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LIPID-LOWERING EFFECT OF DOXAZOSIN AND TERAZOSIN AND THEIR RELATIONSHIP WITH CATALASE ACTIVITY IN A MICE MODEL OF HYPERLIPIDEMIA

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Abstract

The present study aimed to determine the relationship between the lipid-lowering effect generated by the alpha-blocking drugs doxazosin and terazosin with the activity of the enzyme catalase in a mice model of hyperlipidemia. 30 male albino mice were used, which were equally distributed in 5 groups. The blank and hyperlipidemic control groups received 0.5% carboxymethylcellulose (CMC) orally in doses of 10 ml / kg. The drugs doxazosin and terazosin were dissolved in CMC, and then administered orally in doses of 1 mg / 100 g to problem I and problem II groups, respectively; and the drug atorvastatin dissolved in CMC administered orally in doses of 10 mg / Kg to the standard group. The induction of hyperlipidemia was carried out on the ninth day of treatment by administering Triton in a single dose of 400 mg / Kg intraperitoneally to the control, standard, problem I and problem II groups. After 24 hours of triton administration, blood samples were taken to determine the cholesterol, triglyceride and catalase activity values. Analysis of Variance, Nonlinear Regression and Principal Component Analysis were used, with a significance level of $p < 0.05$. In problem I (doxazosin), problem II (terazosin) and standard (atorvastatin) groups with respect to the hyperlipidemic control group, a significant decrease ($p < 0.05$) in cholesterol and triglyceride values was observed. When evaluating the specific activity of catalase, it was found that there is a significant increase ($p < 0.05$) in enzyme activity in problem I, problem II and standard groups compared to the hyperlipidemic control group. A non-linear relationship was observed between cholesterol and triglyceride levels with catalase activity. The results of this study show an inverse non-linear relationship between the lipid-lowering effect of doxazosin and terazosin with the enzymatic activity of catalase in the model tested.

Keywords: *Doxazosin, terazosin, cholesterol, triglycerides, catalase, lipid-lowering, mice*

Introduction

Alpha-blocking drugs are used as the first line in the treatment of benign prostatic hyperplasia (BPH), one of the main causes of consultation for obstructive or irritative urological problems in middle-aged and elderly men; and they are also used as second-line drugs in the treatment of uncontrolled arterial hypertension, in monotherapy or in combination because they are well tolerated [1,2].

Doxazosin and terazosin act on alpha-1 adrenergic receptors, competitively blocking their activity. These receptors are located in blood vessels, bladder and prostate; in this way, by acting on the prostate they produce a reduction in the tone of the prostate muscles, thus relieving obstructive symptoms in BPH, increasing urinary flow and improving symptoms [3].

Pleiotropism, in the pharmacological context, is the ability of a drug to bind to different molecular targets, generating effects beyond the main effect for which it is marketed; drugs such as metformin, some antipsychotics or statins, are examples of this [4,5].

In the mid-nineties of the last century, effects on lipid metabolism by some alpha-blockers began to be reported, one of the last studies in this regard dates from 2001 [6]. The use of these drugs as antihypertensives was later displaced by drugs that modulate angiotensin metabolism [7].

One of the diseases with the highest prevalence in the world is dyslipidemia, it causes around 4 million deaths per year, of which 50 to 60% correspond to developing countries, this pathology is characterized by high levels of cholesterol and triglycerides. Hypercholesterolemia exerts a negative effect on endothelial function, where through a series of metabolic and oxidative alterations the atherosclerotic process begins with the formation of atheromatous plaque, which is the endothelial inflammation product of the infiltration of lipids, and its rupture is responsible for most acute coronary syndromes and even sudden cardiac death [8].

If we take into account that in dyslipidemias increased free radical production is implicated in endothelial dysfunction, then the administration of antioxidants may have a beneficial effect on endothelium [9].

Hyperlipidemia leads to a series of important complications and comorbidities, one of which is arterial hypertension, due to the fact that it generates an increase in adrenergic activity, an increase in sodium and aldosterone concentration and an increase in cardiac output. In addition, arterial hypertension is associated with cardiovascular events such as ischemic stroke, sudden death and myocardial infarction, thus hyperlipidemia and hypertension can cause these events to appear at an early age [10].

