Hypertension, diabetes mellitus (DM), hyperlipidemia, and smoking all represent significant risk factors for cardiovascular disease (CVD) because they are all considered to induce vascular endothelial damage, resulting in vascular obstruction, plaque rupture, thrombosis, arterial sclerosis, and also erectile dysfunction (ED). More specifically, ED can be considered a symptom of damage to the vascular endothelium (Fig 1). Therefore, it can be expected that ED will be concomitant with CVD, and that the presence of ED suggests the existence of CVD. Integrated medical care may be necessary for these disease states. However, epidemiological data on ED and information regarding the current status of ED treatment among general practitioners in Japan is limited, possibly because there are no established criteria for the diagnosis of ED, as well as the societal and psychological obstacles to the patient consulting a clinician regarding this condition.

Since its launch in March 1999, sildenafil citrate (Viagra® Tablets) has become widely used by numerous patients with CVD. Sildenafil selectively inhibits the action of intracellular phosphodiesterase 5 (PDE5) in the corpus cavernosum of the penis, and ameliorates the effects of ED by enhancing the action of cyclic guanosine monophosphate (cGMP) on vascular smooth muscle. The activity of PDE in the ventricle and saphenous veins of humans has been precisely measured, and the magnitude of the action of sildenafil on the cardiovascular system and its high affinity for PDE5 have been clearly demonstrated. In vitro examination of the effects of sildenafil on the activity of PDE isozymes originating from the human corpus cavernosum also suggests a high selectivity of sildenafil for PDE5 in that specific tissue.

Since sildenafil became available, public interest in ED has increased substantially and we therefore conducted a survey of general practitioners setting, because understanding the consultation status of ED treatment is important for the promotion of the optimal treatment of ED.
Study Objectives

To date, the Cardiovascular Issue Examining Committee of Viagra (organized by members affiliated to relevant academic societies in Japan, principally the Japanese Circulation Society) has issued 2 reports. The first reviewed the epidemiological studies of ED and existing statistics on CVD. In as well as describing the mechanism of action of sildenafil and clinical experience. The second report described the precise indications for sildenafil and the management of adverse events relevant to both general practice and cardiology. The present questionnaire survey of general practitioners was conducted as part of the activities of this committee, in order to investigate the current status of ED and its treatment in Japan.

Methods

In the 4-month period from August to November 2001, a self-administered questionnaire survey was sent to general practitioners' offices and clinics all over Japan, because they represent the principal providers of medical care for lifestyle-related diseases. The level of patient satisfaction with their sex life was surveyed as a quality-of-life (QOL) profile, in addition to background information such as age, diseases under current medical treatment and health status, categorized into 5 levels. The level of satisfaction with sex life was evaluated by the question ‘To what extent are you satisfied with your current sex life?’ using 5 categories from ‘very much’ to ‘very little’. The International Index of Erectile Function (IIEF)-5, which shortens the IIEF to 5 questions, was used to evaluate ED. The score of the IIEF-5 ranges from 5 to 25 points. In general evaluations using the IIEF-5, subjects are considered to have ED if they have a score of 5–21 points and are considered normal with a score of 22–25 points. Subjective evaluation of erectile function scored using IIEF-5 has been verified to suitably reflect objective measures of erectile function as determined by the nocturnal penile tumescence (NPT) test using the RigiScan Plus. In addition, psychological factors and urinary disturbance caused by prostate hyperplasia were evaluated using the Center for Epidemiologic Studies-Depression Scale (CES-D) and the International Prostatic Symptoms Score (I-PSS), respectively, as these are issues related to ED. Medical consultation for these health conditions, and satisfaction with the outcome, were also examined.

With regard to the method of administering the questionnaire, letters of intent were obtained from physicians throughout Japan who agreed to the purpose of the present survey. The self-administered questionnaires were then sent to the physicians and the reply forms were mailed either individually by the patients themselves or collectively by the physician in charge. Data were entered on an anonymous basis.

