GUIDE FOR PARAOXONASE ASSAY KIT

1 OVERVIEW

Cardiovascular diseases are the leading cause of death all over the world. About 2/3 of these disorders are coronary artery disease (CAD)(1).

A number of epidemiological studies have shown that some of the risk factors associated with the development of CAD. These risk factors can be interchangeable such as lifestyle, biochemical and physiological characteristics or can be replaced or compensated such as age, gender and heredity factors(2,3).

Should be noted that at the development of coronary artery disease, biochemical parameters of high total and LDL-CHOLESTEROL, low HDL-CHOLESTEROL, hypertension, diabetes mellitus, obesity, and thrombogenic factors effects are larger. In addition physiological effects such as smoking, alcohol, sedentary lifestyle has important role at the development of CAD.

Due to the multifactorial etiology of coronary artery disease have a feature to determine the risk of coronary artery disease, the presence or absence of each risk factor as well as the degree or severity determined, in this context, to the risk factors can not be changed, what can be achieved by changing the existing risk factors shall be calculated (4).

The most important risk factors that play a role in the development of CAD are bad eating habit, smoking, diabetes, hypertension, obesity, oxidized LDL, triglyceride and associated with all low HDL-cholesterol levels (3).

Leading factor that cause coronary artery disease is the atherosclerosis, and the most important risk factor for atherosclerosis is blood lipids. Therefore, the majority of studies on the diagnosis of CAD risk levels of blood lipids, and a lot of developed and developing countries, a large part of the population has higher than normal levels of cholesterol. This is important for the high incidence of CAD (5). CAD risk connection with cholesterol varies according to the type and amount of lipoproteins which get into the structure of cholesterol. While the nature of atherogenic LDL cholesterol, HDL cholesterol, largely in protective. The concentration of LDL and HDL cholesterol level rise fall delays the formation of coronary lesions (6,7).

Atherosclerosis in the coronary arteries, after many years of a very slow process, and to varying degrees, but a disease that causes permanent stenoses. CAD is responsible for the pathogenesis of atherosclerosis alone. Sudden onset of coronary events in a dynamic (coronary artery spasm, coronary artery thrombosis) understood to play an important role. Whether you get a permanent dynamic events developing as the starting point of the coronary arteries to vascular endothelial dysfunction and / or endothelial injury (1).

The endothelium is not only a barrier surrounding the vascular system environment pockets, circulatory homeostasis and blood pressure at the same time balancing the endocrine system acts as a regulating repair events. Endothelial injury in the event of serious pathological events occurs in the cardiovascular system. Hypertension, hypercholesterolemia, and a lot of other risk factors, endothelial function, deterioration and / or endothelial injury and may play an important role, will lead to the development of atherosclerosis and myocardial ischemia(1). Whether to continue with

the process leading up to atherosclerosis, endothelial damage is very serious effects on the development of CAD reveals the importance of the paraoxonase enzyme activity.

2 PARAOXONASE ENZYME

Paraoxonase (PON1) is a glycoprotein which is synthesized by the liver, aromatic carboxylic acid esters which hydrolyse and which is closely tied to HDL esterases (8-11). During oxidation of LDL, HDL, and thus the accumulation of lipid peroxides in many studies of this enzymatic mechanisms reduce lipid peroxides were determined (11-16).

Populations may be affected by environmental factors, and varies according to the activity of paraoxonase (16-20). During the review of the literature, serum PON1 activity was investigated in different countries, and is seen in various diseases.

3 PARAOXONASE RELATIONSHIP WITH DISEASES

Hyperglycaemia and oxidative stress and predispose to atherosclerosis, given the role of DM in serum PON1 arises. 192RR PON1 genotypes and PON1 55LL with IDDM (Diabetes mellitus independent) was observed more frequently in patients. However a study of DM, hypercholestrolemia, renal disease and diseases known to be associated with CAD low serum PON1 activity was independent of genotype have been reported in several studies. Diabetic retinopathy, and low serum PON1 activity was observed in patients with hypertension, lipid peroxidation due to increased susceptibility (22).

