Haemostatic Changes in Patients with Diabetic Nephropathy due to Proteinuria

Diyabetik Nefropatili Hastalarda Proteinüriye Bağlı Hemostatik Değişiklikler

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ABSTRACT

OBJECTIVE: It is known that diabetes may cause to hypercoagulability. The pathogenetic mechanism of coagulation activation is not completely clear and the origin is multifactorial. While chronic hyperglycemia is considered to be the main underlying pathology, there are various comments on the association between glycemic control and haemostatic disorders. In this study, we have aimed to compare patients with diabetic nephropathy and patients with idiopathic nephrotic syndrome with respect to haemostatic differences.

MATERIAL and METHODS: We compared 10 newly diagnosed idiopathic nephrotic syndrome patients with 10 normoalbuminuric, 10 microalbuminuric and 10 macroalbuminuric Type II diabetic patients in terms of haemostatic disorders. We included 12 healthy controls in the study. In all groups, protein C activity, free protein S, Antithrombin III, Factor VII, VIII, IX, XI, plasminogen, fibrinogen and platelet count were evaluated.

RESULTS: Antithrombin III levels of patients with nephrotic syndrome were significantly lower than the control group and macroalbuminuric diabetics but fibrinogen levels were significantly higher than controls. Fibrinogen levels of microlalbuminuric diabetics were significantly higher than controls. Other haemostatic parameters were all in normal range in all patient groups.

CONCLUSIONS: These findings suggest that the mechanism of hypercoagulation works in a different pathway than the hypercoagulation in nephrotic patients.

KEY WORDS: Antithrombin III, Diabetes mellitus, Fibrinogen, Nephrotic syndrome

ÖZ

AMAÇ: Diyabetes Mellitus'da hiperkoagülabiliteye eğilim olduğu bilinmektedir, pıhtılaşma aktivasyonunun patogenetik mekanizması tam olarak açık değildir ve multifaktöriyel orijinlidir. Kronik hipergliseminin altta yatan esas patoloji olduğu kabul edilmekle birlikte, glisemik kontrolün hemostatik bozukluklarla ilgisi konusunda değişik yorumlar mevcuttur. Çalışmamızda, diyabetik nefropatili hastaları idiyopatik nefrotik sendromlu hastalarla hemostatik değişiklikler açısından değerlendirmeyi amaçladık.

GEREÇ ve YÖNTEMLER: Bu amaçla, 10 yeni tanı almış idiyopatik nefrotik sendromlu hastayı normo- mikro- makroalbüminürik evredeki 10'ar tip II diyabetik hasta ve 12 sağlıklı kontrol grubu ile hemostatik parametreler açısından kıyas ettik. Tüm gruplarda aktive protein C, protein S, antitrombin III, Faktör VII, VIII, IX, XI, Plazminojen, fibrinojen çalışıldı.

BULGULAR: Nefrotik sendromlu hastaların kontrol grubu ve makroalbüminürik hastalardan antitrombin III düzeyi anlamlı düşük, fibrinojen düzeyleri ise kontrol grubundan anlamlı yüksek bulundu. Mikroalbüminürik hastaların fibrinojen düzeyi kontrol grubundan anlamlı yüksek bulundu. Tüm gruplarda diğer hemostatik parametreler normal referans aralığı içerisindeydi.

SONUÇ: Bu bulgular diyabetik hastalardaki koagülasyona eğilimin nefrotik sendromlu hastalardaki hiperkoagülasyon mekanizmalarından farklı yönde geliştiğini düşündürmektedir.

ANAHTAR SÖZCÜKLER: Antitrombin III, Diyabetes mellitus, Fibrinojen, Nefrotik sendrom

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INTRODUCTION

In the majority of diabetic patients, mortality occurs due to disrupted coagulation mechanisms. 75% of the thrombotic death risk of 80% occurs due to cardiovascular complications and the remaining 5% occurs due to cerebrovascular events and peripheral vascular complications (1). Important findings such as increased coagulation potential, continuous activation of the haemostatic system, chronic platelet activation and decreased fibrinolytic potential have been demonstrated in diabetic subjects (2-4). The pathogenetic mechanism of coagulation activation in diabetes is not completely clear and is of multifactorial origin. While chronic hyperglycemia is considered to be the main underlying pathology, there are various comments on the association between glycemic control and haemostatic disorders (5).

