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ORIGINAL ARTICLE

Evaluation of Bisphenol-A and its Levels in the Development of Insulin Resistance in Terms of Oxidative Stress

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ABSTRACT

Background: **This study investigated the relationship between oxidative stress and insulin resistance, focusing on both its development and progression, and explored the potential etiological role of bisphenol-A (BPA) toxicity.**
Methods: **A total of 100 individuals participated, including 50 patients diagnosed with insulin resistance and 50 healthy controls. Blood samples were analyzed for oxidative stress biomarkers malondialdehyde (MDA), protein carbonyl (PCO), superoxide dismutase (SOD), and glutathione peroxidase (GPX) using an ELISA device, while BPA levels were measured via LCMSMS. Sociodemographic data, medical histories, and laboratory findings were collected from hospital records. Data analysis was performed with SPSS, and results with $p < 0.005$ were considered statistically significant.**
Results: **Groups were formed according to HOMA levels. The mean HOMA level in the patient group was 3.80 ± 0.91 mg/dL; the HOMA level in the healthy control group was calculated as 1.77 ± 0.44 mg/dL. When laboratory data were examined, no statistically significant differences were observed between groups in ferritin, iron, iron-binding capacity, folic acid, B12, vitamin D, HbA1c, hemoglobin, creatinine, glomerular filtration rate, and TSH levels. When MDA, PCO, SOD, GPX, and BPA levels were analyzed between groups, it was observed that the mean levels of MDA, PCO, and BPA were higher in the patient group, while SOD and GPX levels were lower. When statistically analyzed between groups, differences in MDA, SOD, GPX, and BPA levels were found to be statistically significant, except for PCO levels ($p = 0.038$; 0.004; 0.001; 0.001, respectively). A positive correlation was observed between HOMA and MDA and BPA levels ($p = 0.010$; 0.032, respectively). A strong positive correlation was observed between MDA and BPA, and between SOD and GPX ($p = 0.001$; 0.006, respectively).**
Conclusions: **Oxidative stress was observed as a factor in the course of insulin resistance disease; an increase in the oxidant MDA and a decrease in the levels of the antioxidants GPX and SOD were associated with the disease. BPA toxicity was identified as a risk factor in the development of insulin resistance in our study, which examined it as an etiological factor not only in oxidative stress but also in toxic exposures. To combat insulin resistance, it is necessary to reduce the oxidative stress that develops and avoid substances with expected toxicity.**
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KEYWORDS

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INTRODUCTION

Oxidative stress can occur in most cases where the body's balance is disrupted and can lead to serious pathological problems. One of these is impaired blood sugar

regulation and the development of insulin resistance. In conditions such as polycystic ovary syndrome and diabetes mellitus, which are associated with insulin resistance, the vicious cycle of insulin resistance and oxidative stress is considered a factor that complicates treatment. Evidence can be found in the literature that oxidative stress increases in insulin resistance and that the antioxidant mechanism is disrupted [1,2]. Changes in the antioxidant system have shown that oxidative stress increases as a result of a decrease in antioxidants such as glutathione, superoxide dismutase, and catalase [3]. The relationship between insulin resistance and oxidative stress has been the subject of the literature and has taken its place in the course of the disease that needs to be investigated. When the system cannot cope with the oxidative stress that occurs, it may face antioxidant depletion or insufficient production, leading to cellular damage or resistance [4]. The antioxidants SOD and glutathione peroxidase are considered therapeutic agents [5].

Many biomarkers can be used to assess oxidative stress, such as nitric oxide, bilverdin, and free fatty acids [6,7]. However, these are all endogenous factors. Beyond endogenous factors, the relationship between exogenous exposures and insulin resistance and the oxidative stress they induce encompasses a wide range, from air and water to materials used and food consumed. PM2.5, through direct exposure from the air, has been associated with oxidative stress and has caused hepatic-style insulin resistance [8]. Bisphenol A is a chemical material whose use is increasing worldwide. Its accumulation in the body and the toxicity it creates have been the subject of scientific research [9]. The role of bisphenol A exposure in insulin resistance, both through its toxicity and the oxidative stress it causes, will contribute to public health protection, given the prevalence of insulin resistance.

