Prothrombin Time, Activated Thromboplastin Time, Fibrinogen and D-Dimer Levels and von-Willebrand Activity of Patients with Sheehan's Syndrome and the Effect of Hormone Replacement Therapy on These Factors

Semir PASA[1], Abdullah ALTINTAS[2], Cemil TUMER[3], Mustafa DEMIRCIN[4], Timucin CIL[2], Kadim BAYAN[2], Ramazan DANIS[2], Yekta TUZUN[2], Yahya ATAYAN[1], Orhan AYYILDIZ[2], Mithat BAHCECI[2]

[1] Adiyaman University, Faculty of Medicine, Department of Internal Diseases, Adiyaman
[2] Dicle University, Medical Faculty, Department of Internal Diseases, Diyarbakir
[3] Mustafa Kemal University, Medical Faculty, Department of Physiology, Hatay
[4] Ergani State Hospital, Department of Internal Medicine, Diyarbakir, TURKEY

ABSTRACT

Increased mortality due to atherosclerotic cardiovascular disease has been described in adult patients with hypopituitarism, although the precise underlying mechanisms remain undetermined. Various abnormalities of coagulation and fibrinolysis occur in patients with thyroid diseases. Conversely, there are conflicting reports concerning the effects of growth hormone replacement on coagulation and fibrinolytic pathways in hypopituitary adults, and there is no existing data on the effects of hypocortisolism on thrombotic and fibrinolytic systems. The same controversial data were also obtained in studies which evaluate the effects of estrogen replacement therapy on cardiovascular events in post-menopausal women. The aim of this study was to investigate the effects of Sheehan's syndrome (SS), which is a common cause of hypopituitarism, on haemostatic factors and to assess the effects of L-thyroxin, prednisolone and conjugated estrogen / medroxyprogesterone acetate replacement on these factors. Prothrombin time (PT), activated thromboplastin time (aPTT), fibrinogen and D-dimer levels, and von-Willebrand factor (vWF) activity were compared among 32 patients with SS and 35 control subjects (CS) with similar age. A shorter PT and aPTT, higher fibrinogen and d-dimer levels, and similar vWF activity were determined in patients with SS as compared with CS. In addition, it was determined that hormone replacement treatment did not have a significant effect on coagulation parameters except the fibrinogen and d-dimer levels.

Keywords: Blood coagulation, Hemostasis, Sheehan's syndrome, Hypopituitarism

ÖZET

Sheehan Sendromlu Hastalarda Protrombin Zamanı, Aktive Tromboplastin Zamanı, Fibrinojen ve D-Dimer Düzeyleri, vonWillebrand Faktör Aktivitesi ve Hormon Replasman Tedavisinin Bu Faktörler Üzerinde Etkileri

Altında yatan esas mekanizma çok açık olmasa da erişkin hipofiz yetersizliklerinde aterosklerotik kalp hastalıkları ile ilişkili mortalitede artış olduğu bilinmektedir. Tiroid hastalıklarında çaşitli koagülasyon ve fibrinolizis anormallikleri oluşmaktadır. Buna karşın hipofizer yetersizliklerde büyüme hormonu replasmanının koagülasyon ve fibrinolizis üzerine etkilerine dair eldeki veriler çelişkilidir, kortizolün etkilerine ilişkin veriler ise oldukça kısıtlıdır. Benzer şekilde menopoz sonrası kadınlarda östrojen replasmanının kardiyovasküler olaylar üzerine etkilerine dair veriler de oldukça çelişkilidir. Bu çalışmanın amacı hipofizer yetersizliğin sık nedenlerinden Sheehan sendromunun (SS) hemostatik fakörler üzerine etkilerini incelemek ve L-tiroksin, prednizolon ve konjuge östrojen / medroksiprogesteron asetat replasmanının bu faktörlere etkilerini araştırmaktır. 32 SS hastası ve yaşları benzer 35 kontrolde protrombin zamanı (PT), aktive tromboplastin zamanı (aPTT), fibrinojen düzeyi, D-dimer düzeyi ve von willebrand faktör (vWF) aktivitesi karşılaştırıldı. Sonuçta SS hasta grubunda kontrol grubuna göre daha kısa PT ve aPTT, daha yüksek fibrinojen ve d-dimer düzeyleri ve benzer vWF aktivitesi olduğu saptandı. İlave olarak hormon replasman tedavisinin bu koagulasyon faktörlerinden fibrinojen ve d-dimer düzeyleri dışında diğerleri üzerinde belirgin bir etkileri olmadığını saptadık.

