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Alternations of Hemostatic Balance Induced By a Hypercaloric Diet

KOTEGNON Azonwakin Rodrigue[1,2]*, CHOKKI Steven[2], MICHODJEHOUN Clémentine[2], KOTOMALE Assirius[2], BAH Fatoumata[1], DIENG Abdouramane[1] and BABA-MOUSSA Lamine[3]

[1]Nutritional Sciences Laboratory, Department of Food Sciences and Nutrition, Guinean Higher School of Tourism and Hospitality, Conakry, Guinea

[2]Laboratory of Pharmacology and Improved Traditional Medicines, Department of Animal Physiology, Faculty of Science and Technology, University of Abomey-Calavi, BP 526 Cotonou, Republic of Benin

[3]Laboratory of Biology and Molecular Typing in Microbiology, Faculty of Science and Technology, University of Abomey-Calavi, Abomey Calavi, Benin

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*Corresponding Author Email: akotegnonrodrigue@gmail.com

Abstract

The study entitled "Alterations of Hemostatic Balance Induced by a Hypercaloric Diet" aims to assess the impact of a calorie-rich diet on blood coagulation mechanisms. Hemostasis, a physiological process maintaining vascular integrity, can be disrupted by metabolic disorders linked to obesity. To explore this relationship, twenty-four male Wistar rats were divided into two groups : a control group fed a standard diet and a test group subjected to a hypercaloric diet for 30 days. Body weight, Lee index, and adiposity rate confirmed the induction of an obese state in treated animals. Biologically, these rats exhibited hypercoagulability characterized by significant reductions in bleeding time, coagulation time, aPTT, prothrombin time, and thrombin time, a marked increase in platelet count and D-dimer levels, and a paradoxical decrease in fibrinogen levels. These alterations indicate excessive activation of hemostatic mechanisms, likely triggered by chronic inflammation, oxidative stress, and hepatic dysfunction associated with obesity. The results reveal a profound disruption of hemostatic balance due to the hypercaloric diet, highlighting the vascular risks of nutritional excess. This experimental model supports the importance of a preventive nutritional approach to reduce thromboembolic complications related to obesity.

Keywords

Obesity, Hypercaloric diet, Hemostasis, Hypercoagulability, Wistar rat.

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INTRODUCTION

Hemostasis is a complex and finely regulated physiological process that maintains vascular integrity by ensuring a dynamic balance between procoagulant and anticoagulant mechanisms. It relie on the coordinated interaction between endothelial cells, blood platelets, and plasma coagulation factors, all regulated by specific biochemical mediators and signaling pathways [1]. Any disruption of this balance can lead to pathological states such as thrombosis or hemorrhage. In recent decades, nutritional transition—marked by excessive calorie intake, especially from saturated fats and simple sugars—has emerged as a major risk factor for

various metabolic diseases, including obesity, type 2 diabetes, and cardiovascular disorders [2,3]. These metabolic conditions are often associated with blood hypercoagulability and chronic systemic inflammation, both of which are closely linked to hemostatic imbalance [4,5].

Recent studies have shown that hypercaloric diets, rich in fats and/or sugars, can significantly alter hemostatic parameters even in the absence of clinically established comorbidities. In rats, a widely used and relevant model for metabolic studies, such diets have been correlated with elevated fibrinogen levels, increased platelet counts, and shortened bleeding and clotting times, suggesting a prothrombotic tendency [6].

Furthermore, prolonged exposure to a hypercaloric diet may promote a pro-inflammatory and pro-oxidative state, potentially impairing endothelial function, activating platelets, and altering the expression of coagulation factors [7]. These changes contribute to a thrombogenic environment and increase the risk of vascular complications, including atherothrombosis, in both humans and animal models [8].

In this context, it becomes essential to better understand the mechanisms by which a hypercaloric diet disrupts hemostasis, in order to prevent cardiovascular complications related to nutritional disorders at an early stage. The Wistar rat, due to its physiological similarities with humans in many hematological and metabolic parameters, represents an ideal model for exploring this issue [9].