Developed with the effect of lipid peroxidation and oxidative damage associated with neuronal degeneration, atherosclerosis, Alzheimer's disease, followed examined the relationship between PON1 polymorphism is known, but found no statistically significant results (23). In a study conducted in patients with hepatitis C infection, and these are found to be lower activity of paraoxonase 192RR PON1 polymorphism was found to be higher (24). Low-birth-weight infants PON1 polymorphism in the supply of high amounts of vitamins C and E, and birth weight changes were found. (25).

Rabbit with inflammation model of acute phase serum amyloid A and ceruloplasmin increase of HDL and apo AI, PON1, PAF 'ta demonstrated a significant reduction and HDL anti-inflammatory / antioxidant state of proinflammatory / pro-oxidant has been implicated in the transformation of the situation.

Uremic renal transplant patients at risk for atherosclerosis, low HDL antioxidant capacity in these patients following PON1/HDL and decreased rates of PON1/apoAI considered. Sporadic cases of idiopathic Parkinson PON1 metabolized by environmental neurotoxins B alleles with age and can be held responsible neurodegeneration constitute genetic susceptibility to Parkinson's disease have been proposed. (26). Hyper-paraoxonase and arylesterase activities were lower in children with autism, and the structure of neurotransmitters may be damaged due to an anomaly in these methylation reactions have been reported (27). Lipid oxidation is claimed to be a disease predisposing patients with hyperthyroidism were lower paraoxonase activity (28).

Autoantibodies to a group of patients with positive mmLDL'ye ACA increased significantly decreased PON1 activity and arterial thrombosis R genotype at high risk of developing a tendency for increased observed (29). PON1 activity has been reported systemic amyloidosis.

Plasma lipoprotein levels in fish-eye syndrome is different from normal plasma concentration of HDL cholesterol by 90%, while 89% showed reduced activity of PON1. Tangier's disease on the other hand is another lipoprotein metabolism PON1 enzyme activity could not be determined with the disease (30,31). Infants have the highest PON1 activity pyloric stenosis. Pyloric stenosis correcting operation starts after a week of enteral feeding continues until the height (32). Van Lenten and colleagues rabbit models of acute phase inflammatory HDL, apo A1, and on the other hand increased amyloid A, and ceruloplasmin in PON1 showed dramatically reduced (33).

PON1 activity changes are found in some experimental studies and in one study and considered as part of the inflammatory response, as interesting as chronic PON1 activity reduction, not only increases only atherosclerosis, acute inflammatory conditions also was found to cause more than the droop in body (34).

PON1 activity and concentration of environmental factors such as smoking, alter the activity of suppressing the enzyme. PON1 paraoxanase activity appeared to increase with hormone replacement therapies (21).

Paraoxonase enzyme activity was significantly lower than the control group in a study where the PON1 gene in prostate cancer 102 that a new polymorphism at codon 102, isoleucine and valine and by displacement of this polymorphism has occurred, prostate cancer may be one reason for this polymorphism is suggested (35).

4 MEASUREMENT OF PARAOXONASE

Paraoxonase enzyme activity to develop a variety of methods have been attempted in the past to measure the success that could not be obtained. Furlong (54,55), and Mackness' s (56), although methods are the most widely used methods of implementation difficulties, and remained poor due to analytical errors. Paraoxon difficulties in preparing the solution, spontaneous hydrolysis due to too much on the use of extremely toxic there are serious handicaps.

Due to all these woes, a new, reliable, fast, standardized and automated needs a kit for the "Rel Paraoxonase Assay Kit" offered to scientists in the world in 2007.

"Rel Paraoxonase Assay Test Kit" can be used as a great resource for both manual and automatic introduced the innovation. Also the product is a liquid, ready to use, and long life to be ensured that due to the considerable demand worldwide.

