Evaluation of aortic stiffness in Gilbert syndrome patients: a protective effect of elevated bilirubin levels

Gilbert sendromlu hastalarda aort sertliğinin değerlendirilmesi: Artmış bilirubin düzeyinin koruyucu etkisi

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ABSTRACT

Objective: Gilbert's syndrome (GS) is an autosomal recessive disease that is characterized by an increase in indirect bilirubin (IB). The incidence of atherosclerotic heart disease is decreased in GS. This study aimed to investigate the relation between pulse wave velocity (PWV) and the presence of GS.

Methods: The study included 58 GS patients (32 females, age; 27.12±7.27 years, 26 males, age; 26.63±5.84 years) admitted to the internal medicine clinic of the hospital. The control group included 58 healthy individuals (35 females [27.33±8.06 years old, p=0.716] and 23 males [27.38±6.91 years old, p=0.923]). PWV of both groups was measured from the right carotid and femoral arteries.

Results: Mean age of the GS group was 26.03±8.22 years, while that of the healthy group was 26.60±5.84 years. The GS group's diastolic blood pressure and PWV were significantly lower than those of the control group: 67.76±8.59 mmHg vs 71.72±7.28 mmHg; p=0.008, and 5.63±1.12 m/s vs 6.18±1.22 m/s; p=0.014 respectively. The GS group's high density lipoprotein (HDL) level was significantly higher than that of the control group: 1.4±0.3 mmol/L vs 1.2±0.3 mmol/L, p=0.029.

Conclusion: This study found PWV among GS patients to be lower than that among non-smoking and aged-matched healthy controls.

ÖZET

Amaç: Gilbert sendromu (GS) indirekt bilirubin artışıyla karakterize otozomal resesif bir hastalıktır. Gilbert sendromunda aterosklerotik kalp hastalığı insidansı azalmıştır. Biz bu çalışmada GS'nin varlığı ve nabız dalga hızı (NDH) arasındaki ilişkiyi incelemeyi amaçladık.

Yöntemler: Bu çalışmaya hastanemiz iç hastalıkları kliniğine başvuran 32 kadın (yaş: 27.12±7.27) ve 26 erkek (yaş: 26.63±5.84) olmak üzere toplam 58 GS'li hasta alındı. Kontrol grubu olarak benzer yaş grubunda olan 35 kadın (yaş: 27.33±8.06, p=0.716) ve 23 erkek (yaş: 27.38±6.91, p=0.923) olmak üzere 58 sağlıklı katılımcı çalışmaya dahil edildi. Her iki grubun NDH'si sağ karotis ve femoral arterlerden ölçüldü.

Bulgular: Gilbert sendromu grubunun yaş ortalaması 26.03±8.22 yıl ve sağlıklı grubun yaş ortalaması 26.60±5.84 yıl idi. Gilbert sendromu grubunun diyastolik kan basıncı (67.76±8.59 mmHg) ve NDH'si (5.63±1.12 m/s) kontrol grubundan (71.72±7.28 mmHg, p=0.008; 6.18±1.22 m/s, p=0.014) anlamlı olarak daha düşüktü. Gilbert sendromu grubunun yüksek yoğunluklu lipoprotein düzeyi (1.4±0.3 mmol/L) kontrol grubundan (1.2±0.3 mmol/L mmol/L, p=0.029) anlamlı şekilde daha yüksekti.

Sonuç: Biz bu çalışmada, GS'li hastaların NDH değerlerini sigara içmeyen, yaş uyumlu sağlıklı bireylerden düşük bulduk.

Gilbert's syndrome (GS) is a congenital disorder due to a defect of the UDP-glucuronosyl transferase enzyme. It has been observed in a total of 3% to 17% of Caucasians, and as 12.4% in males and 4.8% in females.[1] GS may not require lifelong treatment. GS patients have high levels of indirect bilirubin (IB), which has been reported as cardioprotective due to its potent antioxidant effect.[2,3] In previous studies it has been shown that IB lowers the incidence of atherosclerotic heart disease by decreasing lipid peroxida-

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tion.[4,5] Another study with a large population reported longer lifespans among GS patients compared to healthy subjects due to the cardioprotective effect of IB.[6]

Abbreviations:

BMI	*Body mass index*
BP	*Blood pressure*
CAD	*Coronary artery disease*
CRP	*C-reactive protein*
GS	*Gilbert's syndrome*
HDL	*High density lipoprotein*
IB	*Indirect bilirubin*
LDL	*Low density lipoprotein*
m/s	*Distance/time*
PWV	*Pulse wave velocity*