Many mechanisms are implicated in the development and progression of insulin resistance. The increasing threat of insulin resistance from a societal perspective, coupled with unhealthy diets and sedentary lifestyles, poses a risk to our young population. Considering the expected lifespan, it is evident how important these individuals are both for themselves and for society. It is important to take precautions, eliminate the etiological causes, and intervene in terms of complications caused by oxidative stress when it occurs. Therefore, in our study, we aimed to evaluate BPA levels in the development of insulin resistance and subsequently assess the relationship with oxidative stress by measuring MDA (malondialdehyde), PCO (protein carbonyl), SOD (superoxide dismutase), and GPX (glutathione peroxidase) levels using the HOMA-IR (Homeostatic Model Assessment) scale.

MATERIALS AND METHODS

Ethical approval and study design

The study commenced after obtaining approval from the Yozgat Bozok University Non-Invasive Clinical Research Ethics Committee (No: 2025-GOKAEK-252_2025.01.22_267). Informed consent was obtained from the participating individuals. The study included 100 individuals: 50 patients diagnosed with insulin resistance who presented to the Internal Medicine Clinic at Yozgat Bozok University, had overt diabetes mellitus, had no history of liver or pancreatic pathology in previous radiological imaging, and had no known medical history, and 50 control subjects who had no pathology detected in their examinations.

Data collection and analysis

Within the scope of the study, biological blood waste samples collected after routine examinations were collected for analysis from individuals who applied to the Internal Medicine Clinic at Yozgat Bozok University. The collected samples were stored at -80 degrees. The preliminary preparation of the samples was carried out at the Multidisciplinary Laboratory of Yozgat Bozok University.

BPA was identified and quantified using ultra-performance liquid chromatography (UPLC) coupled with a triple quadrupole mass spectrometer (Shimatzu 8040, Japan). BPA was extracted from the cartridges, and then the samples (200 µL) were loaded onto SPE cartridges pre-conditioned with 1 mL MeOH and 1 mL ultrapure water. The sorbent was rinsed with 1 mL 25 mM ammonium acetate (AcONH4) and 1 mL MeOH. The cartridges were dried for 5 minutes and the analytes were eluted with 1 mL of MeOH, 1% NH_3. The elution solutions were dried by evaporation under a nitrogen stream at 45°C. Mobile phase A consisted of water containing 0.1% formic acid (HCOOH), while mobile phase B consisted of acetonitrile containing 0.1% formic acid (HCO OH). The valve was switched from the loading position to the elution position in 0.5 minutes and returned to the initial loading position in 5 minutes (Table 1).

The levels of MDA (malondialdehyde), PCO (protein carbonyl), SOD (superoxide dismutase) and GPX (glutathione peroxidase) biomarkers were studied from blood (serum) samples obtained within the scope of the study from patients' routine biological waste blood samples. This analysis was performed using ELISA at the Multidisciplinary Research Laboratory of Yozgat Bozok University Faculty of Medicine. These procedures were carried out by applying routine kit procedures (BT LAB, China for PCO, SOD and GPX; Elabscience, USA for MDA) [10,11]. In addition, the sociodemographic data, medical histories, previous treatments, and laboratory data of the individuals included in the study were recorded from hospital records and medical histories and included in the study.

Exclusion Criteria

Individuals under 18, individuals using drugs that affect liver metabolism, individuals undergoing insulin resistance treatment, individuals diagnosed with diabetes mellitus, individuals with stage 3 or higher chronic renal failure, individuals with diseases involving secretory insulin release such as insulinoma, and individuals with malignancies were excluded from the study.

