

# Hormonal Profile and Advanced Lipid Indices (AIP, TYG) in Experimental Hyperglycemia with Alloxan Monohydrate in Wistar Rats

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## Abstract

**Background:** Diabetes mellitus is a chronic metabolic disease characterized by persistent hyperglycemia and lipid abnormalities contributing to cardiovascular risk. Integrated indices such as the Atherogenic Index of Plasma (AIP) and the Triglyceride-Glucose Index (TyG) offer a synthetic assessment of cardiometabolic risk, but their exploration associated with leptin and  $\beta$ -cell function remains limited in experimental models. This study aimed to evaluate advanced biochemical, hormonal, and lipid changes induced by alloxan in Wistar rats. **Methods:** Twelve male rats were divided into two groups: normoglycemic controls and alloxan-induced diabetics (150 mg/kg, i.p.). Measurements of blood glucose, insulin, leptin, and serum lipids were performed on day 14. HOMA-IR, HOMA- $\beta$ , AIP, and TyG indices were calculated. Statistical analyses used the Mann-Whitney test and linear correlation. **Results:** Diabetic rats showed significant hyperglycemia ( $p < 0.001$ ), insulinopenia with decreased HOMA- $\beta$  ( $p < 0.001$ ), hypertriglyceridemia ( $p = 0.004$ ), and decreased HDL-C ( $p = 0.03$ ). AIP ( $p = 0.002$ ) and TyG ( $p = 0.006$ ) were elevated. Blood glucose correlated positively with AIP ( $r = 0.80$ ;  $p = 0.013$ ), and insulin with HOMA-IR ( $r = 0.90$ ;  $p < 0.0001$ ). **Conclusion:** Leptin did not show significant correlations. Alloxan hyperglycemia induces a pro-atherogenic metabolic signature. AIP and TyG indices are relevant integrated markers of experimental cardiometabolic risk.

## Keywords

Experimental Diabetes, Alloxan, Lipid Indices, Leptin

## 1. Introduction

Diabetes mellitus is a chronic metabolic disease characterized by persistent hyperglycemia resulting from insulin deficiency, insulin resistance, or both mechanisms combined [1]. Beyond carbohydrate abnormalities, it is accompanied by major lipid disturbances including hypertriglyceridemia, a decrease in HDL cholesterol, and an increase in LDL particles which contribute to cardiovascular risk [2] [3]. These abnormalities are often described by isolated parameters, but integrated indices such as the Plasma Atherogenic Index (PAI) and the Triglyceride-Glucose index (TyG) offer a synthetic and predictive assessment of cardiometabolic risk [4]-[6]. AIP, defined as the logarithm of the TG/HDL-C ratio, is correlated with LDL particle size and is a recognized marker of plasma atherogenicity [4] [7]. TyG, calculated from triglycerides and blood glucose, is a simple and validated marker of insulin resistance [5] [6].

Furthermore, leptin is a key adipocyte hormone in energy regulation, involved in the modulation of insulin sensitivity, carbohydrate homeostasis and lipid metabolism [8]. In insulinopenic diabetes, the physiological leptin-insulin relationship can be profoundly altered, leading to hormonal uncoupling that reflects a breakdown in the adipocyte-pancreas dialogue [9] [10]. Joint exploration of this relationship and integrated lipid indices could provide a more detailed reading of the cardiometabolic profile in diabetes.

In our study, we incorporated a diabetic Wistar rat model with alloxan monohydrate, which is a classic experimental model to study the metabolic consequences of selective destruction of pancreatic  $\beta$  cells [11]. While many studies have separately described the effects of alloxan on lipids or hormones, few studies have simultaneously integrated leptin-insulin coupling, advanced lipid indices (AIP, TyG), and  $\beta$ -cell function estimated by HOMA- $\beta$ , in a context of confirmed insulinopenic hyperglycemia.

In this context, the objective of our work is to assess, at a fixed point in the evolution, hormonal markers and integrated lipid indices in alloxan monohydrate diabetic Wistar rats in order to identify a composite metabolic signature associated with cardiometabolic risk. This integrative approach could improve the understanding of hormonal and lipid interactions in insulinopenic diabetes and offer perspectives for the preclinical evaluation of new therapeutic strategies.