Aortic stiffness is a mechanical tension and a reflection of aortic wall elasticity.[7] It increases as a result of oxidative stress-induced endothelial damage. Previous studies have shown an increase of aortic stiffness in relation to hypertension, diabetes mellitus, smoking and aging, all of which accelerate the atherosclerotic process.[8–10] There is a strong relation between coronary artery disease (CAD) severity and aortic atherosclerosis.[11] Aortic atherosclerosis has a direct effect on aortic stiffness, which can be evaluated by the simple, non-invasive method of pulse wave velocity (PWV).[12] In a small population study, PWV of GS patients has been evaluated and found to be lower than that among the control group.[13] The present study aimed to explore PWV difference as a marker of aortic stiffness in patients with and without GS.

METHODS

Study population

The study was a cross-sectional observational study at the Department of Internal Medicine of our Faculty of Medicine conducted between February 2012 and July 2012. It comprised 58 GS patients (32 females, 26 males) and 58 healthy subjects (35 females, 23 males) who were selected from patients admitted to our clinic for routine checkup. An age range of 16 to 45 years was decided upon as GS appears mostly in adolescence, and the incidence of chronic diseases increases after the age of 45. The study was approved in accordance with Helsinki criteria by the local Ethics Committee. (Approval numbers: 2012/20)

Diagnosis of GS

The inclusion criteria of previous GS studies were used.[2,3,14] Thus, GS was diagnosed in the presence of elevation of IB levels, occurring at least twice, measured at the basal and after 15 or 21 days, since IB half-life is prolonged to 14–21 days when bound to albumin.[15]

Inclusion criteria

Patients with mild indirect hyperbilirubinemia (13.68–102.6 µmol/L), normal hepatic enzymes, reticulocyte level <2% measured by reticulocyte smear, lack of hemolytic disease and normal hepatic ultrasonography were considered as GS. Patients without known disease and IB level <11.97 µmol/L were included in the healthy control group.

Exclusion criteria

For both GS and the control group subjects, the following conditions were exclusion criteria: arrhythmias, heart failure, cardiac disease, hypertension, acute or chronic renal failure, peripheral artery disease, dyslipidemia, diabetes mellitus or prediabetes, hyperthyroid or hypothyroid state, cirrhosis, acute and chronic hepatitis, nonalcoholic fatty liver disease, cancer, hematologic diseases, hemolysis, vitamin B12 deficiency, active and chronic infection, chronic drug usage, smoking and use of alcohol.

Pulse wave velocity measurement

Before the procedure, blood pressure (BP) was measured manually with a suitable arm cuff after 10 minutes of rest in the supine position. Measurements were performed 3 times with an interval of one minute from the right arm and the average obtained. Findings within the normal range meant that PWV measurements could be performed. All PWV measurements were performed by a cardiologist using Sphygmocor EM3 (Australia) equipment from the right carotid artery and the right femoral artery and recorded as distance/time (m/s).

Measurement of laboratory tests

Biochemical tests were performed with the photometric assays of an Abbott Architect C16000 analyzer (Abbott Diagnostics, USA). Thyroid-stimulating hormone and vitamin B12 tests were performed using the Chemiluminescent Microparticle Immunoassay (CMIA) method with an Abbott Architect I 2000 analyzer (Abbott Diagnostics, USA). The C-reactive protein (CRP) test was performed using nephelometry with the Coulter Immage 800 device, and the hematologic tests were performed using the Abbott Cell Dyn Ruby analyzer (Abbott Diagnostics, USA).

Statistical analysis

The results were reported as the mean±SD. The data

analysis was performed using the statistical software SPSS for Windows (version 13.1; SPSS, Chicago, IL, USA). All results were analyzed by the Kolmogorov-Smirnov test. The statistical differences of most parameters were analyzed using the independent samples student t-test. Total bilirubin and IB values were analyzed using the Mann Whitney U test. The two-way ANOVA test was used to determine differences between the genders. The relationship between the variables was analyzed with Pearson's correlation. The differences and correlations were considered significant at $p<0.05$.

