International Journal of Diabetes in Developing Countries
https://doi.org/10.1007/s13410-022-01096-x

ORIGINAL ARTICLE

Could the PON1 phenotype play a key role in insulin resistance?

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Received: 3 July 2021 / Accepted: 20 May 2022

Abstract

Aim/objectives Recent studies have shown that Paraoxonase (PON1) enzyme plays a possible role in insulin synthesis by stimulating insulin release from β-cells of the pancreas as well as its anti-atherosclerotic property. In our study, we revealed the relationship between phenotypes of the PON1 enzyme and insulin resistance (IR) and impaired fasting glucose (IFG).

Materials and methods A cohort of 71 IR, 63 IFG, and 68 healthy individuals was examined in this study. The phenotypic distribution was demonstrated by studying PON1 enzyme's Paraoxonase (POase) and Arylesterase (AREase) activity with automated measurement kits.

Results By measuring the ratio of POase activity to AREase activity, 3 different phenotypes (QQ (Risky or Bad Phenotype), QR (Notre Phenotype), and RR (Good Phenotype)) were discovered. The results showed that IR and IFG individuals had riskier phenotypes compared to the control group. In addition, individuals with bad phenotypes were found to be 1.85 and 2.16 times more likely to get IR and IFG, respectively. Both groups were found to be four times more likely to be affected by the bad phenotype (odds ratio: 3.69 and 4.47 respectively).

Conclusion In this present study, the relationship between PON1 enzyme phenotypes and IR was evaluated for the first time in this field. Decreased PON1 activity and poor phenotype may also increase the development of hyperglycemia or diabetes mellitus (DM) due to IR and IFG. It may also predispose to diseases such as atherosclerosis. Therefore, we think that further investigations to explain the possible mechanisms underlying the relationship between PON1 phenotypes, IR and IFG will be useful in the early diagnosis and prevention of *prediabetes.*

Keywords Prediabetes · Paraoxonase · Arylesterase activity · Phenotype · Insulin resistance.

Introduction

Prediabetes occurs when the fasting plasma glucose concentration approaches the lower limit used for the diagnosis of diabetes. This process starts with β-cells of pancreas functional disorders, progressing with insulin resistance and glucose changes [1]. There are two conditions for prediabetes: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG is associated with increased gluconeogenesis development while IGT with peripheral insulin resistance. In cases of simultaneous formation of both, hepatic insulin resistance and increased gluconeogenesis occur [2]. Clinical studies state that individuals with prediabetes may have a high risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases. According to Groop et al., T2DM is a multifaceted disease associated with genetic and clinical heterogeneity [3]. It has been determined that diabetes is associated with macro and microvascular complications, with low PON 1 activity in T2DM patients [4]. Therefore, in prediabetes cases, early diagnosis has great importance for the treatment of these patients [5].

The development of T2DM begins with insulin resistance. This resistance is a condition in which the physiological response to the normal effects of insulin is impaired. In other words, IR can be defined as a subnormal biological response to insulin at a certain concentration or the impairment of the expected effect of insulin on glucose homeostasis, and a lack of response to insulin [6–8]. Insulin resistance is biological

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Published online: 08 June 2022

unresponsiveness to insulin hormones, which occurs with genetic factors, inactivity, obesity, and advancing age [6–9].

Paraoxonase (PON1) is a 45 kDa glycoprotein and shows its enzymatic effect (Paraoxonase, arylesterase, diazonase, etc.) according to the related substrates (paraoxon, phenylacetate, diazoxin, etc.). PON1 hydrolyzes aromatic carboxylic acid esters and is synthesized by the liver and is tightly linked to HDL. This protein prevents oxidation of LDL by hydrolyzing lipid hydroperoxides in vivo. HDL-bonded PON1 slows down the oxidation of LDL and PON1 is a major antiatherosclerotic component of HDL [10]. Therefore, many studies have shown that HDL reduces lipid peroxides by these enzymatic mechanisms during the accumulation of lipid peroxides [11–16]. There are two amino acid polymorphisms in PON1 activity. One of them consists of the substitution of the amino acids methionine and leucine (M/L) at position 55; the other by the substitution of the amino acids arginine and glutamine at position 192 [R/Q]. Three different phenotypes were obtained by the ratio of Paraoxonase (POase) and Arylesterase (AREase) activity of PON1. These phenotypes, which can be easily distinguished on the graph (Fig. 1), are especially due to difference in POase activity. Those with low activity are classified as risky or bad phenotype (QQ); those with medium activity as moderate phenotype (QR), and those with high activity as good phenotype (RR) [17, 18].

