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The Relationship Between Serum Bisphenol A Levels and Diabetic Peripheral Polyneuropathy in Patients with Type 2 Diabetes Mellitus

ABSTRACT

Objective: The present investigation sought to explore the potential link between serum bisphenol A (BPA)—a well-recognized endocrine-disrupting agent—and diabetic peripheral polyneuropathy (PNP) among patients diagnosed with type 2 diabetes mellitus (DM).

Methods: Eighty patients underwent clinical and electrophysiologic assessment of PNP and single-time-point serum BPA quantification by enzyme-linked immunosorbent assay.

Results: The average age and diabetes duration did not differ significantly between patients with PNP and those without. However, fasting glucose, glycosylated hemoglobin (HbA1c), and triglyceride levels were notably elevated in the PNP group relative to non-PNP patients. But serum BPA levels were not statistically different between the groups. Serum BPA levels were negatively correlated with the glomerular filtration rate and HbA1c and positively correlated with the body mass index and high-density lipoprotein cholesterol levels.

Conclusion: No significant association was observed between serum BPA concentrations and the presence of PNP in patients with type 2 DM. These results confirm that known vascular risk factors such as glycemic control are closely related to the presence of PNP.

Keywords Bisphenol A, diabetes mellitus, polyneuropathy

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Introduction

Diabetic neuropathy (DNP) is widely recognized as a major health burden, significantly increasing the risk of illness and death in individuals with type 2 diabetes mellitus (DM).[1] Diabetic peripheral polyneuropathy (PNP) has a lifetime prevalence of about 50% and is the most frequent complication of DM.[2] Peripheral polyneuropathy makes up 75% of DNP.[3] However, the pathogenesis of DNP is still unclear. Although the precise pathophysiological mechanisms of diabetic neuropathy remain unclear, several contributing factors have been identified, including disease duration, poor glycemic control, elevated serum triglycerides, increased body mass index (BMI), smoking, and hypertension.[4] Recent studies also implicate subclinical inflammation and endothelial dysfunction as potential contributors to the development of diabetic PNP.[5]

Recent studies indicate that endocrine-disrupting chemicals (EDC) cause many diseases. Endocrine-disrupting chemicals are compounds that disrupt or mimic the normal functions of all endocrine hormones such as estrogen, androgens, and thyroid, hypothalamic, and pituitary hormones.[6] Bisphenol A (BPA) is an EDC in polycarbonate plastics,[7] and most commonly being exposed by oral route.[8] Bisphenol A is known to be a xenoestrogenic agent capable of binding to the estrogen receptor α, the estrogen receptor β, and the estrogen receptor γ.[9,10] Some studies on the effects of BPA on human health suggest that BPA exposure may be associated with obesity, DM, and metabolic syndrome.[11,12] It is, therefore, a matter of curiosity whether exposure to BPA has been suggested to influence the onset of long-term diabetic complications. Recent evidence has demonstrated a negative association between serum BPA levels and glomerular filtration rate (GFR) among patients diagnosed with type 2 diabetes, indicating that elevated BPA levels have been implicated as a contributing factor in the progression of chronic renal failure within this group.[13] However, the effect of increased BPA exposure on the other microvascular complications of DM such as PNP is unknown. Accordingly, the present study was designed to explore the potential link between serum BPA concentrations and diabetic PNP in patients with type 2 DM.

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Methods

The study population consisted of patients aged 30-65 years with a confirmed diagnosis of type 2 DM and preserved renal function (GFR >60 mL/min/1.73 m^2), who were regularly followed in the endocrinology and internal medicine outpatient clinics. Patients who have another endocrine disease, are smokers, or have an acute or chronic infectious condition, severe heart failure or cardiac arrhythmia, a history of acute myocardial infarction in the past 6 weeks, malignancy, 3 times or more elevation in serum aspartate transferase (AST) and alanine transferase (ALT) levels, or pregnant or lactating patients were excluded from the study. Individuals with hypothyroidism, those receiving statin therapy, or undergoing treatment for neuropathy were not considered eligible, as these conditions could interfere with neuropathy evaluation. The study protocol received approval from the Bursa Yüksek İhtisas Education and Training Hospital Ethics Committee (2011-KAEK-25 2016/1301) on July 13, 2016. All participants provided written informed consent before enrollment.