Anahtar Kelimeler: Koagulasyon, Hemostaz, Sheehan sendromu, Hipofizer yetersizlik

INTRODUCTION

Increased mortality due to atherosclerotic cardiovascular disease has been described in adult patients with hypopituitarism, although the precise underlying mechanisms remain undetermined. Hypopituitarism is associated with a cluster of cardiovascular risk factors including unfavorable body composition, dyslipidemia, reduced insulin sensitivity and endothelial dysfunction.[1-4] These findings are also observed in patients with Sheehan syndrome (SS). SS, which is a common cause of hypopituitarism in developing countries, related with impaired endothelial function and replacement of thyroid and glucocorticoid hormones resulted in improvement in deteriorated endothelial functions.[5] Various abnormalities of coagulation and fibrinolysis occur in patients with thyroid diseases, and may range from subclinical laboratory abnormalities to clinically significant disorders of coagulation and rarely, major haemorrhage or thromboembolism.[6] Thyroid hormones exert effects on different levels of the haemostatic system, such as modulation of fibrinolytic activity and coagulation proteins. Although several reports demonstrated an association of thyroid function and plasma coagulant protein levels, the direction of this relation is still debatable.[7-11] Likewise, there are conflicting reports concerning the effects of growth hormone (GH) replacement on coagulation and fibrinolytic pathways in hypopituitary adults.[12,13] There are no existing data about the effects of hypocortisolism on thrombotic and fibrinolytic system, however the effect of Cushing syndrome is well established.[14] The same controversial data were also obtained in studies which evaluate the effects of estrogen replacement therapy on cardiovascular events, and on coagulation factors in post-menopausal women.[15] Probably since hypopituitarism is a heterogeneous condition arising from a variety of underlying disorders and characterized by multiple coexisting pituitary hormonal deficiencies, diverse results were determined in different studies.

The aim of this study was to investigate the effects of Sheehan's syndrome (SS), which is a common cause of hypopituitarism, on haemostatic factors and to assess the effects of L-thyroxin, prednisolone and conjugated estrogen / medroxyprogesterone acetate replacement on these factors. The markers selected for this study were located in different parts of the coagulation / fibrinolytic pathway. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are basic coagulation tests which determine the integrated actions of the majority of coagulation factors in extrinsic and intrinsic path-ways of blood coagulation cascade. Previous studies have demonstrated that pituitary deficiency in-fluences intrinsic and extrinsic coagulation pathways and the synthesis of vitamin K dependent coagulation factors in rats.[16] VonWillebrand factor (vWF) mediates platelet adhesion, acts as the carrier protein for coagulation factor VIII, and is considered as a reliable marker of endothelial dysfuncti-

on. Fibrinogen acts on blood viscosity, platelet aggregation, and fibrin formation. D-dimer, a fibrin degradation product, is a marker not only of thrombin generation but also of cross-linked fibrin turnover.

PATIENTS AND METHODS

Thirty-two consecutive females with SS aged 24 to 55 years (median 42 years) and 35 healthy female CS (median age 41, range 26 to 53 years) with similar age- and body mass index (BMI) who were admitted to Dicle University, Faculty of Medicine, Department of Internal Diseases between 2003 and 2006 were included in the study. All the CS were selected as healthy females to exclude the sexual and hormonal differences, and were mainly staff members, their relatives or friends. The diagnosis of SS was established with medical history, physical examination and dynamic hormonal evaluations, and was confirmed with magnetic resonance imaging of the pituitary gland. All patients were amenorrheic and had panhypopituitarism. Patients with diabetes, metabolic syndrome, dyslipidemia, coronary or chronic liver disease, using drugs which may affect coagulation tests such as anticoagulants or antiaggregants, and with a history of thromboembolic disease and smoking were excluded. Informed written consent was obtained from all participants.

Blood pressure (BP) of all participants was measured at rested spine in climatized room at 22°C. BMI of patients were calculated as kg/m2. All blood samples for coagulation tests were drawn from the cubital vein after applying short venous pressure in tubes containing 3.2% buffered sodium citrate (volume of blood: volume of citrate= 9:1). The tube was immediately centrifuged at 3000 g for 10 minutes at room temperature to obtain cell and platelet free plasma. PT, aPTT, fibrinogen, d-dimer levels and vWF activity were assayed on the ACL TOP (Instrumentation Laboratory, Milan, Italy) employing proprietary Instrumentation Laboratory reagents (RecombiPlasTin for PT with an International Sensitivity Index of 0.810, ShyntASil for aPTT and Fibronogen-C XL, Clauss method for fibrinogen determinations, respectively). D-dimer was measured employing the new D-dimer quantitative automated latex-enhanced immunoassay on the ACL TOP (Instrumentation Laboratory). Calibrations were performed according to the instructions provided by the manufacturers. After drawing basal blood samples of patients and CS, all patients received 5-7.5 mg/day prednisolone, 100-200 μg/day L-thyroxine, and conjugated estrogen (0.625 mg/day, 1-21 days) and medroxyprogesterone acetate (5 mg/day, 11-21 days) for 12 months. The same coagulation parameters were re-assessed at the end of the follow-up period.