This study therefore aims to evaluate the impact of a hypercaloric diet on the hemostatic balance in Wistar rats by analyzing key blood coagulation parameters, platelet count, and biochemical markers associated with thrombotic risk.

MATERIALS AND METHODS

Study Setting :

The experimental study was conducted at the Laboratory of Pharmacology and Improved Traditional Medicine (LPMTA) of the Faculty of Science and Technology (FAST) at the University of Abomey-Calavi (UAC), Benin. The experiment was carried out over a four-week period.

BIOLOGICAL MATERIAL :

The experiment involved twenty-four (24) male Wistar rats, aged 4 weeks and weighing between 180 and 220 grams at the beginning of the study.

METHODS

The experiment was conducted on twenty-four (24) male Wistar rats, aged between 8 and 10 weeks and weighing between 180 and 220 grams at the beginning of the study. The animals were randomly divided into two homogeneous groups of twelve (12) rats each: a control group (T) fed a standard diet, and a test group (H) subjected to a high-calorie diet. This lipid-rich diet was administered for a period of four (4) weeks with the aim of inducing weight gain and associated metabolic disorders.

The high-calorie diet consisted of 35.56 g/100 g of lipids, 27.33 g/100 g of carbohydrates, and 19.36 g/100 g of proteins, resulting in a high caloric intake conducive to fat accumulation. This formulation was based on experimental nutritional models described by Tchogou [10] and validated by other studies on diet-induced obesity in rats [11,12].

Body weight was measured on Day 0 (D0), Day 14 (D14), and Day 30 (D30) to assess weight progression. In addition, blood samples were collected at D0 (before the diet was initiated) and D30 (after 4 weeks of treatment) to evaluate biological changes, particularly hemostatic parameters, induced by the high-calorie diet. A weight gain of at least 20% compared to the control group was considered a validation criterion for the obesity model, in accordance with standards described by Lee [13].

Evaluated Parameters

Anthropometric Parameters

In this study, several anthropometric parameters were monitored to assess the effect of the high-calorie diet on the nutritional and physical status of the rats. These measurements are essential for confirming the induction of obesity and analyzing its impact on physiological functions, particularly hemostasis.

- **Body Weight (D14 and D30):**

The animals' body weight was measured at regular intervals, specifically on days 14 and 30 of the experiment, to track weight changes resulting from the administration of the high-calorie diet. Monitoring body weight is a central criterion in experimental obesity studies, as it helps evaluate the impact of the diet on body mass gain [14]. A weight gain of at least 20% compared to the control group is considered indicative of an obese state [13].

Weight Gain :

To calculate weight gain, the following formula is used for each group :

Weight gain (g) = Weight on Day 30 – Weight on Day 0

To obtain the percentage of weight gain :

Weight gain (%) = [(Weight on Day 30 – Weight on Day 0) / Weight on Day 0] × 100

Lee Index

The Lee Index is an indicator of obesity in animals and is calculated using the following formula :

$$\text{Lee Index} = \frac{\text{Body weight (g)}}{(\text{Body length})^{1.5}}$$

Body weight: Weight of the animal in grams (g)

Body length: Measured from the nose to the base of the tail, in centimeters (cm)

Biological Parameters Evaluated

To determine the effects of a hypercaloric diet on hemostatic balance, several biological parameters were measured from blood samples collected on days 0 (D0) and 30 (D30). These parameters assess both primary hemostasis (platelet function) and secondary hemostasis (coagulation cascade).