## 2. Materials and Methods

### 2.1. Experimental Animals

Twelve (12) male Wistar rats (*Rattus norvegicus*), aged 13 - 17 weeks and weighing between 150 and 350 g, were used. The animals were kept in standard cages under controlled conditions (12 h/12 h light/dark cycle, temperature  $22^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ), with ad libitum access to water and a balanced standard diet. A 12-h fast was applied before experimental procedures.

The experimental protocol was approved by the Ethics Committee of Marien Ngouabi University and was conducted in accordance with international guide-

lines for the use of laboratory animals [12].

The rats were randomly divided into two groups ( $n = 6$  per group):

- Control Group (T): Healthy control rats.
- Diabetic Group (D): Rats given alloxan monohydrate.

All biological measurements were performed on Day 14 (D14) after induction.

The choice of  $n=6$  rats per group is based on the so-called “Resource Equation Approach” method (degrees of freedom of error method), which recommends keeping the degrees of freedom of error ( $E = N - \text{number of groups}$ ) within an acceptable range, typically between 10 and 20. In our study, we used a sample size of 12 rats, which is in line with the recommendations [13]. Furthermore, this size allows us to test biologically relevant differences with a statistical power of approximately 80% (two-sided test,  $\alpha = 0.05$ ), based on a priori calculations using reasonable effect estimates. Finally, this decision complies with the ethical guidelines of the 3Rs (Reduction) and the recommendations of the ARRIVE guidelines, which require explicit justification of the sample size to ensure scientific rigor while reducing the use of animals [14].

## 2.2. Experimental Induction of Hyperglycemia

Diabetes was induced by a single intraperitoneal injection of alloxan monohydrate (150 mg/kg body weight), dissolved extemporaneously in ice-cold sterile saline (0.9% NaCl) [5]. Control rats received an equivalent volume of saline solution.

To prevent acute post-injection hypoglycemia, 5% glucose solution was administered ad libitum for the first 24 hours after injection.

## 2.3. Diabetes Confirmation and Blood Sugar Monitoring

Blood glucose was measured using a portable glucometer (OnCall Plus II, ACON®). Samples were collected through an incision at the tip of the tail on capillary blood, after a 12-h fast. Measurements were taken on days 1, 3, 5, 7, and 14.

Rats with fasting blood glucose  $> 280$  mg/dL ( $\approx 15.5$  mmol/L) on day 3 post-injection were considered diabetic and retained for the study [15].

## 2.4. Blood Sampling and Sample Preparation

After a 12-h fast on day 14, rats were anesthetized by diethyl ether inhalation. Blood was collected by puncture at the orbital sinus. Samples were centrifuged at 3000 rpm for 10 min, and the resulting serum was stored at  $-80^{\circ}\text{C}$  until biochemical analyses.

## 2.5. Biochemical Assays and Metabolic Indices

The dosage of biochemical parameters was carried out on a CyanStar brand spectrophotometer with Cypress diagnostic reagents, that of insulin was carried out by the ELISA method and the reagents were obtained from the company SunLong Biotech Co., LTD., whose lot number was: SL0373Ra for insulin and SL0441Ra for

leptin. The intra/inter-assay CVs for insulin and leptin are: intra-assay: CV < 12% and inter-assay: CV < 12%.

### 2.5.1. Insulin Resistance and $\beta$ -Cell Function

Insulin resistance and  $\beta$ -cell function were estimated from HOMA formulas described by Matthews *et al.* [16]:

- **HOMA-IR (insulin resistance):**

$$\text{HOMA-IR} = \frac{\text{Glucose (mg/dL)} \times \text{Insulin (\mu U/mL)}}{405}$$

- **HOMA-beta ( $\beta$ -cell function):**

$$\text{HOMA-}\beta = \frac{20 \times \text{Insulin (\mu U/mL)}}{\text{Glucose (mmol/L)} - 3.5}$$

### 2.5.2. Triglyceride-Glucose Index (TyG)

TyG was calculated according to the formula validated by Guerrero-Romero *et al.* [5] [17]:

$$\text{TyG} = \ln \left( \frac{\text{Triglycerides (mg/dL)} \times \text{Glucose (mg/dL)}}{2} \right)$$