Statistical Analysis: Paired sample t test was used for evaluation of pre- and post-treatment parameters (BMI, mean BP, PT, aPTT, fibrinogen); $p<0.05$ was accepted as the statistical significance. Wilcoxon signed ranks test was used to evaluation of pre- and post-treatment d-dimer levels and Mann Whitney U test was used to evaluation of pre- and post-treantment d-dimer levels of patients and control subjects.

RESULTS

The median age of patients with SS was 42 years (ranged 24 to 55 years), and the median age of CS was 41 years (ranged 26 to 53 years). There was no statistically significant difference between the median ages of patients with SS and CS. The mean BMI of patients was 25.66 ± 2.8 kg/m^2 at the time of admission; it was 26.44 ± 2.8 kg/m^2 at the end of follow-up period, and the mean BMI of CS was 25.52 ± 2.6 kg/m^2. There were no statistically significant differences between the BMI of patients and CS both at the time of admission and after treatment, although the mean BMI of patients increased with the treatment ($p= 0.002$). The mean arterial blood pressure (BP) of patients with SS was 76.38 ± 9.8 mmHg before the treatment; it was 81.10 ± 7.5 mmHg after the treatment, and of CS it was 89.73 ± 8.5 mmHg. There were statistically significant differences between the mean BP of patients with SS and CS both at the time of admission and at the end of the follow-up period; and there also was a statistically significant difference between the pre-treatment and post-treatment mean BP of patients ($p< 0.0001$, $p< 0.0001$ and $p= 0.02$, respectively).

The mean PT of patients was 11.54 ± 1.2 sec (range: 9.14 to 15.27 sec) before the treatment, was 12.43 ± 1.1 sec (range: 10.21 to14.94 sec) after the

Table 1. Comparisons of coagulant factors of patients with Sheehan syndrome before treatment (BT) and after treatment (AP), and control subjects (CS)

	Group			p
	BT	**AT**	**CS**	**BT vs CS** **AT vs CS** **BT vs AT**
	(n=32)		**(n=35)**	
BMI (kg/m^2)	25.66±2.8	26.44±2.8	25.52±2.6	NS NS 0.002
Mean BP (mmHg)	76.38±9.8	81.10±7.5	89.73±8.5	<0.0001 <0.0001 0.02
PT (sec)	11.54±1.2	12.43±1.1	12.57±1.2	0.002 0.008 NS
aPTT (sec)	32.47±2.2	31.89±1.9	36.89±3.3	<0.0001 <0.0001 NS
Fibrinogen (mg/dL)	364±89	341±104	316±56	0.007 NS NS
d-dimer (median)	4 (min 2 -max 35)	2 (min 2- max 38)	1 (min 1-max 6)	<0.0001 <0.0001 <0.0001 NS
vWF activity (%)	70±21	74±19	69±21	NS NS NS

BT: Before treatment, AT: After treatment, CS: Control subjects, BP: Blood pressure, BMI: Body mass index, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, vWF: vonWillebrand factor, NS: Not significant.

treatment, and of the CS it was 12.57 ± 1.2 (range: 10.10 to 15.21 sec). There was a statistically significant difference between the pre-treatment PT values of patients and CS (p= 0.002) and between the pre-treatment and post-treatment values of the patients (p= 0.008). The mean prothrombin values increased to the normal value with the treatment and the difference disappeared (p= 0.946). The mean aPTT of patients was 32.47 ± 2.2 sec (range: 28.80 to 38.62 sec) before the treatment, was 31.89 ± 1.9 sec (range: 30.24 to 39.21 sec) after the treatment, and of the CS it was 36.89 ± 3.3 sec (29.7 to 44.3 sec). A statistically significant difference was detected between the patients and the CS in both the initial and the post-treatment aPTT values (p< 0.0001). The treatment did not cause any difference in aPTT of patients with SS (p= 0.316). The mean fibrinogen level of patients was 364 ± 89 mg/dL

