ≥50 years and ESR ≥25 mm/hour. Increases in circulating PRL levels in patients with systemic lupus erythematosus [20] and multiple sclerosis [21] have also been shown by using meta-analyses. In addition, other autoimmune diseases such as polymyalgia rheumatica [22] and psoriatic arthritis [23,24] have been considered to have some relation to the levels of PRL, although direct associations between such diseases and PRL activity have yet to be clarified.

Here, we revealed a correlation between PRL and an inflammatory condition in male patients who visited our general medicine department. It has been reported that acute inflammation upregulates PRL through an extra-pituitary mechanism, while chronic inflammation induces PRL by both pituitary and extra-pituitary pathways [25,26]. ESR is a marker of inflammatory status, particularly in the acute phase reactions seen in cases of infection, autoimmune disease and cancer. ESR is the rate at which erythrocytes settle at the bottom of a test tube in an anticoagulated blood sample, usually over a period of one hour. Some molecules, such as fibrinogen and immunoglobulins, that promote aggregation of erythrocytes can increase ESR [16]. However, an increase in ESR is also observed in patients with anemia, renal failure, or obesity, in aged patients and in female patients [17]. In the present study, serum PRL levels were not correlated with these factors that affect ESR.

Pain was the most frequent initial symptom in our patients. A large proportion of the female patients (78.8%) complained of various types of pain. It has been shown that serum PRL levels are elevated in patients with migraine [27] and in an experimental mouse model of postoperative pain [28]. As for the gender-

dependent difference in inflammatory reactions associated with PRL, it has been suggested that PRL might act on inflammatory cells and signaling in different ways depending on the gender of the patient. An elevated PRL level can modulate endocrine as well as immune responses, and a positive feedback loop in which PRL stimulates the immune system while the products of immune cells stimulate further PRL secretion has been suggested [18, 29]. In basic studies, PRL and its receptors have been shown to have some functional roles in neurogenesis, neuroprotection and neural plasticity, particularly in the hippocampus [12]. From a clinical point of view, hyperprolactinemia has been shown to be related to psychiatric disorders such as depression and anxiety [13]. In the present study, the correlation between serum PRL level and SDS at the time of blood sampling was not significant in either gender, although 8 patients had past histories of psychiatric disorders such as depression, bipolar disorders and eating disorders.

It seems likely that at least some portion of the modulatory effects of PRL on endocrine and immune activities occur in a gender-dependent manner. For instance, knockout of the PRL receptor has been shown to affect ovarian steroidogenesis in estrous female mice but to have no effect on the androgen level in male mice [30]. In our study, gender-dependent differences were found in the interrelationships between levels of serum PRL and other endocrine factors such as thyroid hormone and GH. The pro-nociceptive actions of PRL also seem to be different in males and females, since ablation of the PRL system caused a reduction of hypersensitivity to thermal stimuli in only female mice [28], although the mechanisms contributing to the gender-dependent differences in pain sensitivity remain unclear.

There were some limitations of the present study. Serum PRL levels can be affected by circadian rhythm, stress, medicines and the menstrual cycle. Also, this study was a retrospective single-center study in which sample sizes were relatively small and blood samplings were not always performed in the same period of time. Further studies, including studies using a multi-center database, will be needed to uncover the novel gender-specific roles of PRL in the field of general medicine. Certainly, it is reasonable to measure serum PRL levels when we suspect and/or are following-up hypothalamo- and pituitary-related diseases. However, considering the novel interrelationships between PRL and inflammatory indexes, attention must be given to latent inflammatory conditions even when examining patients with endocrine disorders. In order to clarify the clinical details of the mutual interaction between PRL and inflammation, a prospective study in age- and gender-matched cohorts is needed.

Collectively, in male patients at our general medicine department, PRL levels were significantly related to inflammatory status. Our findings suggest that there are gender-specific differences in the responses and roles of hormones and inflammation pathways in general medicine patients.

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