5 REL ASSAY PARAOXONASE ASSAY KIT

5.1. Kit Components

All reagents are ready to use. Reagent 1 (Buffer): 50 ml of Reagent 2 (substrate): 5ml Calibrator (Lyophilized): 1 vial (Optional)

Calibrator kit available in normal conditions. Due to operating factors described below using the kit calibrator can measure using the value of the factor in the operating procedures. But again, if you want calibrator calibrator human serum paraoxonase assay produced together with the order must

specify Rel. Volume specified on the bottle that you have received as a freeze-dried material prepared by the addition of deionized water used safely.

5.2. Principle of the Test Reaction

Paraoxonase enzyme in the reaction medium in the sample hydrolyzes the substrate paraoxon, and the resulting increase in absorbance of the product, the absorbance spectrum of the appropriate wavelength is monitored kinetically. Nonenzymatic hydrolysis value, the sample value of the net values are calculated by subtracting the enzymatic activity. Results minutes micromolar substrate hydrolysis unit is equal to / is expressed in liters.

5.3. Samples to be used

Serum, heparin plasma, semen plasma sample varieties to be used directly without any treatment. Cell culture and various textures can be used as the sample. But they should be homogenised. This procedure is as follows. Hemolyzed, lipemic sera and calcium binding and hyperbilirubinemia plasmas used anticoagulants should be avoided.

Frequently used in studies of liver, kidney, brain, etc.. soft tissues such as the following is used as a sample homogenate may be prepared according to a procedure.

5.3.1. Soft Tissues Homogenate Preparation Procedure

1 g fresh tissue accepted. * Working Solution are added to 9 ml. Mechanical homogenizer (blender) and crushed. Or crushed in a mortar at 3000 rpm for 5 min. is santrifuge. The supernatant was attempted, such as serum.

* Working Solution:

140 mmol / l KCl (in deionized water) or 50 mmol / L. pH 7.40 Phosphate Buffer (relassay@relassay.com address or by writing to the laboratory is not available +90342230 can be ordered by calling 37 52.)

5.4. Animal Testing

Paraoxonase proteins, which have a wide distribution of mammal species, birds, fish, and invertebrates such as arthropods, animals are not available.

Mammals in many tissues, especially the liver, kidney, small intestine and located in the plasma. Work can be done with serum and tissues of mammals. Nowadays, most rats used for experiments paraoxonase.

Sera from animals studies, that does not bind calcium has been obtained by using the plasma or tissue sample can be used as anticoagulant.

Rel Assay Paraoxonase Kit can be used safely with the animal experiments.

5.5. Storage

5.5.1. Sample Stroge

Paraoxonase enzyme activity, samples to be measured;

Serum / Plasma 2-8 ◦ C in 24 Hours

Serum / Plasma -20 ◦ C to 3 months

Serum / Plasma -80 ◦ C 1 Year

Can stored for dedicated periods.

5.5.2. Kit Storage

Kit should be stored at 2-8 C. Do not freeze. Reagents caps closed, protected from light and moisture. These conditions can be used until the expiration date stated on the product. Mouth opened a little after using the kit is stored in the circumstances set out above, it can be used until the expiration date.

5.6. Warnings and Precautions

Using reagents and wear gloves when working. Do not breathe reagents. Avoid skin contact with reagents. In case of contact, rinse immediately with plenty of water. Reagents any breathing or swallowing, seek medical advice urgently.

6 MANUAL OPERATION PROCEDURE

Sample Volume[A]	25 µl[B]
Reagent 1[C] Volume	500 µl
Reagent 2[D] Volume	25 µl
Wavelength	412 nm[E]
Method	Kinetic (Rate-up)

6.1. Working Steps

Spectrophotometer cuvette placed in 500 mL Reagent 1. Mixed with 25 mL sample is added on. 25 mL of Reagent 2 is added and mixed in turn. Instantly add a timer is started at full-time. Spectrophotometer at 412 nm quickly. also begins to be ABSF. # 30 and 150 ABS is the seconds. This process is applied to all specimens. Results calculated according to the following formula

6.2. Calculation

Result (U / L) = [(ABS 150 seconds - 30 seconds ABS) / 2] x 1202.84 G

6.3. Instructions

A - Sample: Serum, heparin plasma, semen plasma, cell culture and tissue homogenates