Patients with nephrotic syndrome (NS) are also predisposed to hypercoagulability. Studies show that these patients lose the natural anticoagulants such as protein C-S, antithrombin III and plasminogen via urine due to massive proteinuria. This suggests that coagulopathy develops due to the increased production of procoagulants in liver because of the loss of anticoagulants via urine or hypoalbuminemia (6, 7).

In this study, we have aimed to compare patients with diabetic nephropathy and patients with idiopathic nephrotic syndrome with respect to haemostatic differences.

MATERIAL and METHODS

The study was prospectively conducted at Osmangazi University Medical Faculty, Nephrology Department.

30 diabetic patients under follow-up at the Nephrology Polyclinic, diagnosed at least 1 year ago (10 normoalbuminuric, 10 microalbuminuric, 10 macroalbuminuric), 10 patients newly diagnosed with idiopathic nephropathic syndrome and 12 healthy controls were included in the study. All of the diabetic patients (18 female, 12 male) were diagnosed with diabetes mellitus type 2. The disease duration of diabetic patients was 60.3±13.24 months. Among the type 2 diabetic patients, 19 were on insulin and 11 were using oral hypoglycemic drugs. Nephrotic syndrome was defined as plasma albumin <3g/dl and urinary protein excretion >3.5 g/day (derived from a 24-hour urine collection). Oedema was usually but not always present.

The patients receiving anticoagulant therapy or contraceptives, those with a recent thromboembolic event, liver disease, acute or chronic infection or inflammation, and those with creatinine clearance below 35 ml/min were excluded from the study.

The albumin excretion rate was calculated from a 24-hour urine collection after ruling out urinary infection and haematuria. Albumin excretion of 0-30 mg/day was defined as normoalbuminuria, values between 30 to 300 mg/day with at least twice of 30 were defined as microalbuminuria, and excretion above 300 mg/day was defined as macroalbuminuria. The values over 30 mg/day were accepted as the diabetic nephropathy course.

Haemogram, biochemical assays, HbA1C, activated protein C, free protein S levels, antithrombin III (AT-III), fibrinogen, Factor VII, VIII, IX, XI levels, plasminogen, 24-hour urine protein, creatinine, microalbuminuria were evaluated in patient and control groups.

The blood samples required for haematological and biochemical parameters were collected intravenously following 12 hours of fasting.

Biochemical parameters were investigated with the Boehringer Mannheim 747 autoanalyzer using Boehringer Mannheim kits.

Proteinuria in 24-hour urine and HbA1C were investigated with the same method, again with Boehringer Mannheim 747 autoanalyzer using Boehringer Mannheim kits.

Blood samples were collected in Becton Dickinson Vacutainer tubes pre-filled with anticoagulant for all the blood counts, and the counts were performed with the automatic full blood count device Cell-Dyn 3500 R.

Blood samples were collected in tubes containing 3.2% trisodium citrate for fibrinogen, FVII, FVIII, FIX and FXI assays and measurements were performed with the coagulometric method via ACL TOP analyzer using RecombiPlasTin 2G, SynthASiL, Fibrinogen-C XL, FVII, FVIII, FIX, FXI deficient plasma kits from HemosIL.

For protein C activity, free protein S and antithrombin III, the blood samples were intravenously collected into tubes containing 3.2% trisodium citrate following 12 hours of fasting. Protein C activity and free protein S were measured using the chromogenic method with the ACL TOP analyzer and protein C activator and free protein S kits from HemosIL. AT III levels were measured using the Beckmann Array 360 System nephelometer and automatically with Beckmann kits.

Blood samples were intravenously collected into tubes containing 3.2% trisodium citrate for plasminogen analysis. Plasma samples were separated from blood by centrifuging at 3500 rpm for 15 minutes and were stored at -80 ˚C until the analysis. Plasminogen was measured using the kits from HemosIL with ACL TOP analyzer via the chromogenic method.

