

Alterations in Tryptophan Metabolic Pathways in Obese Individuals Adhering to Low-Carbohydrate Intermittent Fasting: Contributions to Oxidative Stress and Hypertension

Nabaa Jawad Kadhim^{1*}, Mustafa Taha Mohammed¹, Rulla Sabah¹

¹Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, Iraq.

Article Info

Article history:

Received: 11, 09, 2025

Revised: 30, 11, 2025

Accepted: 20, 03, 2026

Published: 30, 03, 2026

Keywords:

Kynurenine,
5-hydroxytryptophan,
8-hydroxydeoxyguanosine,
Body mass index,
Adiposity.

ABSTRACT

Low-carbohydrate diets and intermittent fasting (IF) are increasingly used for weight control, particularly in obese women. Modifying dietary behavior forces the body to adapt alternative pathways for energy and nutrient supply. Obesity is associated with oxidative stress and hypertension due to excess body fat. Tryptophan (Trp), an essential amino acid, is metabolized mainly via the kynurenine, 5-hydroxytryptophan (5-HT), and indole pathways. This study examined the effects of lifestyle on Trp metabolism, focusing on the kynurenine and 5-HT pathways, and their association with oxidative stress and hypertension. A total of 120 premenopausal women were enrolled: 40 controls (BMI < 25 kg/m²), 40 non-adherent obese (BMI ≥ 30 kg/m²), and 40 obese adherent to low-carb and IF. Serum analyses included lipid profile, total oxidant status (TOS), total antioxidant capacity (TAC), 8-hydroxydeoxyguanosine (8-OHdG), kynurenine, and 5-HT. Non-adherent obese participants showed significantly higher TOS, 8-OHdG, and kynurenine, with lower TAC and Trp than controls. Adherent obese participants exhibited improvements in TOS, TAC, and kynurenine compared to non-adherent obese, though 8-OHdG and Trp remained unchanged. Oxidative stress correlated with kynurenine in non-adherent obese and with 5-HT in adherent obese. A metabolic shift from kynurenine to 5-HT was observed in the adherent group, negatively correlated with BMI. Kynurenine was associated with increased hypertension risk in both obese groups. In conclusion, adherence to a low-carb diet and IF can shift Trp metabolism from the kynurenine to the 5-HT pathway, reduce oxidative stress, and lower hypertension risk in obese premenopausal women, highlighting the metabolic benefits of lifestyle interventions beyond weight reduction.

This is an open access article under the CC BY license.



Corresponding Author:

Nabaa Jawad Kadhim

Department of Chemistry, College of Science
Mustansiriyah University, Baghdad, Iraq.

Email: nabaa.jawad99@uomustansiriyah.edu.iq



1. INTRODUCTION

Obesity is a clinical condition of elevated body fat mass as a consequence of an imbalance in the intake and expenditure of energy [1] and [2]. The causes of obesity are variable, including metabolic, behavioral, genetic, and social factors metabolic, behavioral, genetic, and social patterns. Moreover, the consequences of obesity are wide, morbid, and in some cases fatal [3]. Obesity consequences include risks of insulin resistance, diabetes, hypertension, liver cirrhosis, cancers, and more. The prevalence of obesity has become a global concern, with the World Health Organization (WHO) classifying it as a global epidemic in males and females, adults and children. The reports of WHO indicate that 2.5 billion (43% of the adult population) of adults were overweight, including 890 million (16% of the adult population) with obesity [4]. Therefore, it has become necessary to study strategies to combat obesity, including raising awareness of the risks of this disease.

Surgical intervention is the most effective approach to remove the body's fat and reduce adiposity in morbidly obese individuals [5]. Nevertheless, multiple techniques have spread recently to control obesity, such as low-carbohydrate (low-carb) adherent [6], keto-diet [7], intermittent fasting (IF) [8], and certain types of physical exercise [9]. The roots of low-carb adherents were introduced in 1972 for controlling weight, which indicates an intake of a low carbohydrate percentage of the daily requirement [10].