A detailed physical examination of all volunteers was performed at the outpatient clinic. Blood pressure was recorded from the brachial artery using a sphygmomanometer when patients were in a sitting position after resting for 5 minutes. Averages were calculated by measuring at 2-minute intervals. Body weight was measured with calibrated digital scales, and BMI was computed as body weight in kilograms divided by the square of height in meters (kg/m^2). The Michigan Neuropathic Screening Test (MNTT) was used to diagnose distal symmetric peripheral neuropathy in patients with type 2 DM. Subsequently, patients underwent electromyography (EMG).[14] Electrophysiological recordings were obtained using a standardized electromyography system (Nihon Kohden MEB9102K).

To ensure a robust and specific definition of diabetic PNP, patients were classified as having PNP only when both MNTT and EMG results were concordantly positive. Individuals with discordant findings were excluded to prevent diagnostic misclassification and maintain internal validity despite the modest sample size.

Laboratory Methods

Venous blood samples were obtained from all participants in the early morning following an overnight fast of 8-12 hours. The blood was centrifuged in glass tubes against the risk of BPA contamination. The obtained serum was again taken in glass bottles and after being covered with aluminum foil to avoid sunlight exposure, it was kept at −80°C for collective measurement of the serum BPA level. Fasting plasma glucose (FPG), serum creatinine, AST, ALT, serum low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol concentrations, total cholesterol and triglyceride values of the patients were measured by Beckman Coulter AU 5800 auto analyzer with high sensitivity spectrophotometric method and glycosylated hemoglobin (HbA1c) values were determined by high-performance liquid chromatography (HPLC) method using Arkray-ADAMS HA-8180v.

Serum BPA levels were measured by the "double sandwich" Enzyme-Linked Immunosorbent Assay (ELISA) method using My BioSource MBS2602664 General Bisphenol A Enzyme-Linked Immunoabsorbent Assay kit (Mybiosource, Southern California, San Diego, USA) with a sensitivity of 3.12 ng/mL. The readings were made by an ELISA reader at a wavelength of 450 nm.

Statistical Methods

Assessment of distributional assumptions was conducted using the Shapiro–Wilk test. Group comparisons were carried out with the independent sample *t*-test when normality was confirmed; otherwise, the Mann–Whitney *U*-test was preferred for nonparametric data. Continuous variables were expressed as mean values with corresponding SDs. Categorical data were analyzed through the Pearson chi-square test or, when appropriate, Fisher's exact test, with results summarized as frequencies and percentages. Correlations between variables were examined using Spearman's rank correlation coefficient. Statistical significance was defined as a two-tailed *P* value below .05. All analyses were conducted using IBM SPSS Statistics software version 22 (IBM SPSS Corp.; Armonk, NY, USA).

No a priori sample-size calculation was performed; this exploratory study included all available participants. "Study Power and Precision" provided in Supplement 1.

Results

A total of 80 individuals diagnosed with type 2 DM (44 women and 36 men) were included in the study. Their mean age was 51.1 ± 5.9 years, and the average duration of the disease was 5.9 ± 5.2 years. In order to demonstrate the presence of diabetic PNP more accurately, patients were grouped as having PNP if both EMG and MNTT results were positive for PNP. Patients with the negative results of both screening tests were considered not to have PNP. Patients who have discordant EMG and MNTT results were excluded. According to this classification, there were 27 patients with PNP and 27 patients without PNP. The average age of patients with PNP was 50.4 ± 5.0 years whereas it was 51.0 ± 6.0 years in patients without PNP. No statistically significant differences were observed between the groups in terms of age, gender, or diabetes duration. Detailed demographic and laboratory data are provided in Table 1.