Statistical Analysis

All data analyses were performed using commercially available software (PASW Statistics 18, SPSS, Inc., Chicago, IL; and SigmaStat 3.5, Systat Software, Inc., San Jose, CA). Continuous variables were demonstrated using n (sample size) and mean, and standard deviation; and categorical variables using n (sample size) and median, and 25th and 75th percentiles.

Continuous normally distributed measurements were compared across the groups using 1-way analysis of variance using the Student-Newman-Keuls method for multiple comparisons. Score variables that did not demonstrate a normal distribution were compared using the Kruskal-Wallis test with the Dunn method multiple comparison tests. Score variables between the 2 groups were compared using the Mann-Whitney U test. Spearman correlation analysis was used to determine correlations among non-normally distributed variables. $P < .05$ was accepted as statistically significant.

Table I: Demographic characteristics and basic laboratory data of the patients and control group.

	Control group (N:12)	**Nephrotic syndrome (N:10)**	**Normoalbuminüric diabetic patient (N:10)**	**Microalbuminüric diabetic patient (N:10)**	**Macroalbuminüric diabetic patient (N:10)**	**p**
Sex(M/F)	7/5	7/3	6/4	7/3	5/5	
*Age(yıl)	35.75±13.98	33.6±12.6	58.5±11.98	59.4±15.14	63±13.38	p<0.001
*height (cm)	170.75±11.87	168±7.21	161.20±10.39	167.5±7.66	162.90±6.14	p>0.05
**weight (kğ)	66.5 (57.5-72.5)	62.5 (58-78)	64.35 (59-72)	76 (70-86)	65 (62-85)	p>0.05
**BMI(kg/m^2)	21.99 (21.01-24.66)	22.21 (21.48-24.92)	25.87 (21.8-27.7)	28.76 (25.73-30)	23.85 (23.55-31.24)	p<0.05
**Hemoglobin b(g/dl) (13.3-17.7)	14.35 (12.5-15.25)	12.05 (11.1-13)	13.45 (11.9-15.5)	12.7 (11.6-14)	12.6 (12.3-13.5)	p>0.05
*WBC(10^3/ul)(3.9-10.6)	7.325±1.98	8.09±2.45	8.66±1.59	8.75±2.27	8.76±2.12	p>0.05
*Platelets count	235000±55.68	307.900±69.67	308400±87.28	308500±8027	284000±91.83	p>0.05
** Glucose (mg/dl)(70-110)	78 (75-82.5)	81.5 (74-90)	130.5 (99-220)	151.5 (117-202)	134 (96-188)	P<0.001
**Total cholesterol, (mg/dl)(112-200)	166.5 (151-186)	288 (179-352)	171.5 (161-209)	167 (145-196)	182.5 (162-213)	p<0.05
**Triglycerides (mg/dl) (25-170)	76.5 (54-97.5)	250.5 (26-295)	136 (85-201)	149 (87-372)	173.5 (89-204)	p<0.001
**HDL –C (mg/dl) (35-70)	54 (46-57.5)	40.5 (36-61)	42 (40-50)	41 (36-53)	44.5 (39-52)	p>0.05
**LDL- C (mg/dl)	100.4 (82.3-114.9)	148 (113.8-209)	105.5 (96.2-123)	83.6 (64-98.4)	103.6 (83-130)	p<0.05
**BUN (mg/dl)(5-20)	14 (12-17)	15.05 (12-26.8)	17.5 (13-30)	18.5 (15-26)	19.9 (11-34.1)	p>0.05
**Cr (mg/dl)(0.5-1.6)	0.75 (0.7-0.85)	0.9 (0.6-1.4)	0.84 (0.6-1.13)	0.8 (0.61-1)	1.15 (0.8-1.2)	p>0.05
**Total Protein (g/dl)(6-8.5)	7.75 (7.5-7.95)	5.1 (4.3-5.7)	7.6 (7-7.8)	7.55 (6.4-8.2)	6.8 (6.7-7.7)	p<0.001
*Albumin (g/dl)(3.5-5)	4.62±0.35	2.48±0.53	4.45±0.33	4.4± 0.68	4.08±0.5	p<0.001
*CrCl (ml/dk)	101.37±13.33	90.54±42.63	92.56±27.80	85.31±35.32	75.76±39.9	p>0.05
**Proteinüri a (mg/gün)	90.34 (71.25-111.5)	5143 (4525-7290)	128.1 (87.9-166.59)	333.28 (240-593.76)	834.6 (604-1082)	p<0.001
**Microalbuminüria (mg/gün)	10.3 (6.73-12.42)	1416 (838-2405)	8.36 (5.8-21.56)	128.76 (63.9-194)	538.8 (429-669)	p<0.001