### 2.5.3. Athérogenic Index of Plasma (AIP)

AIP was determined according to the method described by Dobiasova and Frohlich [4]:

$$\text{AIP} = \log_{10} \left( \frac{\text{Triglycerides (mmol/L)}}{\text{HDL-C (mmol/L)}} \right)$$

## 2.6. Statistical Analysis

Data were expressed as mean  $\pm$  standard deviation (M  $\pm$  SD). The distribution of variables was verified by the Shapiro-Wilk test. For comparison between the two groups (Controls/Diabetics), the non-parametric Mann-Whitney test was used. The relationships between biochemical variables (glycemia, insulin, leptin) and metabolic indices (HOMA-IR, HOMA- $\beta$ , TyG, AIP) were assessed by linear correlation analysis. Depending on the normality of the distributions, Pearson correlation (normal variables) or Spearman correlation (non-normal variables) was applied. A significance threshold of  $p < 0.05$  was used for all analyses. Statistical processing was performed using GraphPad Prism software version 5.0 (GraphPad Software, San Diego, CA, USA).

## 3. Results

### 3.1. Weight and Glycemic Profile

To induce hyperglycemia, we determined weight and blood glucose in Wistar rats from two groups of our study population ( $n = 6$ ) at D1, D3, D5, D7 and D14. Our data showed a statistically significant difference,  $p = 0.04$  for weight (**Figure 1**)

and  $p = 0.03$  for blood glucose (Figure 2).

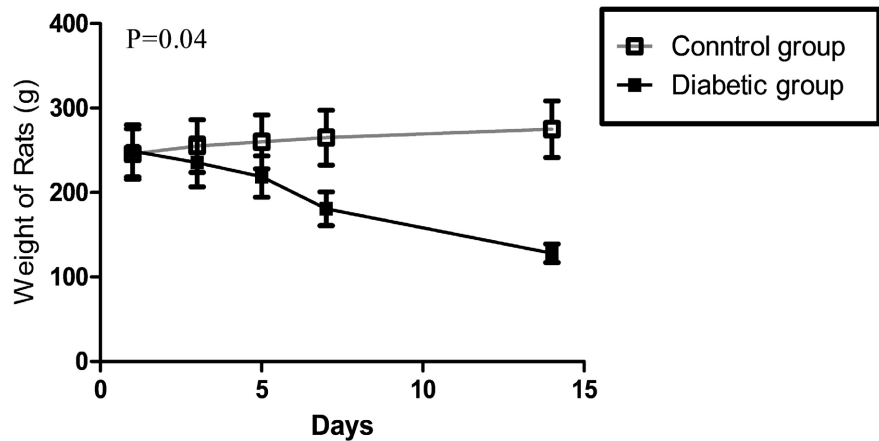


Figure 1. Weight measurement on D1, D3, D4, D5 and D14.

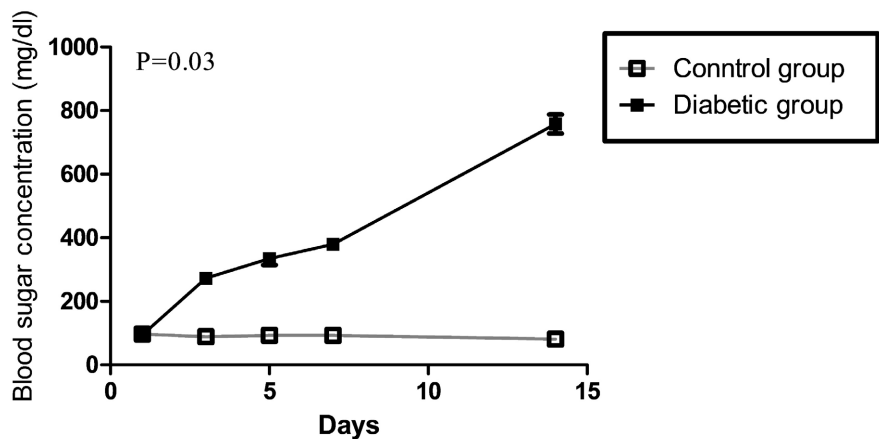


Figure 2. Blood sugar measurement on D1, D3, D4, D5 and D14.

