Cukurova Medical Journal

Araştırma Makalesi / Research Article

Effects of Gilbert's Syndrome on Lipid Profile, Levels of Serum Uric Acid, Glucose and Insulin Resistance

Lipid Profili, Serum Ürik Asit, Glukoz ve İnsülin Direnci Üzerine Gilbert's Sendromunun Etkileri

Medine Cumhur Cüre[1], Erkan Cüre[2], Aynur Kırbaş[1], Süleyman Yüce[2], Ayşe Ertürk[3]

[1]University of Recep Tayyip Erdogan School of Medicine. Departments of Biochemistry, [2]Internal Medicine and [3]Departments of Infectious Disease, RİZE

Cukurova Medical Journal 2014;39(3):.443-450.

ABSTRACT

Purpose: The protective effect of bilirubin on atherosclerotic heart disease in Gilbert's syndrome (GS) is well known. The aim of the study was to evaluate whether the atherosclerotic risk factors such as uric acid (UA), insulin resistance, glucose and lipid profiles are reduced in patients with GS compared with healthy subjects.

Material and Methods: Thirty-four male and 38 female a total of 72 GS patients and a similar age group of 72 healthy individuals (34 males and 38 females) were included in the study. Both groups were between 16-45 years old and all patients were were non-smokers and drinkers. The levels of UA, lipids, glucose, insulin and C-reactive protein (CRP) were examined. HOMA-IR index were estimated.

Results: GS patient's UA is 4.2 ± 0.8 mg/dL, control group's UA is 4.8 ± 1.1 mg/dL. GS patient's HOMA-IR is 1.8 ± 0.6, control group's HOMA-IR is 2.0 ± 0.4. GS patients had significantly lower levels of UA ($p < 0.001$), insulin ($p = 0.021$), HOMA-IR ($p = 0.039$), triglycerides (TG) ($p = 0.005$), low-density lipoprotein (LDL) ($p = 0.036$) and CRP ($p = 0.006$) compared with the control group. Even insignificantly, GS patients had lower levels of total cholesterol whereas high-density lipoprotein (HDL) ($p < 0.001$) was found to be higher.

Conclusion: Our results shown that in GS patients, increased bilirubin levels are associated with decrease in UA, insulin, LDL, TG, and increased HDL. In GS patients, low level of UA, insulin and lipid profile may be contributed to cardioprotective effect.

Key Words: Gilbert's syndrome; uric acid; lipids; blood glucose; insulin resistance

ÖZET

Amaç: Gilbert's sendromunda (GS) aterosklerotik kalp hastalığı üzerine bilirubinin koruyucu etkisi iyi bilinmektedir. Bu çalışmanın amacı ürik asit (ÜA), insülin direnci, glukoz ve lipid profilleri gibi aterosklerotik risk faktörlerinin sağlıklı bireylerle karşılaştırıldığında GS'li hastalardadüşük olup olmadığı araştırmaktır.

Materyal ve Metod: 34 erkek ve 38 kadın toplam 72 GS'li hasta ve benzer yaş grubunda 72 sağlıklı birey (34 erkek ve 38 kadın) bu çalışmaya dahil edildi. Her iki grupta 16-45 yaş aralığında ve sigara ve alkol tüketimi yoktu. ÜA, lipidler, glukoz, insülin ve C-reaktif protein (CRP) seviyelerine bakıldı. HOMA-İR indeks hesaplandı.

Bulgular: GS'li hastalarda ÜA 4.2 ± 0.8 mg/dL, kontrol grubunda ise ÜA is 4.8 ± 1.1 mg/dL idi. GS'li hastalarda HOMA-İR 1.8 ± 0.6, kontrol grubunda ise 2.0 ± 0.4 idi. GS'li hastalarda ÜA ($p < 0.001$), insülin ($p = 0.021$), HOMA-İR ($p = 0.039$), trigliserid (TG) ($p = 0.005$), düşük dansiteli lipoprotein (DDL) ($p = 0.036$) ve CRP ($p = 0.006$) kontrol grubuna göre anlamlı düşük seviyede bulundu. İstatistiki anlamlı olmasa bile, GS'li hastalarda total kolesterol düşük bunun aksine yüksek dansiteli lipoprotein (YDL) yüksek bulundu.

