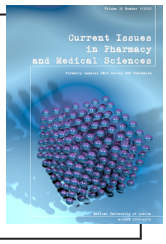
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Assessing the role of serum Pentraxin-3 (PTX3) levels in hypothyroidism patients as risk marker of insulin resistance

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ABSTRACT

Introduction. Hypothyroidism is a common endocrine disorder that affects millions of people worldwide. The diagnosis and monitoring of this condition often rely on thyroid hormone levels, which can be limited in their accuracy. Pentraxin 3 (PTX3) is a protein family that is involved in the innate immune response and is distinguished by its distinct pentameric structure.

Aim. To evaluate the utility of serum PTX3 levels in detecting and monitoring hypothyroidism.

Materials and Methods. A case-control design of the study included 90 participants between the ages of 20 and 50 years. These participants were divided into three groups: overt hypothyroidism (OH), subclinical hypothyroidism (SCH), and a control group of healthy individuals. Anthropometric data, including age, sex, weight, height, body mass index (BMI), and hormonal parameters were measured and recorded for each participant.

Results. Our work demonstrates that serum PTX3 levels were significantly elevated in individuals with hypothyroidism, compared to those with normal thyroid function ($p<0.001$). Furthermore, PTX3 levels correlated positively with TSH levels ($r=0.62$, $p<0.001$) and negatively with T4 levels ($r= -0.53$, $p<0.001$).

Conclusion. The findings suggest that serum PTX3 levels can be a useful biomarker for detecting and monitoring hypothyroidism, particularly in cases of SCH. The study's exclusion criteria made sure that no other systemic illnesses or medication use could have tainted the findings. Therefore, the use of plasma PTX3 levels in hypothyroidism detection and monitoring may prove to be a valuable clinical tool in the future.

INTRODUCTION

Hypothyroidism is a condition where the body does nott produce enough thyroxin hormone due to a malfunction in the thyroid gland. The condition can be categorized as primary, which originates in the thyroid gland, or secondary/central, which results from issues in the hypothalamus or pituitary gland. Subclinical hypothyroidism is a subtype of primary hypothyroidism, characterized by elevated TSH levels despite normal blood free T4 and T3 levels [1].

Approximately 2-5% of all people with subclinical hypothyroidism develop overt hypothyroidism every year. Treatment is recommended for patients with both clinically apparent and subclinical hypothyroidism who have TSH levels over 10mIU/L. Depression, memory and cognitive impairments, and impaired motor coordination are only some of the neuropsychiatric symptoms that may accompany hypothyroidism. The total prevalence is 10%, although it is much higher among the elderly, particularly among women [2].

Although there is widespread agreement that obesity and hypothyroidism go hand in hand, the debate continues over whether or not the two conditions are causally related. While overt hypothyroidism is linked to slight weight gain, the link between subclinical hypothyroidism and obesity is less clear [3]. The causes and manifestations of hypothyroidism are diverse and multifaceted. Some of the most common signs include an increase in body mass, thinning hair, sensitivity to cold, sluggishness, constipation, dry skin, and even a change in one's voice. However, hypothyroidism symptoms might differ in appearance and intensity depending on age, gender,

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and other variables. There is an elevated risk of morbidity and death associated with untreated hypothyroidism [4]. Furthermore, those with type 2 diabetes mellitus (DM-II) are more likely to acquire hypothyroidism [5].

Hyperlipidemia, a possible contributor to the increased risk of CAD, may be a result of the rising prevalence of overt hypothyroidism [6]. Hashimoto's thyroiditis, a kind of autoimmune thyroid disease, is the most common cause of hypothyroidism. Lack of iodine in the diet, however, is the leading cause of hypothyroidism across the world. Hypothyroidism may now be diagnosed with a simple blood test, and treatment consists of administering synthetic thyroid hormone [7].