BMI, body mass ındex; **WBC,** white blood count; **LDL-C,** low-density lipoprotein cholesterol; **HDL-C,** high- density lipoprotein cholesterol; **BUN,** blood urea nitrogen; **Cr,** creatinine; **CrCI,** creatinine clearance
Values are given as mean (SD) or median (range).
* One Way Analysis of Variance, mean(SD)
** Kruskal-Wallis test, median(Q1-Q3)

Table II: Comparison between the haemostatic paramaters of patient groups and control groups.

	Control group (N:12)	Nephrotic syndrome (N:10)	Normoalbuminüric diabetic patient (N:10)	Microalbuminüric diabetic patient (N:10)	Macroalbuminüric diabetic patient (N:10)	p
*Protein.S (%) (55-140)	91.017±19.44	87.75±22.69	89.41±18.85	89.91±28.16	77.19±24.05	p>0.05
*Protein.C aktivity(%) (70-130)	112.3±13.04	133.5±29.72	122.30±22.61	117±21.11	116.30±26.51	p>0.05
**ATIII (mg/dl) (25-36)	32.1 (25.3-45.9)	24.35 (20.6-25.6)	29.5 (26.8-32.5)	31.1 (23.6-34.3)	31.5 (27.9-36.4)	p<0.05
*FVII (%) (50-150)	118.31±21.76	128.06±35.52	116.74±35.94	120.2±20.72	103.76±25.26	p>0.05
*FVIII (%) (50-150)	106.76±25.86	136.18±24.61	142.08±44.92	133.94±42.63	107.21±21.36	p<0.05
*FIX (%) (50-150)	118.23±31.16	122.24±37.17	111.19±25.52	131.14±39.50	119.75±31.94	p>0.05
*FXI (%) (50-150)	103.83±27.50	99.29±27.53	125.88±14.83	120.34±31.90	123.06±50.17	p>0.05
*Plazminogen(%) (80.2-132.5)	102.50±18.59	91.67±15.06	99.40±16.46	105±16.51	105.90±15.91	p>0.05
**Fibrinogen(mg/dl) (200-400)	280.5 (270.5-301.5)	496 (429-625)	337 (265-366)	412 (361-433)	383 (288-525)	p<0.001

ATIII, antithrombin 3; **FVII,** factor 7; **FVIII,** factor 8; **FIX,** factor 9; **FXI;** factor 11
Values are given as mean (SD) or median (range).
* One Way Analysis of Variance, mean(SD)
** Kruskal-Wallis test, median(Q1-Q3)

RESULTS

The demographic characteristics and the basic laboratory data of the patients and control group are presented in Table I, and the haemostatic data in Table II.

The height, body weight, haemoglobin (Hb), white blood count (WBC), platelet count, high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen (BUN), creatinine (Cr), and creatinine clearance (CrCI) data were similar between the patients and the control group (p> 0.05). The age of patients in NS and control groups (33.6±12.6 and 35.75±13.98 years, respectively) were statistically lower than the normoalbuminuric, microalbuminuric and macroalbuminuric ones among diabetic patients (58.5±11.98, 59.4±15.14 and 63±13.38 years, respectively) (p<0.001) while the ages were similar between the NS and control groups (p>0.05). Body mass index (BMI) of the microalbuminuric diabetic patients was higher than the control group with statistical significance (28.76 mg/m^2 (25.73-30) and 21.99 mg/m^2 (21.01-24.66), respectively) (p<0.05) while the BMI of other groups were similar (p>0.05). We found difference between the groups regarding total cholesterol levels, yet we could not calculate this during the multiple comparison; however, the median value of the patients with NS was significantly higher compared to other groups (p<0.05).