Doxazosin metabolites have been reported to have antioxidant properties in *in vitro* tests, which could be very useful to prevent atherosclerosis in hypertensive patients, especially when other comorbidities such as dyslipidemia and diabetes are associated [11]. Then, there is evidence of the hypocholesterolemic and antioxidant effect of doxazosin; effects that have not been proven with other alpha-blockers but that indicates a potential effect against endothelial dysfunction that occurs in various conditions.

Catalase as part of the endogenous antioxidant enzymatic system is responsible for transforming hydrogen peroxide (H_2O_2) formed by oxidative stress that occurs in low-density lipoproteins that are increased in cases of dyslipidemia. In this way, the enzymatic activity of catalase on H_2O_2 allows the formation of oxygen and water, attenuating the impact of free radicals in the body [12,13].

In the present investigation we determined the relationship between the activity of the catalase enzyme and the lipid-lowering effect generated by the alpha-blocking drugs doxazosin and terazosin in a mice model of hyperlipidemia.

Methods

Sample preparation and dosage

Doxazosin (Pfizer), terazosin (IQFarma) and Atorvastatin (Pfizer) were dissolved in 0.5% carboxymethylcellulose (Dropaksa) (CMC). The atorvastatin dose was 10 mg / Kg orally; and the

dose of 1 mg / 100 g orally for both alpha-blocking drugs was calculated based on the body weight of the specimens, taking into account pharmacokinetic parameters and previous studies [4,14]. The administration of the drugs was carried out using an orogastric cannula.

Selection of specimens

30 *Mus musculus* Balb/c male specimens of 2 months of age and weighing between 40 and 50 g were randomly selected. They were acquired from the bioterium of the Faculty of Pharmacy and Biochemistry of the National University of Trujillo-Peru, kept in plastic cages, ambient temperature (24.1 ± 0.37 ° C), under the same nutritional conditions and water *ad libitum*.

Experimental model

The induction of hyperlipidemia was carried out with the administration of 10% Triton X-305 intraperitoneally diluted in saline. With this agent, an increase in blood cholesterol and triglycerides is obtained [15].

We worked with five groups, of six mice each: The Blank group and the Control group received 10 ml / Kg of 0.5% CMC orally; the Problem I and Problem II groups received 1 mg / 100 g of doxazosin or terazosin orally, respectively; and the Standard group received 10 mg / Kg of atorvastatin orally. Treatments were administered for 10 days; and on day 9 Triton X-305 was administered at the dose of 400 mg / kg intraperitoneally to the Control, Standard, Problem I and Problem II groups.

Cholesterol and Triglyceride Quantification

Exsanguination of the specimens was performed; the blood sample taken from the submandibular venous sinus after anesthesia (ketamine 15 mg/kg; xylazine 2 mg/kg) and was collected in Eppendorf tubes and subsequently centrifuged at 3 500 rpm for 15 min to obtain blood serum. Cholesterol and triglyceride quantification were carried out enzymatically using kits of determination by Spinreact [16,17]. Briefly, 10 µL of serum is mixed with 1 mL of enzyme solution, incubated at 37 ° C for 5 minutes, then absorbances were read at a wavelength of 505 nm (GENESYS 20 Thermospectronic spectrophotometer). In the same way, the procedure was carried out without a sample and also with a standard. Finally, the concentrations were expressed in mg / dl.

Catalase Activity Assessment

The enzyme catalase has a dual activity, catalytic function by breaking down hydrogen peroxide and peroxide allowing the oxidation of hydrogen donors. For its determination, the method described by Aebi was followed, the blood was collected in tubes with citrate, they were centrifuged at 3 500 rpm, then the pellet was washed three times with PBS. From the sediment the hemolysate is obtained in a 1 / 500 ml dilution [18].

The following system was prepared: Blank: 1 ml of phosphate buffer pH 7 and 2ml of the hemolysate dilution, Unknown: 2ml of hemolysate dilution and 1ml of hydrogen peroxide at 30mM, which was added when the cuvette was in the spectrophotometer and immediately absorbances were recorded every 10 seconds up to 120 seconds.

The catalase activity expressed in U / ml was obtained by multiplying the variation in absorbance by the factor 41,550 and it allows establishing that 1 µmol of the substrate is being transformed during one minute of reaction. However, the specific activity of catalase makes it possible to express the proportion of an enzyme as a function of the concentration of proteins present in the sample. In this way, to calculate the specific activity of catalase, the hemoglobin concentration of the specimens is needed and the catalytic activity of catalase is divided by the value of hemoglobin, the result being expressed in U / mg of hemoglobin.