An acute inflammatory protein known as pentraxin 3 (PTX3) belongs to the same family as the well-known cardiovascular biomarker C-reactive protein (CRP). PTX3 and CRP are both considered to be members of the C-reactive protein family [8]. PTX3 is made in reaction to bacterial products, interleukin-1, and tumor necrosis factor, which all cause inflammation. However, it does not come about because of interleukin-6. PTX3 is made by a few different kinds of cells, like macrophages and blood endothelial cells, but not by the liver [9-11]. Since PTX3 is generated by vascular endothelial cells and macrophages rather than the liver, it is possible that PTX3 levels may more accurately represent the inflammatory condition of the vasculature than CRP does. Indeed, researchers have discovered an elevation in plasma levels of PTX3 in individuals who had been diagnosed with acute myocardial infarction (AMI) [12]. In addition, several research organizations have recently released studies that reveal higher levels of plasma PTX3 in individuals suffering from a variety of cardiovascular illnesses [13,14].

The aim of study is to discern whether plasma PTX3 levels may serve as a potential biomarker for hypothyroidism. However, there is currently a lack of data regarding plasma PTX3 levels in large healthy populations.

MATERIALS AND METHODS

This was case-control study design that took place at Al-Hakim Teaching Hospital in Najaf, Iraq, between October 2022 and February 2023. Hormonal parameters were measured and recorded with anthropometric data such as age, sex, weight, height and body mass index (BMI). 90 subjects between the ages of 20 and 50 participated in the research. Thirty people were classified as having overt hypothyroidism (OH) patients (20 females: 10 males), thirty as having subclinical hypothyroidism (SCH) patients (19 females: 11 males) and 30 were used as a control group of healthy (17 females: 13 males) individuals. Patients with elevated TSH>4.5 μIU/mL and normal T4 and T3 values were classified as having subclinical hypothyroidism, whereas those with elevated TSH>10 μIU/mL and low T4 and T3 values were classified as having overt hypothyroidism. Patients were excluded if they had thyroidectomy, cancer, anemia, or any other clear systemic disease or chronic illness, or were taking any medication that may influence lipid metabolism.

The body mass index (BMI) of the study participants was determined by taking their weight in kilograms and dividing it by their height in meters squared:

$$BMI = weight/height^2 \ (kg \cdot m^{-2}) \qquad [15].$$

After subjects fasted for 12 hours, venipuncture samples were taken. Serum was extracted by centrifugation at 3000 Xg for 15 minutes. Serum levels of Thyroid stimulating hormone (TTSH), Triiodothyronine (TT3), Thyroxin (TT4), PTX3, and fasting insulin (FIN) were measured using enzyme-linked immune sorbent assay (ELISA) KITS (Melsin Medical Company, China). Quantitative results were established by applying the colorimetric approach. High density lipoprotein cholesterol (HDL), total cholesterol (TC), and triglyceride (TG) levels were established by way of kits from BIOLABO (France) Homeostatic model assessment-insulin resistance (HOMA-IR) index was calculated as:

$$HOMA/IR = glucose\ (mg/dL) \cdot insulin\ (U/mL)/405$$

$$HOMA\beta = 360\ insulin/(Glucose - 63) \qquad [16].$$

Low density lipoprotein cholesterol (LDL-C) and (VLDL-C) were measured by the indirect method, using Friedewald's equation [17].

STATISTICAL ANALYSIS

In order to determine whether or not there were differences between the research variables, the Kruskal-Wallis test was run via the SPSS v.27 software program (SPSS Inc., Chicago, Illinois, United States). The link between analyte levels within each research group was analyzed using Pearson's correlation coefficient, which was applied to assess the association between the two variables. In addition, receiver operating characteristic (ROC) curves were created using the MedCalc program in order to evaluate the efficacy of biomarkers in the diagnosis and prognosis of hypothyroidism. As a means of evaluating the reliability of the test, the area under the curve (AUC) was computed. The threshold for statistical significance was established at P less than 0.05 and P less than 0.01, which indicates that differences with a probability of less than 5% or 1% were deemed to be statistically significant.

RESULTS AND DISCUSSION

The baseline characteristics of the study are shown in Table 1, which contains a data comparison between OH group patients, SCH group patients, and healthy controls (HC) group. There were no statistically significant differences in age or sex between the groups. In contrast to the healthy control group, patients with hypothyroidism groups exhibited substantially higher mean levels of FSG, insulin, BMI, serum TSH, TG, TC, VLDL-C, LDL-C, PTX3, FIN and HOMA/IR. The only group where the HOMAβ did not vary significantly from the healthy control group was the one with subclinical hypothyroidism. In addition, the mean

levels of blood T3, T4, TG, TC, and PTX3 were all greater in the overt hypothyroidism group than in the subclinical hypothyroidism group.