RESULTS

Patient and control groups did not differ in terms of demographic and basal clinical analyses (Table 1). No smoker or diabetic was included in either group. A family history of CAD was positive in 5 GS patients and 7 healthy subjects. Mean age of the GS group was 26.03±8.2 years, body mass index (BMI) 21.98±4.15 kg/m^2, waist circumference 78.02±11.4 cm, systolic BP 104.66±13.1 mmHg, diastolic BP 67.76±8.5 mmHg, and PWV 5.63±1.1 m/s. Mean age of the control group was 26.6±5.8 years, BMI 22.16±3.6 kg/m^2, waist circumference 78.97±9.3 cm, systolic BP 108.28±11.41 mmHg, diastolic BP 71.72±7.21 mmHg, and PWV 6.18±1.2 m/s. Patient characteristics are shown in Table 1.

Total bilirubin ($p<0.001$) and IB ($p<0.001$) of the GS group were significantly higher than the control group. While PWV ($p=0.014$) and diastolic BP ($p=0.008$) of the GS group were found to be significantly lower, high density lipoprotein (HDL) ($p=0.029$) was significantly higher in this group than in the control group. There were no significant differences between the two groups with respect to age, BMI, waist circumference, systolic BP, fasting glucose, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine and lipid parameters ($p>0.05$). The laboratory values are shown in Table 2.

The results of gender subgroup analysis in the GS and control groups are shown in Table 3. Both systolic and diastolic BPs of healthy male subjects were significantly higher than in the other three subgroups. While PWV among healthy males was higher than in the other three groups, PWV among the GS male group was significantly lower than in the healthy males. PWV of GS females was significantly lower than in the other three subgroups. The subgroup analyses are shown in Table 3.

In the correlation analysis for both groups, a negative correlation was found between PWV and total bilirubin ($p=0.034$), and IB ($p=0.038$) and HDL ($p=0.029$) respectively. A positive correlation was found for PWV and glucose ($p<0.001$), hemoglobin ($p=0.007$), age ($p=0.038$), BMI ($p=0.036$) and waist circumference ($p=0.003$) respectively. The correlation result of PWV and IB are shown Table 4.

DISCUSSION

The study found PWV and diastolic BP among GS patients to be significantly lower than those in the control group. Even though systolic BP, low density lipoprotein (LDL) and CRP among the GS group were lower than in the control group, the difference did not reach statistical significance. IB, total biliru-

Table 1. Clinical characteristics and PWV of the non-smoking non-diabetic groups

	Gilbert's syndrome (n=58)	Control (n=58)	*p*
Gender (Male/Female [n])	32/26	35/23	0.907
Age (years)	26.03±8.22	26.60±5.84	0.668
Body mass index (kg/m^2)	21.98±4.15	22.16±3.64	0.813
Waist circumference (cm)	78.02±11.48	78.97±9.33	0.627
Systolic blood pressure (mmHg)	104.66±13.14	108.28±11.41	0.116
Diastolic blood pressure (mmHg)	67.76±8.59	71.72±7.28	0.008
Xulse wave velocity (m/s)	5.63±1.12	6.18±1.22	0.014

Values are presented as mean±SD and number Student's t-test for independent samples.

Table 2. Results of laboratory parameters of the two groups

	Gilbert's syndrome patients	Healthy subjects	*p*
	Mean±SD	Mean±SD	
Aspartate aminotransferase (IU/L)	17.28±4.25	17.45±4.79	0.838
Alanine transaminase (IU/L)	15.28±8.78	15.10±9.55	0.920
Fasting plasma glucose (mmol/L)	5.21±0.50	5.32±0.52	0.187
Total bilirubin (μmol/L)	35.95±12.07	12.09±5.11	0.001
Indirect bilirubin (μmol/L)	25.57±11.97	6.02±3.46	0.001
Gamma-glutamyl transpeptidase (IU/L)	17.17±12.02	16.34±7.64	0.659
C-reactive protein (mg/dL)	0.18±0.33	0.38±1.11	0.183
Creatinine (μmol/L)	62.88±8.85	67.21±8.83	0.114
Blood urea nitrogen (mmol/L)	9.77±4.04	9.27±2.95	0.453
Thyroid stimulating hormone (mIU/L)	1.61±0.69	1.60±0.96	0.972
Hemoglobin (g/dL)	13.85±1.43	13.47±1.85	0.226
Platelets (x10^9/L)	254.60±57.96	251.01±44.76	0.710
White blood cell counts (x10^9/L)	6.56±1.74	6.84±1.52	0.351
Total cholesterol (mmol/L)	4.22±0.71	4.23±0.69	0.635
Triglycerides (mmol/L)	0.93±0.46	0.92±0.39	0.414
Low density lipoprotein (mmol/L)	2.50±0.53	2.56±0.60	0.474
High density lipoprotein (mmol/L)	1.43±0.36	1.24±0.33	0.029

Student's t-test for independent samples (for TB and IB were used Mann Whitney U test).