No statistically significant differences were observed between the groups with respect to BMI (31 ± 6.5 vs. 29.4 ± 2.7 kg/m^2), systolic blood pressure (SBP) (120.0 ± 12.7 vs. 116.7 ± 8.8 mm/Hg), diastolic blood pressure (DBP) (78.1 ± 8.3 vs. 76.7 ± 8.3 mm/Hg), creatinine (0.8 ± 0.2 vs. 0.8 ± 0.2 mg/dL), GFR (94.7 ± 21.0 vs. 101.0 ± 22.6 mL/min/1.73 m^2), albumin/creatinine ratio (ACR) (65.9 ± 164.0 vs. 31.2 ± 51.6 mg/g), AST (28.0 ± 14.9 vs. 27.3 ± 10.7 U/L), ALT (34.1 ± 18.2 vs. 35.5 ± 21.9 U/L), LDL cholesterol (132.3 ± 38.6 vs. 129.7 ± 31.2 mg/dL), HDL cholesterol (45.3 ± 11.4 vs. 50.7 ± 14.99 mg/dL) and total cholesterol (222.4 ± 49.4 vs. 213.2 ± 39.6 mg/dL). The mean FPG (228.9

MAIN POINTS

- To the authors' knowledge, this is the first research to evaluate the relationship between circulating bisphenol A (BPA) concentrations and diabetic peripheral polyneuropathy in individuals with type 2 diabetes mellitus. No direct relationship was found between BPA concentrations and the presence of diabetic neuropathy.
- Bisphenol A levels were significantly correlated with several metabolic risk factors, including body mass index and glomerular filtration rate.
- These findings suggest that BPA may exert indirect metabolic effects, highlighting the potential role of environmental toxins in the pathophysiology of diabetes.

Table 1. Demographics and Laboratory Results of Diabetic Patients with and Without Peripheral Polyneuropathy

	With PNP (n = 27)	Without PNP (n = 27)	*P*
Age (years)	50.4 ± 5.0	51.0 ± 6.0	NS
Female, n (%)	13 (48.2)	15 (55.6)	NS
Male, n (%)	14 (51.8)	12 (44.4)	
Duration of diabetes (years)	6.9 ± 6.4	5.0 ± 3.7	NS
BMI (kg/m^2)	31 ± 6.5	29.4 ± 2.7	NS
SBP (mmHg)	120.0 ± 12.7	116.7 ± 8.8	NS
DBP (mmHg)	78.1 ± 8.3	76.7 ± 8.3	NS
FPG (mg/dL)	228.9 ± 91.0	179.1 ± 89.5	**.030**
HbA1c (%)	9.8 ± 2.2	8.0 ± 2.2	**.008**
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	NS
GFR (mL/min/1.73 m^2)	94.7 ± 21.0	101.0 ± 22.6	NS
ACR (mg/g)	65.9 ± 164.0	31.2 ± 51.6	NS
AST (U/L)	28.0 ± 14.9	27.3 ± 10.7	NS
ALT (U/L)	34.1 ± 18.2	35.5 ± 21.9	NS
LDL cholesterol (mg/dL)	132.3 ± 38.6	129.7 ± 31.2	NS
HDL cholesterol (mg/dL)	45.3 ± 11.4	50.7 ± 14.9	NS
Total cholesterol (mg / dL)	222.4 ± 49.4	213.2 ± 39.6	NS
Triglyceride (mg/dL)	219.9 ± 88.3	162.1 ± 58.3	**.006**
Bisphenol A (ng/mL)	7.4 ± 2.5	7.7 ± 3.0	NS

The data are given as mean ± SD. Bold values indicate statistically significant differences ($p < 0.05$).
ACR, albumin/creatinine ratio; ALT, alanine aminotransferase; AST, Aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA1c, glycosylated hemoglobin;HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant; PNP, peripheral polyneuropathy; SBP, systolic blood pressure.

± 91.0 vs. 179.1 ± 89.5 mg/dL) and HbA1c levels (9.8 ± 2.2% vs. 8.0 ± 2.2%) were higher in patients with PNP compared with the patients without PNP (*P* = .03 and *P* = .008; respectively). Serum triglyceride levels were also found higher in patients with PNP when compared with the patients without PNP (219.9 ± 88.3 vs. 162.1 ± 58.3 mg/dL) (*P* = .006). Mean serum BPA level was 7.4 ± 2.5 ng/mL in the patients with PNP whereas it was 7.7 ± 3.0 ng/mL in the patients without PNP. Serum BPA concentrations did not differ significantly between the 2 groups (*P* = .708), (Table 1) (Figure 1).