Table 1. Clinical characteristics of participants with and without Hypothyroidism

Parameters	Control (n=30)	Patients (n=60)		p value
		SCH (n=30)	OH (n=30)	
Sex (Fe/M)	17/13	19/11	20/10	--
Age (Years)	36.50 ±7.09	39.50 ±9.41	39.75 ±10.57	0.207a 0.172b 0.0016c
BMI(Kg/m2)	27.08 ±4.46	30.86 ±5.39	33.31 ±7.81	0.018a 0.001b 0.120c
TT3 (ng/mL)	2.13 ±0.56	1.85 ±0.39	1.43 ±0.74	0.068a 0.001b 0.007c
TT4 (ng/mL)	101.78 ±9.58	92.91 ±19.99	69.79 ±26.59	0.089a 0.001b 0.001c
TSH (µIU/mL)	2.95 ±0.90	8.47 ±3.62	19.19 ±15.69	0.024a 0.001b 0.001c
T-CHO (mg/dL)	171.90 ±14.32	183.30 ±23.31	195.87 ±24.79	0.041a 0.001b 0.025c
TG (mg/dL)	101.90 ±12.06	156.80 ±40.48	180.84 ±54.27	0.001a 0.001b 0.023c
HDL-C (mg/dL)	38.37 ±3.00	21.17 ±4.34	21.07 ±4.78	0.001a 0.001b 0.925c
VLDL-C (mg/dL)	20.38 ±2.41	31.36 ±8.10	36.12 ±10.85	0.001a 0.001b 0.023c
LDL-C (mg/dL)	113.15 ±13.90	130.77 ±21.70	138.68 ±19.98	0.001a 0.001b 0.107c
FSG (mg/dL)	87.85 ±2.70	104.91 ±9.30	110.10 ±9.71	0.001a 0.001b 0.129c
FIN (µU/mL)	7.15 ±0.90	12.00 ±1.95	13.30 ±1.64	0.001a 0.001b 0.060c
HOMA/IR	1.53 ±0.23	3.13 ±0.69	3.63 ±0.67	0.001a 0.001b 0.046c
HOMA/β	66.18 ±8.33	61.99 ±6.64	49.75 ±6.50	0.188a 0.001b 0.001c
PTX3 (ng/ml)	0.11 ±0.08	0.30 ±0.18	0.98 ±0.4	0.067a 0.001b 0.001c

