



## Research Article

# The Role of GABA and Insulin Regulated Aminopeptidase on Insulin Resistance and GLUT4 in Prediabetes and Type 2 Diabetes Mellitus

Ismael Sadeq Khashan\*, Maysaa Jalal Majeed

Department of Biochemistry, College of Medicine, University of Baghdad, Baghdad, Iraq

\* Corresponding author's email: [Ismael.Sadek1109f@comed.uobaghdad.edu.iq](mailto:Ismael.Sadek1109f@comed.uobaghdad.edu.iq)

### ABSTRACT

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**Keywords:** gamma-aminobutyric acid, Insulin-regulated aminopeptidase, low glucose transporter protein-4, type 2 diabetes, insulin resistance



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**Background:** Different proposed mechanisms for insulin resistance have been put forth to understand the relationship and changes in insulin resistance. Looking at the levels of insulin, the neurotransmitter gamma-aminobutyric acid, glucose transport type 4, and the newly discovered enzyme insulin regulated aminopeptidase may provide an integrated perspective on insulin resistance.

**Objectives:** To study the role of serum gamma-aminobutyric acid and insulin regulated aminopeptidase enzyme levels in pathogenesis of insulin resistance and translocation of glucose transport type 4 in patients with type2 diabetes mellitus and pre-diabetes ones.

**Subjects and methods:** Ninety individuals were divided into three age- and BMI matched groups (diabetics, prediabetics, healthy) were assessed for glycated hemoglobin (turbidometry method), fasting serum glucose (colorimetric method), serum insulin (electrochemiluminescence immunoassay method), homeostatic model assessment for insulin resistance, serum gamma-aminobutyric acid, glucose transporter type 4, and insulin regulated aminopeptidase measured by the sandwich ELISA method. The cut-off value was adopted according to the World Health Organization, individuals with their fasting serum glucose lower than 110 mg/ml, and glycated hemoglobin level not more than 5.7 % are considered healthy individuals.

**Result:** The mean ( $\pm$ SD) values of serum insulin regulated aminopeptidase, gamma-aminobutyric acid and glucose transport type 4 showed significantly lower levels with greater increases in insulin resistance, represented by the significant decrease in diabetics group who have high insulin resistance compared with pre-diabetics and healthy individuals' groups ( $p < 0.05$ ). They also significantly decrease in individuals with the pre-diabetic stage compared to healthy individuals without insulin resistance ( $p < 0.05$ ). Significant negative correlations were found between HOMA-IR values and each of GABA, IRAP, and GLUT4.

**Conclusion:** Decreasing gamma-aminobutyric acid may promote insulin resistance and prediabetes/diabetes onset. Decreased insulin regulated aminopeptidase levels suggest a role alongside glucose transport type 4 in glucose uptake, allowing screening for prediabetes risk.

## Introduction

Diabetes mellitus (DM) is a chronic medical condition with elevated blood glucose levels. This is caused by insufficient insulin production or resistance to insulin, a hormone made by the pancreas (1,2). The World Health Organization (WHO) states that type 2 diabetes (T2DM) stems from improper insulin action in the body. Over 95% of diabetic cases are type 2 diabetes, which is mainly connected to obesity and sedentary lifestyle (3,4)

Pancreatic beta cells produce significant gamma-aminobutyric acid (3,4). In adults, GABA is an inhibitory neurotransmitter (7,8), but in developing brains, it promotes cell growth and maturation (9). In beta cells, GABA boosts insulin release (10), while alpha cells inhibit glucagon secretion (11-12).

Patients with T2DM often have low glucose transporter protein-4 (GLUT4), impairing glucose transport and causing insulin resistance (13). This impairment is linked to decreased translocation of GLUT4 to the cell membrane (14). Insulin-regulated aminopeptidase (IRAP) interacts with GLUT4. Insulin triggers the movement of both GLUT4 and IRAP to the cell surface. This facilitates glucose entry and cleaves off the extracellular portion of IRAP (IRAPe), discharging it into circulation. However, in T2DM, IRAP translocation is impaired, decreasing IRAPe cleavage. Thus, IRAP may contribute to insulin function and diabetes (15).

