ZANCO Journal of Pure and Applied Sciences
The official scientific journal of Salahaddin University-Erbil
https://zancojournals.su.edu.krd/index.php/JPAS

ISSN (print):2218-0230**, ISSN (online):** 2412-3986**, DOI: http://dx.doi.org/10.21271/zjpas**

RESEARCH PAPER

Association between HOMA-IR with ketoacidosis and lipid profile markers in diabetic nephropathy patients

Zrar Saleem Kareem Almarzany
Department of Biology, Faculty of Science and Health, Koya University Koya KOY45, Kurdistan Region – F.R. Iraq

A B S T R A C T:

The study designed to study the relationship between the homeostatic model assessment of insulin resistance (HOMA-IR) with ketoacidosis markers and hyperlipidemia in patients with non-insulin-dependent diabetes mellitus (NIDDM) and chronic kidney disease at end-stage renal disease (ESRD). Disturbance of the mechanisms which maintain normal blood pH and lipid profiles is a defining feature of chronic metabolic diseases such as diabetes and kidney failure. The present research included 90 patients and 30 healthy subjects. Serum insulin, fasting blood sugar (FBS), glycated hemoglobin % (HbA1c %) and HOMA-IR levels, lipid profile parameters and ketoacidosis markers were estimated in all groups. Statistical analysis showed that high HOMA-IR was significantly associated with lipid profiles and ketoacidosis markers in patients' groups when compared with control. Receiver operating characteristic (ROC) curve analysis investigated HOMA-IR as a significant risk factor for diabetic nephropathy (DN) in ESRD patients. The present finding regarding ROC curve analysis observed that IR is dependently associated with ketoacidosis and lipid profile abnormalities in NIDDM, ESRD and DN patients. Also, the study suggested HOMA-IR as a consequence and risk factor in DN at ESRD.

Keywords:

KEY WORDS: Insulin resistance, ketoacidosis, hyperlipidemia, NIDDM, ESRD, Diabetic nephropathy.
DOI: http://dx.doi.org/10.21271/ZJPAS.33.2.6
ZJPAS (2021) , 33(2);59-66 .

1. INTRODUCTION

NIDDM is the most common form of diabetes in which the primary problem is due to insulin resistance (Shekhane and Muslih, 2019). T2DM can damage kidneys by hyperglycemia that makes the kidneys filter blood hardly resulting in diabetic nephropathy (DN), (Zhou *et al.*, 2015). The pathophysiology of DN is difficult and incompletely understood. Whereas hyperglycemia is clearly essential, the role of IR is increasingly recognized (Filippone *et al.*, 2014).

* **Corresponding Author:**
Zrar Saleem Kareem Almarzany
E-mail: zrar.saleem@koyauniversity.org
Article History:
Received: 06/10/2020
Accepted: 29/11/2020
Published: 18/04 /2021

focused on IR which is presented in chronic renal failure and recent evidence proposes the presence of IR in the early renal disease stages. DN patients have increased cardiovascular mortality rates due to the IR which is proposed as a contributing factor, this is emphasizes the importance of IR mechanisms on DN (Schrauben *et al.*, 2019). However, the precise mechanisms of IR on the lipids profile and ketoacidosis markers remains poorly understood. Till now it is unclear if IR alone contributes to an elevated risk of essential clinical outcomes in kidney failure (Shang *et al.*, 2019). The study aimed to study the association between IR and DN and to investigate the potential mechanisms linking IR with lipid profile and ketoacidosis markers.

MATERIAL AND METHOD

The study included 120 age and sex-

matched persons and classified into the following groups: Group 1 (control group): This group included 30 healthy persons (16 males and 14 females) whose mean age range in years (50.40 ± 5.1). Group 2 (NIDDM): This group included 30 patients with T2DM under medical treatment and have normal GFR level (15 males and 15 females) with ages range in years (55.5 ± 4.82). Group 3 (ESRD patients): 30 patients with end-stage renal disease (17 males and 13 females) under medical treatment and hemodialysis (twice a week with 3 hours dialysis every time) with mean age ranged in years (50.70 ± 2.27 years). Group 4 (NIDDM+ ESRD): 40 patients with diabetic nephropathy at ESRD (14 males and 16 females) under medical and on hemodialysis treatment with their mean age range in years (53.90 ± 4.75). All the studied groups had normal CRP level and were subjected to personal interview through a specifically designed questionnaire form. Standard current criteria were applied for the diagnosis of T2DM in differentiating the diabetic types.