(range: 206 to 654 mg/dL) before the treatment, was 341±104 mg/dL (ranged 188 to 652 mg/dL) after the treatment, and of the CS it was 316 ± 56 mg/dL (range: 189 to 412 mg/dL). There was a statistically significant difference between the pre-treatment mean fibrinogen level of patients with SS and CS (p= 0.007). This difference disappeared with the treatment. There was no statistical significant difference between the post-treatment mean fibrinogen levels of patients and the CS (p= 0.152), and also between the pre-treatment and the post-treatment mean fibrinogen levels of patients (p= 0.083). Median d-dimer level was 4 (2-35) before the treatment, was 2 (2-38) after the treatment, and of the CS it was 1 (1-6). A statistically significant difference was detected between the patients and the CS in both the initial and the post-treatment d-dimer values (p< 0.0001). And the treatment resulted with statistically significant decrement in d-dimer levels of patients with SS (p< 0.0001). Mean vWF activity was 70 ± 21% (ranged 47 to 135%) before the treatment, was 74 ± 19% (ranged 46 to 122 %) after the treatment, and of the CS it was 69 ± 21% (ranged 41 to 133%). There was no statistically significant difference between the pre-treatment mean vWF activity level of patients and the CS, between the post-treatment mean vWF activity level and CS, and also between the pre-treatment and the post-treatment mean vWF activity level of patients with SS (p= 0.646, p= 0.859 and p= 0.443, respectively).

Coagulant factors of patients with SS and of CS at baseline and after the treatment and their comparisons are shown in Table 1.

DISCUSSION

Patients with SS have a shorter PT and aPTT, higher fibrinogen and d-dimer levels, and similar vWF activity compared to healthy subjects. Additionally, hormone replacement treatment consisting of L-thyroxin, prednisolone and conjugated estrogen / medroxyprogesterone acetate did not result in correction of these coagulation parameters except fibrinogen and d-dimer levels. Fibrinogen level decreased to its normal value after hormone replacement. D-dimer levels decreased significantly with the treatment but the decrement did not reached to the levels of healthy control subjects.

Hypopituitarism results in deficiencies of many hormones and it is not easy to determine the real cause of the haemostatic changes. Most studies focused on the effects of thyroid and growth hormones on plasma proteins and blood viscosity, but the results are often contradictory. Mostly, hypocoagulable states have been described in the literature in patients with hypothyroidism. Mild mucocutaneous bleeding (epistaxis, gum bleeding, menorrhagia, bruising), but also, rarely, severe post-traumatic and post-surgical bleeding may occur.[17] FVIII and vWF have been found to be decreased in patients with overt hypothyroidism.[18,19] Franchini et al.[20] studied this association between vWF and hypothyroidism in detail. First, they screened 131 consecutive subjects with low vWf levels for thyroid hormone levels.[20,21] Eight of the 131 individuals (6.1%) with low vWF levels had a concomitant subclinical hypothyroidism as documented by normal thyroid hormone levels, and raised TSH concentrations. Three of them (37.5%) had bleeding symptoms. Thyroid hormone replacement therapy showed that haemostatic parameters had returned to normal in all patients. Second, they studied 1342 consecutive patients with various thyroid diseases who were candidates for thyroid surgery.[22] A preoperative screening including prothrombin time, activated partial thromboplastin time and platelet function analyser (PFA-100) identified 39 patients (2.9%) with abnormalities. Of these, 35 had von Willebrand's disease (type 1 in 33 cases and type 2A in 2 cases). However, all these patients were euthyroid at the time of the screening. The reduced level of several coagulation factors in hypothyroid patients has been attributed to the generalized decrease of protein synthesis. However, an old but well-designed study performed in patients with myxoedema showed a reduced clearance of factors II, VII, IX and X from plasma.[23] This might lead to higher concentration of coagulant in hypothyroidism. Recently, increased fibrinogen and d-dimers[8,24], and FVII:C/FVII:Ag[25] were reported in patients with overt hypothyroidism, suggesting a hypercoagulable state. In contrast, Burggraaf et al.[9] have reported that excess T3 was associated with elevated levels of fibrinogen, whereas plasminogen was decreased. Moreover, the level of tissue plasminogen activator in hyperthyroidism was reduced, and fibrinolytic activity decreased due to vascular endothelial

dysfunction compared with control patients.[10] Interestingly, patients with moderate hypothyroidism, who were consistently shown to be at high risk for cardiovascular disease, have decreased fibrinolytic activity.[26] In the current study, the decreased PT and aPTT may be related with increased levels of coagulants such as fibrinogen and fibrin degradation products (d-dimer), which is caused by its decreased clearance. L-T4 replacement resulted in decreased fibrinogen and d-dimer levels, probably due to increase in its clearance, but PT and aPTT did not reach normal levels. Some different coagulation factors or other replaced hormones such as estrogen may be responsible for these results.