Statistical analysis

Statistical analyses were performed using the SPSS 20.00 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) statistical programme. Descriptive statistics were given as mean ± standard deviation for continuous variables and as % for categorical variables. The Kolmogorov-Smirnov test was used to determine whether the groups were normally distributed. Measurement values between groups were evaluated using the independent samples *t*-test and ANOVA tests for continuous variables and the chi-squared test for categorical variables. Correlation analyses were performed using the Pearson's Correlation Test. p-values < 0.05 were considered statistically significant, whereas p-values < 0.001 were considered indicative of a more stronger level of statistical significance (for all tests).

RESULTS

The study included 100 individuals, comprising 50 individuals with diagnosed insulin resistance and 50 healthy control subjects. Of the 100 individuals included in the study, 28 were male and 72 were female. The minimum age was 18, the maximum age was 65, and the mean age was calculated as 40.83 ± 11.42. No statistically significant differences were found between the groups in terms of age and gender ($p = 0.334$ and $p = 0.645$, respectively).

Groups were formed according to HOMA levels. The mean HOMA level in the patient group was 3.80 ± 0.91 mg/dL; the HOMA level in the healthy control group was calculated as 1.77 ± 0.44 mg/dL. The fasting blood glucose levels of the individuals included in the study were 98.90 ± 10.23 mg/dL on average in the patient group and 91.36 ± 7.94 mg/dL on average in the control group. The insulin level was 15.61 ± 3.27 IU in the patient group and 7.89 ± 1.79 IU on average in the control group. When the laboratory data were examined, no statistically significant differences were observed between the groups in terms of ferritin, iron, iron-binding capacity, folic acid, B12, vitamin D, HbA1c, hemoglobin, creatinine, glomerular filtration rate, and TSH levels (Table 2).

When MDA, PCO, SOD, GPX, and BPA levels were analysed between groups, it was observed that the mean levels of MDA, PCO, and BPA were higher in the patient group, while SOD and GPX levels were lower. When analyzed between groups, the differences in MDA, SOD, GPX, and BPA levels, except for PCO levels, were found to be statistically significant ($p = 0.038$; 0.004; 0.001; 0.001, respectively) (Table 3).

A positive correlation was observed between HOMA and MDA and BPA levels ($p = 0.010$ and 0.032, respectively). A strong positive correlation was observed between MDA and BPA, and between SOD and GPX ($p = 0.001$ and 0.006, respectively). (Table 4).

A negative correlation was observed between vitamin B12 levels and MDA and BPA levels ($p = 0.005$ and 0.040, respectively). No significance was detected for other data in Table 5.

DISCUSSION

In our study, insulin resistance was evaluated using multifaceted parameters and its relationship with toxic exposures was assessed. Firstly, the absence of statistically significant differences between groups in ferritin, iron, iron-binding capacity, folic acid, vitamin B12 and D levels, hemoglobin, creatinine, glomerular filtration rate, and TSH levels was particularly valuable in observing the effect with isolated MDA, PCO, SOD, GPX, and BPA levels in the groups. This result strengthened our study. A study by Mo and colleagues showed that iron overload causes insulin resistance by inhibiting the JAK2/STAT3/SLC7A11 signalling pathway, particularly in transfusion-dependent patient groups, and that insulin resistance can be improved with the use of iron chelators [12]. In our study, iron may not have been shown as a risk factor for insulin resistance because vitamin and mineral levels were not at toxic levels. In another study conducted in the United States, which evaluated the relationship between iron levels expected from population screening and insulin resistance, 2,993 participants were examined, and it was shown that insulin resistance decreased as iron levels increased. In this study, the increase in iron levels referred to an increase from anemia levels to optimal values, not to toxic levels of iron [13]. We did not find the iron and ferritin levels to be associated with insulin resistance in our study. This difference may be due to the origin of the study which neither reflects the diet nor the lifestyle of our society. A study on multivitamin supplementation in the treatment of insulin resistance also found that B vitamin complexes are beneficial in insulin resistance [14]. Although no study has been conducted on its evaluation as an etiological factor in the literature, it has been observed that it may also be included in treatment. However, this study concluded that it has positive effects on oxidative stress; it has not been shown to be directly related to vitamin B12 levels, as in our study. Another study based on treatment also found that in individuals with metabolic dysfunction, those receiving medical treatment containing vitamin B12 showed improvement in metabolic dysfunction compared to the placebo group in a double-blind, randomized controlled trial. Insulin resistance, which is evaluated within metabolic dysfunction, was also included in the generalized

Table 1. Gradient program for online SPE–LC analysis of BPA.