Blood samples were obtained after overnight fasting. Samples of venous blood (3 ml) were collected by sterile disposable syringes and transferred into a disposable plastic test tube. Serum was separated by the centrifugation at (1000g for 15 minutes). The separated serum was investigated for serum glycated hemoglobin (HbA1c), fasting blood glucose (FBS), (Majeed *et al.*, 2019), Lipid profile parameters included (total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG)), ketoacidosis markers included (pH, amylase, ketones, HCO3, anion gap, osmolality) by using the biochemical KENZA analyzer diagnostic kit (4 KENZA 240TX /Hitachi-USA) with a full automated biochemical analyzer, French. Insulin resistance (IR) was calculated by the homeostatic model assessment of IR (HOMA-IR) formula.

$$\mathbf{HOMA-IR} = (\mathbf{fasting\ serum\ glucose} \times \mathbf{fasting\ serum\ insulin})/\mathbf{22.5}$$

Consideration of Ethics and written informed consent

Approval of the study was obtained from Koya University/Faculty of science and health/ Department of Biology, office of the Academic Ethical Committee with ethics study number (49). All patients had signed informed written consent as an acceptance for the study project.

RESULTS

Table (1) showed that serum insulin levels were markedly elevated (P<0.001) in all groups when related to the control group. There was a significant increase (P<0.001) in serum insulin of the group of NIDDM+ESRD when related to the group of ESRD. While serum insulin level in ESRD was markedly low (P<0.001) when compared with NIDDM. The serum level of FBS was markedly increased at (P<0.001) in all groups when correlated with the control subjects. The FBS was elevated in a significant way at (P<0.001) group of NIDDM+ESRD when related to both ESRD and NIDDM groups. FBS level in ESRD was significantly (P<0.001) low when compared with NIDDM. Statistical analysis revealed significant elevation in HbA1c % at (P<0.001) in groups of NIDDM and NIDDM+ESRD in relation with the control group. There was a significant increase (P<0.001) in HbA1c % in group of NIDDM+ESRD when related to ESRD group. Also HbA1c level was highly significantly at (P<0.001) in the group of NIDDM when compared with the ESRD group. HOMA-IR significantly elevated at (P<0.001) in groups of NIDDM, ESRD and NIDDM+ESRD in relation to the group of control. HOMA-IR was significantly high (P<0.001) in NIDDM+ESRD when compared with both ESRD and NIDDM groups. Also, HOMA-IR of NIDDM was significantly increased at (P<0.001) when compared with ESRD (P<0.001).

Some biochemical parameters related to ketoacidosis markers in the present study revealed that pH did not change in groups of NIDDM, ESRD and NIDDM+ESRD when correlated with the control group. Anion gap was markedly elevated at (P<0.001) in groups of NIDDM, ESRD and NIDDM+ESRD as correlated with the control group. In NIDDM+ESRD anion gap was elevated at level (P<0.01) in comparison with NIDDM group. Serum HCO3 level was markedly decreased at (P<0.001) in NIDDM, ESRD and NIDDM+ESRD groups when compared with the control. HCO_3 was markedly decreased at (P<0.001) in NIDDM and ESRD groups when compared with the NIDDM+ESRD group. Osmolality in serum was markedly decreased in NIDDM group (P<0.001) and NIDDM+ESRD

group at (P<0.01) when correlated with the control group. There was a significant elevation at (P<0.001) in the osmolality of group of ESRD in comparison to NIDDM+ESRD groups at (P<0.001). Furthermore, osmolality of ESRD group showed significant elevation at (P<0.001) in relation to NIDDM group. Ketonemia was significantly increased in NIDDM, ESRD and NIDDM+ESRD subjects at (P<0.001) when compared with the control subjects. Ketonemia was markedly decreased in groups of NIDDM and ESRD at (P<0.001) when compared with the NIDDM+ESRD group.