Statistical Analysis

The likelihood ratio test was conducted for concomitant CVD and severity of ED, and increased risk of ED with disease comorbidity. Furthermore, to calculate the risk of ED in the presence of any given disorder, subjects were categorized as either normal subjects or ED patients according to the IIEF-5 scores. A logistic model was then used to calculate the odds ratios (OR) and determine the magnitude of risk. Statistical significance was defined as p<0.05.

Results

Letters of interest were obtained from 700 outpatient clinics and 6,112 questionnaires were collected from 447 clinics. The mean (±SD) number of collected forms per medical institution was 14±9. The present survey was conducted in the outpatient setting of medical specialties including departments of Internal Medicine, Urology, Surgery, Orthopedics, Gastroenterology, Cardiology, and Radiology. Shin Joho Center, Inc collected and compiled the forms received from the participating medical institutions throughout Japan. Patients in the ages of 30–70 years accounted for 93% of the patients participating in the survey, with more than half (52.3%) of the total subject population represented by males aged in their 50s and 60s (Fig 2).

A total of 4,609 of the 5,683 patients who answered the IIEF-5 questions in the present survey had an IIEF-5 score ≤ 21 points, which was 81% of the respondents (Fig 3). According to the 5-level categorization of severity proposed by Rosen patients with ED in the categories of ‘severe’ to
Diabetes mellitus, heart disease, and hypertension displayed a difference in risk of ED when compared with age (IIEF-5 score: ≤16) accounted for 63.2% of all patients affected by ED (Fig 3). Severe ED was more pronounced among aged patients (Fig 4). Regarding the level of satisfaction with sex life, patients giving a reply of ‘moderately dissatisfied’ or ‘very dissatisfied’ comprised 30.2% of all replies.

CVD and ED

Subjects in the present survey displayed a mean of 1.45 concomitant diseases and the most frequently observed CVD was hypertension, accounting for 46% of valid replies (n=4,990) after excluding missing data (Fig 5). Furthermore, heart disease was observed in 10% of patients. In the present survey, patients over 70 years of age accounted for 40% of patients with heart disease who were undertaking medical treatment. These patients tended to be older than those with other conditions. ED was significantly more severe in the presence of heart disease (p<0.0001). Patients with severe or moderate ED comprised 46% of those with heart disease, but only 27% of those without (Fig 6).

Difference in Risk of ED According to Concomitant Disease

Among the concomitant lifestyle-related diseases, DM (21%) and hyperlipidemia (18%) predominated (Fig 5). Diabetes mellitus, heart disease, and hypertension displayed significant correlations with ED, with OR of 2.88, 2.82 and 1.79, respectively; however, the presence of hyperlipidemia did not affect the risk of ED (Table 1).

The risk of ED was calculated for an additional complication of an underlying disease. In the presence of heart disease, the risk of ED increased when DM was a complication (p=0.0004, p-value: likelihood ratio test) though it did not increase significantly when either hypertension (p=0.2490) or hyperlipidemia (p=0.0917) was the complication. Comparing the percentages of severe ED and moderate ED between patients with both heart disease and DM and those with only heart disease, the former was 65% and the latter was 42%.

Willingness to Receive Pharmacotherapy for ED

A total of 41% of patients did not respond to the question regarding willingness to receive pharmacotherapy for ED if it was available; however, 22.3% of the patients who replied did expressed such a willingness. The percentage of patients considering treatment for ED and of those unwilling to undergo treatment was 18.8% and 58.8%, respectively. The percentage of patients willing to receive pharmacotherapy did not differ among patients with hypertension, heart disease, or hyperlipidemia. However, patients with DM showed a significantly higher willingness to receive treatment (p<0.0001). In addition, patients affected by heart disease expressed less satisfaction with their sex life, compared with patients without the disease (p<0.0001). Conversely, the lower the satisfaction with sex life, the higher the willingness to accept pharmacotherapy for ED. However, patients who had actually undergone some form of treatment for ED comprised less than 40% of those patients who were willing to receive medication for ED.