B - µL: Microliter

C - Reagent 1: Paraoxonase kit in the box, a large bottle of liquid reagent

D - Reagent 2: Paraoxonase kit in the box, a small bottle of liquid reagent

E - nm: nanometer; spectrophotometer wavelength unit to be set

F - ABS: "Absorbance". Of reading spectrophotometer unit

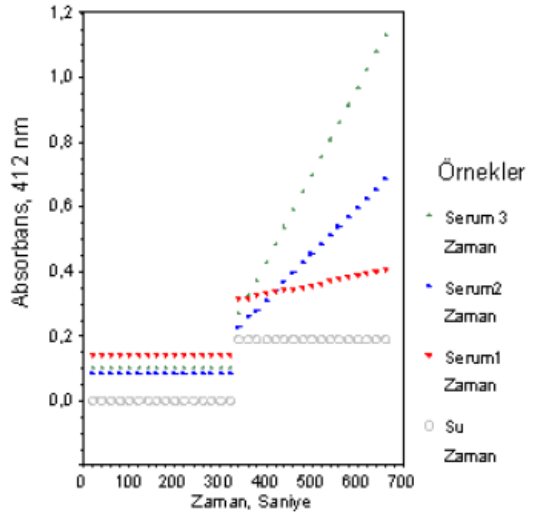
G - 1,202.84: 1 cm of light direction factor is considered. If the light path is different than 1 cm, the new factor in the calculation; 1202.84 's are obtained by dividing the value of the light path in cm.

7 OPERATING PROCEDURE (Automated Analyzer)

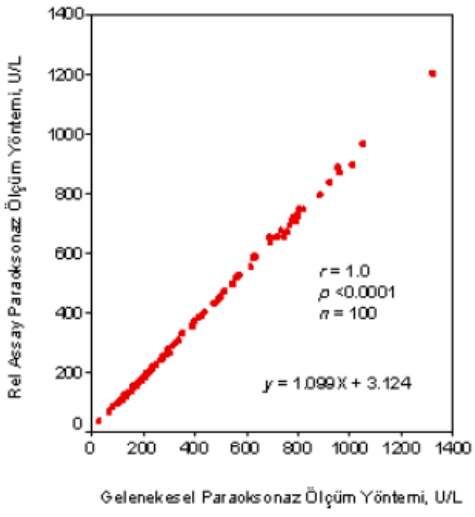
Application by entering the following data can be automated analyzer. Show the menus are different types of automated devices. Each device has its own algorithm. But the following data for each device is shared between the parameters and their values. Apart from that, the values must be defined on the device, the device responsible for firm staff are available in the application.

Sample Volume	25 µl
Reagent 1 Volume	500 µl
Reagent 2 Volume	25 µl
Wavelength	412 nm
Method	Kinetic (Rate-up)
Calibration	Factor (1202,84)
Unit	U/l

7.1. Reaction Kinetics and Performance



Sekil 1. Yüksek, orta ve düsük paraoksonaz aktivite düzeylerine sahip serumlar ile suyun otomatik analizörde zaman – absorbans degiskenli, Rel Assay Paraoksonaz testinin reaksiyon kinetikleri.



Sekil 2. Rel Assay paraoksonaz ölçüm yöntemiyle geleneksel paraoksonaz ölçüm yöntemi'nin karsilastirilmasi ve korelasyon grafigi.

7.2. Test% CV values

Sera Pools	%CV
High	**4.1**
Medium	**1.7**
Low	**1.5**

8 ASSESSMENT OF THE TEST

There are two different genetic factors that affect the activity of paraoxonase enzyme. Paraoxonase 55 and 192 effect on the activity of amino acid type.

PON1 55 position, leucine (L genotype) rather than methionine (M genotype) is less than the arrival of the effect on activity (39). However, 192 glutamine instead of arginine in position to arrive at least 8-fold reduced activity. 192 of the enzyme thus Paraoxonase Aminoasitinin Arginine (R) or glutamine (Q) activity that affects serious meaning. Paraoxonase of the individuals associated with this enzyme activity determines the properties of being resistant to the disease or sensitive. # 192 High activity allele is RR, QR activity when the activity is low when the medium and QQ.