Sonuç: Bizim çalışmamızın sonuçları GS'li hastalarda artmış bilirubin seviyesinin düşük ÜA, insülin, DDL, TG ve artmış YDL seviyeleri ile ilişkili olduğunu gösterdi. GS'li hastalarda, düşük seviyedeki ÜA, insülin ve lipid profili kardiyoprotektif etkiye katkı sağlıyor olabilir.

Anahtar Kelimeler: Gilbert's sendromu, ürik asit, lipidler, kan glukozu, insülin direnci

INTRODUCTION

Uric acid (UA) is an end product of purine metabolism. UA is known to act as an antioxidant and oxygen radical remover, but recent publications have shown it to be a pro oxidant. It increases the oxidation of low-density lipoprotein (LDL) so it increases free oxygen radicals, as a result inflammation, insulin resistance and endothelial dysfunction[1,2]. A relationship has been found among dyslipidemia, UA level, hypertension, impaired glucose tolerance, diabetes and atherosclerotic diseases[2-4]. Levels of UA and dyslipidemia have been found to be related to the left ventricular hypertrophy and myocardial infarction[5].

Gilbert syndrome (GS) was first described in 1901 by Gilbert and Lereboulle. GS is an autosomal recessive disease, which is a benign condition that does not progress to chronic liver disease or fibrosis6. Bilirubin glucuronidation is decreased due to a partial defect in UDP-glucuronosyl transferase enzyme, so levels of indirect bilirubin (IB) are increased7. Most of the time, the diagnosis is incidental. Generally it requires no treatment.

Bilirubin is known to be a potent antioxidant. It has been reported to have a cardioprotective effect8. Chronic inflammation has been found to be lower in GS patient groups. These patients have decreased lipid peroxidation so they have lower oxidative stress[9]. Due to the reduction of the inflammatory process and lipid peroxidation, oxidative stress is low and, as a result, it decreases atherosclerosis. The elevated levels of bilirubin and decreasing levels of TG, LDL, UA, insulin and increasing level of HDL in GS patients may have an effect on the slowing down of the atherosclerotic process.

The aim of this study was to evaluate whether the cardiovascular events risk markers such as triglycerides (TG), LDL, insulin resistance and UA are reduced in patients with GS compared with healthy subjects.

MATERIALS and METHODS

Patients

GS diagnosed according to previous studies[10-12]. Seventy-two patients diagnosed with GS (38 females, 34 males) who had applied to the internal medical clinic in the hospital were included in this study. A control group of 72 healthy persons (38 females, 34 males), who were non-smokers and drinkers were included. Both groups were between 16- 45 years old.

Inclusion criteria were as follows: Increased levels of IB (0.8 mg/dL≤) with normal levels of lactate dehydrogenase (LDH) were not considered as hemolysis and corrected reticulocyte counts were done with a reticulocyte smear to the patients with lower 2% included from the study. Healthy subjects with IB < 0.7 mg/dL who had not any known disease were included in the control group.

Exclusion criteria for both groups were as follows: Having heart disease, chronic renal failure, diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, hyperthyroidism, hypothyroidism, acute or chronic liver disease, cancer or any other chronic disease, acute or chronic infection, chronic drug user, smoking, drinking alcohol, hipoalbuminemia, hematologic diseases such as myelodysplastic syndrome, leukemia, lymphoma and vitamin B_{12} deficiency. Increased levels of IB with elevated levels of LDH were considered as hemolysis and excluded from the study[13]. Corrected reticulocyte counts were done with a reticulocyte smear to the patients with normal levels of LDH, and the levels of more than 2% were excluded[14].

Diagnosis of GS

There is no indication for liver biopsy in patients with GS. If a biopsy is performed, it will show normal liver tissues[15]. The previous laboratory tests of patients who met the above criteria were reviewed, and the elevation of IB at least twice at different times was accepted as GS. Patients with elevated levels of IB, who had no previous laboratory results were called after 15 days for retesting and persistent elevation, were included in the study.

Measures of Laboratory Tests

UA, glucose, lipid parameters and other biochemical tests were performed with the photometric assays of the Abbott Architect C16000 analyzer (Abbott Diagnostics, USA), and the thyroid stimulating hormone (TSH) and vitamin B12 tests were performed by the Chemiluminescent Microparticle Immunoassay (CMIA) method of the Abbott Architect I 2000 immunology analyzer (Abbott Diagnostics, USA). Insulin was measured using CMIA (Chemiluminescent microparticle immunoassay) (Abbott, Architect system, USA).