Based on EMG findings, 36 patients were identified with PNP and 44 without. No differences were detected between the groups in terms of age or gender distribution. However, patients with PNP showed significantly elevated levels of FPG, HbA1c, and triglycerides compared with those without PNP (*P* = .009, *P* = .002, and *P* = .018, respectively). Other assessed parameters did not demonstrate significant intergroup variation. The mean serum BPA concentrations were 7.1 ± 2.7 ng/mL in the PNP group and 8.5 ± 3.5 ng/mL in the non-PNP group, with the difference failing to achieve statistical significance (*P* = .088).

Based on MNTT classification, 44 patients were assigned to the PNP group and 36 to the non-PNP group. The 2 groups were comparable with respect to age and gender distribution. No notable differences were identified between the groups in terms of diabetes duration, BMI, DBP, FPG, HbA1c, creatinine, GFR, ACR, AST, ALT, LDL cholesterol, HDL cholesterol, and total cholesterol levels. Systolic blood pressure and triglyceride levels were found higher in the patients with PNP when compared with the patients without PNP (*P* = .036 and *P* = .027, respectively). The mean serum BPA concentrations were 8.3 ± 3.3 ng/mL in patients with PNP and 7.4 ± 3.1 ng/mL in those without PNP; but this variation was not statistically meaningful (*P* = .185).

Correlation analysis revealed that MNTT symptom scores were positively and significantly associated with diabetes duration ($r = 0.225$; *P* = .045), HbA1c levels ($r = 0.254$; *P* = .023), LDL cholesterol ($r = 0.225$; *P* = .045), total cholesterol ($r = 0.306$; *P* = .006), and triglycerides ($r = 0.393$; $P < .001$). The physical examination scores of MNTT were positively correlated with serum HbA1c levels only ($r = 0.269$; *P* = .016).

Correlation analysis revealed that serum BPA levels of patients were negatively correlated with the GFR ($r = -0.231$, *P* = .039) and HbA1c ($r = -0.289$; *P* = .009) levels of patients. Serum BPA concentrations

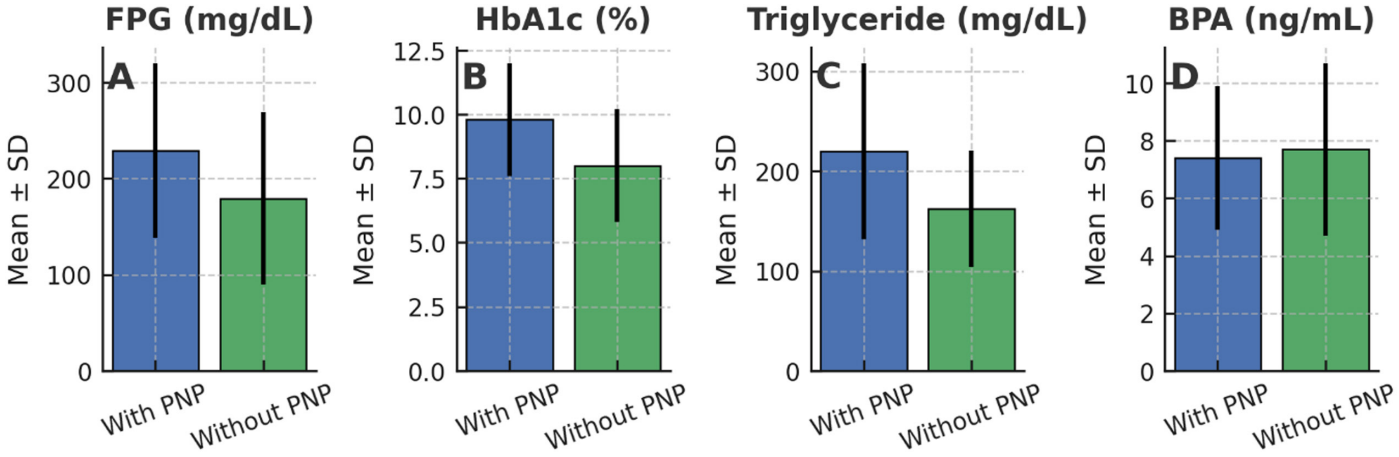

Figure 1. Comparison of significant metabolic parameters and serum bisphenol A (BPA) levels between diabetic patients with and without peripheral polyneuropathy (PNP). (A) Fasting plasma glucose levels were significantly higher in patients with PNP than in those without PNP (*P* = .030). (B) Glycated hemoglobin values were also higher in the PNP group (*P* = .008), reflecting poorer glycemic control. (C) Serum triglyceride concentrations were significantly increased among patients with PNP compared with those without PNP (*P* = .006). (D) Mean serum BPA concentrations did not differ significantly between groups (*P* > .05). Bars represent mean ± SD.