### 3.2. Biochemical Parameters

Table 1 presents the biochemical and hormonal parameters of Wistar rats according to the groups studied (Controls/Diabetics) in our study. Compared to controls, diabetic rats showed a significant increase in blood glucose ( $p < 0.001$ ), LDL-Cholesterol ( $p = 0.01$ ) and triglycerides ( $p = 0.004$ ), associated with a decrease in HDL-cholesterol ( $p = 0.03$ ). Insulinemia also showed a marked decrease in the diabetic group ( $p = 0.002$ ), reflecting insulinopenia characteristic of the alloxan monohydrate model.

Regarding metabolic indices, diabetic rats showed a significant elevation of AIP ( $p = 0.002$ ) and TyG ( $p = 0.006$ ), reflecting a more atherogenic lipid and carbohydrate profile. The HOMA- $\beta$  index was significantly reduced in the diabetic group ( $p < 0.001$ ), confirming the failure of  $\beta$ -cell function, while the HOMA-IR ( $p = 0.15$ ) showed a tendency to increase, without reaching statistical significance.

These results suggest a profound imbalance in carbohydrate-lipid metabolism, with an increased cardiometabolic risk in diabetic animals.

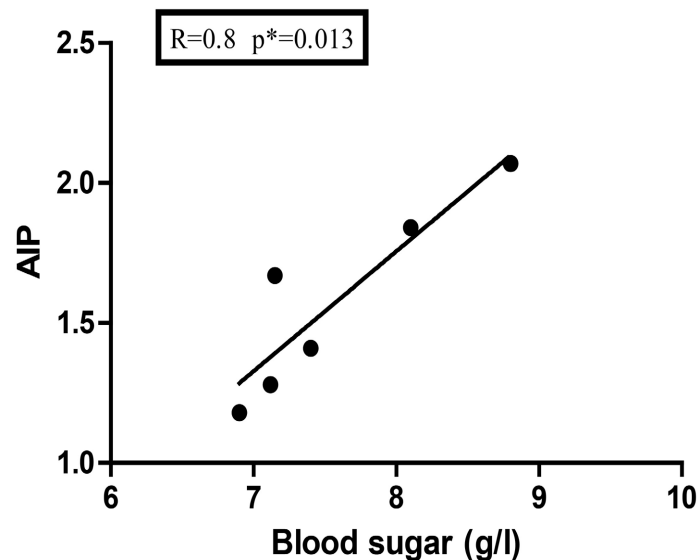
**Table 1.** Metabolic, hormonal parameters and cardiometabolic risk indices in control and diabetic rats.

Parameters	Controls	Diabetics	P Value
	n = 6	n = 6	
Blood Sugar (mg/dL)	98.3 ± 12.4	356.7 ± 48.5	<0.001***
LDL-C (mg/dL)	22.4 ± 5.1	38.6 ± 7.9	0.01*
Triglycerides (mg/dL)	78.6 ± 14.2	142.8 ± 22.7	0.004**
HDL-C (mg/dL)	46.5 ± 8.7	31.2 ± 6.8	0.03*
Insulin (μU/mL)	11.2 ± 2.1	4.6 ± 1.3	0.002**
AIP (log TG/HDL-C)	0.16 ± 0.04	0.65 ± 0.09	0.002**
TyG index	4.35 ± 0.19	4.93 ± 0.24	0.006**
HOMMA-β	112.4 ± 24.8	35.6 ± 12.1	<0.001***
HOMMA-IR	2.7 ± 0.6	3.3 ± 0.8	0.15
Leptin (ng/mL)	6.8 ± 1.5	5.9 ± 1.4	0.2

**Abbreviations:** HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HOMA-β: Homeostatic Model Assessment of β-cell function; TyG: Triglyceride-Glucose Index; AIP: Atherogenic Index of Plasma. Statistical test: Mann-Whitney. Significant: \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001.