The CRP test was performed with the nephelometric method of the Coulter Immage 800 device (Beckman, USA), and HBsAg, anti-HCV and anti-HIV were tested with the Roche Cobas E 601 macroelisa device (Roche Diagnostics, England). The hematologic tests were performed by the Abbott Cell Dyn Ruby analyzer (Abbott Diagnostics, USA).

Homeostasis Model Assessment + Insulin resistance (HOMA+IR) was computed by the following formula[16]: HOMA-IR = fasting plasma glucose (FPG) (mmol/L) × fasting serum insulin (mU /mL)/22.5. The cut off value was taken 2.7 for HOMA-IR[17].

Statistical analysis and Ethic issue

The results were reported as the mean±SD and median. The data analysis was performed using the statistical software SPSS for Windows (version 13.1; SPSS, Chicago, IL, USA). All the results were analyzed by applying the Kolmogorov Smirnov test for the determination of the normal and abnormal data distribution. The statistical significance of the differences in all parameters between the GS and the control group were analyzed using the independent sample t-test. Subgroups analyses were done by One Way Anova, followed by Bonferroni analysis. The relationship between the variables was analyzed with the Pearson's correlation. The differences and correlations were considered significant at $p < 0.05$. The study was approved by the local ethics committees, and informed consent from each participant was obtained (Approval number's: 2012/85).

RESULTS

Ages of GS group 30±11 years, body mass index (BMI) 23.5±4.6 kg/m^2, aspartate aminotransferase (AST) 18±5 IU/L, alanine aminotransferase (ALT) 19±13 IU/L, total bilirubin (TB) 2.0±0.6 mg/dL, IB 1.5±0.7 mg/dL, glucose 94±8 mg/dL, insulin 7.7±2.5 µIU/mL, HOMA-IR 1.8±0.6, CRP 0.2±0.2 mg/dL, BUN 28.6±11 mg/dL, creatinine 0.7±0.1 mg/dL, total cholesterol (TC) 173±28 mg/dL, TG 92±51 mg/dL, LDL 102±24 mg/dL, high-density lipoprotein (HDL) 53±11 mg/dL, UA 4.2±0.8 mg/dL.

Ages of the control group 28±5 years, BMI 23.8±3.2 kg/m^2, AST 20±8 IU/L, ALT 23±16 IU/L, TB 0.8±0.2 mg/dL, IB 0.4±0.2 mg/dL, glucose 94±9 mg/dL, insulin 8.5±1.3 µIU/mL, HOMA-IR 2.0±0.4, CRP 0.4±0.4 mg/dL, BUN 24±8 mg/dL, creatinine 0.7±0.1 mg/dL, TC 180±29 mg/dL, TG 124±70 mg/dL, LDL 110±25 mg/dL, HDL 45±13 mg/dL, UA 4.8 ±1.1 mg/dL.

When comparing the two groups, TB and IB were found to be significantly higher in GS ($p<0.001$, $p<0.001$). HDL was significantly found to be higher in GS group ($p<0.001$). UA ($p<0.001$), insulin ($p=0.021$), HOMA-IR ($p=0.039$), CRP ($p=0.006$), TG ($p=0.05$) and LDL ($p=0.036$) were significantly lower in GS group. The results are shown in Table 1.

When dividing the two groups into two subgroups according to gender; UA level of GS male group was 4.1±0.9 mg/dL while in the males of the control group UA was found to be 5.7±0.9 mg/dL (p<0.001). HDL level of GS male group was 49±11 mg/dL, the control group male was 40±8 mg/dL (p=0.001). TG level of GS male group was 153±76 mg/dL while the control group male was 99±59 mg/dL (p<0.001). Other results by Anova are shown in Table 2.

There was a negative correlation between TB and UA (r^2=0.053, p<0.01), insulin (r^2=0.069, p=0.002), HOMA-IR (r^2=0.060, p=0.004) and TG (r^2=0.037, p<0.05). There was a negative correlation between IB and UA (r^2=0.066, p<0.01), insulin (r^2=0.058, p=0.004), HOMA-IR (r^2=0.048, p=0.010) and TG (r^2=0.058, p<0.01). There was a positive correlation between TB and IB compared to HDL [respectively; r=0.172, p<0.05; r=0.227, p<0.01)].

Table 1. The main characteristics and laboratory parameters of the two groups.