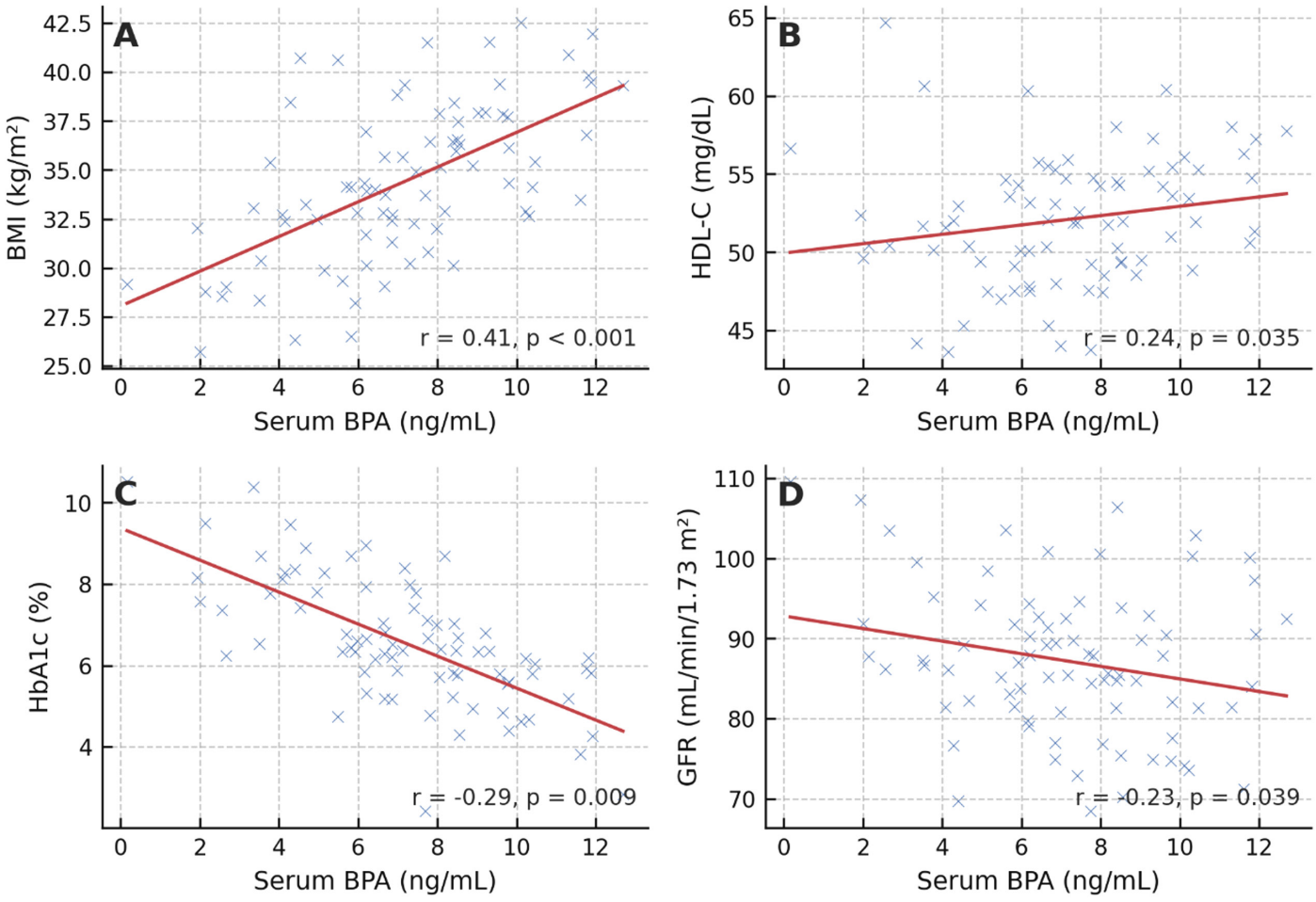

Figure 2. Correlations between serum bisphenol A (BPA) concentrations and selected metabolic parameters in patients with type 2 diabetes. (A) Serum BPA levels showed a weak positive correlation with body mass index ($r = 0.41$, $P < .001$). (B) A weak positive correlation was also observed with high-density lipoprotein cholesterol ($r = 0.24$, $P = .035$). (C) BPA was inversely correlated with glycated hemoglobin ($r = -0.29$, $P = .009$). (D) A weak negative correlation was found between BPA and estimated glomerular filtration rate ($r = -0.23$, $P = .039$). Red lines represent linear regression fits with 95% CIs.

showed a positive correlation with BMI ($r = 0.410$; $P < .001$) and HDL cholesterol levels ($r = 0.236$; $P = .035$) (Figure 2).

This study also examined the association between serum BPA levels and microvascular complications, including retinopathy. According to fundus examination findings, participants were divided into 2 subgroups: diabetic retinopathy (DRP) (n = 13) and non-DRP (n = 67). The mean serum BPA level was 8.19 ± 4.35 ng/mL in the DRP group and 7.80 ± 2.99 ng/mL in the non-DRP group. This difference was not statistically significant ($P = .830$).

Discussion

In this cross-sectional study of adults with type 2 DM, there was no significant association between serum BPA concentrations and the presence of diabetic PNP. This negative finding represents the central outcome of this research and suggests that, within the range of BPA exposure observed, circulating BPA levels may not contribute directly to the development of PNP. Despite the absence of a relationship between BPA and PNP, these findings reaffirm the well-established association between poor glycemic control, elevated triglycerides, and neuropathy risk, underscoring that traditional vascular and metabolic factors remain the predominant determinants of PNP in diabetic patients.

Although there is not a definitive diagnostic method described in the guidelines for PNP diagnosis, the general consensus is to diagnose using multiple diagnostic methods.[14] For this reason, a grouping was made by evaluating the results of MNTT and EMG tests to strengthen the diagnosis of PNP in this study. A total of 54 diabetic patients with (n = 27) and without PNP (n = 27) were analyzed statistically. Serum BPA concentrations showed no meaningful variation between diabetic patients with and without PNP. Likewise, subgroup analyses based solely on EMG or MNTT findings revealed no significant differences in serum BPA levels across groups.