### 3.3. Linear Correlation Analysis

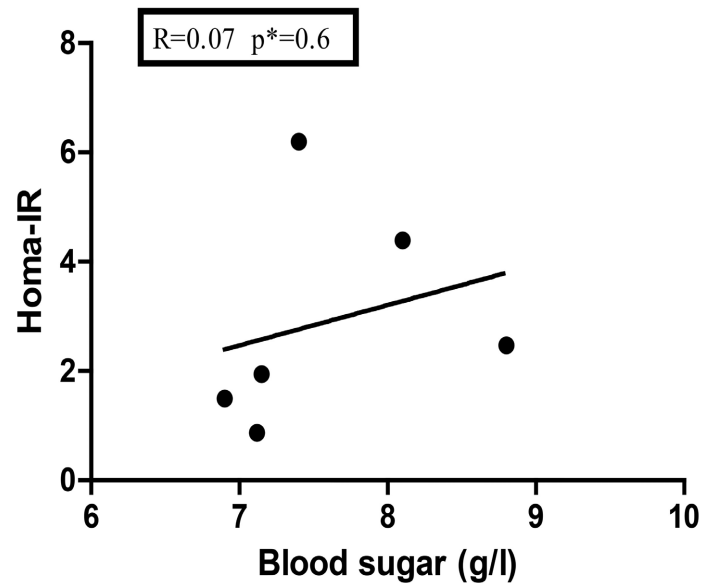
Correlation analysis of our results revealed distinct associations between hormonal parameters and integrated indices of cardiometabolic risk.

**Figure 3.** Linear correlation between Blood Glucose and AIP.

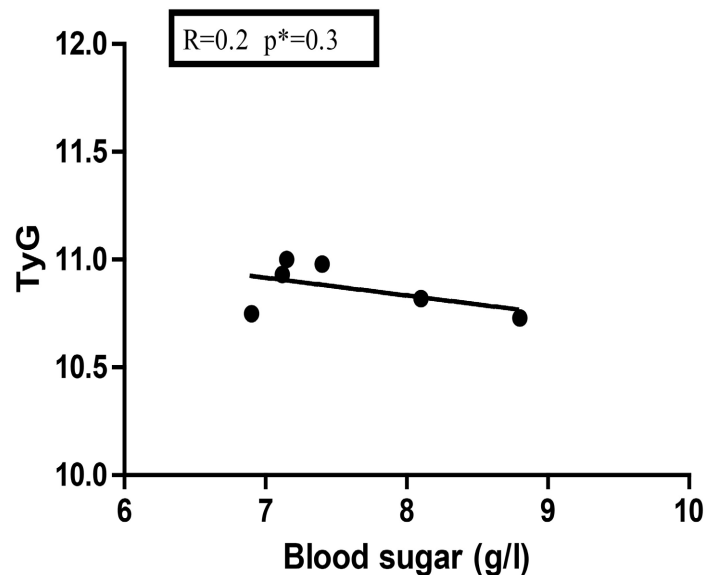
Blood glucose showed a strong positive correlation with AIP ( $r = 0.80$ ;  $p = 0.013$ ) **Figure 3**, indicating a direct link between hyperglycemia and plasma ath-

erogenicity. In contrast, no significant association was observed with HOMA-IR ( $r = 0.07$ ;  $p = 0.60$ ) **Figure 4** or TyG index ( $r = 0.20$ ;  $p = 0.30$ ) **Figure 5**. Insulinemia showed a highly significant positive correlation with HOMA-IR ( $r = 0.90$ ;  $p < 0.0001$ ) **Figure 6**, validating the relevance of this index in the assessment of insulin resistance in our model. No correlation was detected with AIP ( $r = 0.01$ ;  $p = 0.80$ ) **Figure 7** or TyG ( $r = 0.08$ ;  $p = 0.57$ ) **Figure 8**.

Leptin showed no significant correlation with lipid parameters AIP ( $r = 0.08$ ,  $p = 0.5$ ) **Figure 9** or metabolic indices HOMA-IR ( $r = 0.14$ ,  $p = 0.45$ ) **Figure 10**; TyG ( $r = 0.009$ ,  $p = 0.9$ ) **Figure 11**, suggesting a decoupling of this adipokine from global metabolic regulation in this insulinopenic context.