Determination of Hemoglobin

For the determination of hemoglobin, a blood sample was taken from the specimens with the help of capillaries heparinized, which were placed in a microcentrifuge and the hemoglobin values expressed in g / dl were found by means of hematocrit [19].

Statistical

The effect of the drugs on cholesterol, triglycerides and catalase activity was analyzed using one-way ANOVA, Tukey's post hoc tests and DMS (statistical program SPSS v.22.0). The graphs

were made using GraphPad Prism 7 Demo. The cholesterol, triglycerides and catalase activity values were subjected to a non-linear regression analysis (inverse, quadratic, power and S), then they were regrouped by means of the Principal Component Analysis (PCA) with Varimax rotation and Kaiser normalization (SPSS v.22.0 and Origin Pro 2019 Demo). In all cases, a confidence level of 95% was considered ($p < 0.05$).

Ethics

All the activities that were carried out in the present investigation were followed according to the norms of the ethics committee for the handling of animals approved by the Ethics Committee of the National University of Trujillo [20].

Results

In Table 1 shows the cholesterol and triglyceride levels expressed in mg / dl in each study group. It can be seen that the control group shows a significant increase ($p<0.05$) of +79.24% and +111.41% in cholesterol and triglyceride levels respectively, compared to the blank group. Furthermore, in the Problem I, Problem II and Standard groups there is a significant correlation ($p < 0.05$) in both parameters compared to the control group. In addition, the catalytic and specific activity of the catalase enzyme is shown, where a significant reduction of -62.83% and -55.75%, respectively, can be observed in the control group compared to the blank group. However, in the Problem I, Problem II and Standard groups, a significant increase in both enzymatic activities is observed.

Graph 1 shows a curvilinear estimate of the cholesterol level and the specific catalase activity by means of a non-linear inverse and quadratic modeling; and graph 2 shows the curvilinear estimate of triglyceride levels and the specific catalase activity by means of a non-linear potential and S modeling. Graph 3 together with Table 02 allow us to observe all variables, cholesterol and triglycerides levels and the enzymatic activity of catalase, in two clearly differentiated rotated components. On the one hand, enzymatic activity and specific activity of catalase; and cholesterol and triglycerides on the other.

In addition, in Table 2 are the variables in the distribution matrix with rotated components, according to the PCA; variables with values close to unity are considered in a component.

Discussion

The objective of the present investigation was to determine the relationship between the lipid-lowering effect generated by the alpha-blocking drugs doxazosin and terazosin with the activity of the enzyme catalase in a mice model of hyperlipidemia.

When evaluating the results of cholesterol and triglycerides of the different experimental groups, shown in Table 01, it is evident that the highest values of cholesterol and triglycerides correspond to the control group, which received triton as an inducing agent of hyperlipidemia. This agent has surfactant properties, generating destabilization of receptors that allow the uptake of blood lipids, such as liver LDL receptor, preventing the entry of cholesterol into the hepatocyte; thus generating an increase in cholesterol levels; also inhibits the action of lipoprotein lipase which leads to an increase in triglycerides [21,22].

The drugs doxazosin, terazosin and atorvastatin were administered to problem I, problem II and standard groups respectively, and showed a significant decrease in cholesterol and triglyceride values compared to the control group; being with doxazosin - 42.67%, $p < 0.05$; - 49.65%, $p < 0.05$; with terazosin -51.17%, $p < 0.05$; -49.66%, $p < 0.05$; and with atorvastatin -42.54%, $p < 0.05$; -48.70%, $p < 0.05$ respectively. Statins, such as atorvastatin, act by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and thus limit cholesterol synthesis [23]. The group with the best reduction in cholesterol levels was problem II, who received terazosin for 10 days; and with regard to reduction in triglyceride levels, the standard groups, problem I and problem II presented a significant decrease ($p < 0.05$) compared to the control group.

These results are consistent with the study carried out by Gong et al., in which they report that patients with BPH associated with hypercholesterolemia and who were treated with terazosin obtained a significant reduction of 12.73% in total cholesterol. Regarding triglycerides, a

significant reduction of 36.42% was obtained at 6 months of treatment [24]. On the other hand, Hernández et al. found that treatment for four weeks with terazosin produced a significant 8.71% decrease in total cholesterol and a 14.31% reduction in triglyceride values [25].