Primary and Secondary Hemostasis Parameters

- **Bleeding Time (BT)**
  Bleeding time evaluates platelet functionality as well as vascular wall integrity. It is a key indicator of primary hemostasis. Any prolongation may indicate thrombopathy or decreased platelet function.
- **Clotting Time (CT)**
  Overall clotting time reflects the plasma's ability to form a stable clot. This test provides a global assessment of the coagulation process, including both intrinsic and extrinsic pathways.
- **Activated Partial Thromboplastin Time (aPTT)**
- The aPTT measures the efficiency of the intrinsic coagulation pathway. Prolongation of aPTT may reveal deficiencies in factors VIII, IX, XI, or XII.
- **Prothrombin Time (PT)**
  PT assesses the extrinsic coagulation pathway. It is sensitive to deficiencies in factors II, V, VII, and X, and also monitors liver function or potential activation of coagulation.
- **Plasma Fibrinogen Assay:**
  Fibrinogen is a major coagulation factor, converted into fibrin during clot formation. An increase or decrease in its concentration may indicate inflammation or excessive consumption during coagulation disorders, respectively.
- **Platelet Count :**
- Platelet count quantifies the cellular elements essential to primary hemostasis. Thrombocytosis may indicate a pro-thrombotic state, while thrombocytopenia can cause bleeding disorders.

Statistical Analysis

- Software : GraphPad Prism 8
- Tests : Student's t-test or one-way ANOVA (with Tukey's post hoc test if needed)
- Significance threshold: $p < 0.05$

RESULTS

Anthropometric Parameters

Body Weight Variation

Administration of the hypercaloric diet for 4 weeks led to a significant weight gain in rats from the H group compared to the control group. These data are illustrated in Figure 1.

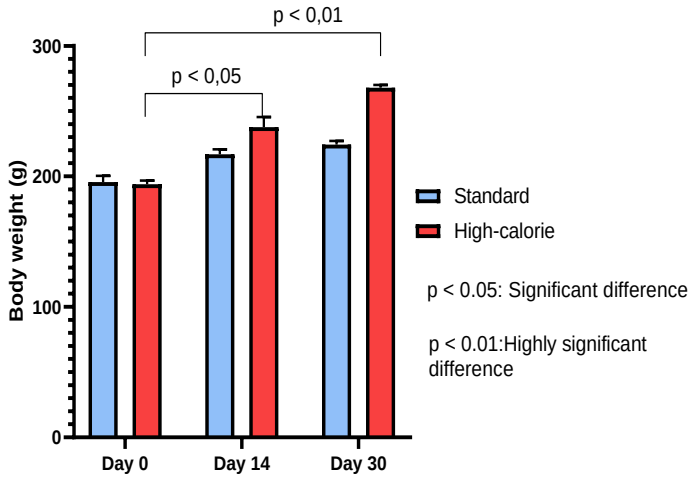

Fig 1 : Variation in body weight of animals subjected to a standard diet and a hypercaloric diet.

At the beginning of the experiment (Day 0), the average body weights of rats were comparable between the two groups. The control group had a mean weight of 195.6 ± 4.8 g, while the hypercaloric group had 194.1 ± 2.8 g, with no statistically significant difference ($p > 0.05$).

By Day 14, an increase in body weight was observed in both groups, but it was more pronounced in the hypercaloric group. The control group averaged 216.95 ± 3.76 g, whereas the hypercaloric group reached 237.67 ± 7.74 g. This difference begins to reflect the impact of the hypercaloric diet on body mass gain.

At Day 30, rats fed the hypercaloric diet showed a significant weight gain, with an average of 267.86 ± 2.13 g, compared to 224.37 ± 2.76 g in the control group. The difference of more than 40 g between groups was statistically significant ($p < 0.05$), confirming the effectiveness of the hypercaloric diet in inducing obesity in Wistar rats.