Time (minute)	Mobile phase composition	Flow rate (mL/minute)	Valve position
0.0 - 0.5	80% A/20% B	1.0	loading
0.5 - 0.6	0% A/100% B	0.1	elution start
0.6 - 8.0	0% A/100% B	1.0	elution
8.0 - 9.0	80% A/20% B	1.0	re-equilibration
9.0 - 10.0	80% A/20% B	1.0	loading

Table 2. Laboratory data of individuals included in the study (two groups).

	Mean	STD	Minimum	Maximum	p
Glucose (mg/dL)	96.01	12.52	77.00	123.00	0.031 *
Insulin (IU)	11.75	4.68	4.38	23.90	0.001 **
Ferritin (ng/mL)	44.01	48.93	5.48	334.00	0.396
Iron (µg/dL)	74.20	31.31	17.00	139.00	0.135
UIBC (µg/dL)	288.14	74.25	59.00	420.00	0.132
Folate (ng/mL)	8.15	3.94	2.14	17.40	0.273
Vit B12 (pg/mL)	519.09	160.89	342.00	1,576.00	0.559
Vit D (ng/mL)	19.53	7.85	6.51	49.10	0.022 *
HbA1C (%)	5.41	0.38	4.60	6.60	0.320
Hemoglobin (g/dL)	13.89	1.63	9.60	18.30	0.766
Creatinine (mg/dL)	0.74	0.15	0.44	1.21	0.635
GFR	105.18	15.02	62.00	138.00	0.484
TSH (µIU/mL)	2.48	2.63	0.03	23.90	0.476
HOMA (mg/dL)	2.78	1.23	0.90	6.61	0.001 *

STD Standard deviation.

Table 3. Analysis of MDA, PCO, SOD, GPX, and BPA values between.

	Patient (n = 50)		Control (n = 50)		p
	Mean STD	Std. Error (range)	Mean STD	Std. Error (range)	
MDA (ng/mL)	1.35 ± 0.74	0.10 (5.20)	1.11 ± 0.33	0.46 (1.85)	0.038 *
PCO (ng/mL)	2.00 ± 1.34	0.18 (6.60)	1.78 ± 1.02	0.15 (4.60)	0.364
SOD (ng/mL)	10.15 ± 3.43	0.48 (19.63)	15.72 ± 12.75	1.80 (62.90)	0.004 **
GPX (ng/mL)	194.23 ± 68.21	9.64 (295.59)	242.87 ± 10.71	10.71 (331.92)	0.001 **
BPA (pg/mL)	3.29 ± 2.43	0.21 (6.85)	2.43 ± 0.95	0.13 (4.08)	0.001 **

p-values * and ** represent significance at 5% and 1%.

result [15]. Since no pre- and post-treatment evaluation was performed in our study, vitamin B12 levels were found to be ineffective as an etiological factor. The study on B12 levels in the etiology of metabolic syndrome was conducted specifically on this topic and also addressed insulin resistance. The study concluded that

Table 4. Relationship between HOMA and MDA, PCO, SOD, GPX, and BPA levels.

	MDA	PCO	SOD	GPX	BPA
HOMA	0.256 **	0.010	-0.162	-0.166	0.215 *
MDA	1.000	-0.015	0.032	0.112	0.322 **
PCO		1.000	-0.109	-0.126	0.025
SOD			1.000	0.272 **	0.050
GPX				1.000	0.044
BPA					1.000

p-values. * and ** represent significance at 5% and 1%.