Lipid profile tests observed a marked increase in TC level in NIDDM (P<0.01), ESRD (P<0.01) and NIDDM+ESRD at (P<0.001) when compared with the control group. The serum level of TG was markedly elevated in groups of NIDDM, ESRD and NIDDM+ESRD at (P<0.001) when correlated with the control group. TG was slightly low in the group of NIDDM at (P<0.05) as compared with the NIDDM+ESRD group. The level of HDL was low in groups of NIDDM (P<0. 05), ESRD (P<0.001) and NIDDM+ESRD at (P<0.001) in comparison with control group. HDL was high in NIDDM group at (P<0.001) when compared with the group of NIDDM+ESRD. Also a significant increase at (P<0.001) in HDL was shown in NIDDM group when compared with group of ESRD. Serum LDL level was significantly increased at (P<0.001) in NIDDM, ESRD and NIDDM+ESRD when compared with control group.

Receiver characteristics curve for HOMA-IR in the studied patient groups

Biomarkers and risk factors for NIDDM, ESRD and NIDDM+ESRD, were performed by ROC curves. ROC for HOMA-IR as shown in figure (1) was (1.000, 0.981 and 1.000) at (P<0.001) respectively, in groups of NIDDM, ESRD and NIDDM+ESRD. The result indicated HOMA-IR as a major marker for diabetic nephropathy.

Correlation between HOMA-IR with pH, anion gap, HCO3, osmolality and ketonemia in NIDDM group, ESRD group and NIDDM+ESRD group

Pearson's correlation analysis as observed in table (2) for NIDDM group, showed that HOMA-IR significantly correlated with anion gap (r= -0.599, p= 0.001), HCO3 (r=0.696, p= 0.001), Ketonemia (r=-0.437, p= 0.001), Osmolality (r= 0.475, p= 0.001) and pH (r=0.522, p=0.001). In ESRD group, HOMA-IR significantly correlated with anion gap (r= 0.509, p= 0.001), HCO3 (r=-0.669, p= 0.001), Ketonemia (r=0.448, p= 0.001), Osmolality (r= 0.156, p= NS) and pH (r=--0.601, p=0.001). In DN at ESRD group, HOMA-IR significantly correlated with anion gap (r= -0.712, p= 0.001). HCO3 (r=0.811, p= 0.001), Ketonemia (r= -0.730, p= 0.001), Osmolality (r= 0.290, p= 0.005) and pH (r=0.779, p=0.001).

Correlation analysis in table (3) in NIDDM group indicated that HOMA-IR significantly correlated with TG at (r= -0.400, p=0.001), Cholesterol at (r= -0.411, p=0.001), HDL at (r= 239, p=0.02) and LDL at (r= -0.700, p=0.001). ESRD group showed significant correlation between HOMA-IR with TG at (r= 0.672, p=0.001), Cholesterol at (r= 0.465, p=0.001). HDL at (r= -0.527, p=0.001) and LDL at (r= -0.464, p=0.001). Furthermore, NIDDM+ESRD group, showed that HOMA-IR significantly correlated with TG at (r= -0.599, p=0.001), Cholesterol at (r= -0.311, p=0.002), HDL at (r= 0.567, p=0.001) and LDL at (r= -0.770, p=0.001).

Table (1): Mean values (Mean ± S.E) of some assayed biochemical parameters for control group and patients in groups of NIDDM, ESRD and diabetic nephropathy

Parameters	Control N=30	NIDDM N=30	ESRD N=30	NIDDM+ESRD N=30
insulin (pmol/L)	10.000 ± 1.362	39.150±1.000 *** +++	26.750±2.014 *** ###	48.217 ± 1.018 ***
FBS (mg/dl)	118.010±4.031	257.530±7.730 *** ### +++	130.140±5.110 *** ###	294.340 ±4.111 ***

