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Relationship between blood lead (Pb) concentration with risk of diabetes mellitus in women living in mining area

Novia Luthviatin[1,2*], Onny Setiani[3], Bagoes Widjanarko[4] and Mohammad Z. Rahfiludin[5]

[1]Public Health Doctoral Study Program, Faculty of Public Health, Universitas Diponegoro, Semarang, Indonesia; [2]Faculty of Public Health, Universitas Jember, Jember, Indonesia; [3]Department of Environmental Health, Faculty of Public Health, Universitas Diponegoro, Semarang, Indonesia; [4]Department of Health Promotion, Faculty of Public Health, Universitas Diponegoro, Semarang, Indonesia; [5]Department of Public Health Nutrition, Faculty of Public Health, Universitas Diponegoro, Semarang, Indonesia

*Corresponding author: novia@unej.ac.id

Abstract

Diabetes is a global health concern with significant implications for individuals and societies. Diabetes results from a complex interaction between genes and environmental factors, including metal exposure. Lead or plumbum (Pb) is a heavy metal pollutant and is predicted to be associated with the morbidity of diabetes. The aim of this study was to assess the relationship between blood Pb level and possible risk factors (body mass index insulin resistance, carbohydrate intake, sugar intake, and physical activity) with fasting blood sugar (FBS) level in women living in the mining area. A cross-sectional study was conducted in a mining area of Indonesia located in Pemali District, Bangka Belitung Regency, involving women aged 30–49, selected through purposive sampling. Logistic regression was used to assess the relationship between the risk factors and FBS level, while the Spearman correlation was used to analyze the correlations between the risk factors and FBS level. Our data indicated that blood Pb concentration and other risk factors (carbohydrate intake, sugar intake and physical activity) were neither associated nor correlated with FBS level. However, as predicted, insulin resistance was associated with FBS level with OR: 9.66; 95%CI: 1.13–82.29; *p*=0.038. In addition, the Homeostatic Model Assessment Insulin Resistance (HOMA-IR) score was also correlated with FBS level (*r*=0.316, *p*=0.002). This study highlights the level of Pb is not associated with the risk of diabetes in women living in mining area.

Keywords: Blood Pb concentration, diabetes mellitus, fasting blood sugar, insulin resistance, mining area

Introduction

Diabetes is a metabolic disorder identified by insufficient insulin production by the pancreas or ineffective insulin utilization by the body, impacting blood sugar regulation [1]. Diabetes, a chronic and severe disease, has a profound impact on the life and health of individuals and communities worldwide. The International Diabetes Federation estimated the worldwide cost of treating adult diabetes in 2017 was USD 850 billion [2]. The global diabetic population is projected to reach 629 million by 2045, with nearly 4 million deaths attributed to high blood glucose [3]. Indonesian Basic Health Research 2013–2018 revealed an increase in diabetes prevalence among individuals aged 15 years and above, from 1.5% to 2% [4,5].

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Diabetes is diagnosed when fasting blood sugar (FBS) levels reach ≥126 mg/dL in the presence of signs and symptoms [2]. Elevated FBS is a key component of metabolic syndrome, along with central obesity, high blood pressure, and dyslipidemia, including elevated triglycerides, high levels of low-density lipoprotein cholesterol (LDLC), and low levels of high-density lipoprotein cholesterol (HDLC) [6]. FBS levels also indicate insulin resistance, the central feature of diabetes, which develops years before diabetes onset [7]. People with diabetes are at increased risk of heart disease, peripheral arterial and cerebrovascular disease, obesity, cataracts, erectile dysfunction, and nonalcoholic fatty liver disease [1].

Obesity and weight gain are associated with the development of diabetes [7]. The International Diabetes Federation has shown that the onset of diabetes can be delayed or even prevented by lifestyle changes through physical activity and a healthy diet [8]. Lack of physical activity is associated with weight gain or inability to control weight, which is a risk factor for diabetes [9]. Low physical activity will also reduce glucose absorption by peripheral insulin, which is mediated by glucose resistance due to decreased muscle cell sensitivity [9]. Insulin is a peptide hormone essential for energy metabolism, such as glucose, fat, and protein, and maintaining homeostasis [10]. The Homeostatic Model Assessment Insulin Resistance (HOMA-IR) formula is used to calculate the abnormal body responses to the hormone insulin, also called insulin resistance. HOMA-IR is a well-established index that assesses insulin resistance by comparing fasting glucose and circulating insulin levels. Higher HOMA-IR values indicate greater insulin resistance [11]. Moreover, the consumption of carbohydrates and sugar also cause an increase in blood glucose levels [12].