Table 5. Relationship between vitamin levels and MDA, PCO, SOD, GPX, and BPA levels.

	Folate	Vit B12	Vit D	MDA	PCO	SOD	GPX	BPA
Ferritin	0.073	-0.035	0.086	0.096	0.004	0.064	0.086	0.040
Folate	1.000	0.260	0.075	0.060	0.227	0.116	0.064	-0.293
Vit B12		1.000	0.157	-0.345 **	-0.090	-0.054	0.117	-0.256 *
Vit D			1.000	-0.068	-0.098	0.106	0.099	-0.107

p-values. * and ** represent significance at 5% and 1%

B12 levels were insignificant in the etiology of metabolic syndrome. Only B2 levels were clinically significant [16]. This supports the conclusion we reached. Similar studies on folate have also predicted that folate supplementation would be beneficial in the treatment of insulin resistance [17]. A study conducted on rats also observed that folate supplementation increased insulin sensitivity [18]. A review concluded that although no significant relationship was found between folate levels and insulin resistance, the effect of folic acid supplementation on glycemic improvement should be investigated [19]. Similarly, in our study, folate levels were not observed as an etiological factor in insulin resistance; a double-blind, randomized controlled trial is needed to evaluate its place in treatment. Numerous studies can be listed on insulin resistance, whether due to vitamin deficiencies or congenital and acquired causes of anemia. Considering that we are sufficiently aware of vitamin deficiencies, insulin resistance studies conducted in individuals with Fanconi anemia and B thalassemia may be considered more valuable in observing the pure effect of this condition. Insulin resistance was detected in 23% of children with Fanconi anemia and 37.25% of those with B thalassemia [20, 21]. The fact that no relationship was found between hemoglobin level and insulin resistance in our study was thought to be due to the participants' hemoglobin values being within a more optimized range. This result indicates that neither vitamin efficacy nor anemia were decisive factors in our study, that the results are consistent with those in the literature, and that this finding enhances the study's power in demonstrating isolated toxicity.

The kidneys are the most important organ in the elimination of insulin from the body. Therefore, the effect of creatinine and glomerular filtration rate on insulin resistance was investigated, and no significant findings were obtained in our study. A study conducted on cats also found that insulin resistance in cats with chronic kidney disease, as assessed by the HOMA scale, was lower than in the healthy group, and the difference was statistically significant [22]. In a cross-sectional study by Li and colleagues, insulin resistance was found to be associated with chronic kidney disease, and chronic kidney disease progression decreased with insulin resistance treatment [23]. Although the glomerular filtration rate was low in our study, the difference may not have been significant because individuals with stage 3 or lower renal failure were not included in the study. This situation demonstrated that moderate levels of glomerular filtration rate did not affect the presence of insulin resistance.

The relationship between insulin resistance and thyroid disorders has been demonstrated in numerous studies. In particular, high TSH levels have been found to be closely related to insulin resistance by disrupting insulin signalling [24]. However, since the majority of patients in our study were euthyroid and no difference in thyroid dysfunction was observed between groups, thyroid dys-

function played an insignificant role in the development of insulin resistance in our study. Again, this strengthened our study's ability to assess toxicity. Our research revealed that insulin resistance is caused by disturbances in the oxidant-antioxidant system. Elevated MDA levels and decreased GPX and SOD levels were found to be risk factors for insulin resistance ($p = 0.038$; 0.001; 0.004). Furthermore, a correlation was observed with elevated HOMA levels; as the HOMA score increased, MDA levels rose, indicating increased oxidative stress ($p = 0.010$). The positive correlation we found between the antioxidants SOD and GPX ($p = 0.006$) provided evidence that antioxidant mechanisms are affected in a multifaceted and simultaneous manner and that the antioxidant mechanism is weakened in insulin resistance. The literature similarly discusses the oxidative stress created by insulin resistance and the resulting vicious cycle. The study by Şenyiğit and colleagues also showed that impaired glycemic control increases oxidative stress and is associated with increased MDA levels and decreased GPX and SOD levels [25]. Insulin resistance may cause MDA increase due to the process that causes metabolic syndrome and lipid peroxidation. An intervention aimed at reducing this increased lipid peroxidation may provide protection against related complications. Nemati and colleagues found evidence that MDA-containing antioxidant therapy may improve insulin resistance [26]. There are studies that address the use of multi-faceted supplements instead of antioxidant therapy in insulin resistance [27]. PCO, a protein carbonyl oxidant, was not associated with insulin resistance in our study. Although it was high in the patient group, the difference was not statistically significant. This result can be interpreted as indicating that oxidative stress caused by lipid metabolism by-products is the etiological factor in insulin resistance, and that protein content has no effect at moderate levels. Insulin resistance causes oxidative stress, but PCO is not among the mediating biomarkers. In a study by Liang and colleagues, PCO was found to exacerbate and be partially associated with glucose dyshomeostasis; however, a definitive association was not established [28].