Weight reduction, reduced blood pressure (BP), better fasting blood glucose, insulin resistance, and lipoproteins like triglycerides (TGs) and high-density lipoprotein cholesterol (HDL-C) are all associated with the advantages of a low-carb diet [11]. However, since they might be low in plant-based sources like fruits, vegetables, and fiber and rich in animal-based ones like red meat, Their safety, however, remains a topic of debate. It has been demonstrated that this raises the risk of cancer morbidity and mortality as well as cardiovascular disease (CVD) [12]. The intake of the other macronutrients decreases when the intake of one is high. Therefore, Rather than relying on a single macronutrient when examining health benefits, consumption of carbohydrates, fats, and proteins should be taken into account together [13]. On a similar aspect, pursuing an IF diet pattern of eating has been gaining popularity in this realm. IF refers to eating patterns that target a pattern of dedicated periods (ranging from 12 h to several days) with consumption of little or no calories [14]. Short-term (6-month) calorie restriction has been demonstrated to dramatically enhance insulin sensitivity, mitochondrial function, and several cardiovascular risk factors in overweight people. Clinical investigations suggest that calorie restriction may have several positive consequences on overweight individuals beyond weight loss, most likely as a result of these physiological changes. However, studies on obesity interventions conducted over the past few decades have shown that most people struggle to maintain daily calorie restriction for prolonged periods [15].

Tryptophan (Trp) is an essential amino acid whose metabolism can affect physiological processes. The main pathways of Trp metabolism are kynurenine, 5-hydroxytryptophan (5-HT), and the indole pathway [16]. Physiological processes are regulated in part by Trp metabolism. The Kynurenine pathway regulates inflammation, metabolism, immunological feedback, and neurological processes, all of which impact the course of disease [17]. Sleep, gut-brain axis communication, and intestinal homeostasis can all be controlled by the 5-HT pathway. Trp is immediately converted to indole, indole derivatives, tryptamine, and skatole by the gut flora [18]. These compounds include receptor ligands for aromatic hydrocarbons, which support intestinal barrier function and immunological homeostasis [16]. Oxidative stress, on the other hand, is a physiological abnormality caused by electron imbalance, creating species that are oxidizing agents [19]. Most of these species are oxygen-centered, which are known as reactive oxygen species (ROS), and are both physiological and pathological mediators according to their levels [20]. Oxidative stress is found in almost every metabolic disorder, including obesity [21]. The onset of oxidative stress can be considered as a trigger for major health consequences, where the risks of obesity are strongly involved in oxidative stress [21-23]. Antioxidants are present endogenously and exogenously to neutralize these oxidizing agents, in a way that reduces oxidative stress [24]. In this study, kynurenine and 5-HT, two major pathways of Trp, were investigated in non-adherent obese and low-carb-IF adherent obese to predict the fluctuations that occur in Trp metabolism according to the lifestyle of obese subjects. Moreover, the hypertension risks of kynurenine and 5-HT were also investigated, with the association of each metabolic pathway with oxidative stress.

2. Method

2.1 Subject

The study included the collection of 120 female subjects over three groups according to lifestyle. The control group included 40 subjects with a body mass index (BMI) <25 kg/m², while the non-adherent obese group included 40 subjects with a BMI >30 kg/m². The third group, consisting of obese individuals adhering to a low-carb-IF regimen, included 40 subjects with a BMI >30 kg/m². All of the included subjects were adult females (>18 years) and at premenopausal age (<45 years), and were collected from Baghdad, Iraq. In the adherent obese group, subjects followed the diet system for 4-6 months, and those with lower or higher periods were excluded from the study. Additionally, individuals with autoimmune disorders, cancer, or those who were pregnant or lactating women were excluded from the study. The sample collection was taken from Nov 2024 to Feb 2025, and the study was ethically approved by the College of Science, Mustansiriyah University, Baghdad, Iraq (Ref. BCSMU/0824/00015C).

2.2 Sample

Solution polymerization was used in the following manner to carry out the polymerization reaction: After dissolving a sodium saccharin compound (0.01 mol) and acrylic acid (0.01 mol, 0.72 g) in 30 milliliters of benzene, the mixture was degassed by nitrogen gas was purged for N – allyl saccharin formed. After cooling, methanol (25 mL) was added, and the mixture was refluxed for 10 hours with AIBN (0.008 mol, 1.3 g) added. This caused the polymer precipitate to develop and solidify on schedule. According to the following equations: Serum samples were analyzed for Trp, kynurenine, 5-HT, and 8-hydroxydeoxyguanosine (8-OHdG) using ELISA kits from ARS Biochem (China) by using Human ELISA microplate reader (Germany).