Studies on diabetic neuropathy suggest that persistent and marked hyperglycemia is the major factor contributing to the development of neuropathy in patients with either type 1 or type 2 DM.[15] Recent studies have shown that dyslipidemia, hypertension, and cigarette smoking may also be risk factors in addition to hyperglycemia.[16,17] According to the European Diabetes Study Group (EURODIAB) study, peripheral neuropathy was observed in 23.5% of type 1 diabetes patients following an average follow-up of 7.3 years. The onset of

neuropathy was associated with serum triglycerides, BMI, smoking status, hypertension, as well as the length of diabetes and HbA1c values.[18] Another study involving 427 patients with diabetic neuropathy reported that triglyceride levels were significantly related to the progression of diabetic neuropathy independent of glycemic control, type of diabetes, and insulin administration following a 1-year observational period.[17] These results showed that patients with PNP had elevated FPG, HbA1c, and triglyceride levels. In contrast, BMI and duration of diabetes did not differ significantly between groups. These findings suggest that common vascular risk factors may also pose a risk for developing neuropathy.

Diabetic PNP is the most common neurological complication of type 2 DM.[18] This has prompted extensive research efforts aimed at clarifying the pathogenesis of PNP and identifying potential treatment strategies. The results of published studies suggest that the increase in growth factors; platelet-derived growth factor, T-lymphocyte activation regulator, tumor necrosis factor-alpha (TNF-α), intercellular adhesion molecule (ICAM), leptin, osteoprotegerin, granulocyte-colony stimulating factor, vascular cell adhesion molecule, C-reactive protein (CRP) and fibrinogen may play a role in the etiopathogenesis of PNP.[5] In a recent study, it was observed that patients with PNP had increased high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), TNF-α, IL-1 receptor antagonist (IL-1RA) and soluble ICAM while serum adiponectin levels of these patients were found decreased.[19] Collectively, these observations support the hypothesis that chronic subclinical inflammation plays a pivotal role in peripheral neuropathy.