Chemical exposure is unavoidable in our daily lives, and its effects can be multifaceted on health. The BPA exposure we examined is a known endocrine disruptor, and examples such as food containers, water bottles, toys, and medical devices can be extended, indicating exposure at every stage [29]. Our study examined the relationship between insulin resistance and BPA, and found BPA toxicity to be a risk factor for insulin resistance ($p = 0.001$). As BPA exposure increased, the HOMA score was also found to be correlated with it ($p = 0.032$). This showed that the amount of toxicity could be effective in the course of the disease. Increased BPA was found to be associated with oxidative stress and correlated with MDA levels ($p = 0.001$). This result provides strong evidence of BPA's role in the development of insulin resistance, both through its own toxicity and through oxidative stress. There are no recent studies in the literature on the relationship between BPA exposure and polycystic ovary syndrome [30,31]. Although polycystic ovary syndrome and insulin resistance are considered to be associated, our isolated study on insulin resistance is different in this respect. BPA has been proven to be a risk factor for insulin resistance. Yang and colleagues have associated BPA with diabetes mellitus, showing that it causes impaired glycemic control control [32]. In our study, BPA was observed to cause insulin resistance, both directly and through oxidative stress, and this was supported by correlations in the literature with endocrine diseases with which it is associated.

Our investigation into the antioxidant effect of vitamin levels and their role in the treatment of insulin resistance also showed that MDA levels increased as B12 levels decreased ($p = 0.005$). Raising B12 levels to protect against oxidative stress may be beneficial in patient groups with insulin resistance. The inverse correlation observed between vitamin B12 levels and BPA supports the conclusion that BPA exposure may have reduced B12 absorption ($p = 0.040$). It can be concluded that foods containing BPA should also be avoided in cases of vitamin B12 deficiency. However, studies demonstrating that BPA inhibits the absorption of labelled B12 molecules in the gastrointestinal tract are needed to confirm this.

In conclusıon; insulin resistance is quite common in society and poses a threat to our youth due to the dietary habits and immobility brought about by modern life. Although there are many causes in its etiology, the vicious cycle in the course of insulin-resistant individuals is noteworthy for clinicians. Among the causes of this condition, oxidative stress has been observed as a factor; an increase in MDA, an oxidant, and a decrease in GPX and SOD levels, antioxidants, have been associated with the disease. Not only oxidative stress but also toxic exposure has been investigated as an etiological factor in our study, and BPA toxicity has been identified as a risk factor in the development of insulin resistance. To combat insulin resistance, it is necessary to break the oxidative stress that occurs and avoid substances with expected toxicity.

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Ethics Approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Yozgat Bozok University

Clinical Research Ethics Committee (No: 2025-GOKA EK-252_2025.01.22_267).

Consent to Participate:
Informed consent was obtained from all individual participants included in the study.

Consent for Publication:
The authors confirm that human research participants gave informed consent for the collection and processing of their data within the study.

Data Availability:
The data sets used during the current study are available from the corresponding author on reasonable request.

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There is no conflict of interest.

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