The fibrinogen value of the patients with NS was significantly higher than the control group and the normoalbuminuric diabetic patients (496 mg/dl (429-625), 280.5 mg/dl (270.5-301.5), 337 mg/dl (265-366), respectively) (p<0.001); the fibrinogen value of microalbuminuric diabetic patients was also significantly higher than the control group (412 mg/dl (361-433), 280.5 mg/dl (270.5-301.5) respectively) (p<0.001) while the fibrinogen values were similar between the other groups (p>0.05). AT-III value of the patients with NS was significantly lower than the control group and the macroalbuminuric diabetic patients (24.35 mg/dl (20.6-25.6), 32.1 mg/dl (25.3-45.9), 31.5 mg/dl (27.9-36.4), respectively) (p<0.05) while the AT-III values were similar between the other groups (p>0.05). We found different levels of FVIII across the group yet we could not calculate this during the multiple comparison; however, the FVIII level was within the normal reference range of our laboratory. The groups did not show any difference in terms of protein S level, protein C activity, FVII, FIX, FXI, and plasminogen values (p>0.05).

DISCUSSION

In this study, antithrombin III levels of patients with nephrotic syndrome were significantly lower than the control group and macroalbuminuric diabetics but fibrinogen levels were significantly higher than controls. Fibrinogen levels of microlalbuminuric diabetics were significantly higher than controls. Other haemostatic parameters were all in normal range in all patient groups.

Elevated levels of fibrinogen is a marked abnormality in patients with nephrotic syndrome (6, 8-10, 11, 12). In the study by Takeda and Chen, the elevated plasma fibrinogen level was observed to be a result of urinary protein loss and the proportionally increased synthesis (13). In our study, plasma fibrinogen level of

patients with nephrotic syndrome was significantly higher than the control group and normoalbuminuric diabetic patients, while it was similar to those of micro- and macroalbuminuric diabetic patients. While the fibrinogen level of normoalbuminuric patients was not different from the control group in our study, the fibrinogen level of microalbuminuric patients was significantly higher than the control group; however, the lack of a difference between the fibrinogen levels of macroalbuminuric patients and the control group suggests that this situation is not related to proteinuria. In that case, the hyperfibrinogenemia in type II diabetes may be occurring due to a different mechanism than the hyperfibrinogenemia in nephrotic syndrome. As the reason of this, Knöbl et al. suggested the adhesion of monocytes with the disrupted endothelium due to diabetic vasculopathy, which leads to release of interleukin 6, causing increased hepatic synthesis of fibrinogen (14). The majority of the studies report elevated fibrinogen levels in Type II diabetic patients with or without a microvascular disorder (15).

There are articles reporting loss of coagulation inhibitors such as protein C and protein S in patients with nephrotic syndrome due to massive proteinuria and increased production in the liver as compensation (16, 17); therefore, the plasma levels of these proteins are either normal or increased but the protein C activity or the functional level of protein S may be decreased (16, 17). We found normal levels of protein C activity and protein S, which were not different than the control group. Similar to our study, Aslan et al. classified Type II diabetic patients into subgroups based on urinary albumin excretion: group 1 (<30 mg/ml), group 2 (30-140 mg/ml) and group 3 (>140 mg/ml), and performed assays for protein C antigen and protein C activity. While the mean protein C-antigen (ag) levels in group 1, 2 and 3 were lower than the control group, the protein C activity levels of the 3 groups were not different than the control group (18). According to this study, the finding that even the normoalbuminuric patients (group 1) had low levels of protein C suggests the lack of association with urinary excretion of natural anticoagulants. However, we believe that it is necessary to investigate the urinary levels and conduct further studies to ensure the accuracy of this observation. In our study, the protein C activity levels and the protein S levels of patients with nephrotic syndrome were not different than the control group and the diabetic patients at normo-micro-macroalbuminuric phases.