Turkey's population is made on samples taken from healthy subjects in our study reached the following data. These values race, age, on the diet, chronic diseases and the use of non-dependent variable.

Groups	Concentrations (U/L)	% of Population
Low Activity	<200	%46
Medium Activity	200-400	%44
High Activity	>400	%10

This study has been prepared in accordance with the international literature in the light of scientific data. Turkish population samples were made in this study as were used. This study used samples from healthy individuals 20-60 years of age. It should be noted that each laboratory determine its own reference range. This study is the study of a sample prepared by the manufacturer itself. The manufacturer does not accept responsibility for any problems arising from the use of this data.

9 QR 192 PON1 polymorphism (phenotyping)

Although two separate enzyme paraoxonase and arylesterase algılanırsada, studies, and research has shown that, as well as human serum paraoxonase arylesterase as the enzyme activity of a single gene product that has been processed. Publications, showing that even with the activity of this enzyme laktonaz available (40). In humans, 7 long arm of chromosome q-q-3.21 and 1.22 can be defined between the PON1 paraoxonase gene family, PON2 and PON3 has 3 members in the form. Developmental perspective, create a structural similarity as a result of gene duplication genes. PON1, PON2 and PON3 genes of mammals; nüklelotid similarities at the level of 81-90%, while the level of amino acid similarity is 79-90%. PON1 106 codon (lysine), while PON2 and lysine PON3'te available. For years, studies with PON1, human serum capacity to hydrolyze xenobiotics, and to investigate the relationship between atherosclerosis. PON2 and PON3, due to the lack of research on how well anlaşılamamışlardır PON1. Also, while plasma PON1 and PON3 gene product, is said to be localized in

intracellular PON2'nin (41,42). PON2 and PON3 gene family, some of the research conducted in recent years contributed to the activity of PON1 and PON2 and PON3 HTLase 's so precious in CAD PON1 reported that at least (43). But we talk about the fact that PON1 paraoxonase and arylesterase activity of PON1 from talking about it. There are two amino acid polymorphisms in PON1. One of them 55 position leucine with methionine (M / L) in the change of amino acids, the other 192 amino acids arginine and glutamine in position by the displacement of [R / Q (Q instead of some sources A genotype, R B genotype is used instead)] occurs. PON1 polymorphism in the promoter region than it has five other known polymorphisms. Makes the difference in the distribution of polymorphic populations of individuals. Arylesterase polymorphism does not affect the activity, independent of changes in the activity of PON1 arylesterase activity, based on the concentration of the protein can be considered as an indication. So paraoxonase; activity show polymorphism also has arylesterase activity (44). PON1 55 position, leucine (L genotype) rather than methionine (M genotype) is less than the arrival of the effect on activity (39). However, 192 glutamine instead of arginine in position to arrive at least 8-fold reduced activity. PON activity polymorphism, PON1192R isoform, paraoxon PON1192Q form faster hydrolysis, while isoform PON1Q192 diazokson, somon'u hydrolyzes faster (45).