Since IR and IFG pose a risk for diabetes mellitus-related diseases and cause various complications in the chronic period, early diagnosis and correct treatment of patients would benefit society. Accordingly, it is obvious that any scientific study to be conducted on them would have great importance. Studies related to IFG, IR, and PON1 enzymes are limited. Therefore, this study can contribute to the literature. In our study, both paroxanase and arylesterase activity of PON1 enzyme in individuals with IFG and IR were studied and the phenotype they had was investigated with these data. For this purpose, the possible role of the PON1 enzyme was investigated with data obtained from the control and patient groups.

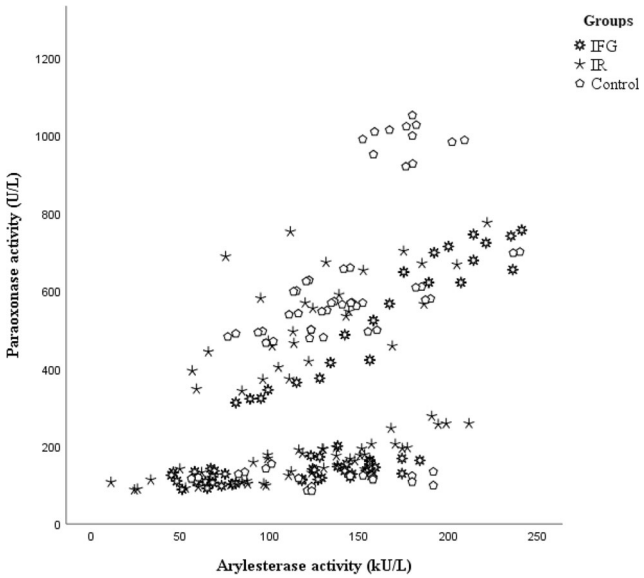

Fig. 1 Paroxanase and arylesterase activities of groups

Material and method

Ethical statement and clinical information

After blood samples were taken from the patients who applied to the Bezmialem Vakıf University Health Research and Application Center Endocrine Polyclinic, their weight, height, and body mass index (BMI) were recorded.

Study design and blood tests

Considering the World Health Organization (WHO) diabetes diagnosis criteria and statistical power analysis (5% type 1 error level and 80% power level), 71 individuals (31 women and 40 men) IR, 63 individuals (28 women and 35 men) IFG, and 68 individuals (30 females and 38 males) were included in the study as a control group. Samples were collected between August and October 2019.

After 8–10 h of fasting, blood was drawn into Hemogram and Gel tubes. HbA1c was studied from hemogram tubes. After the blood samples in the gel tubes were centrifuged at 3600 rpm for 6 min, glucose, HDL-cholesterol, LDL-cholesterol, triglyceride, and insulin were studied in an autoanalyzer device (Abbott Architect Illinois, USA). Patients with blood glucose levels below 126 mg/dL were divided into groups by glucose tolerance test.

The HOMA-IR measurement method, which was first described by Matthews and her colleagues, is made with the help of mathematical data that allows quantitative measurement of insulin resistance. Unlike other tests, it determines basal insulin resistance. With the HOMA formula, insulin resistance and β-cell function (HOMA-β) are processed and are calculated [19]. The HOMA index and the insulin resistance index values are directly proportional, and insulin resistance also increases in conditions where the HOMA level is high. Considering the prevalence in the Turkish population, it has been reported that insulin resistance occurs at levels above 2.4–2.7 HOMA values [20]. The HOMA-IR index is calculated in mg/dL by multiplying the fasting plasma glucose value with the insulin value and dividing the result by 405. The HOMA-IR was calculated according to the formula: (fasting glucose level (nmol/L) x fasting insulin level (microU/L) /22.5). Scientist Eriksson described the insulin resistance measurement as an “early period predictor” in the Type 2 DM process [21].

Those with a fasting glucose lower than 110 mg/dL or less than 110 mg/dL in the 2nd hour after loading 75 g OGTT and HOMA-IR < 2.5 were accepted as the control group. Those with a fasting glucose between 110 and 125 mg/dL and those with a glucose between 110 and 140 mg/dL at 2 h after 75 g OGTT loading and those with The HOMA-IR < 2.5 were included in the impaired fasting glucose group (IFG (+) IR (−)). In addition, those with a fasting glucose between 110 and 125 mg/dL and those with a glucose between 110 and 140 mg/dL at the 2nd hour after 75 g OGTT loading and HOMA-IR > 2.5 were included in the IFG combining IR group (IFG (+) IR (+)). Thus, the impaired fasting glucose group and the groups with insulin resistance were completely separated from each other. HOMA-IR calculation was obtained by dividing the product of fasting blood glucose (FBG) and insulin by the number 405. In addition, some of the samples were transferred to Eppendorf tubes and stored at −80. After the samples reached the planned number, the tubes were dissolved, and enzyme activities were studied.