The present study aims to investigate the role of IRAPe and GABAs in insulin resistance in T2DM.

## Subjects and Methods

Ninety individuals aged more than 45 years and with a body mass index greater than 29.9 kg/m<sup>2</sup> were enrolled. They were grouped into three groups:

- The first group consisted of 30 type 2 diabetic patients diagnosed based on WHO standards (16) with diabetes duration more than 5 years (this was to ensure disease-related changes in the measured parameters would be apparent), irrespective of their HbA1c values.
- The second group contained 30 prediabetic individuals identified by WHO guidelines (16) matched by age and BMI to the diabetics.
- The third Group: Healthy individuals without insulin resistance, confirmed by measuring their serum insulin level, fasting glucose and blood HbA1c, were also selected to match the age and BMI of the other two groups.

Five milliliters of blood were drawn via vein puncture between 8:00 AM and 10:00 AM from each subject after an overnight fast of eight hours.

The gender distribution was matched among groups to exclude the effect of sex hormones. Exclusion criteria were patients with renal dysfunction, heart disease, hypertension, insulin dependence, hyperthyroidism, hypothyroidism, Cushing's disease, acromegaly, chronic liver disease, type 1 diabetes, and pregnant women.

The study was reviewed and granted ethical approval by the Scientific Committee of the Biochemistry Department at the College of Medicine, University of Baghdad, and the Ministry of Health (Iraq). The study was conducted from January 2022 to December 2022, and participants were recruited from the Diabetic and Endocrinology Center in Baghdad-Al-Rusafa. The clinical diagnosis

was depended to world health organization (WHO) criteria of type 2 diabetes (16).

Participants were required to complete questionnaires as a means of obtaining their consent for the study and to gather information from both healthy subjects and patient groups.

Fasting serum insulin was assessed using an automated Roche Cobas e411 immunoassay that operates on the electrochemiluminescence principle. Insulin resistance was estimated via the homeostatic model assessment of insulin resistance (HOMA-IR) index, calculated as (fasting serum insulin (μIU/mL) x fasting serum glucose (mg/dL))/405 (17).

Serum levels of insulin regulated aminopeptidase (IRAPe) were measured by a double antibody sandwich ELISA method using ELISA kits from ELK Biotechnology Co., Ltd.

Fasting serum glucose (FSG) and glycated hemoglobin (HbA1c) were quantitatively analyzed using the automated spectrophotometric analyzer Roche Cobas c111.

Statistical analysis was completed using SPSS version 20 and Minitab 18 (18). Continuous variables are presented as mean ± standard deviation. One-way ANOVA was used to compare between three group means. Post hoc analysis utilized Fisher's least significant difference test. Pearson's correlation coefficient (r) assessed associations between continuous variables. P values less than 0.05 were considered statistically significant.

## Results

There were non-significant differences in mean values of age and BMI among and between the study groups, indicating they were well matched for these characteristics, as shown by the non-significant p-values greater than 0.05.

As it was expected (when the groups were chosen) result of the diagnostic tests for insulin resistance: serum fasting glucose, blood HbA1c, serum insulin and HOMA-IR showed significant (p-value ≤0.05) differences among and within the groups which is deepened to the World Health Organization criteria (16). Table (1) shows the level of serum fasting glucose, serum insulin, blood HbA1c and HOMA-IR for each group.

Table 2 demonstrates the levels of serum IRAPe, GABA, and Glut4 were significantly decrease with a greater increase in insulin resistance, represented by the significant decrease in mean values of these parameters in diabetics who have high insulin resistance compared with prediabetics and healthy individuals (p-value < 0.05). The mean values of (IRAPe, GABA, and Glut4) levels also significantly decrease in individuals in the pre-diabetic stage compared to healthy individuals without insulin resistance (p < 0.05).

The levels of HOMA-IR showed significant negative correlations (p-value <0.05) with serum IRAP (r = -0.816, p < 0.0001), GABA (r = -0.696, p < 0.0001), and Glut4 (r = -0.745, p < 0.0001) respectively, at a high level of significance (P-value ≤ 0.0001), as shown in the figures 1, 2, and 3.