	Gilbert's syndrome (n=72) (mean±SD) (n=72) (mean±SD)	**Healthy subject (n=72) (mean±SD)**	**P values**
Age (years)	30±11	28±5	0.151
Sex (M/F) (n)	34/38	34/38	1.00
BMI (kg/m^2)	23.5±4.6	23.8±3.2	0.612
UA (2.6-6) (mg/dL)	4.2±0.8	4.8 ±1.1	0.001
FPG (70-110) (mg/dL)	94±8	94±9	0.565
Insulin (µIU/mL)	7.7±2.5	8.5±1.3	0.021
HOMA-IR	1.8±0.6	2.0±0.4	0.039
AST (0-55) (IU/L)	18±5	20±8	0.055
ALT (5-34) (IU/L)	19±13	23±16	0.086
BUN (15-43) (mg/dL)	28.6±11	24±8	0.080
Creatinine (0.6-1.1) (mg/dL)	0.7±0.1	0.7±0.1	0.780
TB (0.2-1.2) (mg/dL)	2.0±0.6	0.8±0.2	0.001
IB (0.1-0.7) (mg/dL)	1.5±0.7	0.4±0.2	0.001
CRP (0-0.8) (mg/dL)	0.2±0.2	0.4±0.4	0.006
TC (0-199) (mg/dL)	173±28	180±29	0.153
TG (0-149) (mg/dL)	92±51	124±70	0.005
LDL (0-130) (mg/dL)	102±24	110±25	0.036
HDL (35-70) (mg/dL)	53±11	45±13	0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, Body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; F, Female; FPG, fasting plasma glucose; HDL, High density lipoprotein; IB, indirect bilirubin; LDL, Low density lipoprotein; M, Male; TB, Total bilirubin; TC, Total cholesterol; TG, Triglycerides; UA, Uric acid.

Table 2. Subgroup analysis of Gilbert and the control group by ANOVA

	UA (2.6-6) (mg/dL)	TC (0-199) (mg/dL)	TG (0-149) (mg/dL)	LDL (0-130) (mg/dL)	HDL (35-70) (mg/dL)	TB (0.2-1.2) (mg/dL)	IB (0.1-0.7) (mg/dL)
1-GS M (n=34)	4.1±0.9	171±25	99±59	102±21	49±11	2.4±0.9	1.8±0.8
2-GS F (n=38)	4.2±0.8	175±31	90±46	102±26	55±11[d]	1.8±0.6[a]	1.3±0.5[a]
3-HS M (n=34)	5.7±0.9[ab]	182±31	153±76[ab]	111±26	40±8[ab]	0.6±0.2[ab]	0.4±0.1[ab]
4-HS F (n=38)	3.9±0.6[c]	178±27	92±46[c]	109±23	51±15[c]	0.6±0.3[ab]	0.4±0.2[ab]

The results mean±SD. Abbreviations: GS, Gilbert syndrome; HDL, High density lipoprotein; HS, healthy subject; IB, indirect bilirubin; LDL, Low density lipoprotein; M, Male; TC, Total cholesterol; TG, Triglycerides; TB, Total bilirubin; UA, Uric acid.

[a]comparison is made with GS male, p<0.001
[b]comparison is made with GS female, p<0.001
[c]comparison is made with HS male, p<0.001
[d]comparison is made with GS male, p<0.026

DISCUSSION

In the literature, there is a single study of UA examination on GS patient, and limited study available for lipid parameter examination. Previous study reported that levels of UA, TC, LDL, TG and HDL were similar in the GS and control groups[18]. In this study, the number of experimental is quite a few, however in the current study it is rather enough for GS patients. In contrary to previous study[18], UA level is significantly low in GS patients. Another study reported that levels of TC, LDL, TG, and glucose in GS group were similar control group, but GS group had significantly lower levels of high sensitive CRP and oxidized LDL[19]. Interestingly, the study reported that level of HDL in GS group were lower than control group[19]. Contrary to previous study, in the current study; UA, insulin resistance, TG, and LDL were significantly lower in GS patients compared to the control group. HDL was found to be significantly higher in GS patients than control group. Similar to previous study, the levels of glucose were found to be same in the two groups. A study by Boon et al. has shown that levels of LDL, and TG were strongly lower while HDL levels were not significant, but higher GS group compared to the control group, and glucose levels were similar between the two groups[20]. This study's LDL and TG values are similar with our study, however our study is found strongly high for HDL level. In addition, number of individuals in our study is quite enough for GS illness. Another study reported that level of LDL in GS group was lower than control group, whereas level of HDL in GS group was higher than control group[11]. In the same time that this study resulted similarly with our study, the lipid panel in the GS patients is not evaluated as primer; results are given in order to enforce other findings. On the other hand, UA level is never examined in this study.