Enzyme activities

Paraoxonase (POase) and Arylesterase (AREase) activity was studied with commercially available Rel Assay Diagnostic kits (Rel Assay Diagnostics, Gaziantep, TURKEY). POase activity was determined by the kinetic measurement of the p-nitrophenol product at 412 nm, which is formed in the basic environment where the enzyme's substrate paraoxon and its cofactor calcium are present at 412 nm. The result was calculated using the molar absorption coefficient of the p-nitrophenol molecule (18,290 M–1 cm^{-1}) and was defined as Unite/L.

AREase activity was measured by the increase in the concentration of the phenol product formed in the presence of phenylacetate, the substrate of the enzyme. Enzymatic activity was calculated using the molar absorption coefficient of the produced phenol (1310 M–1 cm−1). It was determined by defining each 1 μmol of phenol produced by measurement at 340 nm as 1 Unite/L [22].

PON1 enzyme polymorphism was determined according to the distribution of POase and AREase activities. POase activity was placed on the Y-axis and AREase activity was placed on the X-axis and the groups were determined with 3 different polymorphisms. Three phenotypes were identified as homozygous low activity AA (QQ), heterozygous medium activity AB (QR), and homozygous high activity BB (RR).

Exclusion criteria from the study

Patients who used medication for any disease such as diabetes mellitus, cardiovascular, neurological, liver, rheumatoid arthritis, anemia, and kidney disease were excluded from the study. Individuals with cancer or a history of cancer, those diagnosed with hepatitis and blood pressure, and those using serum lipid lowering, antipsychotic, insulin, and antioxidant drugs were not included in the study. Pregnant individuals and women with a history of gestational diabetes and individuals who are not suitable for the age range, children, and infants were not included.

Statistical analysis

The data obtained from the study were analyzed using IBM SPSS Statistics v.27.0 package program. To analyze the relationship between the dependent and independent variables, a logistic regression method was used. The differences between independent variables were analyzed by independent sample *t* test, and the relationship between variables was analyzed with Pearson correlation coefficient. The mean and standard deviation were calculated as descriptive statistics. Since variance homogeneity in POase and AREase activities was not fully ensured, a nonparametric Mann-Whitney *U* test was also applied, and the results were similar to those obtained from parametric tests. Statistically, $p < 0.05$ values were considered significant. The relationship between the groups was examined using the Chi-square test. As a result of the chi-square analysis, good phenotype, and bad phenotype risk analysis (risk estimate and odds ratio) were performed, and the results were presented (Tables 2 and 3). In addition, Phi and Cramer *V* values were also added to the table to reveal the effect values of the significance level.

Results

Demographic, clinical, and laboratory findings of participated individuals are shown in Table 1. The data on age, sex, and BMI displayed not significant difference between the 3 groups ($p > 0.05$). Fasting glucose levels in peripheral bloods of IFG (+) IR (−) and IFG (+) IR (+) patients have been found to be significantly higher compared to controls ($p < 0.05$). In both groups, HbA1c, LDL, total cholesterol, and triglyceride were significantly higher compared to the control ($p < 0.05$). IFG (+) IR (−) and IFG (+) IR (+) patients' HDL values were lower than the control groups. PONase and AREase activities were significantly lower in both groups when compared with the control. There were nonsignificant correlations between Paraoxonase and lipid profiles (HDL, LDL, and total cholesterol) ($p > 0.05$) (Table 1). Paraoxonase and arylesterase activities of groups and phenotypic distributions of groups were given in Fig. 1 and Table 2, respectively. Since the overall incidence of BB (RR) polymorphisms in populations is very low, BB (RR) and AB (QR) polymorphisms were used together to represent moderate activity in the risk analysis