**Figure 4.** Linear correlation between blood glucose and Homa-IR.



**Figure 5.** Linear correlation between blood glucose and TyG.

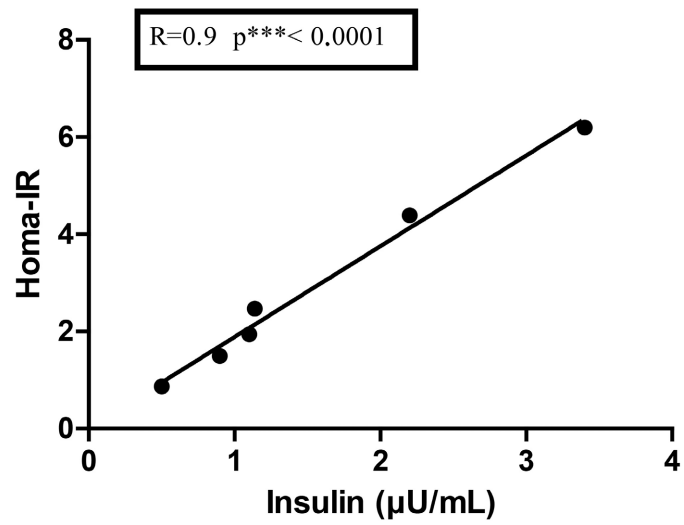


Figure 6. Linear correlation between insulin and Homa-IR.

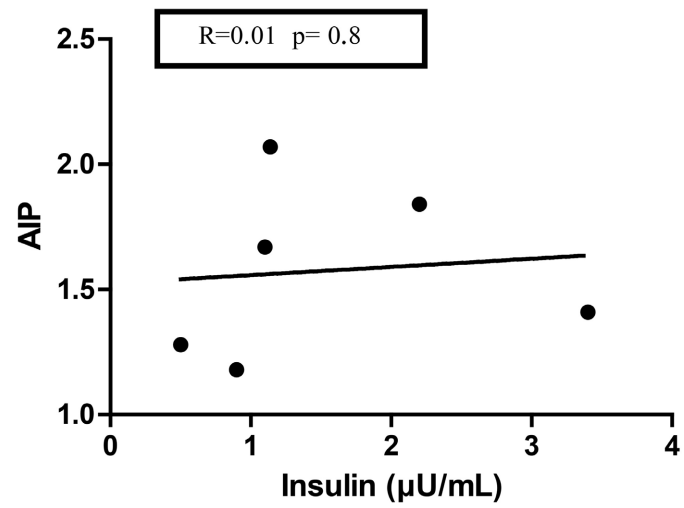


Figure 7. Linear correlation between insulin and AIP.

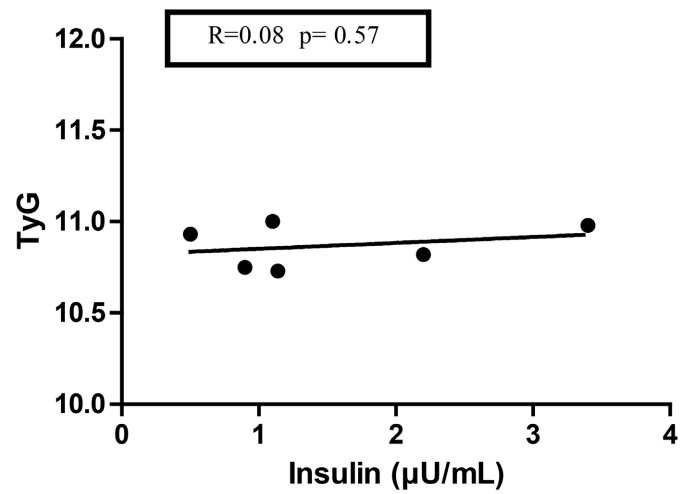


Figure 8. Linear correlation between insulin and TyG.

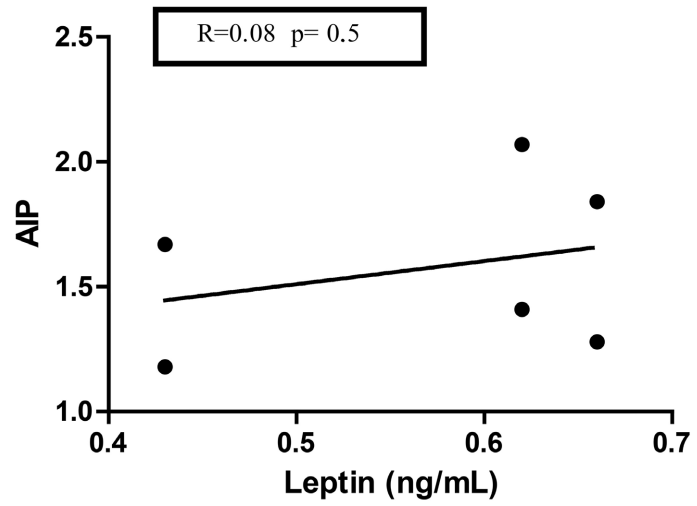


Figure 9. Linear correlation between leptin and AIP.