Growth hormone deficiency (GHD) has been considered the main underlying factor influencing increased mortality of hypopituitary patients. While many other factors, such as excessive glucocorticoid or thyroxine replacement, can contribute to the increased cardiovascular mortality, the direct effect of GHD is highly likely. GHD produces negative effects on cardiovascular function, directly on the heart and endothelium and indirectly via its impact on hypercoagulability, abdominal obesity, insulin resistance, serum lipids, atherosclerosis, decreased exercise performance, pulmonary capacity, and endothelial function.[27] A small number of studies have shown higher levels of fibrinogen, plasminogen activator inhibitor 1 (PAI-1), and tissue plasminogen activator antigen (tPA) in patients with GHD compared with controls.[12,28,29] There has been relatively less study of the effects of GH replacement on haemostatic markers, and these studies have yielded variable results. Recent data in hypopituitary adults with GHD do suggest elevated levels of both fibrinogen and vWF with positive correlations observed between other surrogate markers of endothelial dysfunction. Conversely, acute blocking GH action in healthy males using the GH receptor antagonists, pegvisomant, led to reduction in vWF levels.[30-32] Smith et al.[33] have demonstrated elevated levels of the haemostatic markers, vWF, factor VIII, and fibrinogen in patients with GHD despite stable physiological GH replacement, suggesting perturbation of endothelial function and the persistence of a prothrombotic tendency. In contrast, Gomez et al.[34] studied the peripheral fibrinolytic markers, inflammatory cytokines and endothelial function in hypopituitary adults with GHD, and they suggested that these patients do not present an abnormal coagulation activation reflected even in a moderate decrease in the d-dimer in untreated GHD. Miljic et al.[16] evaluated the changes in PT and aPTT during replacement therapy with human recombinant GH in GHD adults. They found no statistically significant differences in fibrinogen level, PT and aPTT values between patients and healthy controls. In the current study, we found a statistically significant difference in fibrinogen and d-dimer levels, PT and aPTT in patients with SS compared with controls with similar age- and BMI. It is not easy to determine the main etiological cause of this result because of the deficiencies of several hormones which may effect the coagulation factors. However, the correction of fibrinogen levels and decrement of d-dimer with hormone replacement therapy consisting of L-thyroxine, prednisolone, and conjugated estrogen / medroxyprogesterone acetate suggested that the effect of thyroid hormones may be important. Another limitation of our study is the inability to perform GH replacement because of economical status of our country. Therefore, we could not evaluate the effects of GH on coagulation system.

Adrenal insufficiency is not commonly complicated by bleeding or thrombotic episodes. An association with the anti-phospholipid syndrome (APS) has been described.[35,36] Adrenal failure is present in 10%-26% of patients with catastrophic APS. The pathophysiologic mechanism is not clearly understood, but an adrenal vein thrombosis could provoke an adrenal haemorrhagic infarction.[37]

Reduction in levels of sexual hormones is associated with an increased risk of coronary heart disease as a result of changes in lipid profile, clotting and fibrinolytic factors, and vessel function, all of which are likely to be caused by the loss of estrogen protection. Menopause is associated with elevated levels of coagulation factors such as factors VII and VIII in addition to fibrinogen. Similar results may be expectable in hypopituitarism, despite lack of clinical data on patients with SS.[38]

In conclusion, we found a shorter PT and aPTT, higher fibrinogen and d-dimer levels, and similar vWF activity that may result in a hypercoagulable state in patients with SS compared to healthy subjects. The most possible causes are decreased cle-

arance of coagulant factors, increased fibrinogen and d-dimers, and FVII:C/FVII:Ag due to hypothyroidism; higher levels of fibrinogen, plasminogen activator inhibitor 1 (PAI-1), and tissue plasminogen activator antigen (tPA) of patients with GHD, patients with SS or elevated levels of coagulation factors such as factors VII and VIII in addition to fibrinogen due to ovarian hypoactivity compared with controls. Larger scale studies are needed to clarify the main pathogenetic mechanisms underlying this hypercoagulable state.

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Correspondence

Dr. Semir PAŞA

Adıyaman Üniversitesi Tıp Fakültesi

İç Hastalıkları Anabilim Dalı

Adıyaman / TURKEY

Tel: (+90.416) 223 16 90

İş Fax: (+90.416) 223 16 93

e-mail: semirpasa@dicle.edu.tr

semirp@hotmail.com