Averrage weight gain

Figure 2 shows the Averrage weight gainof rats fed a standard diet and those fed a high-calorie diet

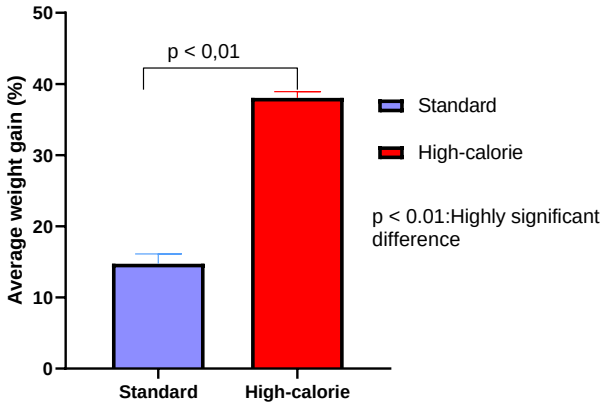

Fig 2 : Averrage weight gain

At the end of the experimental period, a significant difference in weight gain was observed between the two groups. The control group showed an average weight gain of 28.77 g, representing a 14.73% increase compared to the initial body weight. In contrast, the high-calorie group recorded a much higher average weight gain of 73.81 g, corresponding to a 38.04% increase.

Determination of the Lee Index

Figure 3 shows the Lee index of rats fed a standard diet and those fed a high-calorie diet.

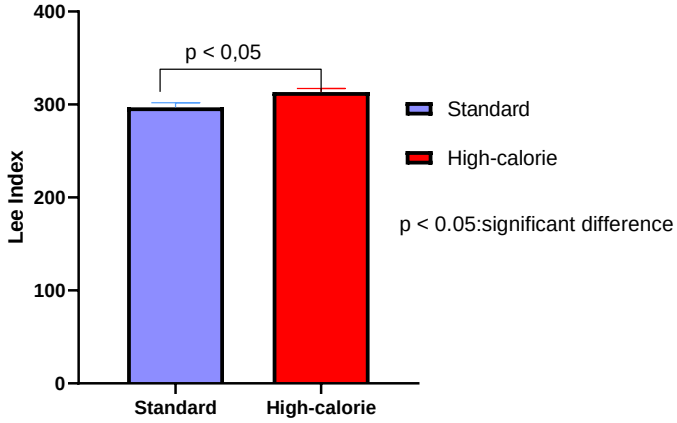

Fig 3 : Determination of the Lee Index

The results show that the Lee index was significantly higher in the high-calorie group compared to the control group, both on Day 14 and Day 30.

In animals subjected to the high-calorie diet, the Lee index exceeded the threshold value of 300, which is generally considered indicative of an obese state in rats. This elevation reflects an excessive accumulation of adipose tissue, confirming the impact of the energy-rich diet on body composition.

In contrast, rats in the control group showed a Lee index below this threshold, indicating normal

physiological weight gain without notable fat overload.

Biological Parameters Assessed

Determination of Bleeding Time

Figure 4 shows the bleeding time recorded in rats subjected to the standard diet and those subjected to the hypercaloric diet.

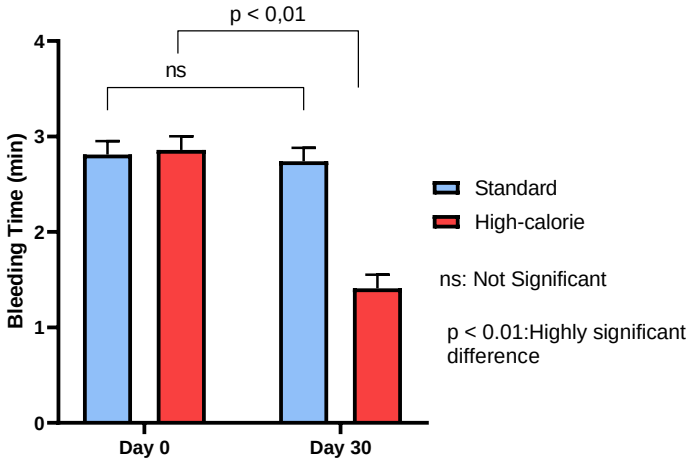

Fig 4 : Bleeding time recorded in rats subjected to the standard diet and those subjected to the hypercaloric diet

Bleeding time, key indicator of primary hemostasis, did not show any significant variation in the control group between day 0 (2.81 ± 0.13 min) and day 30 (2.74 ± 0.12 min), with a p-value of 0.42. This suggests stable platelet function and vascular integrity in the absence of a hypercaloric diet.