HbA1C (%)	5.850±0.260	7.900±0.180 *** +++	6.583±0.237 ###	8.000±0.258 ***
HOMA-IR	0.91±0.250	3.741±0.291 *** ### +++	1.999±1.051 * ###	5.359±1.090 ***
Blood pH	7.394 ± 0.006	7.265 ± 0.005	7.298 ± 0.004	7.260 ± 0.003
Anion gap (mmol/L)	17.29 ± 0.581	30.920 ± 1.118 *** ##	33.380 ± 1.630 ***	37.020 ± 1.230 ***
HCO_3 mmol/L)	23.090 ± 0.262	15.230 ± 0.205 *** ###	14.760±0.224 *** ###	13.200 ± 0.190 ***
Osmolality(mOsmol/Kg)	292.0 ± 1.024	269.6 ± 2.565 *** +++	295.8±5.585 ###	273.4 ± 5.094 **
Ketonemia(mmol/L)	0.419 ± 0.020	1.530 ± 0.140 *** ###	1.563±1.182 *** ###	2.466 ± 0.112 ***
TC (mg/dl)	178.800±1.637	238.800±10.190 **	241.300±10.990 **	253.9 ± 15.100 ***
TG (mg/dl)	127.800±7.000	281.000 ± 27.640 *** #	322.600 ± 8.372 ***	359.500 ± 16.420 ***
HDL-C (mg/dl)	57.410 ± 2.200	48.610 ± 2.273 * ### +++	30.690 ± 0.953 ***	37.150 ± 2.024 ***
LDL-C (mg/dl)	76.600 ± 4.258	172.600 ± 3.416 ***	175.200 ± 4.208 ***	174.300 ± 3.690 ***

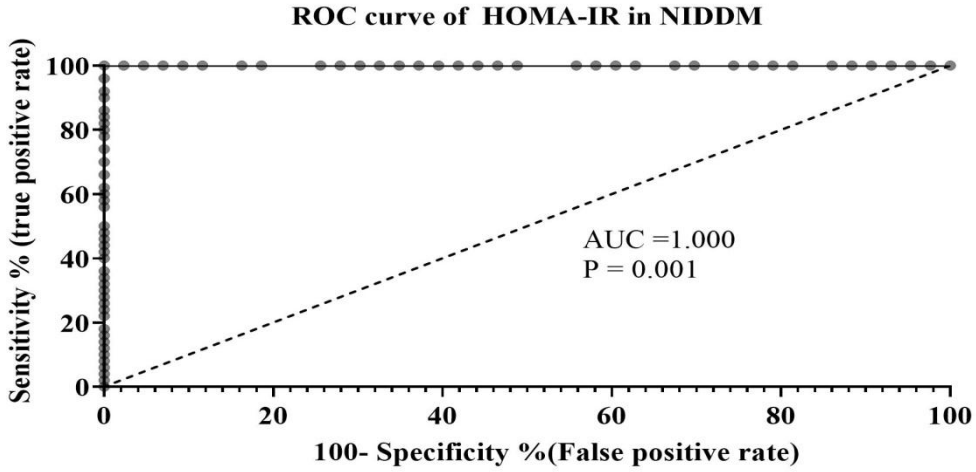
Statistical changes between groups of NIDDM, ESRD and NIDDM+ESRD in comparison with control group is expressed with star (*) symbol (* P<0.001) while statistical changes between NIDDM+ESRD with NIDDM and ESRD groups are expressed as hash (#) symbol (# # #P<0.001), while statistical changes between NIDDM and ESRD subjects are shown with cross (+) symbol (+++ P<0.001).**

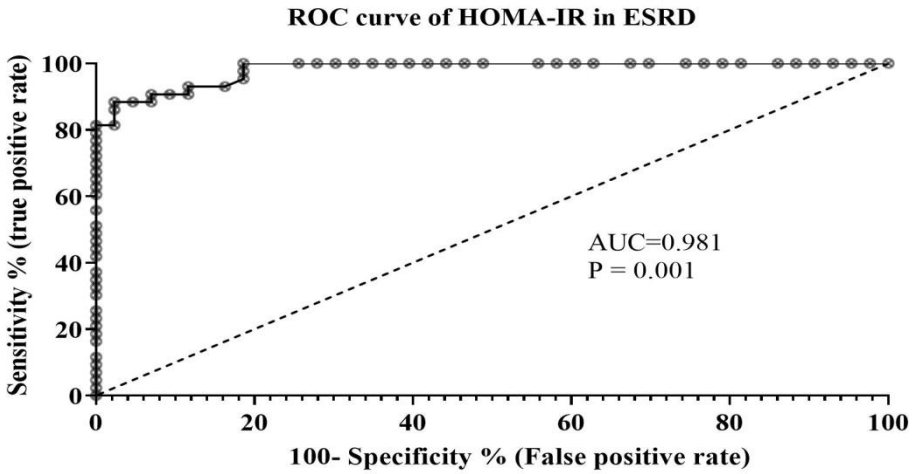
Table (2): Correlation between HOMA-IR with pH, anion gap, HCO3, osmolality and ketonemia in NIDDM group, ESRD group and NIDDM+ESRD group