Diabetes is influenced by genetic factors like ethnicity and family history, as well as environmental factors including obesity and lead (plumbum or Pb) exposure [2]. Pb is one of the four most dangerous heavy metal pollutants toxic to human health and associated with higher FBS levels, metabolic syndrome, and increased diabetes risk [13,14]. A study reported that Pb was significantly associated with the morbidity of diabetes [12], and elevated levels of urine Pb were associated with an increased risk of diabetes [15]. Pb exposure from unregulated pollution and industrialization contributes to glucose uptake disruption and other complications [16].

In Indonesia, the examination of Pb levels in humans has not been a priority, even in high-exposure areas like Pemali Sub-district, Bangka District, Kepulauan Bangka Belitung Province. This province, known for Indonesia largest white tin production area, suffers from environmental damage due to the tin industry [17,18], resulting in heavy metal pollution in its waters [14-17]. Heavy metals such as arsenic (As), chromium (Cr), copper (Cu), plumbum (Pb), zinc (Zn), ferrum (Fe), cadmium (Cd), and stannum (Sn) are prevalent, with Pb being the most abundant [19,20]. These heavy metals accumulate in organisms through the food chain [21,22]. According to data from the Bangka District Health Office, the prevalence of diabetes in Bangka Regency was 2.67%, with Pemali Sub-district ranking third highest for diabetes in 2020[23]. The prevalence of diabetes in Kepulauan Bangka Belitung Province is higher in women than men [4,5].

Pb accumulation in the body leads to acute and chronic poisoning, resulting in genetic and reproductive problems [24]. Women with a blood pb concentration of 10 g/dL are at risk for premature birth, low birth weight, infertility, miscarriage, early childhood neurological defects, and maternal hypertension [25]. Fetal growth is directly affected by the bioaccumulation of Pb in the blood, ranging from 10–15 ng/dL [25]. Other studies found that elevated Pb level was associated with high risks of gestational diabetes [26,27]. Further research is needed to fully understand the association of blood Pb concentration with the risk of diabetes, especially among female subjects. Therefore, the aim of this study was to analyze the relationship between blood Pb concentration, insulin resistance, carbohydrate intake, sugar intake, and physical activity with FBS in women.

Methods

Study design, setting and sampling

A cross-sectional study was conducted at the Pemali primary healthcare center (*Puskesmas*), Bangka District, Bangka Belitung Regency, Kepulauan Bangka Belitung Province, Indonesia, in

2022. Samples were selected based on purposive sampling of 91 women with the minimal sample was 89 based on calculations using the Slovin formula.

Participants and criteria

This study included women aged between 30 and 49 years old who had never been diagnosed with diabetes before and living in the study area have Pb exposure for ≥20 years. Women who were active or passive smokers, had a diet program, were pregnant or breastfeeding, and had one or both parents suffering from metabolic syndrome were excluded from the study. Respondents were selected based on women's participation in community-based preventive and promotive care (*Posyandu*) activities managed by Pemali *Puskesmas* in 2022. During the *Posyandu* activities managed by Pemali *Puskesmas* in 2022, there were 795 women involved. Out of the total, 230 were judged eligible based on the criteria and 91 women were willing to participate and signed the informed consent.

Data collection

After signing the informed consent form, 3 mL of venous blood sample was collected from participants by a competent laboratory staff into an ethylenediaminetetraacetic acid (EDTA) tube to measure fasting blood glucose and insulin hormone level. Blood samples were directly transferred to Depati Bahrin Laboratory, Sungailiat, Indonesia, where the blood samples were subsequently centrifuged to separate the blood serum. The serum obtained was divided into two: FBS level was measured at Depati Bahrin Laboratory and the rest of the sample was sent to GAKI Laboratory at Universitas Diponegoro, Semarang, Indonesia, to measure the insulin level using the enzyme-linked immunosorbent assay (ELISA) method using the Calbiotech Insulin Elisa Kit (Calbiotech, California, USA).

Data on the blood Pb concentration were obtained by taking an additional 5 mL of whole blood sample from a vein. The Pb concentration was measured using an atomic absorption spectrophotometer method [28] in GAKI Laboratory, Universitas Diponegoro, Semarang, Indonesia.