In contrast, rats subjected to the hypercaloric diet exhibited a highly significant reduction in bleeding time, from 2.86 ± 0.17 min to 1.41 ± 0.07 min (p = 0.0008). This decrease may indicate excessive activation of primary hemostasis, reflecting a pro-thrombotic state. It could result from platelet hyperactivity or vascular imbalance induced by the metabolic stress associated with obesity. These findings suggest that a hypercaloric diet disrupts the hemostatic system from its earliest stages.

Clotting time

Figure 5 shows the coagulation time recorded in rats fed a standard diet and those fed a high-calorie diet.

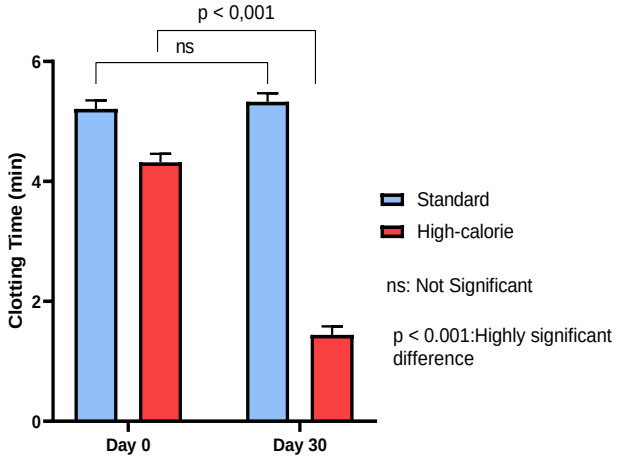

Fig 5 : Coagulation time recorded in rats subjected to a standard diet and those subjected to a high-calorie diet.

In rats fed a standard diet, coagulation time did not show any significant variation between day 0 (5.21 ± 0.14 min) and day 30 (5.33 ± 0.11 min), with a p-value of 0.16. This reflects a stable global coagulation process in the absence of nutritional overload.

In contrast, rats subjected to the high-calorie diet exhibited a highly significant decrease in coagulation

time, dropping from 4.32 ± 0.19 min to 1.44 ± 0.08 min (p = 0.0001). This reduction indicates accelerated coagulation activation, possibly linked to a procoagulant state induced by obesity. The shortened coagulation time may reflect blood hypercoagulability, a condition frequently observed in chronic inflammatory states or metabolic syndrome.

Activated partial thromboplastin time

The figure 6 shows the activated partial thromboplastin time recorded in rats fed with the standard diet and those fed with the high-calorie diet.

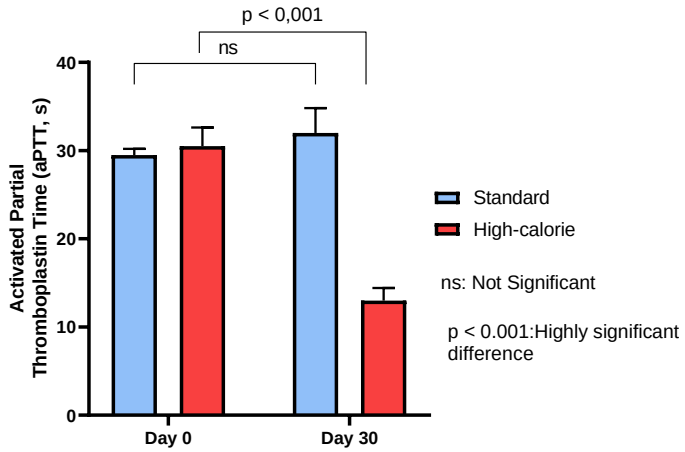

Fig 6 : activated partial thromboplastin time recorded in rats fed with the standard diet and those fed with the high-calorie diet.