Moreover, TGs, cholesterol, and HDL-C were analyzed using Human kits (Germany) by using a PD-303 Apel visible spectrophotometer (Japan). The level of total oxidant status (TOS) and total antioxidant capacity (TAC) was analyzed using spectrophotometric methods according to Erel [25-27]. Oxidative stress index (OSI), low-density, and very low-density lipoprotein cholesterol (LDL and VLDL) were determined by the following equations:

$$\text{OSI} = \frac{\text{TOS}}{\text{TAC}} \quad (1)$$

$$\text{LDL (mg/dL)} = \text{Cholesterol} - \text{HDL} - \text{VLDL} \quad (2)$$

$$\text{VLDL} \left(\frac{\text{mg}}{\text{dL}} \right) = \frac{\text{TGs}}{5} \quad (3)$$

2.3 Statistical Analysis

The data were analyzed by using SPSS 26.0 software for analysis of variances (ANOVA), least significant difference (LSD), Pearson's correlation coefficient (r), receiver operating characteristics (ROC), and multinomial logistic regression to estimate the risk of the tested markers for hypertension according to lifestyle.

3. RESULTS AND DISCUSSION

The results indicated significantly ($p < 0.05$) higher values of BMI, waist to hip ratio (WHpR), and waist to height ratio (WHtR) in adherent and non-adherent obese subjects compared to controls (Table 1). Moreover, the values of BMI, WHpR, and WHtR were significantly lower in the adherent obese compared non-adherent obese group. Both of the obese groups contained a comparable percentage of subjects who expressed hypertension. Data analyzed using ANOVA followed by LSD test for continuous variables and Chi-square test for categorical variables.

Table 1. Characteristics of the studied subjects.

Parameter	Control	Non-adherent obese	Adherent obese	p-value	
Number	40	40	40		
Age (year)	29.80±7.33	32.05±8.17	31.93±6.97	0.325	
BMI (kg/m ²)	23.02±1.64a	34.39±3.23b	33.85±3.47b	< 0.001	
WC (cm)	75.60±6.91a	107.05±13.27b	91.65±8.35c	< 0.001	
WHpR	0.752±0.068a	0.868±0.065b	0.797±0.076c	< 0.001	
WHtR	0.467±0.038a	0.672±0.082b	0.575±0.061c	< 0.001	
Weight class	Normal	40 (100%)	0 (0%)	0 (0%)	< 0.001
	Obesity class I	0 (0%)	24 (60%)	29 (72.5%)	< 0.001#
	Obesity class II	0 (0%)	14 (35%)	8 (20%)	< 0.001#
	Obesity class III	0 (0%)	2 (5%)	3 (7.5%)	< 0.001#
Blood pressure	Normotensive	38 (95%)	17 (42.5%)	18 (45%)	< 0.001#
	Hypertensive	2 (5%)	23 (57.5%)	22 (55%)	< 0.001#
Physical exercise	Daily	15 (37.5%)	4 (10%)	27 (%)	< 0.001#
	2-3 times/week	7 (17.5%)	9 (22.5%)	1 (%)	< 0.001#
	1 time/week	11 (27.5%)	11 (27.5%)	9 (%)	< 0.001#
	Never	7 (17.5%)	16 (40%)	3 (%)	< 0.001#

Mean±SD; N(%). Different letters indicate significant differences between groups according to LSD test. # Significant differences in Chi-square test.

The levels of cholesterol, TGs, VLDL-C, and LDL-C were increased significantly ($p < 0.05$) in adherent and non-adherent obese subjects compared to control, with a significant decrease of HDL-C. Moreover, TGs level was reduced significantly ($p < 0.05$) in adherent obese compared to the non-adherent group (Table 2). The level of Trp was decreased significantly ($p < 0.05$) in non-adherent obese subjects (27.71±7.54 ng/mL), and adherent obese subjects (29.78±8.81 ng/mL) compared to control (35.22±11.84 ng/mL), with no significant differences ($p > 0.05$) between the two groups of obese subjects. Moreover, kynurenine level was increased significantly ($p < 0.05$) in non-adherent obese subjects (307.45±144.10 ng/L) compared to control (247.02±91.68 ng/L) and adherent obese subjects (210.32±78.94 ng/L). A non-significant ($p > 0.05$) lower level of kynurenine was observed in adherent obese subjects compared to control.