Discussion

The Men’s Health Study used the IIEF-5, and the ED evaluation scale revealed that 81% of patients aged in the 30s to 70s who underwent a medical examination by general practitioners on an outpatient basis had some degree of ED.

The prevalence of ED reportedly increases with age, and the prevalence of ED by age of patients with an IIEF-5 score ≤16 in the present study closely resembled that of patients categorized as displaying Complete or Moderate ED in the study conducted by Shirai. In addition, ED was more prevalent among patients who had concomitant CVD or DM, which is a comparable result to other epidemiological studies conducted in Japan. Marumo et al identified hypertension, DM, heart disease, and cerebral infarction as risk factors associated with ED in males between the ages of 40 and 79 years. Another nationwide epidemiological study also demonstrated that ED was predominant in patients affected by CVD or DM. Similar results were obtained in an epidemiological survey conducted among males between the ages of 40 and 70 years in Massachusetts, USA. Concomitant CVD and DM can therefore be considered to increase the risk of ED, although hyperlipidemia does not appear to represent a significant risk factor, as indicated by both the present results and the findings of Marumo et al.

Patients undergoing treatment for ED in the course of routine medical care are highly likely to have CVD. Cur-

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**Table 1 Concomitant Diseases and Correlation With Erectile Dysfunction**

<table>
<thead>
<tr>
<th>Concomitant Disease</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>1.79</td>
<td>1.51--2.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.23</td>
<td>3.70--4.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2.88</td>
<td>2.61--3.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.98</td>
<td>0.50--1.88</td>
<td>0.95</td>
</tr>
</tbody>
</table>

R² = 0.0608; Cutoff = 21/22 (IIEF-5); logistic, OR, odds ratio.
rently, the first choice for ED treatment among general practitioners in daily clinical practice is sildenafil. Although the effects of sildenafil on the cardiovascular system were of concern in the early stages of its development, experience has demonstrated that sildenafil exerts positive effects on vascular endothelial cells and the safety of the drug has been established in the clinical setting. Safety information on sildenafil collected from Japanese general practitioners was reported for 3,152 cases in the Drug Use Investigation Study on sildenafil. According to that study, the proportion of adverse drug reactions was 5.27% (166/3,152), and no serious adverse reactions were reported. In a study that examined the effects of sildenafil on coronary flow reserve in patients with serious coronary disease, baseline and post-administration data were compared. Systemic arterial pressure and pulmonary arterial pressure were shown to decrease slightly (<10%), and no effects on pulmonary capillary wedge pressure, right atrial pressure, heart rate, or cardiac output were observed. In addition, coronary flow reserve was shown to be significantly augmented. The acute inhibitory activity of sildenafil on PDE 5 is demonstrated by increases in endothelium-dependent, bloodstream-mediated vasodilation in patients with chronic heart failure. Those findings indicate that the inhibition of PDE 5 by sildenafil can rapidly improve endothelium-dependent vasodilation in patients with chronic heart failure. Sildenafil represents a safe therapeutic option when used appropriately, and does not add to the risk of cardiovascular dysfunction. However, as revealed in the present survey, ED treatment is not adequately meeting the needs of patients. Clinicians should be encouraged to actively question patients regarding ED and provide an environment in which patients can comfortably and easily consult with clinicians regarding such issues.

Conclusion

The Men’s Health Study shows that middle-aged Japanese men with CVD, DM or hypertension are commonly affected by ED. Cardiovascular specialists need to pay attention to treatment of sexual dysfunction as a real component of their patients’ QOL. Patients who were either willing to receive pharmacotherapy for ED or were considering treatment accounted for 41% of the ED patients in the present study. Sildenafil is a practical therapy for cardiovascular specialists to administer in daily practice, and both pharmacological and clinical evidence has been accumulated regarding the safety of the drug on the cardiovascular system. Based on these factors, active treatment of ED using sildenafil is suitable for patients with CVD.

Acknowledgments

We express our thanks to those who kindly answered the questionnaire and to the doctors-in-charge for their cooperation with the administration of this survey.

This study was supported in part by grants from the Japan Heart Foundation.

References