In the control group fed a standard diet, the activated partial thromboplastin time (aPTT) remained relatively stable between day 0 (29 ± 0.54 s) and day 30 (31 ± 0.47 s), with no significant variation (p = 0.39). This indicates that the intrinsic coagulation pathway was not affected in the absence of lipid overload.

However, in rats subjected to the high-calorie diet, a highly significant decrease in aPTT was observed, dropping from 32 ± 0.67 s to 13 ± 0.99 s (p < 0.0001). This marked reduction reflects an acceleration of the coagulation process via the intrinsic pathway, indicating a pronounced procoagulant state.

Prothrombin time

The figure 7 shows the prothrombin time recorded in rats fed with the standard diet and those fed with the high-calorie diet.

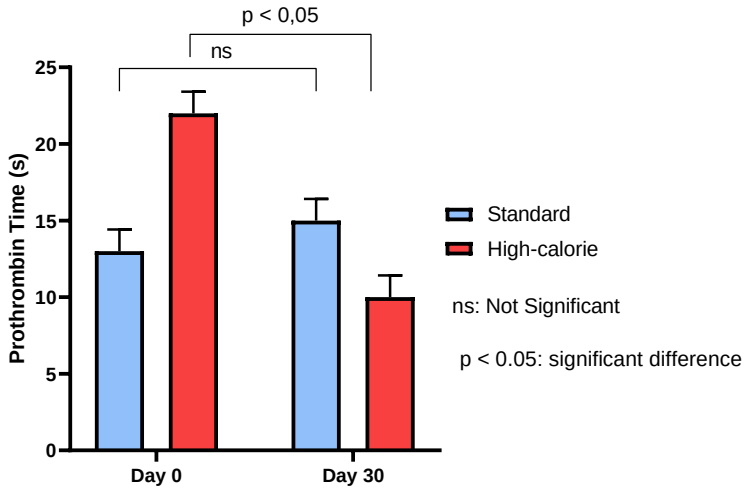

Fig 7 : Prothrombin time recorded in rats subjected to a standard diet and those subjected to a high-calorie diet.

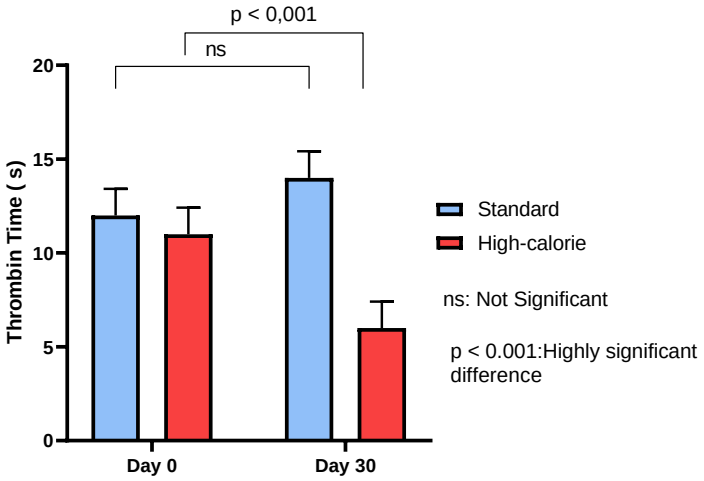

Fig 8 : Thrombin time recorded in rats subjected to the standard diet and those subjected to the high-calorie diet

In the control group fed a standard diet, no significant change in thrombin time was observed between day 0 (12 ± 1.03 s) and day 30 (11 ± 1.06 s), with a p-value of 0.46. This indicates stability in the final step of coagulation, corresponding to the conversion of fibrinogen to fibrin.

In contrast, animals subjected to a high-calorie diet showed a highly significant reduction in thrombin time, decreasing from 14 ± 0.98 s to 6 ± 0.18 s (p = 0.0005). This decrease reflects an acceleration of fibrinogen conversion to fibrin, indicating activation of coagulation at an advanced stage.