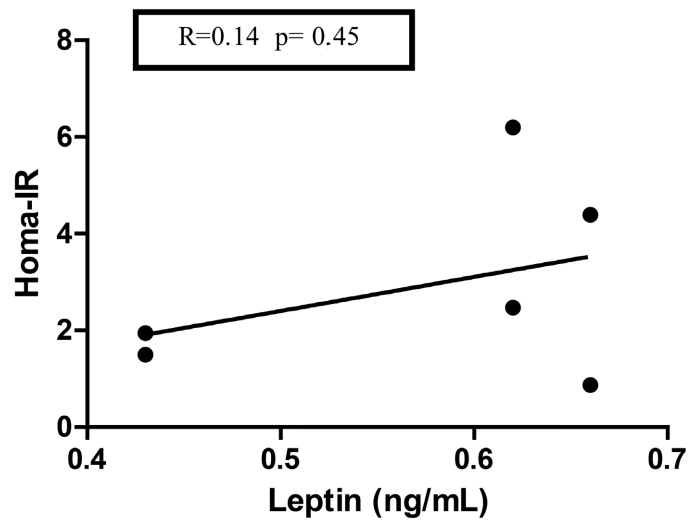


Figure 10. Linear correlation between leptin and Homa-IR.

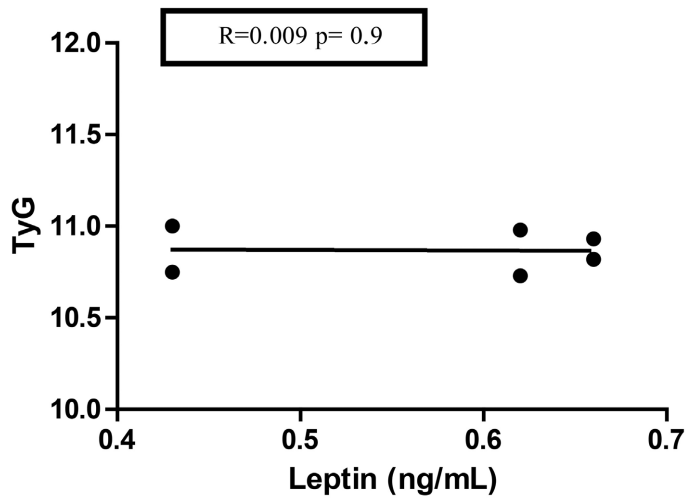


Figure 11. Linear correlation between leptin and TyG.