Table1: Mean ( $\pm$  SD) values of blood HbA1c, Fasting serum glucose, serum insulin and HOMA-IR in diabetes mellitus (DM), prediabetes and the healthy control group.

Parameter	Study group	No.	Mean $\pm$ SD	P value	LSD P-value
FBG (mg/dl)	Patients with diabetes type2 (a)	30	204.68 $\pm$ 42.33	0.000	*
	individuals with Pre-diabetes (b)	30	123.65 $\pm$ 3.09		**
	Healthy individuals (c)	30	89.8 $\pm$ 10.20		***
HbA1c%	Patients with diabetes type2 (a)	30	9.33 $\pm$ 1.33	0.000	*
	individuals with Pre-diabetes (b)	30	5.92 $\pm$ 0.18		**
	Healthy individuals (c)	30	4.76 $\pm$ 0.42		***
Insulin ( $\mu$ U/ml)	Patients with diabetes type2 (a)	30	21.02 $\pm$ 15.69	0.000	*
	individuals with Pre-diabetes (b)	30	18.38 $\pm$ 12.60		**
	Healthy individuals (c)	30	7.73 $\pm$ 3.62		***
HOM-IR	Patients with diabetes type2 (a)	30	10.81 $\pm$ 8.50	0.000	*
	individuals with Pre-diabetes (b)	30	5.61 $\pm$ 3.83		**
	Healthy individuals (c)	30	1.70 $\pm$ 0.77		***

\*Groups A vs B, \*\*A vs C, and \*\*\*B vs C show statistically significant differences ( $p \leq 0.05$ ).

Table 2 Mean ( $\pm$  SD) values of IRAPe, GABA and GLUT4 of subjects with diabetes mellitus (DM), prediabetes and the healthy group.

Parameter	Study group	No.	Mean $\pm$ SD	P value	LSD P-value
S. IRAP (ng/ml)	Patients with diabetes type2 (a)	30	0.46 $\pm$ 0.09	0.000	*
	individuals with Pre-diabetes (b)	30	0.55 $\pm$ 0.19		**
	Healthy individuals (c)	30	0.66 $\pm$ 0.16		***
S. GABA (pg/ml)	Patients with diabetes type2 (a)	30	40.93 $\pm$ 0.09	0.000	*
	individuals with Pre-diabetes (b)	30	69.83 $\pm$ 0.19		**
	Healthy individuals (c)	30	131.7 $\pm$ 57.4		***
S. GLUT4 (ng/ml)	Patients with diabetes type2 (a)	30	1.94 $\pm$ 0.32	0.000	*
	individuals with Pre-diabetes (b)	30	2.60 $\pm$ 1.54		**
	Healthy individuals (c)	30	4.37 $\pm$ 2.20		***

\*Groups A vs B, \*\*A vs C, and \*\*\*B vs C show statistically significant differences ( $p \leq 0.05$ ).

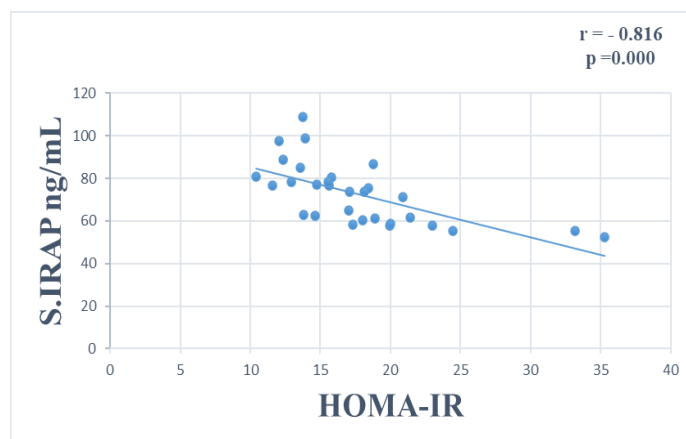


Figure 1: The Correlation between HOMA-IR with S. IRAP in T2DM Patient Groups.