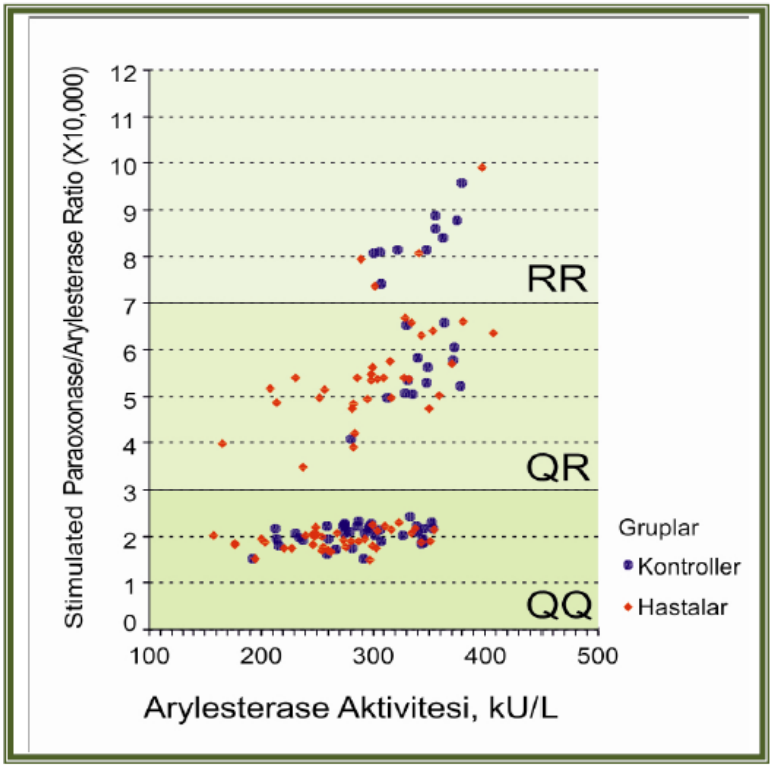
Allozymes paraoxonase phenotyping by quantitative and qualitative methods have been developed with the discovery that they are different. 1984 BN La Du et al. The method according to the method is termed the dual substrate (46); two isoenzyme salt and pH of both phenotypes identified by different responses. Responding to the salt has a high enzyme activity against B Allozim paraoxonase. Paraoxonase activity 1M (Molarity) when stimulated with activity as NaCl, while the decrease in arylesterase activity were determined. Trimodal distribution observed in this analysis. Large-low activity peak "low activity homozygotes-AA", a small peak of high activity "heterozygotes and the EU", the small peak of activity in the "high-activity homozygotes-BB" represents. The most common homozygous-AA (QQ), the second EU-heterozygous (QR), at least one homozygous-BB (RR), respectively. Shows the distribution of polymorphic paraoxonase large interethnic variability.

Related human gene, also termed as HUMPONA for paraoxonase. Low paraoxonase activity in patients with CAD is located in the hypercholesterolemic and diabetes. Because these groups, lipid peroxidation products, lipid oxidation products aterosklerozis'in accelerates the development and increases the human şilomikronlarında. PON1 activity is also closely related to dietary intake in söylenmektedir.Diyette fruit, tea and butter increased PON1 activity and dietary content of carbohydrate, protein, MUFA, PUFA, vitamin E, flavonoids, and there are studies that report that correlate with Qercetin (49) High levels of PON1 from PON155LL'nin paraoxon hydrolytic activity of the purified PON1192RR and the high, the low PON1192QQ and PON155MM this activity. Paraoxon hydrolysis activity of the protein encoded by the allele Q R allele eight times higher. Intermediate step activity homozygotes (50). Methyl paraoxon substrate specificity similar to the steps, as well as other oksonlarda klortion-oxone and Armin observed. On the other hand paraoxon hydrolytic activity of paraoxonase capacity to protect LDL from oxidation with alloenzyme completely reversed. Thus, PON155MM / HDL and PON1 are associated with individuals who alloenzim PON1192QQ the biggest addition to being capable of protecting the nerve gases such as sarin alloenzyme diazoxon and salmon, and take an active role in hydrolysis (51,52).

RR allele was quite low in the Turkish population, the eastern populations showed lower values close to the European race (53). Q low activity allele in Europe, Canada and the United States is high,

Australia, Aboriginal, Zambia, and Zimbabwe is low. Around 50% of European populations followed bimodalite low activity isoform and decreases with distance from Europe. Unimodal distribution in Africa and in Eastern countries, it is less common breeds low-activity genotype frequency.

9.1. Phenotyping Study



Paraoxon enzyme paraoxonase (Paraoxonase) and phenylacetate (Arylesterase) activity rate, which is the phenotype of three individuals, QQ, QR and RR from which one can be identified as belonging to. Paraoxonase'ın determined by dual substrate phenotyping, high linearity with genotype analysis. PON1 192Q / R rel for phenotyping assay kits Stimulated Arylesterase Paraoxonase and easily by using the automatic and fast to get results.

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