## 4. Discussion

The main objective of our study was to evaluate the impact of experimental hyperglycemia induced by alloxan on biochemical, hormonal parameters and advanced lipid indices (AIP, TyG) in Wistar rats. In this study, we induced diabetes with alloxan monohydrate at a dose of 150 mg/kg. Our results are consistent with those obtained with other diabetes-inducing agents, such as streptozotocin, although alloxan is less stable and requires precise dose adjustment [18]. Several studies report stable hyperglycemia from 48 h post-injection, with levels above 250 mg/dL, the diagnostic threshold used in many animal protocols [19]. Thus, we observed a reduction in body weight in rats in the diabetic group, with a significant difference ( $P = 0.04$ ,  $n = 6$  per group) from the fifth day and these results are similar to other studies conducted on Wistar rats [20] [21]. In general, the reduction in body weight in diabetes mellitus is due to the stimulation of gluconeogenesis production. Indeed, an acceleration of the protein and fat breakdown process leads to a significant reduction in body weight, which in turn leads to increased muscle atrophy and loss of tissue protein [22]. This information confirms that hyperglycemia leads to a reduction in body weight. Similarly, other studies suggest that body weight loss can be attributed to the lipolytic effects of glucocorticoids on adipose tissue. In addition to accelerating lipolysis, glucocorticoids promote proteolysis and stimulate gluconeogenesis. These metabolic effects are probably related to the lack of insulin, a lipogenic hormone [23]. At the same time, an increase in blood glucose was observed as early as the third day after administration of alloxan monohydrate at a dose of 150 mg/kg body weight ( $p = 0.03$ ,  $n = 6$  per group) in rats in the diabetic group and these results are consistent with those of other researchers [24] regarding the onset of hyperglycemia. Our results show that insulinopenic diabetes is characterized by persistent hyperglycemia, decreased insulin levels and HOMA- $\beta$ , atherogenic dyslipidemia, as well as significant elevations of AIP and TyG. Indeed, alloxan is known to induce selective destruction of pancreatic  $\beta$  cells via the generation of free radicals, leading to severe insulinopenia [11] [25]. This impairment was confirmed in our study by the marked elevation of blood glucose and the fall in HOMA- $\beta$ , in agreement with the work of Lenzen *et al.* and more recent studies validating the alloxan model as an experimental tool for insulin-dependent diabetes [15] [26]. At the same time, our data highlighted hypertriglyceridemia and a significant decrease in HDL-C, which corresponds to the classic metabolic alterations described in experimental and clinical diabetes [2] [27]. Such disturbances promote the accumulation of LDL-C which is highly atherogenic [3] and explains the significant elevation of AIP observed in our study, in agreement with recent work confirming its value as a marker of plasma atherogenicity [4] [7]. Furthermore, the increase in TyG confirms its relevance as a simple marker of insulin resistance and cardiometabolic risk, recognized both in preclinical research and in clinical practice [5] [17].

Correlationally, the observed positive relationship between blood glucose and AIP underlines the direct link between glucose imbalance and plasma athero-

genicity, while the correlation between insulin and HOMA-IR confirms that the latter is an index of insulin resistance. In our model, HOMA-IR did not reach the threshold of statistical significance, even though the TyG index was significantly higher. This discrepancy can be explained by the fact that HOMA-IR is based on a combination of fasting insulin and blood glucose levels, and mainly reflects insulin resistance in the context of compensatory hyperinsulinism. However, in a situation of severe insulinopenia such as that induced by alloxan, insulin levels fall sharply, which reduces the sensitivity of HOMA-IR and partially masks the existence of peripheral insulin resistance. Conversely, TyG, calculated from blood glucose and triglycerides, remains an important indicator of insulin resistance even in the absence of hyperinsulinism, because it directly reflects the alteration of carbohydrate-lipid metabolism. Thus, our results suggest that in models of insulinopenia, TyG constitutes a more sensitive marker than HOMA-IR for detecting latent insulin resistance or insulin resistance aggravated by lipid disturbances [28] [29].

Conversely, leptin showed only weak correlations, probably due to severe insulinopenia induced by alloxan, thus breaking the physiological leptin-insulin dialogue described in less extreme metabolic contexts [8] [9]. Overall, our results reinforce the idea that integrated indices such as AIP and TyG outperform the interpretation of isolated parameters, providing a synthetic and predictive view of cardiometabolic risk. These findings are consistent with those of studies conducted in both human populations and animal models [6] [5] [7] [17].

However, some limitations must be highlighted, including the small sample size and the lack of longitudinal follow-up, which limit the scope of the conclusions. Nevertheless, the integrative approach adopted, combining composite indices and key hormones, gives increased relevance to our results and opens up interesting perspectives. In the future, expanded studies including other adipokines such as adiponectin or resistin, as well as inflammatory markers, would be necessary to better clarify the role of adipocyte-pancreas dialogue in the pathogenesis of diabetes and its cardiovascular complications. [30] [31].

## 5. Conclusion

Our integrative approach demonstrates that the alloxan model of insulinopenic diabetes is accompanied by a complex metabolic profile, where AIP and TyG constitute valuable synthetic markers of cardiometabolic risk. These indices surpass isolated measures in reflecting global metabolic perturbation in this experimental setting. Their use could strengthen the relevance of preclinical studies testing new therapies.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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