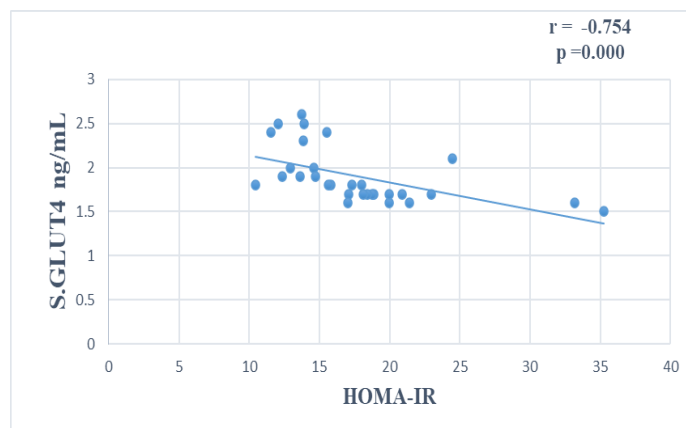


Figure 2: The Correlation between HOMA-IR with S. GLUT4 in T2DM Patient Groups.

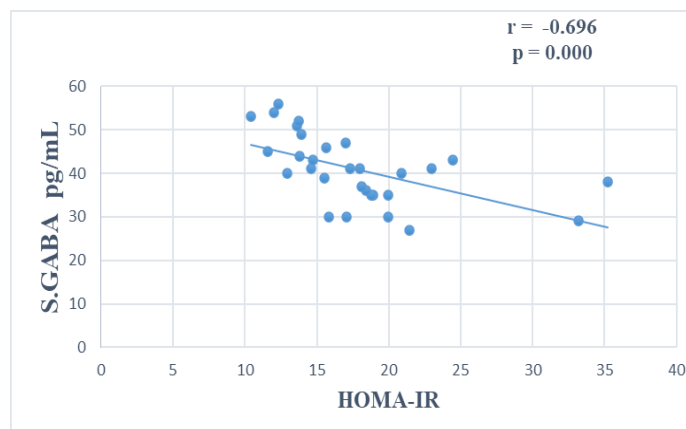


Figure 3: The Correlation between HOMA-IR with S. GABA in T2DM Patient Groups.

## Discussion

The control group was age-matched to the patients to preclude age as a confounding variable. The non-significant results for age suggest it did not substantially affect the outcomes related to insulin resistance and muscle mitochondria. Age does correlate with body composition changes that could contribute to insulin resistance development with aging (19).

obesity can kickstart diabetes progression through causing insulin resistance. Fat tissue in obese people discharges higher quantities of non-esterified fatty acids, glycerol, hormones, and inflammation-promoting cytokines. The secretion of these substances from adipose tissue leads to insulin resistance in obese individuals. To isolate the effect only on the studied markers, the influence of age was excluded. In type 2 diabetes, individuals do not use endogenous insulin efficiently (insulin resistance) and do not produce enough insulin (insulin deficiency). A low HOMA-IR indicates sensitivity to insulin, where a small amount of insulin effectively maintains blood sugar balance. Conversely, a high HOMA-IR is associated with a greater degree of insulin resistance. A higher value of HOMA-IR reflects increased insulin resistance (20).

Blood levels of the neurotransmitter gamma-aminobutyric acid (GABA) are reduced when insulin resistance is present. GABA is thought to be secreted by cells to "calm" and "ready" them for subsequent surges of insulin release. With low or absent GABA, dysfunction and inflammation risks increase in both type 1 and type 2 diabetes mellitus. Phelps and colleagues found GABA is pulsatile, spiking at intervals akin to normal insulin pulses, and helps control the timing of insulin secretion. Additionally, GABA release is independent of glucose levels. Activating GABA receptors regulates beta cell activity through internal autocrine signaling cascades (21). In agreement with the present findings, prior research proposed Low blood GABA associates with insulin resistance. Possible reasons for insufficient GABA include nutrient deficiencies depleting GABA, stress decreasing GABA, and mitochondrial enzymes altering GABA production and breakdown (22). Additionally, another study found extracellular glutamine stimulates beta cell GABA secretion by delivering glutamate for the GABA synthesizing enzyme GAD (23). The mitochondrial enzyme GABA transaminase (GABA-T) likely also has a role, generating succinic semialdehyde by transamination GABA with alpha-ketoglutarate (24). This catabolism of GABA can impact the TCA cycle through producing succinate from succinic semialdehyde. Alternatively, glucose-provoked changes in mitochondrial function may alter the rate of GABA breakdown and release (25).