Parameters		HOMA-IR (NIDDM)	HOMA-IR (ESRD)	HOMA-IR (NIDDM+ESRD)
Anion gap	**r**	-0.599	0.509	-0.712
	p	0.001	0.001	0.001
HCO3	**r**	0.696	-0.669	0.811
	p	0.001	0.001	0.001
Ketonemia	**r**	-0.437	0.448	-0.730
	p	0.001	0.001	0.001
Osmolality	**r**	0.475	0.156	0.290
	p	0.001	0.151	0.005
pH	**r**	0.522	-0.601	0.779
	p	0.001	0.001	0.001

Table (3): Correlation between HOMA-IR with cholesterol, TG, HDL, LDL in NIDDM group, ESRD group and NIDDM+ESRD group

Parameters		HOMA-IR (NIDDM)	HOMA-IR (ESRD)	HOMA-IR (NIDDM+ESRD)
TG	**r**	-0.400	0.672	-0.599
	p	0.001	0.001	0.001
Cholesterol	**r**	-0.411	0.465	-0.311
	p	0.001	0.001	0.002
HDL	**r**	0.239	-0.527	0.567
	p	0.021	0.001	0.001
LDL	**r**	-0.700	0.464	-0.770
	p	0.001	0.001	-0.599





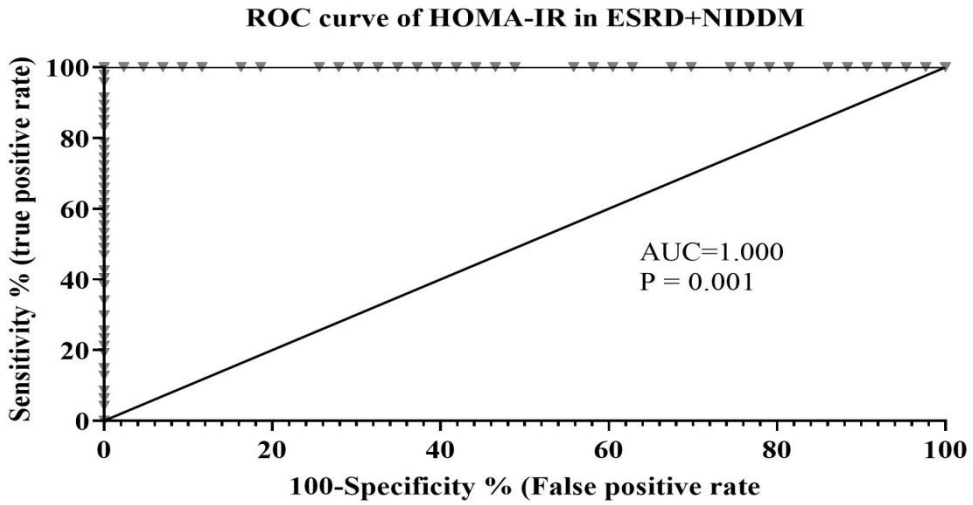


Figure (1): ROC curve shows the sensitivity and specificity of HOMA-IR in NIDDM groups, ESRD groups and NIDDM+ESRD groups.

DISCUSSION

Effects of HOMA-IR on Serum lipids markers in NIDDM, ESRD and NIDDM+ESRD groups

Serum lipids were significantly altered when compared with control. Serum lipids may be independent risk factors in both NIDDM and ESRD. Some previous studies results are inconsistent with the current result (Chen *et al.*, 2013) which revealed that component of metabolic syndrome like hypertriglyceridemia does not relate with serum lipoproteins and indicated them as an independent risk factor of developing metabolic syndrome.

However, there are few studies on the correlation of lipid profile levels in serum with IR in patients NIDDM and ESRD in the Kurdistan region. Therefore, the association of serum lipids and diabetic nephropathy requires to be explored more in our population. The major finding of this study was that high levels of cholesterol, TG, LDL with low HDL was correlated with increased risk of NIDDM and ESRD in both sex in accordance with Zhang *et al.,* (2014) study who showed that serum lipids and lipid ratios in both men and women were associated with CKD and diabetes.