An explanation for the decrease in cholesterol and triglyceride values was made by Jatwa and Kar, they relate this effect to a regulation of thyroid function. The relationship between the imbalance of thyroid hormones and serum lipids involves processes such as beta oxidation at the muscle and liver level, through beta adrenergic stimulation, in addition to accelerating the turnover of LDL. In this way, terazosin would generate a change in thyroid hormone values, which allowed us to observe a decrease in cholesterol and triglyceride values; however, the exact mechanism of action is not entirely clear [26].

After showing the reduction of blood lipids in the experimental groups it was decided to evaluate on the catalase activity, because this enzyme is part of a group of endogenous enzymes that react against oxidative mechanisms, involved in dyslipidemias [27]. When comparing the control group against the problem I and II groups and the standard group in table 1, a significant increase ($p < 0.05$) in the catalytic and specific activity of catalase is shown, with the highest values found in the standard group the which was treated with atorvastatin.

As mentioned, statins exert their lipid-lowering effect by inhibiting HMG-CoA reductase, which limits the rate of cholesterol synthesis through mevalonate; however, they also inhibit the synthesis of isoprenoid derivatives, which is related to their pleiotropic effects. They reduce lipid peroxidation, act against hydroxyl radicals, and also reduce lipoprotein oxidation in various oxidative systems, reducing the damage that free radicals can exert in the body [28,29]. In this way, atorvastatin would act as an exogenous antioxidant, thus allowing the enzymatic activity of catalase to increase. Furthermore, among the problem groups, higher values were found in problem group II that was treated with terazosin (Table 01).

With regard to alpha-blockers, Ishimitsu et al. propose that these drugs would also suppress the activity of the enzyme HMG-CoA reductase, involved in the biosynthesis of cholesterol; increasing the activity of the LDL receptor, which facilitates the catabolism of LDL cholesterol; also, they increase the activity of lipoprotein lipase that facilitates triglyceride catabolism [30].

In graphs 1 and 2 it can be observed that the specific activity of catalase is higher when the values of both cholesterol and triglycerides are low; at the same time, the enzymatic activity decreases when there are high levels of cholesterol and triglycerides. In this way, an inverse relationship is established between the specific activity of catalase and the concentration of serum cholesterol and triglycerides. This is verified with graph 3 and table 2 through the distribution of variables in rotated components; since if we place ourselves in component 1 we can notice that here the values of the variables cholesterol and triglycerides are close to unity (0.944 and 0.964 respectively) while the variables of catalytic and specific activity of the catalase enzyme show an inverse correlation moving away zero (-0.732 and -0.722 respectively).

Consequently, we can show that the alpha-blocking drugs studied, terazosin and doxazosin, have the ability to reduce cholesterol and triglyceride levels, in turn increasing catalase levels in a model of induced hyperlipidemia, giving a prospect to these drugs as antioxidant agents.

Finally, our findings attempt to reassess the use of alpha-blockers in processes involving hyperlipidemia and other diseases that cause an unbalance of oxidative species, triggering oxidative stress, in addition to the effects already known as vasodilator and prostate muscle relaxant.