Table 3. Subgroup analysis of pulse wave velocity and laboratory parameters in GS and control groups

	Indirect bilirubin	Systolic BP	Diastolic BP	Pulse wave velocity
Gilbert syndrome male	30.80±13.75	106.12±11.56	69.58±8.71	6.03±1.01
Gilbert syndrome female	20.55±8.61¶	104.30±15.32	67.05±9.62	5.33±1.12^{W}
Healthy subject male	6.86±5.11$^{¶\#}$	115.80±8.45$^{\pi\#}$	76.90±5.89$^{¥\#}$	6.59±1.34$^{\#}$
Healthy subject female	5.15±3.48$^{¶\#}$	104.47±11.30$^{\chi}$	69.80±7.02$^{\beta}$	5.94±1.15^{ER}
*F	57.30	4.86	6.17	5.22
*P	0.001	0.003	0.001	0.002

Values are presented as mean±SD. BP: Blood pressure; *: Two way ANOVA; ¶: p<0.001; ¥: p=0.003; πp=0.008, Wp=0.035 vs. GSM group; #: p<0.001, Ep=0.047 vs. GSF group; χ: p<0.001, β: p=0.002, Rp=0.033 vs. HSM group.

bin and HDL levels among GS patients were significantly higher than those of the control group. While PWV has a positive correlation with glucose, BMI, waist circumference, age, aspartate aminotransferase, alanine aminotransferase and hemoglobin, it has a negative correlation with IB and HDL. Elevated levels of HDL are known to be protective against CAD. Thus, high PWD levels are expected in patients with low HDL. As IB is an end product of hemoglobin metabolism, the presence of a strong relation between IB and hemoglobin is considered normal. Elevated hemoglobin levels in patients without anemia has been reported to have a strong positive relation with arterial stiffness and cardiac mortality in hypertensive patients.[16] The present study found a strong positive relation between PWD and hemoglobin, and a strong positive correlation between liver function tests and PWD. The strong relation of simple steatosis and non-

Table 4. Pearson correlation coefficients between indirect bilirubin, pulse wave velocity and measured parameters

	Indirect bilirubin		Pulse wave velocity	
Variable	r	*p*	r	*p*
Gender	-0.229	0.013	-0.258	0.005
Age	0.099	0.290	0.193	0.038
Body mass index	0.001	0.998	0.195	0.036
Waist circumference	0.052	0.579	0.277	0.003
Systolic blood pressure	-0.128	0.172	0.167	0.074
Diastolic blood pressure	-0.152	0.103	0.136	0.145
Pulse wave velocity	-0.194	0.038		
Aspartate aminotransferase	0.037	0.696	0.219	0.018
Alanine transaminase	0.080	0.393	0.312	0.001
Fasting glucose	-0.046	0.625	0.291	0.001
Total bilirubin	0.966	0.001	-0.197	0.034
Indirect bilirubin			-0.194	0.038
Gamma glutamyl transferase	0.148	0.112	0.266	0.004
C-reactive protein	-0.131	0.162	0.120	0.198
Creatinine	-0.046	0.624	0.158	0.089
Blood urea nitrogen	0.126	0.178	0.043	0.646
Thyroid stimulating hormone	0.091	0.333	-0.023	0.810
Hemoglobin	0.264	0.004	0.248	0.007
Platelets	-0.026	0.784	0.076	0.418
White blood cell counts	-0.036	0.701	0.164	0.078
Total cholesterol	0.049	0.603	0.016	0.864
Triglyceride	0.089	0.340	0.124	0.185
Low density lipoprotein	-0.030	0.749	0.060	0.522
High density lipoprotein	0.146	0.118	-0.192	0.029

alcoholic steatohepatitis with atherosclerosis is well known. In these patients a relationship between liver function tests and PWV has been reported.[17] However, even though no steatosis was found in our patients, there was a strong positive correlation between liver function tests and PWV. The association of age, waist circumference, BMI and decreased levels of HDL with atherosclerosis is well known. The present study may help in determining the inverse relation between IB levels and PWV.