Table 1 Demographic clinical and laboratory findings

Parameters	IFG(+) IR(−) (*N*=63)	IFG(+) IR(+) (*N*=71)	Control (*N*=68)	*p*
Age	49.53 ± 10.93	45.32 ± 12.73	44.21 ± 14.34	ns
BMI (kg/m^2)	22.3 ± 1.1	23.7 ± 1.4	21.5 ± 0.9	ns
Glucose (mg/dL)	109.74 ± 9.06 [a]	112.93 ± 10.41 [a]	90.91 ± 4.46 [b]	< 0.01
HbA1c (%)	5.46 ± 0.28 [a]	5.72 ± 0.41 [a]	5.23 ± 0.24 [b]	< 0.05
Insulin (μIU/mL)	5.82 ± 2.47 [b]	13.75 ± 3.82 [a]	6.28 ± 3.04 [b]	< 0.05
LDL (mg/dL)	133.82 ± 39.46 [a]	130.20 ± 30.74 [a]	105.61 ± 36.84 [b]	< 0.05
Triglyceride (mg/dL)	128.71 ± 48.64 [b]	142.46 ± 63.48 [a]	120.92 ± 66.62 [b]	< 0.05
HDL (mg/dL)	51.17 ± 11.3 [a]	44.91 ± 9.34 [a]	56.68 ± 16.61 [b]	< 0.05
Total Cholesterol (mg/dL)	205.15 ± 53.83 [a]	203.06 ± 49.65 [a]	169.22 ± 42.99 [b]	< 0.05
Paraoxonase activity (U/L)	276.48 ± 220.4 [a]	307.96 ± 204.2 [b]	505.30 ± 301.4 [c]	< 0.01
Arylesterase activity (kU/L)	131.49 ± 52.75 [a]	120.65 ± 47.99 [a]	142.29 ± 38.82 [b]	< 0.05

a, b, c Within rows. Means followed by the same letter are not significantly different according to ($p < 0.05$)

$p > 0.05$ shown as ns (not significant)

calculation. Thus, individuals were divided into 2 groups as bad polymorphism (QQ) and good polymorphism (QR, RR) (Table 2). In the chi-square analysis, the frequency of IFG (+) IR (−) and IFG (+) IR (+) was significantly higher in patients with poor phenotype. As seen in Table 3, the risk of developing IFG (+) IR (−) with bad phenotypes was 2.16 times higher than those with good phenotype (Relative risk); in other words, those with IFG (+) IR (−) had a bad phenotype. The probability of being affected was determined as 4.47 times higher (Odds ratio). However, the risk of getting IFG (+) IR (+) was 1.85 times higher than those with good phenotype (Relative risk). In other words, those caught IFG (+) IR (+) were found to be 3.69 times more likely to be affected by the bad phenotype (Odds ratio) (Table 3).

Discussion

In our current study, PONase and AREase activity was significantly lower in individuals with IFG (+) IR (−) compared to controls. We found that individuals with bad phenotypes had 2.16 times higher risk of getting IFG (+) IR (−) than normal individuals. In addition, individuals with IFG (+) IR (−) were found to be 4.47 times more likely to be affected by the bad phenotype. PONase activity has a relationship with IFG (+) IR (−) as well as IFG (+) IR (+). Although there are a few activity studies on insulin resistance and impaired fasting glucose, the phenotypic study was evaluated for the first time in this study. We speculate that having a bad phenotype in individuals with IFG (+) IR (+) may bring along lipid metabolism disorders. However, because of metabolic and endocrine disorders, it sets the ground for possible future coronary artery disease. Therefore, low PON1 enzyme activity may become an important criterion in the diagnosis of such diseases. In line with this theoretical and applicable information, patients with the PON1 phenotype may have a higher risk of developing insulin resistance or impaired fasting glucose. The probability of observing, diagnosing, and treating many health problems such as DM and coronary artery disease in advance increases.

The paraoxonase gene family has 3 members, namely PON1, PON2, and PON3. These are located on the long arm of human chromosome 7 between q-21.3 and q-22.1. It is believed that the product of PON1 and PON3 genes is in

Table 2 Phenotypic distributions of groups

Parameters	Control	IFG(+) IR(−)	IFG(+) IR(+)	*p*
Bad phenotype	20[b]	41[a]	43[a]	< 0.001
	% 29	% 65	% 61	
Good phenotype	48[b]	22[a]	28[a]	< 0.001
	% 71	% 35	% 39	
Total	68	63	71	

a, b, c Within rows. Means followed by the same letter are not significantly different according to ($p < 0.05$)

$p > 0.05$ shown as ns (not significant)

Table 3 Relative risk and odds ratios

Parameters	IFG(+) IR(−)	IFG(+) IR(+)	*p*
Odds ratio	4.47	3.69	< 0.001
Relative risk	2.16	1.85	< 0.001
Phi and Cramers V	0.357	0.323	

The *p* value obtained as a result of the control group comparison is indicated

IFG(+) IR(−): individuals who got impaired fasting glucose but not insulin resistance