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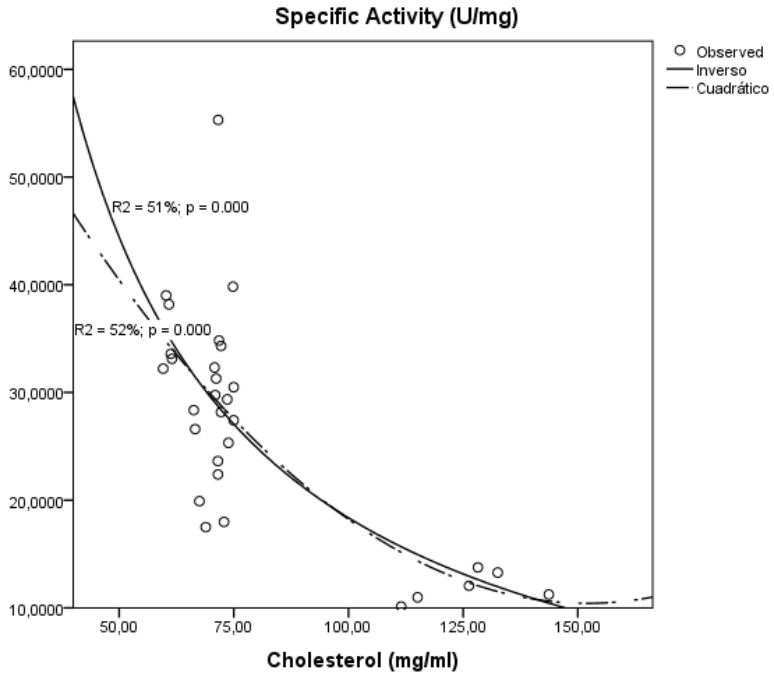
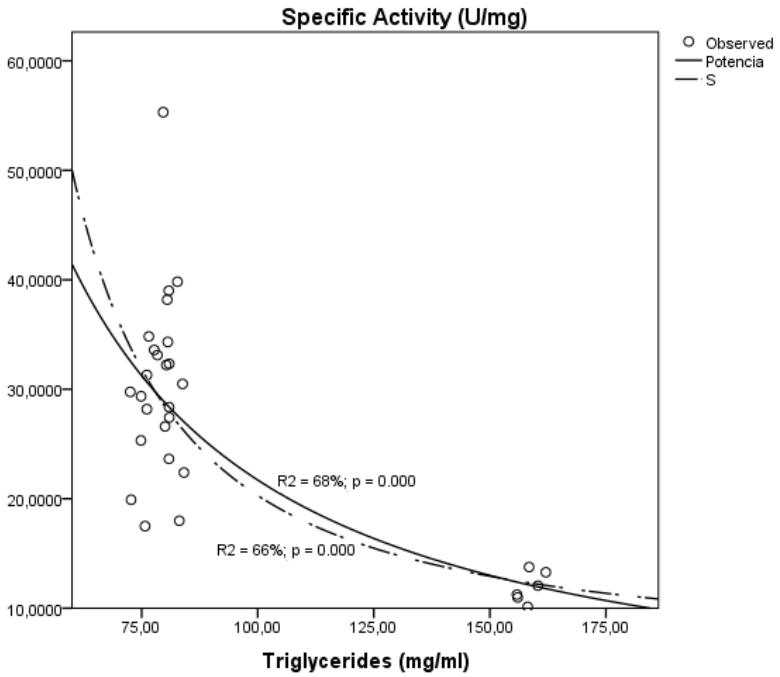
Table 01. Mean levels of Catalytic Activity (U / mL) and Specific (U / mg Hb) of catalase (CAT) according to study groups

	Blank	Control	Problem I	Problem II	Standard
Cholesterol (mg/dL)	70,41 ± 1,83	126,21 ± 11,75* (+79,24%)	72,36 ± 1,24# (-42,67%)	61,62 ± 2,38#,& (-51,17%)	72,52 ± 3,27# (-41,82%)
Triglycerides (mg/dL)	74,96 ± 1,82	158,47 ± 2,43* (-111,42%)	79,79 ± 4,02# (-49,65%)	79,78 ± 1,38# (-49,66%)	81,30 ± 1,63# (-48,18%)
Catalytic activity CAT (U/mL)	4098,88 ± 1105,18	1523,62 ± 140,06* (- 62,83)	3996,62 ± 802,97# (+ 162,31%)	5418,83 ± 629,70#,& (+ 255,65%)	5756,96 ± 186,76#,& (+ 277,85%)
Actividad específica CAT (U/mgHb)	26,91 ± 6,77	11,91 ± 1,40* (- 55,75%)	25,17 ± 5,11# (+ 111,39%)	34,08 ± 3,96#,& (+ 186,23%)	35,66 ± 10,79#,& (+ 199,48%)