UA is an end product of purine metabolism that is used as an early marker of endothelial dysfunction and atherosclerosis[21]. The relation between cardiovascular disease and UA levels were shown in previous studies[22,23]. In our study the levels of UA of the GS group compared to the control group were found to be decreasing. The absence of an increase in the levels of UA may be

due to the potent antioxidant effect of bilirubin. Endothelial dysfunction via lipid peroxidation and inflammation is a marker for atherosclerosis. Increasing the levels of circulated LDL increase lipid peroxidation. The CRP level demonstrates the intensity of inflammation. In the current study, levels of LDL and CRP were found to be significantly low. So increasing levels of bilirubin, which is a potent antioxidant, in GS patients prevents adverse cardiovascular events.

Even though glucose levels of both groups were normal, serum insulin and HOMA-IR index of GS group were significantly lower than the control group. Long term inflammation process due to insulin resistance may participate in the pathogenesis of atherosclerosis[24]. Previous studies have shown that sustained hyperinsulinemia to be a potential trigger factor for endothelial dysfunction[25]. The persistent insulin resistance is a result of an alteration in insulin signaling. Decreased *endothelial* nitric oxide (NO) synthase (eNOS) can lead to endothelium dysfunction by insulin resistance[26]. Nitric oxide is caused vasodilatation in vessels. Persistent low levels of eNOS lead to decreased level of nitric oxide; therefore, low level of NO lead to endothelial disfunction[27]. Our study has shown HOMA-IR index of GS patients to be lower than the control group. There was a negative correlation between IB and insulin resistance. Low insulin resistance levels in GS patients may indicate a protective effect against atherosclerotic heart disease. Additionally, persistent hyperinsulinemia not only increases serum levels of TG and LDL but also decreases serum levels of HDL[28]. That explains why we found low levels of TG and LDL is addition to high HDL levels in GS patients.

High TG levels and low HDL levels have been shown to be related to increased cardiovascular events. At the same time, this condition is a part of metabolic syndrome. In this study, in comparison to the control group, lower levels of TG and higher levels of HDL have been found. Due to the results are significant, low levels of CRP and LDL may be related to the antioxidant effect of bilirubin and may be the reason that cardiovascular events are less likely to occur in GS patients. High levels of HDL in GS patients may be ensured a lower cardiovascular risk.

UA level is generally higher in males than females[29]. In this study GS males had higher levels of HDL and lower levels of UA than the healthy males so have fewer incidences of cardiovascular events. Also, low level of TG in GS males is a protective factor against cardiac diseases. In the current study GS females had higher levels of HDL and lower levels of UA than the healthy females, but these parameters were not significant. When compare these findings between females with GS and control group, it may be thought that cardiovascular disease would be seen less. The current study has shown that the effect of bilirubin as an antioxidant may be more prominent in GS male and female patients.

As a result, the relationship of cardiovascular events with high levels of serum UA, insulin resistance, LDL, TG, CRP and low levels of HDL has been shown. We have found that GS patients have obviously low levels of UA, insulin resistance, LDL, CRP and TG while HDL was high. Thus, we conclude that, in parallel with the literature, GS patients have a cardioprotective effect[30-32]. In addition to previous study, it is put forth in our study that in GS patients, decreased of UA, insulin resistance and lipid parameters may have relation with low risk of cardiovascular disease.

The limitations of the study

In comparison with previous studies, as well as the number of experimental is enough; the limited number of the subjects may have influenced the results of the study.

ACKNOWLEDGEMENTS

No financial support and no other potential conflict of interest relevant to this article was reported. The authors would like to thank all the Gilbert's patient who took part in this research.

Source of support, conflict of interest: Authors of this study have no financial relationships involved for this study and there is no conflict of interests. The authors did not receive grants or outside funding in support of their research or preparation of this manuscript.

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Yazışma Adresi / Address for Correspondence:
Dr. Medine Cumhur Cüre
University of Recep Tayyip Erdogan, School of Medicine,
Department of Biochemistry,
Islampasa mahallesi,
53100 RİZE
Phone: +90-464-213-0491-1874
Fax: +90-464-217-0364
Email: medinecure@yahoo.com

Geliş tarihi/Received on: 23.01.2014
Kabul tarihi/Accepted on:28.02.2014