Variables

The dependent variable of the study was the risk of diabetes, referred to the level of FBS. The FBS was categorized as normal if <126 mg/dL and high if ≥126 mg/dL. Screening for diabetes symptoms and other diabetes diagnostic criteria such as occasional plasma glucose, oral glucose tolerance test, or HbA1C level measurement was not performed in this study.

The independent variables consisted of age, occupation, educational attainment, body mass index (BMI), blood Pb concentration, insulin resistance, carbohydrate intake, sugar intake, and physical activity. Educational attainment was categorized into low (elementary-senior high school) and high (diploma or bachelor's degree). Blood Pb concentration was obtained from the atomic absorption spectrophotometer method. Carbohydrate and sugar intakes were obtained by recording the household size of each food raw material consumed by respondents in the food recall questionnaire, then the sugar and carbohydrate intake were calculated in grams through the Nutri Survey Application. For statistical analysis purposes, the age (median 39 years), blood Pb concentration (median 47.5 μg/dL), carbohydrate intake (median 262.7 g), and sugar intake (median 11 g) were grouped into two categories based on the median value of each variable.

BMI, insulin resistance, and physical activity were categorized based on standards. BMI was categorized based on the WHO classification (underweight if BMI<18.5 kg/m^2, normal if BMI 18.5–22.9 kg/m^2, overweight if BMI 23–24.9 kg/m^2, obesity I if BMI 25–29.9 kg/m^2, and obesity II if BMI≥30 kg/m^2). Measurement of insulin resistance based on the HOMA-IR calculation formula:

$$\text{HOMA} - \text{IR} = \frac{\text{Fasting blood sugar}\left(\frac{\text{mg}}{\text{dL}}\right) \times \text{Fasting insulin}\left(\frac{\text{IU}}{\text{L}}\right)}{405}$$

Insulin resistance was categorized if the $\text{HOMA} - \text{IR score} \geq 2$.

Measurement and categorization of physical activity based on the International Physical Activity Questionnaire (IPAQ) [29]. Low physical activity if metabolic equivalent unit (MET) <600/week, moderate if MET 600–1,499 and high if MET ≥1,500/week.

Statistical analysis

The univariate and multivariate logistic regression test was used to analyze the relationship between blood Pb concentration and other possible risk factors (age, occupation, educational attainment, BMI, insulin resistance, carbohydrate intake, sugar intake, and physical activity) with FBS level. The Spearman correlation test was used to analyze the correlations between blood Pb concentration and other possible risk factors with FBS level. Statistical significance was considered at *p*-value less than 0.05.

Results

Characteristics of participants

A total of 91 women were included in the study, and all variables' distribution was presented in **Table 1**. More than 50% of the women aged 40–49 years, and most of them were housewives (86.8%). Almost all participants were at a low educational attainment level (93.4%) and about 28.6% were obese. More than 50% of the participants had high blood Pb concentrations, insulin resistance, low carbohydrate intake, and high sugar intake. About 37.4% had high physical activity, and almost all of them had high normal FBS (93.4%).

Table 1. Characteristics of women from high Pb exposure are included in the study (n=91)

Variables	Frequency	Percentage
Age		
30–39	45	49.5
40–49	46	50.5
Occupation		
Housewives	79	86.8
Other	12	13.2
Educational attainment		
Low	85	93.4
High	6	6.6
Body mass index (BMI)		
Underweight	5	5.5
Normal	23	25.3
Overweight	19	20.9
Obesity I	26	28.6
Obesity II	18	19.8
Blood Pb concentration		
Low	45	49.5
High	46	50.5
Insulin resistance		
Normal	44	48.4
Resistance	47	51.6
Carbohydrate intake		
Low	51	56
High	40	44
Sugar intake		
Low	43	47.3
High	48	52.7
Physical activity		
Low	33	36.3
Moderate	24	26.4
High	34	37.4
Fasting blood sugar (FBS) level		
Normal	85	93.4
High	6	6.6

Factors associated with FBS level

Univariate logistic regression analysis found that age, occupation, educational attainment, BMI, blood Pb concentration, carbohydrate intake, sugar intake, and physical activity were not

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associated with FBS level (**Table 2**). However, insulin resistance was significantly associated with FBS level (p=0.038). Individuals with insulin resistance were 9.66 times more likely to have high FBS level as compared to those respondents with normal insulin (OR: 9.66; 95%CI: 1.13–82.29) (**Table 2**). Multivariate logistic regression analysis confirmed that only insulin resistance was associated with FBS level (OR: 10.73; 95%CI: 1.18–97.16, p=0.035) (**Table 3**).