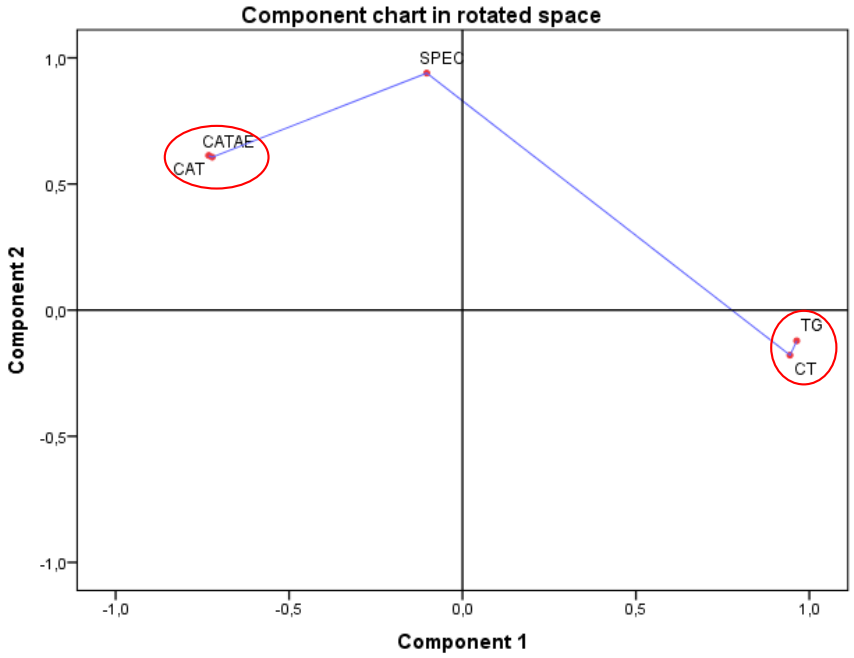
*: p <0.05, compared to the White group; #: p <0.05 compared to the Control group; &: p < 0.05, purchased with Problem I group. The White group is normolipemic, the Control group is hyperlipemic, the Problem group I receives Doxazosin 10 mg / kg, Problem II Terazosin 10 mg / kg and the Standard group receives Atorvastatin 10 mg / kg.



Graph 01. Curvilinear estimation of cholesterol and specific enzymatic activity of catalase (U / mg), through non-linear modeling (inverse and quadratic)



Graph 02. Curvilinear estimation of triglyceridemia and specific enzymatic activity of catalase (U / mg), through non-linear modeling (potency and S)



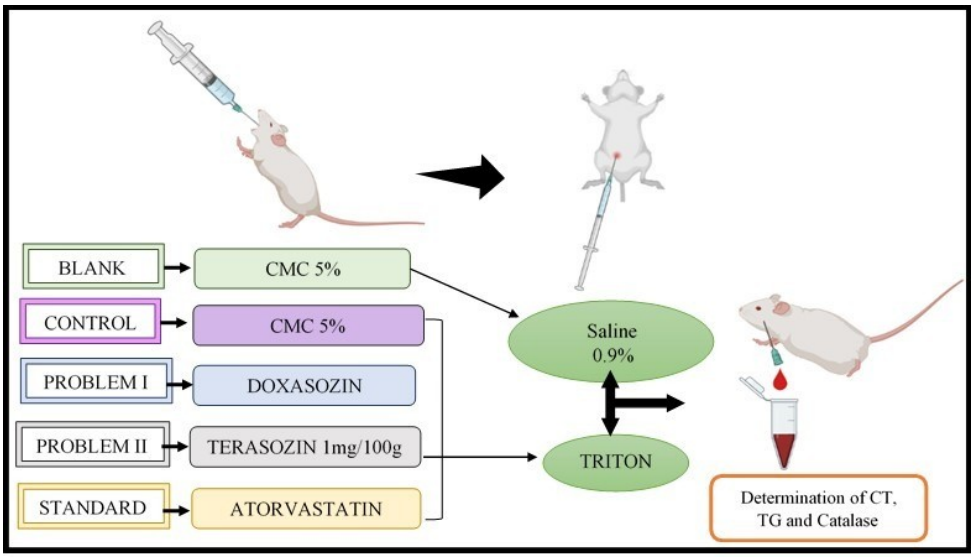
Graph 03. Variables grouped into two components in rotated space, according to PCA

CAT: Catalase enzymatic activity; CATE: Specific enzymatic activity of catalase; TG: triglycerides; TC: Total cholesterol; SPEC: Specimen; PCA: Principal Component Analysis

Table 02. Distribution matrix of variables in rotated components, according to PCA

	Component	
	1	2
Cholesterol (mg/dL)	**0,944**	**-0,178**
Catalytic Activity (U/mL)	-0,732	**0,613**
Specific Activity (U/mg)	-0,722	**0,606**
Tryglicerides (mg/dL)	**0,964**	**-0,122**
Specimen	-0,103	**0,940**

Rotation method: Varimax with Kaiser normalization



Scheme N°1. Experimental design. (Created with BioRender.com)