The pathophysiology of aortic stiffness includes excessive activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, lipid peroxidation and nitric oxide-induced vasodilation.[18] An excess of reactive oxygen radicals leads indirectly to aortic stiffness by leading to endothelial dysfunction and endothelial injury.[19] At the same time, elevated levels of these radicals decrease nitric oxide production from endothelial cells and increase the release of vasoconstrictor substances such as endothelin-1.[20] Additionally, the impairment of nitric oxide-induced vasodilation increases the severity of vasoconstriction, leading to endothelial injury and vessel stiffness.[20] Previous studies have demonstrated that small dense LDL, oxidized LDL and LDL in GS patients is lower than in healthy subjects.[2,3,14,21,22] Studies conducted on GS patients and subjects with high IB have revealed IB to be a strong antioxidant, preventing the oxidative stress that leads to the formation of oxygen radicals and decreasing lipid peroxidation.[21,22] Therefore, the incidence of atherosclerotic heart disease has been reported as decreased in GS

patients in comparison to healthy subjects. A study conducted by Arslan et al. revealed PWV level of GS patients to be lower than controls, and reported bilirubin as preventing arterial stiffness by decreasing oxidative stress.[13] In the present study, even though the differences were not statistically significant, levels of CRP and LDL of GS group were lower than the control group. CRP indicates systemic inflammation. Several studies have shown many inflammatory markers to be associated with aortic stiffness and PWV.[23,24] In the current study, low levels of CRP and LDL indirectly indicate bilirubin's potent effect in lowering oxidative stress in GS patients. Endothelial injury might be prevented by preservation of nitric oxide bioavailability and nitric oxide-dependent vasodilation might induce the reduction of oxidative stress in GS patients.

Reactive oxygen radicals induced by oxidative stress lead to endothelial dysfunction, and thus vessel inflammation leads to the production of local angiotensin converting enzyme and angiotensin II.[25] Angiotensin II induces superoxide radical formation by increasing vascular NADPH oxidase.[26] As a result, the process of aortic stiffness starts with low nitric oxide level, high oxidative stress and vascular complications induced by activated mediators[24,27] and atherosclerotic heart diseases and hypertension may develop. It is known that an association exists among PWV, BP and arterial elasticity. Several studies have shown systolic and diastolic BPs of GS patients to be lower than in healthy control groups.[2,28] In the current study, while diastolic BP of the GS group was significantly lower, systolic BP difference did not reach statistical significance. The low diastolic and systolic blood pressure in GS patients may be related to the potent antioxidant effect of bilirubin in decreasing oxidative stress and preventing the release of angiotensin induced by oxidative stress.

Hyperglycemia and insulin resistance are associated with oxidative stress and endothelial dysfunction.[29] Previous studies have shown a negative association between IB level and obesity, insulin resistance and BP.[30,31] Recently, increased bilirubin level has been reported as increasing insulin sensitivity.[32] In a study, epicardial adipose tissue thickness, which is a good indicator of atherosclerosis, was found to be lower in GS patients than in healthy subjects.[14] In the same study, serum adiponectin levels were found to be high. It is known that adiponectin has anti-atherosclerotic effects.[33] Bilirubin may prevent endothelial dysfunction in GS patents by decreasing insulin resistance and plasma glucose level, and thus decreasing formation of aortic stiffness.

Subgroup analysis by gender has shown PWV among GS males to be significantly lower than among healthy males. PWV of GS females was lower than GS males, and both healthy females and males. As is well known, male gender is a risk factor for CAD. It is known that in women, estrogen has a protective effect against CAD, and breakdown of estrogen is reduced in patients with GS.[34] Estrogen levels in GS women may be higher than in healthy women, and therefore the cardioprotective effects of estrogen may be observed more in GS women. PWV is a good indicator for atherosclerosis,[35] so it may be suggested that GS patients might be protected when compared to healthy subjects, with this effect being more pronounced in GS females.

Study limitations

The study was small in scale and limited to patients under 45 years. However, atherosclerosis may be seen at young ages. This study has shown a strong relation between PWV and age. Further, larger studies are required to examine the influence of GS on the long-term prognosis and development of cardiovascular events in order to define the protective effect of IB on the atherosclerotic process.

Conclusion

This study found that PWV among subjects diagnosed with GS was lower than among a control group of non-smoking, age-matched healthy subjects. The study also found levels of serum CRP, LDL and the levels of diastolic and systolic blood pressure to be lower among the GS group than in the control group.

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