Additional evidence indicates gamma-aminobutyric acid, which has an insulin-like beneficial effect, also raised the glucose infusion rate during a euglycemic clamp. Gamma-aminobutyric acid's capacity to ameliorate insulin resistance is credited to increasing GLUT4 while decreasing gluconeogenesis and glucagon receptor gene expression. Gamma-aminobutyric acid co-localizes with insulin in pancreatic beta cells and acts as an anti-diabetic factor. It exerts anti-diabetic effects by promoting beta cell proliferation and modulating the immune system (26).

Glucose transporter protein type-4 (GLUT4) vesicles contain amount of other proteins, most of which play key roles in the translocation process (27). Notably, among these vesicular proteins, there is an aminopeptidase that shows a close and stoichiometric relationship with GLUT4. Insulin-regulated aminopeptidase (IRAP), a protein directly involved in insulin-mediated glucose uptake and

associated with GLUT4, emerges as a potential biomarker for insulin resistance (28). The results of this study concur with that suggestion. This phenomenon occurs due to the influence of insulin, which prompts the translocation of GLUT4 vesicles, causing them to merge with the cellular surface membrane, the circulating levels of IRAP are expected to reflect the amount of both IRAP and GLUT4 that undergo translocation to the plasma membrane, thus providing an indication of the degree of insulin sensitivity (29).

When insulin binds, insulin-regulated aminopeptidase (IRAP) is co-transported and moves together with GLUT4 to the plasma membrane of skeletal muscle and adipose tissues, which are key glucose storage sites. This occurs in a proportional way. after this, the external piece of IRAP (IRAPs) is clipped and let out into the circulation. But in people with type 2 diabetes (T2D), the shifting of IRAP triggered by insulin is notably lowered (30-31).

Based on these findings, this protein has garnered significant interest due to its extracellular domain being enzymatically cleaved and released into the bloodstream. This suggests that the levels of IRAP present in the bloodstream should correlate with the amounts of both IRAP with GLUT4 translocated to the cell membrane in response to insulin stimulation. Consequently, this could potentially function as an indicator of insulin sensitivity (32).

Several possible mechanisms may explain the reduced serum levels of insulin regulated aminopeptidase (IRAP) observed in prediabetic and type 2 diabetic patients: 1) Decreased production and activity of IRAP could occur in tissues like muscle and fat due to the high insulin and insulin resistance associated with prediabetes and T2D. This reduction of IRAP may disrupt insulin regulation (33), 2) The movement of IRAP from intracellular vesicles to the cell surface relies on insulin. Insulin resistance could impair this traffic, lowering IRAP surface levels and serum measurements (34), 3) Inflammation and oxidative stress tied to insulin resistant conditions may increase IRAP breakdown. Immune cytokines and reactive oxygen molecules can promote pathways that degrade IRAP (35), and 4) Metabolic irregularities in prediabetes and T2D could disturb the processes controlling IRAP secretion from tissues into the bloodstream. This may diminish IRAP release into circulation (36).

## Conclusion

The decrease in GABA levels impacts insulin resistance, potentially causing imbalances in insulin regulation and contributing to the development of prediabetes and diabetes. Furthermore, the decline in IRAP levels may suggest its role in conjunction with GLUT4 in glucose transport, offering a potential approach for widespread screening of populations at risk for prediabetes.

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This research did not receive any specific fund.

## Conflict of Interest

Authors declare no conflict of interest.

## Data availability

Data are available upon reasonable request.

## ORCID

Ismael Khashan  
Maysaa Majeed

[0009-0009-1133-5301](https://orcid.org/0009-0009-1133-5301)  
[0009-0002-8884-6715](https://orcid.org/0009-0002-8884-6715)

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