The results of BPA studies, known as EDC, suggest that serum and urinary BPA levels may be associated with type 2 DM and diabetic nephropathy.[11,13] In addition, Choi et al[20] demonstrated that BPA may lead to systemic inflammation independent of obesity and insulin resistance. Persistent inflammation has been recognized as a major contributor to the pathogenesis of PNP as well as other diabetes-related complications.[5] But the role of BPA as an endocrine disruptor in this process is still unclear. Bisphenol A is thought to exert many effects through estrogen receptors. It is also known that estrogen inhibits neurocyte degeneration like a neuroprotective and neuroregulatory agent.[21] Bisphenol A can stimulate estrogen receptors though it binds the receptors with low affinity compared to natural estrogens.[22] It disrupts the densities of the estrogen receptor even at low doses in the brain, reducing the sensitivity of the receptor to natural estrogens.[23] This suggests that the positive effects of estrogen on neurons may be blocked by BPA. Although both chronic inflammations caused by BPA and its antiestrogenic effects suggest that BPA may be implicated in the development of PNP, there is no association between serum BPA levels and PNP in this study. To the authors' knowledge, no previous study has specifically evaluated the association between PNP and BPA.

In the present analysis, serum BPA levels showed a negative correlation with GFR ($r = -0.231$; $P = .039$) and HbA1c ($r = -0.289$; $P = .009$) while positive correlations were observed with BMI ($r = 0.410$; $P < .001$) and HDL levels ($r = 0.236$; $P = .035$). Another study demonstrated that urinary BPA levels were positively associated with obesity, independent of age, race, gender, education, physical activity, and serum creatinine levels.[24] Although the effect of BPA on weight is thought to be related to estrogen receptors,[25] some studies have reported that BPA exerts an "obesogenic" effect by inducing adipocyte differentiation and adipogenesis-related gene expression.[26] In some laboratory studies, it has been emphasized that neurological effects that occur in animals exposed to BPA may lead to weight gain. Rats exposed to BPA have been reported to gain more weight when fed high-fat food than the control group. These findings suggest that exposure to BPA may disrupt the hypothalamic energy balance leading to dietary-related metabolic disturbances and obesity.[27] The major metabolite of BPA, BPA glucuronide, which is thought to be inactive, has also been shown to induce adipogenesis without any estrogenic activity.[28] The relationship between BPA exposure and obesity has been widely explored, with numerous studies suggesting a potential association. This is explained by different mechanisms in different studies. These findings also demonstrated a positive correlation between serum BPA levels and BMI, supporting previously reported data. Nonetheless, conflicting evidence exists, as both human and animal studies have shown no significant link between BPA exposure and weight gain.[29] Therefore, additional research is warranted to clarify the metabolic implications of BPA.

In a study by Kim et al,[30] HDL and non-HDL cholesterol levels were found higher in BPA-exposed rats than in the control group. Numerous studies have consistently demonstrated that estrogen contributes to an increase in circulating HDL cholesterol levels.[31] Increased serum HDL cholesterol levels in BPA-exposed rats were thought to be related to the estrogenic effect of BPA. Consistent with prior reports, the present findings demonstrated a positive correlation between serum BPA concentrations and HDL cholesterol levels. However, no significant association was identified between BPA and non-HDL cholesterol.

The potential relationship between serum and/or urinary BPA concentrations and glycemic control remains of interest. Prior investigations have reported a notable positive association between urinary BPA levels and glycemic regulation, as reflected in HbA1c values. High urinary BPA concentrations were linked to the increased hs-CRP, visceral fat amount, BMI, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index values.[20,32] In this cross-sectional study, fasting morning venous blood samples were analyzed to determine serum BPA concentrations. Interestingly, a negative correlation was identified between serum BPA and HbA1c levels, contrary to the positive association reported in previous studies. To investigate the association of glycemic control and HbA1c, measurement of urinary BPA levels instead of serum BPA levels with the short half-life or serial serum BPA measurements for the documentation of chronic exposure might be more accurate.