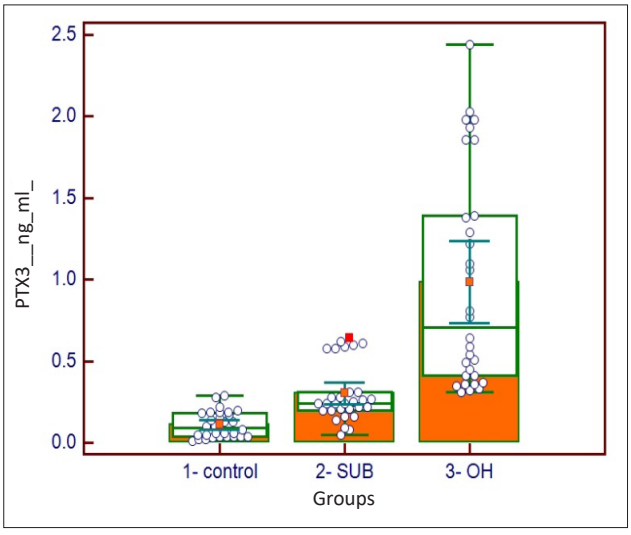


Figure 1. Comparison of serum PTX3 in OH, SCH and Control groups

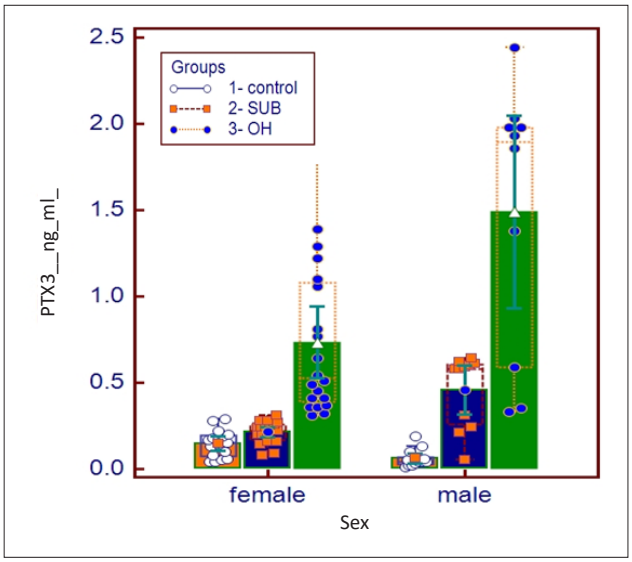


Figure 2. Comparison of serum level of PTX3 in male and female OH, SCH and HC groups

The correlation analysis is as shown in Table 2. Accordingly, the serum level of PTX3 in the SCH patient group has a positive significant correlation with TG, VLDL-C and LDL-C, while serum level of TT3 and TT4 display a negative significant correlation with PTX3 in this patient group.

Table 2. Correlation analysis of serum PTX3 level with biochemical parameters in the enrolled patients of the SCH group

Parameters	Pearson's Correlation (r)	P value
Age (years)	0.15	0.42
BMI (kg/m²)	0.10	0.60
TSH(µIU/mL)	0.10	0.61
TT3(ng/mL)	-0.520**	0.00
TT4(ng/mL)	-0.31	0.04
T-CHO (mg/dL)	0.379*	0.03
TG (mg/dL)	0.20	0.05
HDL-C (mg/dL)	-0.01	0.96
VLDL-C(mg/dL)	0.20	0.05
LDL-C(mg/dL)	0.364*	0.03
FSG (mg/dL)	0.15	0.43
FIN (µU/mL)	0.05	0.78
HOMA/IR	0.10	0.59
HOMA/β	-0.06	0.75

As evident in Table 3, the serum level of the PTX3 OH patient group has a significant negative correlation with TT3, TT4 and HOMA/β, while holding an appositive significant correlation with age, BMI, TC, TG, LDL-C, VLDL-C, FIN and HOMA/IR levels in OH group patients.

Table 3. Correlation analysis of serum PTX3 level with the investigated biochemical parameters in the enrolled patients of the OH group

Parameters	Pearson's Correlation (r)	P value
Age (Years)	0.331	0.031
BMI (Kg/m²)	0.310	0.033
TSH(μIU/mL)	0.082	0.668
TT3(ng/mL)	-0.569**	0.001
TT4(ng/mL)	-0.512**	0.004
T-CHO (mg/dL)	0.501**	0.005
TG (mg/dL)	0.406*	0.026
HDL-C (mg/dL)	-0.165	0.385
VLDL-C(mg/dL)	0.406*	0.026
LDL-C(mg/dL)	0.441*	0.015
FSG (mg/dL)	0.001	0.997
FIN (μU/mL)	0.217	0.050
HOMA/IR	0.276	0.051
HOMA/β	0.216	0.050

Table 4 and Figure 3 reveal the statistical results of the Receiver Operating Characteristic (ROC) analysis for the biomarker PTX3. The ROC curve for PTX3 shows a Cut-off value in the SCH group at >0.19, AUC at 0.892, Sensitivity at 80.0, Specificity at 90.0 and P-value at 0.001.

Table 4. Statistics output of ROC analysis of Markers between healthy and Sub clinical Hypothyroidism patients

Variables	PTX3
Area Under Curve (AUC)	0.892
P-value	<0.001
Cut-off value	>0.19
Sensitivity	80.0
Specificity	90.0