IFG(+) IR(+): individuals who got both impaired fasting glucose and insulin resistance

plasma, while PON2 is in the cell. PON2 and PON3 are not understood as well as PON1 due to the lack of research on them. In past studies with PON1, the relationship between human serum capacity, hydrolysis of xenobiotics, and atherosclerosis has been investigated [11, 15, 17, 23–25]. The phenotypic distribution in humans causes the formation of a polymorphism. With paraoxonase enzyme polymorphism, the PON1 192R isoform hydrolyzes the paraoxon faster than the PON1 192Q form, making the elimination of Ox-LDL formed in the body more effective. Individuals who have poor PON1 phenotype with low activity can get coronary artery disease faster [15, 17, 25]. Paraoxonase activity may also closely be related to dietary intake. There are studies reporting that fruit, tea, and butter in the diet increase Paraoxonase activity and correlate with protein, Monounsaturated, Polyunsaturated, Vitamin E, flavonoids, and Quercetin [26]. Paraoxon hydrolytic activity of PON1192RR and PON155LL purified from high level PON1 is the highest, while this activity is the lowest in PON1192QQ and PON155MM. The paraoxon hydrolysis activity of the protein encoded by the R allele is eight times higher than the Q allele. The intermediate step of the activity is homozygous [27].

It is clear that paraoxonase activity may be associated with many diseases or conditions in the body, as well as with cardiovascular diseases and diet. Paraoxonase activity has been found to be low in patients who develop diseases known to be associated with coronary artery disease, such as obesity, DM, hypercholesterolemia, and renal failure, serum diabetic retinopathy, and hypertension [15, 16, 28]. Recently, it has been shown that the expression of human PON1 can prevent the development of diabetes in mice through its antioxidant properties and stimulation of β-cell of pancreas insulin release, suggesting a possible role for PON1 in insulin biosynthesis. PON1 may be a powerful antioxidant and antidiabetic enzyme [29].

Increasing the fat ratio in the body causes insulin resistance leading to obesity. Accordingly, central obesity, dyslipidemia, and genetic factors may cause the onset and development of insulin resistance [7]. Similar to the above studies, the PON1 activity of individuals with insulin resistance was studied in our current study, and the phenotype was investigated with the obtained data. It was observed that PONase and AREase activity was significantly lower in individuals with insulin resistance. In addition, individuals with bad phenotypes were found to have 1.85 times higher risk of getting IR than normal individuals. However, individuals with IR were found to be 3.69 times more likely to be affected by the bad phenotype (odds ratio). Considering these data obtained from previous studies, there may be a strong relationship between low PON1 activity and IR. However, it can be stated that PON1 plays a protective role in IR, as in many diseases, especially coronary diseases.

According to the 2019 WHO guidelines, IFG was evaluated as an impaired step in carbohydrate metabolism [30]. A fasting blood glucose level of 110–125 mg/dL (6.1 to 6.9 mmol/L) is defined as impaired fasting glucose [30]. IFG, which is also considered as an intermediate metabolic disorder, is stated to be an important risk factor in terms of diabetes and/or cardiovascular diseases [31]. Lu et al. conducted a study on 284 patients, supporting our findings. According to this study, they found that PON1 activity was significantly lower in patients with coronary heart diseases and IFG compared to the control group. The activity and structure of PON1 can be changed during glucose and/or lipid oxidation process. There are components that inhibit PON1 activity, such as advanced glycation end products in patients with DM. However, PON1 can decrease its activity by glycosylation itself. In the same study, altering the physicochemical properties of HDL may affect PON1 activity in HDL metabolism, and decreased HDL size and unesterified cholesterol accumulation in the HDL particle, increasing PON1 release and impairing its capacity to stabilize enzyme activity [32].

The main limitation of the current study is the lack of sufficient IGT sample size for significant statistical analysis to compare PONase and AREase activity and therefore, their effect on above-mentioned diseases could not be compared. Additionally, the number of studies which dealt with PONase and AREase activity and phenotype distribution was not sufficient enough to compare with our current study.

As a result, observing changes in PON1 activity may contribute to the prediction of diffuse, severe, or multiple disease lesions in patients with IR, IFG, or complications. The decrease in PON1 activities may increase the development of hyperglycemia, DM, and atherosclerosis due to IR and IFG. Therefore, it would be useful to conduct further research to explain possible mechanisms underlying the relationship between the PON1 phenotype, IR, and IFG. Further clinical, molecular, and biochemical studies are required to reveal all possible functions of PON1.

Acknowledgments This project was supported by the Bezmialem Vakif University scientific research project. Thank you to the commission.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval This study was carried out with the permission no 06/08/2019–13,038 obtained from Bezmialem Vakif University Non-Interventional Research Ethics Committee.

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