Individuals with reduced renal function (GFR <60 mL/min/1.73 m^2) were excluded from participation. In the remaining cohort, serum BPA concentrations demonstrated an inverse correlation with GFR. This may be related to the elimination of BPA by the urine,[33] but it may also suggest that BPA exposure may contribute to the onset of diabetic nephropathy, as demonstrated by the study of Hu et al.[13] However, this study was designed primarily to examine the relationship between serum BPA and PNP, and additional studies focusing on diabetic retinopathy and diabetic nephropathy are needed to clarify the association of serum BPA with these complications.

The present study is subject to several limitations. Primarily, this study design is cross-sectional and has a small patient group. The ELISA technique was preferred to measure serum BPA levels for its applicability and cost. Measurement of serum BPA levels by ELISA

has lower sensitivity compared with the other methods.[34] There are studies measuring the serum BPA levels as well as urinary BPA in the literature. Serial BPA measurements were used in the study by Hu et al,[13] which is investigating the association of diabetic nephropathy and BPA exposure. However, this study measured only serum BPA, without including urinary BPA assessments. Another important consideration is that this study did not assess dietary or environmental sources of BPA exposure. Since BPA exposure primarily occurs through ingestion of contaminated food, beverages, or packaging materials, the lack of such contextual exposure data limits the ability to adjust for potential confounding. Consequently, unmeasured variation in dietary habits, lifestyle, or environmental contact may have influenced serum BPA concentrations and contributed to residual confounding in the observed associations. The limitations are provided in Supplement 2.

In conclusion, while no significant association was observed between serum BPA levels and peripheral neuropathy, these findings reinforce the link between PNP and glycemic control. Previous reports have demonstrated associations between BPA and diabetic nephropathy,[13] and recent data suggest that among phenolic compounds, BPA uniquely shows a positive association with all-cause mortality in individuals diagnosed with diabetic retinopathy, independent of confounding factors.[35] These data highlight BPA as a potential modifiable risk factor in diabetic microvascular complications. Given the exploratory, cross-sectional nature and limited sample size, causal inferences cannot be drawn; these findings should be interpreted as hypothesis-generating. Although the sample size was modest and the design cross-sectional, the present study serves as an exploratory step toward understanding the potential contribution of environmental endocrine disruptors such as BPA to diabetic microvascular complications. Prospective longitudinal studies with larger cohorts are warranted to further elucidate its role in neuropathy, nephropathy, and retinopathy.

In this cohort of adults with type 2 diabetes, serum BPA levels showed no association with diabetic PNP. Glycemic control and lipid parameters remained the dominant correlates. Future prospective studies incorporating repeated liquid chromatography–tandem mass spectrometry (LC-MS/MS) BPA measurements and urinary biomarkers are needed to confirm these findings.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Bursa Yüksek İhtisas Education and Training Hospital Ethics Committee (Approval No.: 2011-KAEK-25 2016/1301; Date: 13.06.2016).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Supplement 1. Study Power and Precision

No a priori power analysis was performed because the study included all eligible participants during the enrollment period. To provide transparency, we calculated the minimal detectable effect (MDE) under standard logistic-regression assumptions ($\alpha = 0.05$, power = 0.80). Given a total sample size of 80 and a diabetic peripheral polyneuropathy prevalence of approximately 34%, the study had 80% power to detect an odds ratio of 2.0 or greater per 1-SD increase in serum BPA. Smaller true effects may therefore have remained undetected.

Supplement 2. Limitations

This study has several limitations. First, serum bisphenol A (BPA) was measured only once using a commercially available ELISA kit, which has lower analytical sensitivity and specificity compared with LC-MS/MS. A single time-point measurement may have introduced random exposure misclassification, likely biasing the association toward the null. Second, urinary BPA levels were not assessed, even though urinary measurements are considered more reliable for estimating recent BPA exposure; therefore, residual misclassification of exposure cannot be excluded. Third, to enhance diagnostic accuracy and minimize potential bias, diabetic peripheral polyneuropathy (PNP) was defined only when both the Michigan Neuropathy Screening Test (MNTT) and electromyography (EMG) findings were concordantly positive. Although this stringent definition reduced the available sample size, it provided high diagnostic specificity and minimized potential criticism regarding the accuracy of neuropathy diagnosis. Finally, the cross-sectional design precludes causal inference, and larger prospective studies are warranted to confirm these findings.