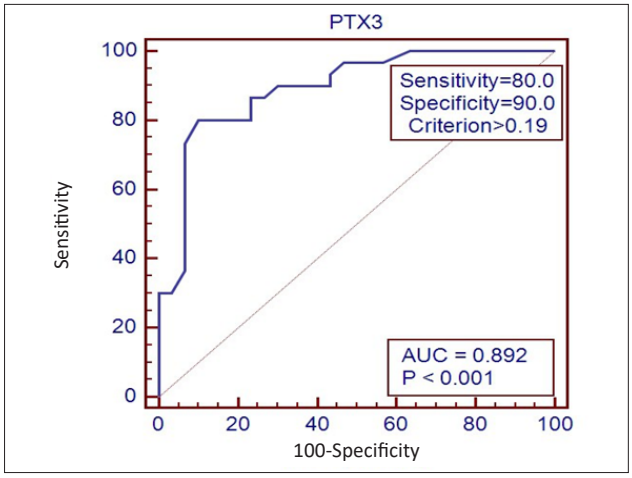


Figure 3. The ROC curve of PTX3 between healthy control group and SCH patients

Table 5 and Figure 4 show the statistical results of the Receiver Operating Characteristic (ROC) analysis for the biomarker PTX3. The ROC curve for PTX3 displays a Cut-off value in the OH group at >0.2, AUC at 0.997, Sensitivity at 100, Specificity at 93.3 and P-value at 0.001.

Table 5. Statistics output of ROC analysis of Markers between healthy and Overt Hypothyroidism patients

Variables	PTX3
Area Under Curve (AUC)	0.997
P-value	<0.001
Cut-off value	>0.2
Sensitivity	100
Specificity	93.3
Accuracy (Youden Index)	0.933
Positive Predictive Value (PPV)	93.721
Negative Predictive Value (NPV)	100.00

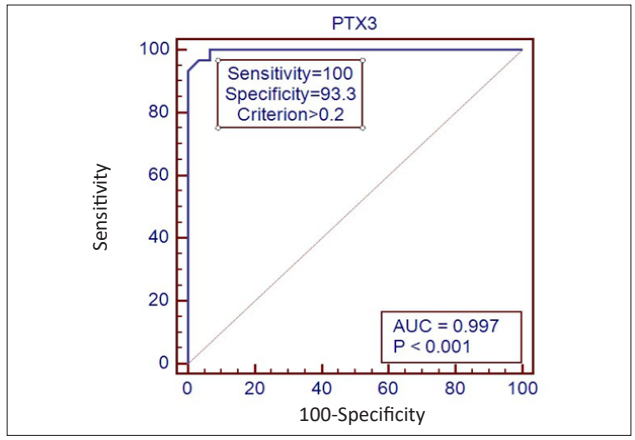


Figure 4. The ROC curve of PTX3 between the healthy control group and OH patient groups

To our knowledge, this is the first study to evaluate the association between PTX3 and thyroid dysfunction. Here, we we found PTX3 to be significantly enhanced in the OH and SCH groups compared to HC groups. In addition, we observed that serum PTX3 level was increased in the OH patients group in direct proportion to the increased severity of hypothyroidism (with increased TSH and decreased TT4. Also, serum PTX3 levels were independently associated with TT3and TT4 and lipid profiles (TG, TC, VLDL-C) and insulin resistance in the overt hypothyroidism patients group. A similar trend was seen in PTX3 levels and incidences of metabolic diseases [18-21].

Hypothyroidism is characterized by insufficient production of thyroid hormone by the thyroid gland. A sluggish metabolism causes a host of unpleasant side effects, including lethargy, weight gain, constipation, dry skin and an overall diminished capacity to generate heat. Hypothyroidism is more prevalent in the elderly and more frequent in women than in males. Still, it is not picky about age and may strike anybody at any time. Hashimoto's thyroiditis, an autoimmune illness, is the most prevalent cause of hypothyroidism; however, thyroid surgery, radiation treatment, and certain medications can contribute to the condition [22].

Thyroid dysfunction may be characterized by a wide range of non-specific symptoms, and the diagnosis of this condition is mostly predicated on the identification of anomalies in biochemical processes. The thyroid hormones thyroxin (T4) and tri-iodothyronine (T3) have a complicated inverse association with the pituitary hormone thyrotropin (TSH), which is also known as thyrotropin [23]. TSH levels are the most sensitive indication of thyroid health

in a person because there is a negative feedback process between TSH and thyroid hormones [24].

If an individual has high TSH levels and low free T4 levels, they are diagnosed with overt hypothyroidism. If TSH levels are high, but circulating T4 levels are normal, it is considered subclinical hypothyroidism [25]. Thyroid hormones are known to impact carbohydrate metabolism, leading to insulin resistance (IR). Both hyperthyroidism and hypothyroidism can cause this effect [26]. Hypothyroidism, whether subclinical or overt, has been linked to an increased risk of coronary artery disease. This is thought to be due to the effects of low thyroid hormone levels on lipid metabolism and vascular function [27]. Insulin resistance is a condition related to glucose regulation, in which the response of the liver, muscle, adipose tissue, and other body tissues to insulin is less than what is expected [28].