Table 2. Univariate logistic regression analysis of factors associated with fasting blood sugar (FBS) level among women from high lead exposure

Variables	Fasting blood sugar (FBS) level		OR (95%CI)	*p*-value
	Normal	High		
Age (year)				
30–39 (reference)	44	1	1	
40–49	41	5	1.25 (0.31–4.99)	0.752
Occupation				
Housewives (reference)	74	5	1	
Other	11	1	1.24 (0.14–10.87)	0.847
Educational attainment				
Low (reference)	79	6	1	
High	6	0	0.98 (0.19–5.17)	0.978
Body mass index (BMI)				
Underweight (reference)	5	0	1	
Normal	23	0	0.27 (0.33–2.02)	0.196
Overweight	18	1	0.17 (0.43–0.66)	0.010
Obesity I	24	2	0.28 (0.71–1.11)	0.070
Obesity II	15	3	0.62 (0.17–2.26)	0.464
Blood Pb concentration				
Low (reference)	42	3	1	
High	43	3	2.04 (0.43–9.45)	0.363
Insulin resistance				
Normal (reference)	43	1	1	
Resistance	42	5	9.66 (1.13–82.29)	0.038*
Carbohydrate intake				
Low (reference)	47	4	1	
High	38	2	1.06 (0.25–4.56)	0.933
Sugar intake				
Low (reference)	39	4	1	
High	46	2	1.22 (0.28–5.42)	0.792
Physical activity				
Low (reference)	31	2	1	
Moderate	22	2	0.82 (0.12–5.53)	0.515
High	32	2	0.62 (0.11–3.32)	0.834

*Statistically significant at p<0.05

Table 3. Multivariate logistic regression analysis of factors associated with fasting blood sugar (FBS) level among women from high lead exposure

Variables	Fasting blood sugar (FBS) level		OR (95%CI)	*p*-value
	Normal	High		
Body mass index (BMI)				
Underweight (reference)	5	0	1	
Normal	23	0	0.35 (0.02–6.52)	0.479
Overweight	18	1	2.72 (0.22–33.56)	0.436
Obesity I	24	2	1.26 (0.11–14.93)	0.857
Obesity II	15	3	0.80 (0.04–16.23)	0.886
Insulin resistance				
Normal (reference)	43	1	1	
Resistance	42	5	10.73 (1.18–97.16)	0.035*

*Statistically significant at p<0.05

Factors correlated with FBS level

We further analyzed the correlation between blood Pb concentration and some other factors (insulin resistance score, carbohydrate intake score, sugar intake score and physical activity score) (**Table 4**). The data indicated that blood Pb concentration was not correlated with FBS levels. However, as predicted, there was a positive correlation between insulin resistance (HOMA-IR scores) and FBS levels (r=0.316; p=0.002).

Table 4. Correlation of blood Pb concentration, insulin resistance, carbohydrate intake, sugar intake, and physical activity with fasting blood sugar (FBS) levels

Variable	Fasting blood sugar (FBS) level	
	r	*p*-value
Blood Pb concentration	0.016	0.881
Insulin resistance	0.316	0.002*
Carbohydrate intake score	0.077	0.471
Sugar intake score	0.042	0.694
Physical activity score	0.070	0.508

Discussion

The calculation results revealed that the respondent's HOMA-IR was 0.2–10.7 when the HOMA-IR index ≥2 is considered to indicate insulin resistance. Insulin resistance was significantly associated with FBS level (OR: 10.73; 95%CI: 1.18–97.16; p=0.038) as well as correlated with FBS level (r=0.316, p=0.002). Individuals with insulin resistance were 10.7 times more likely to have high FBS as compared to those respondents with normal insulin. HOMA-IR increases along with FBS levels. These results were reinforced by another study showing that the annual changes of HOMA-IR were associated with FBS in subjects who did not have diabetes. Subjects with pre-diabetes were associated with a more rapid increase of insulin resistance [7].

Insulin resistance is a critical pathophysiological link between risk factors and diabetes prevalence. Improving insulin resistance is one of the primary targets in diabetes treatment [30]. The rate of insulin resistance progression correlates with pancreatic β-cell activity, indicating an adaptive response to maintain glucose homeostasis and delay or prevent diabetes onset [7]. Research in Japan describes that the ratio of HOMA-β to HOMA-IR, an indicator of impaired β-cell compensation for insulin resistance, gradually decreases from 9 years to 1 year before the onset of diabetes. This shows that β-cell decrease compensation for insulin resistance may contribute to the onset of type 2 diabetes [31].