Blood platelet count

Figure 9 shows the blood platelet count recorded in rats subjected to the standard diet and those subjected to the hypercaloric diet.

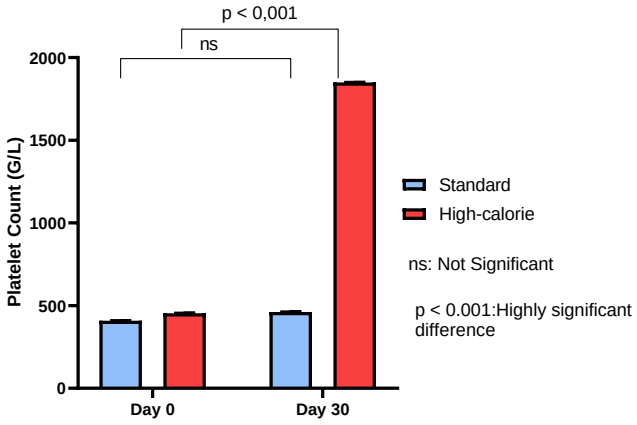

Fig 9 : Blood platelet count recorded in rats subjected to the standard diet and those subjected to the hypercaloric diet

In the control group of rats fed a standard diet, platelet counts remained stable between day 0 (409.21 ± 32.21 G/L) and day 30 (454.16 ± 21.14 G/L), with no statistically significant difference (p = 0.11). This stability reflects a normal balance of primary hemostasis, without excessive activation of platelet production.

In contrast, the group subjected to the high-calorie diet showed a highly significant increase in platelet count, rising from 462.4 ± 43.39 G/L to 1850.7 ± 16.14 G/L (p < 0.0001). This marked thrombocytosis could reflect a pro-inflammatory and pro-thrombotic state, frequently associated with obesity.

D-dimer levels

Figure 10 shows the D-dimer levels recorded in rats subjected to the standard diet and those subjected to the high-calorie diet.

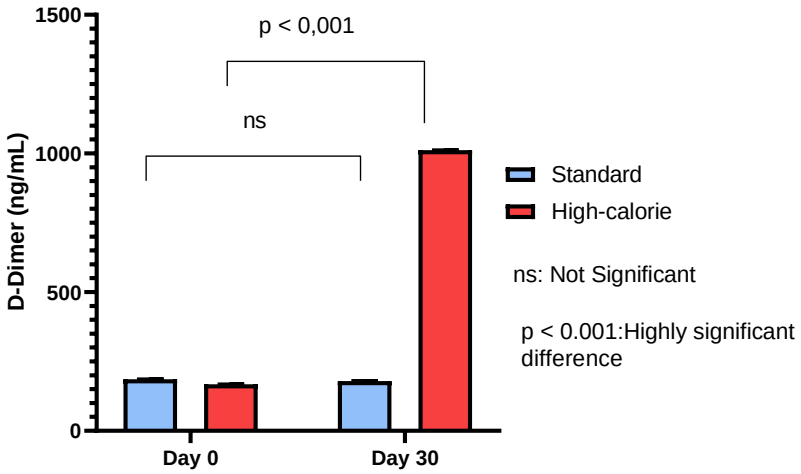

Fig 10 : D-dimer levels recorded in rats subjected to the standard diet and those subjected to the high-calorie diet.

In rats subjected to the hypercaloric diet, a highly significant increase in D-dimer levels was observed, rising from 168.97 ± 4.10 ng/mL to 1013.30 ± 220.13 ng/mL (p = 0.0027). In contrast, in the standard diet group, D-dimer levels remained stable (186 ± 5.06 vs. 179 ± 4.38 ng/mL; p = 0.36).

Fibrinogen levels

Figure 11 shows the fibrinogen levels recorded in rats subjected to the standard diet and those subjected to the high-calorie diet.