Furthermore, several previous studies showed that high levels of cholesterol and triglyceride might play an essential role in the pathogenesis of diabetic nephropathy by preceding in the genesis of glomerulosclerosis (Chen *et al.*, 2013).

A study was done by Domingueti *et al.*, (2016) showed that LDL, TC, and TG-rich apoB- containing lipoproteins may relate to decreasing in kidney function in kidney failure at ESRD. Another potential confounder such as high serum glucose and insulin is presented. Low HDL level is another component of metabolic syndrome which was in accordance with results of Zhang *et al.*, (2014) study which stated that elevated metabolic syndrome components are related to CKD and diabetes. IR in DM patients and ESRD predict subsequent events of cardiovascular mortality which results from both environmental and genetic factors and contributes to type 2 diabetes mellitus and dyslipidemia (Bianchi *et al.*, 2016). Abnormalities of lipoprotein metabolism occur as a result of the apolipoproteins alterations, lipid transfer proteins, lipolytic enzymes, and receptors of lipoprotein from the early disease stages. However, recently, the main cause is due to the aggravate in IR which promotes atherogenic dyslipidemia (Mikolasevic *et al.,* 2017). The interaction between IR and triglyceride levels is bidirectional. Hypertriglyceridemia and increased free fatty acids contribute to IR, but the relative contribution is not known till now (Guthoff *et al.*, 2017).

Effects of HOMA-IR on metabolic ketoacidosis markers in NIDDM, ESRD and NIDDM+ESRD groups

Ketoacidosis results from rapid changes in blood glucose and insulin responsiveness which alter serum tonicity and osmolality. Variations in insulin kinetics in patients with NIDDM and ESRD present researchers with an additional challenge determining the mechanism of IR outcomes of patients with ESRD and those without significant kidney disease (Rosenstock and Ferrannini, 2015).

IR inhibits the ability of glucose to enter cells, the result becomes an increased reliance on fat oxidation for energy production. Blood will turn to an acidic medium since hyperketonemia causes accumulation of glucose in the blood and urine. Although diabetic ketoacidosis occurs mainly in patients with type 1 diabetes, it is not surprising in some patients with NIDDM which was in accordance with (Yu *et al.*, 2018 and Mottalib *et al.,* 2019). The current study showed that metabolic acidosis is another consequence in NIDDM and ESRD that has been associated with the development of IR. The main cause is the disability to excrete acid and production of excess acid in the setting of progression of IR in NIDDM and chronic renal failure (Chen and Abramowitz, 2014 and Dobre *et al.*, 2015).

Furthermore, acidosis with an increased anion gap observed in all studied groups of both NIDDM and ESRD in agreement with studies of Chen and Abramowitz, (2014) and Schaapveld-Davis *et al.*, (2017). Anion gap elevation is related to low serum bicarbonate. Some factors have been supposed to affect metabolic acidosis which progress diabetes and kidney disease such as activation of ammonia-induced complement, increased endothelin (ET) and aldosterone production due to IR (Chen and Abramowitz, 2014). Some researchers proposed that ammonia reacted biochemically in order to activate the alternative complement pathway. Therefore, progressive kidney injury could further instigate

the compensatory elevation in single-nephron ammonia genesis which was observed in diabetes and ESRD (Schaapveld-Davis *et al.*, 2017).

Elevated aldosterone can also act to decrease GFR caused by acidosis, by its pro-fibrotic and hemodynamic mechanisms. Aldosterone mediates increased acidification of distal nephron in the metabolic acidosis setting, and kidney disease prevention with alkali in the rat remnant kidney model which was related to decreased aldosterone production in kidney cortex (Schembolan *et al.*, 2011).

Conclusion

Lipid profile and ketoacidosis markers showed significant correlation with the studied HOMA-IR. Regarding ROC curve analysis, the result indicated HOMA-IR as an essential biomarker for diabetes and ESRD.

Ethical Requirements enforcement

- Declaration of the author that there are no potential conflicts of interest associated with this manuscript.
- The research involved human participants with informed consent.
- Informed consent: The respondents have received an informat ive consent form and the objective of the research was clarif ied to them.
- Ethical approval: All procedures undertake n in studies involving human subjects is in compliance with the ethical guidelines of t he institutional and/or national study com mittee at which the studies were conducted with IRB and Ethics Committee approval has been obtained.

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