Detecting and mitigating insulin resistance (IR) early is crucial as it is a significant and initial causative mechanism for cardio metabolic diseases, and early detection and intervention have a vast potential to reduce the disease burden [29]. The study showed that individuals with subclinical hypothyroidism (SCH) and overt hypothyroidism (OH) have elevated serum insulin levels compared to healthy individuals. Insulin resistance, characterized by impaired response of cells to insulin, is a risk factor for diabetes and cardiovascular diseases. The observation of increased insulin resistance index in hypothyroid patients is significant as it indicates a higher risk for developing diabetes and metabolic syndrome in these individuals [30].

Prior study by Yamasaki et al. demonstrates that the serum level of PTX3 is a useful biomarker of innate immunity and systemic inflammation, and it is known to be synthesized and stored in the vasculature. In response to inflammatory stimuli mediated by cytokines, it is rapidly released. The expression of PTX3 may have a role in local inflammatory reactions and the innate immune response [31].

A study by Rafagat et al. revealed that serum PTX3 is a marker that connects inflammation with cardiovascular disease (CVD) since it is secreted by cell compartments involved in the initiation and development of CVD. Its high levels in elderly individuals with hypertension can predict frailty due to its role in causing vascular damage. Circulating PTX3 quantity increases in clinical disorders affecting the cardiovascular system [21].

PTX3 is an innate immune system soluble pattern recognition receptor that regulates tissue homeostasis [20]. PTX3 has been studied as a possible biomarker for a variety of illnesses, including sepsis, small-vessel vasculitis and acute myocardial infarction [19]. PTX3 may also act as an early measure of illness severity and prognosis in sepsis. Furthermore, PTX3 levels are higher in systemic inflammatory patients and have been suggested to act as a sensitive measure of vascular inflammation as part of the innate immune system [19]. The humoral soluble pattern recognition molecule known as PTX3 is an extremely important component of the innate immune response and inflammation, as well as tissue damage and remodeling. Moreover, recent research has indicated that PTX3 has a role in the pathophysiology of a number of different autoimmune disorders [32].

The circulating of PTX3 is an important component of the innate immune system, and its synthesis as an acute-phase protein is essential for the body's homeostatic responses to tissue damage and inflammation. Its multiple roles include orchestrating leukocyte recruitment and trafficking, promoting clearance of dying cells and autoantigens, and protecting the vasculature. Its actions are necessary for the resolution of inflammation and tissue repair [33]. In diseases where inflammation does not resolve, PTX3 continues to be produced and serves as a valuable biomarker for patient stratification and predicting clinical outcomes. Understanding the mechanisms of PTX3's homeostatic role may lead to novel therapies for regulating leukocyte migration and the resolution of inflammatory processes [20]. PTX3 has been found to have a dual role in oncogenesis, both promoting and inhibiting tumor growth depending on the context. Its ability to modulate the immune response and interact with the extracellular matrix have been suggested as key mechanisms underlying its involvement in cancer biology [18].

CONCLUSION

We concluded that there are significant higher level of PTX3 in patients with overt and subclinical hypothyroidism than in the healthy control. Thus, PTX3 may be relatively independent marker for prognosis of subclinical to overt cases or to metabolic complications in hypothyroidism patients as a potential risk factor for this disease.

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DECLARATION OF INTEREST

The authors certify that they do not have any conflicting interests.

ETHICAL CLEARANCE

All participants (both controls and patients) or their parents or legal guardians gave written informed permission in accordance with the most stringent ethical requirements. All local, national, and international ethical and privacy regulations were followed, and the research was approved by the institutional ethics board at the University of Kufa (1311/2023). The Declaration of Helsinki of the World Medical Association, the Belmont Report, the CIOMS Guideline, and the International Conference for Harmonization of Good Clinical Practice are all examples of such regulations. In addition, the ICH-GCP (International Council for Harmonization Good Clinical Practice) standards for human research safety are adhered to by our institutional review board.

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