Most participants in this study with high FBS also had insulin resistance (83.3%). The progression rate of IR significantly predicts the incidence of diabetes, while high FBS indicates higher HOMA-IR [7]. A study of female respondents showed an indirect relationship between insulin resistance and FBS through the sagittal abdominal diameter (SAD). The close relationship between SAD and insulin resistance suggests that it may serve as an indicator of visceral fat associated with poor glucose regulation [32]. Visceral fat accumulation over time may also increase insulin resistance through dysregulation of adipokines, which are at risk of causing diabetes [31]. Obesity correlates with insulin resistance, where insulin sensitivity decreases with weight gain. A potential mechanism underlying obesity-induced insulin resistance is fat accumulation in the liver and skeletal muscle, inflammation, mitochondrial dysfunction, endoplasmic reticulum stress, and lipotoxicity [33,34]. Increasing physical activity also can slow insulin resistance progression. Physical activity has diverse effects on insulin and glucose metabolism through acute changes leading to contraction-mediated glucose uptake via glucose transporter 4 and chronic adaptations leading to insulin-stimulated glucose uptake [35].

This study results revealed that the respondent's blood pb concentration was 11–94 μg/dL. Blood Pb concentration with no negative effects on health has not been identified; blood Pb concentrations as low as 5 μg/dL and 10 μg/dL are associated with a range of effects, including cardiovascular disease in adults [36]. There was no association between blood Pb concentration and FBS in women in the Pemali District, and it also had no correlation with the FBS level. The proportion of respondents with high FBS was balanced in the low and high blood Pb concentration category. These results strengthen research in China, which states that Pb serum levels were correlated with reproductive hormones, while reproductive hormones were not correlated with FBS level. These results are different from another study showing that blood Pb concentration will increase FBS levels and the risk of DM [13,14,37,38].

The most common sources of pb exposure in the general population include workplace exposure [39], paint [40], water, ingestion of pb-contaminated household dust [41], herbal supplements [42], and so on. However, some research states that only low-level Pb exposure primarily affected FBS [43]. In our study, the study subjects were collected from a high Pb exposure area in Pemali District as a mining area. The primary source of pb exposure in our study population is from mining processes that pollute the surrounding environment (water and animals) and enter the human body through the ingestion route. Previous studies stated that the tin industry in almost all areas of the Bangka Belitung Islands Province caused Pb pollution in rivers, seas, and lakes of former mining excavations [19,44]. The Pb content in the water of the former mining excavated lake and marine animals (fish, snails, and shellfish) exceeds the maximum level set [45,46].

A study in the US revealed that exposure to all mixed metals (lead (Pb), zinc (Zn), copper (Cu), selenium (Se), hydrargyrum (Hg), and cadmium (Cd) leads to changes in glucose homeostasis and is positively associated with the development of DM, while Pb has the smallest impact on FBS compared to other metals [37]. Metal exposure from unregulated pollution and industrialization contributes to glucose uptake disruption and other complications. Accumulation of mixed metal induces oxidative stress and causes dysfunction, apoptosis, death of β-cells and degeneration of proteins, lipid peroxidation, and damage to nucleic acid [16].

Preclinical studies found that pb exposure was pro-diabetic in the obese model, causing glucose intolerance in rats [47]. In addition, glucose intolerance was also observed when rats were exposed to Pb acetate in drinking water [48]. Pb can increase the activities of gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in rodent liver with a mild increase in fasting glucose and glucose intolerance [49]. Pb exposure in rodents can affect key liver gluconeogenesis enzymes, resulting in impaired FBS and hyperglycemia. However, potential mechanisms related to the relationship between Pb exposure and insulin resistance in humans still need to be further investigated due to species differences, duration and dose of Pb exposure, population selection, sample size, and insulin resistance assessment methods [43].

Conclusion

Our data indicated that blood Pb concentration was neither associated nor correlated with FBS level in women living with high Pb exposure. However, further prospective study is warranted to validate the result. Nevertheless, as predicted, there was a relationship between insulin resistance and FBS levels.

Ethics approval

This research has been approved by the Health Ethics Commission, Faculty of Public Health, Universitas Jember, Indonesia, with registration number 245/KEPK/FKM-UNEJ/VIII/2022. Informed consent was obtained from each respondent before the interview.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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