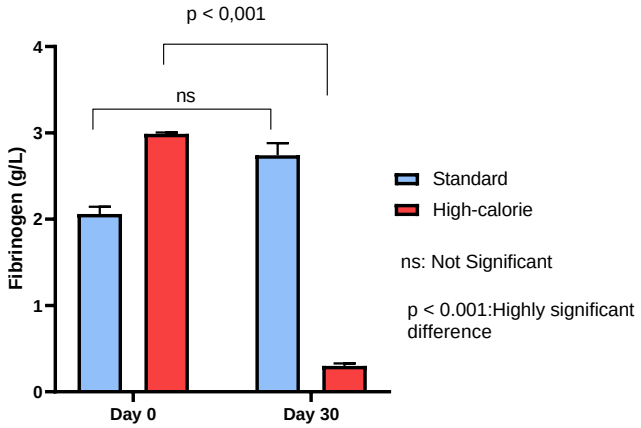

Fig 11 : Fibrinogen levels recorded in rats subjected to the standard diet and those subjected to the high-calorie diet.

In rats subjected to a hypercaloric diet, fibrinogen levels significantly decreased compared to the control group (2.74 ± 0.29 g/L vs. 0.23 ± 0.02 g/L; p = 0.0001). This marked reduction could indicate an inhibitory effect of the hypercaloric diet on the synthesis or release of fibrinogen, a key glycoprotein involved in coagulation. It may also reflect impaired liver function or a modified inflammatory response.
In contrast, no significant change in fibrinogen levels was observed in the standard diet group (p = 0.76), suggesting stability of this parameter under normal nutritional conditions.

DISCUSSION :

The results of the present study show that the administration of a high-calorie diet for 30 days induces significant obesity in Wistar rats, as evidenced by increases in body weight, Lee's index, and adiposity rate. This obesity model is well established and consistent with the work of Rinaldi, who demonstrated that prolonged exposure to a diet rich in fats and/or sugars leads to an accumulation of visceral adipose tissue [16,17].

From a hemostatic perspective, the high-calorie diet caused major alterations indicating a prothrombotic state. The significant shortening of bleeding time and the marked increase in platelet count suggest activation of primary hemostasis. This phenomenon is often observed in the context of obesity, where chronic low-grade inflammation, oxidative stress, and endothelial dysfunction promote platelet hypersensitivity [18,19].

Activation of secondary hemostasis is also demonstrated by the significant reduction of all coagulation times (clotting time, aPTT, prothrombin time, and thrombin time), indicating hypercoagulability affecting the intrinsic, extrinsic, and common pathways. These findings agree with those reported by Tripodi and Sagripanti, who described an elevation of procoagulant factors and increased thrombin activity in obesity [20,21].

However, the significant decrease in fibrinogen levels in the high-calorie group contrasts with some literature data. This paradox may be explained by increased fibrinogen consumption due to excessive coagulation activation, impaired hepatic synthesis linked to diet-induced steatosis, or even a direct toxic effect on hepatocytes [22,23].

At the same time, the marked increase in D-dimer levels suggests secondary activation of fibrinolysis in response to excessive clot formation, reflecting a state of latent thrombosis [24,25]. Altogether, these disturbances indicate a profound disruption of hemostatic balance related to a cascade of metabolic and inflammatory mechanisms triggered by the high-calorie diet.

These results reinforce clinical evidence showing that obesity is a major thromboembolic risk factor associated with systemic alterations in hemostatic regulation [26,27]. Thus, this study highlights the pathophysiological implications of hypercaloric feeding on vascular health and underlines the necessity of appropriate nutritional management in preventing hemostatic disorders associated with obesity.

CONCLUSION

In summary, this study demonstrates that a high-calorie diet profoundly disrupts hemostatic balance in Wistar rats by inducing obesity associated with systemic hypercoagulability. These results call for a better understanding of the mechanisms through which energy-rich diets may promote thromboembolic events, including in humans, and highlight the importance of nutritional intervention in the prevention of cardiovascular disorders related to obesity.

Conflicts of Interest

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

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