The thrombosis in nephrotic patients has been suggested to be associated with the AT-III deficiency due to increased urinary loss, and the inability of low AT-III levels to activate the procoagulant factors (19). Studies have shown low AT-III levels in patients with nephrotic syndrome (7). Also in our study, the AT-III levels were lower than the normal range in patients with nephrotic syndrome, showing a statistically significant difference compared to the control group. Chan et al. found normal plasma AT-III levels in diabetic and non-diabetic patients with nephropathy and proteinuria over 1g/day, while they found higher levels of urinary AT-III in patients with diabetic nephropathy and attributed this to the non-selective protein loss in advanced diabetic nephropathy or the urinary loss due to increased local concentrations of AT-III resulting from intraglomerular thrombosis (20). This study shows the loss of natural anticoagulants via urine in severely diabetic nephropathy and therefore appears to support our hypothesis. Differing from ours, the mean creatinine clearance of the patients is below 35 ml/min and the daily protein excretion is approximately 4 g/day in this study. As massive proteinuria usually accompanies renal dysfunction and taking into account the effects of uremic nephropathy on coagulation, we excluded the patients with creatinine clearance below 35 ml/min and the ones with proteinuria at nephrotic borderline. We also could not investigate AT-III levels in the urine. In our study, the AT-III level of the nephrotic patients was lower than the diabetic patients in the macroalbuminuric phase with a statistically significant difference, and was similar to normo- and microalbuminuric diabetic patients; however, the AT-III level of diabetic patients was within the normal reference range. The finding that AT-III level of the nephrotic patients was similar to normo- and microalbuminuric diabetic patients while it was lower than the macroalbuminuric patients suggests that AT-III is not lost via proteinuria but the urinary levels should be investigated to ensure the accuracy of this observation. There was a negative association between the degree of proteinuria and AT-III level in patients with nephrotic syndrome, although this was not statistically significant ($r = -236$, $p > 0.05$).

In patients with nephrotic syndrome, Factor IX, XI and XII are likely to be lost in urine due to their low molecular weight. While the level of Factor IX varied, the levels of factor XI and XII were low in patients with nephrotic syndrome. The levels of co-factors, Factor V and VIII were increased (21). Kanfer and colleagues demonstrated F VIII activity exceeding 200% in 22 of 57 patients with nephrotic syndrome (9). These changes lead to increased synthesis of these proteins from the liver due to decreased plasma oncotic pressure, F V and VIII are not found in the urine of patients with nephrotic syndrome, and this may be related to their molecular size (21). In our study, the factor levels of the patients with nephrotic syndrome and the normo-micro-macroalbuminuric diabetic patients were within the normal reference range of our laboratory. The coagulation and fibrinolysis alterations in urine and glomerulus of patients with nephrotic syndrome are not fully understood and there are controversial results. Generally, the plasma plasminogen concentration is decreased in nephrotic syndrome (22-24). This has been associated with the low level of serum albumin and the degree of proteinuria (25,26). In our study, we found a lower plasminogen level in patients with nephrotic syndrome compared to the control group, although this difference was not statistically significant. There was no difference regarding plasminogen levels between the normo-micro-macroalbuminuric patients and the patients with nephrotic syndrome.

As a result of our study, we find it difficult to attribute the hypercoagulability in patients with nephrotic syndrome to the elevated fibrinogen, which we consider as possibly related to proteinuria, and the mild AT-III deficiency. There are articles reporting that nephrotic syndrome accompanies acquired hypercoagulability; however, it leads to thrombotic events in the presence of an underlying genetic thrombophilia (27, 28). Furthermore, use of diuretics and steroids are also thought to facilitate thrombosis. Similarly, the lack of haemostatic problems in diabetic patients in macroalbuminuric phase make it difficult to explain the hypercoagulation mechanism with proteinuria alone. In addition, it is difficult to explain hypercoagulation mechanism with proteinuria alone in these patients as the different glycemic control levels and different treatment approaches in diabetics with various levels of vascular complications, and various type and duration of diabetes may have an impact on haemostatic parameters. Another limitation of our study is the limited number of our patients and the younger age in patients with nephrotic syndrome while the type II diabetic patients were at an advanced age.

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