The level of 5-HT, on the other hand, increased in adherent obese subjects (53.10±18.44 ng/mL) significantly ($p < 0.05$) compared to non-adherent obese subjects (44.01±11.49 ng/mL), but not control (49.33±13.30 ng/mL), which was non-significantly differenced with non-adherent obese subjects as well (Table

2). The level of TOS was increased significantly ($p < 0.05$) in non-adherent obese subjects (4.65 ± 2.28 H₂O₂ μ M Eq/L) compared to control (3.27 ± 1.46 H₂O₂ μ M Eq/L) and adherent obese group (3.84 ± 1.28 H₂O₂ μ M Eq/L). Nevertheless, no significant ($p > 0.05$) difference in TOS level was observed between control and adherent obese subjects. The level of TAC was decreased significantly ($p < 0.05$) in non-adherent obese subjects (0.69 ± 0.26 Vit. C mM Eq/L) and adherent obese subjects (1.07 ± 0.40 Vit. C mM Eq/L), compared to control (1.65 ± 0.38 Vit. C mM Eq/L). Moreover, the level of TAC was significantly lower in non-adherent obese subjects compared to adherent obese subjects. The level of 8-OHdG was increased significantly ($p < 0.05$) in non-adherent obese subjects (13.02 ± 5.84 ng/mL) and adherent obese subjects (11.40 ± 3.23 ng/mL) compared to control (9.23 ± 4.11 ng/mL), with no significant difference between the two groups of obese subjects (Table 2). Data were analyzed using ANOVA followed by LSD post hoc test.

Table 2. Serum markers of lipid profile, Trp metabolism, and oxidative stress.

Parameter	Control	Non-adherent obese	Adherent obese	p-value
Cholesterol (mg/dL)	147.10 \pm 20.26a	165.25 \pm 29.92b	160.90 \pm 25.36b	0.005
TGs (mg/dL)	89.85 \pm 33.74a	163.40 \pm 55.55b	124.95 \pm 54.88c	<0.001
HDL (mg/dL)	42.85 \pm 3.31a	39.53 \pm 6.41b	38.65 \pm 6.45b	0.003
VLDL (mg/dL)	17.97 \pm 6.75a	32.68 \pm 11.11b	24.99 \pm 10.98c	<0.001
LDL (mg/dL)	86.28 \pm 22.75	93.05 \pm 25.87	97.26 \pm 21.52	0.112
Trp (μ mol/L)	35.22 \pm 11.84a	27.71 \pm 7.54b	29.78 \pm 8.81b	0.002
Kynurenine (ng/L)	247.02 \pm 91.68a	307.45 \pm 144.10b	210.32 \pm 78.94a	<0.001
5-OHT (ng/mL)	49.33 \pm 13.30a/b	44.01 \pm 11.49a	53.10 \pm 18.44b	0.024
TOS (H ₂ O ₂ μ M Eq/L)	3.27 \pm 1.46a	4.65 \pm 2.28b	3.84 \pm 1.28a	0.002
TAC (Vit. C mM Eq/L)	1.65 \pm 0.38a	0.69 \pm 0.26b	1.07 \pm 0.40c	<0.001
OSI	2.22 \pm 1.57a	7.60 \pm 5.05b	4.08 \pm 1.88c	<0.001
8-OHdG (ng/mL)	9.23 \pm 4.11a	13.02 \pm 5.84b	11.40 \pm 3.23b	0.001

Mean \pm SD; N(%). Different letters indicate significant differences between groups according to LSD test.

Among non-adherent obese subjects, a positive correlation was observed between TOS & BMI, TOS & OSI, TOS & kynurenine, OSI & BMI, OSI & kynurenine, kynurenine & BMI, kynurenine & WC, kynurenine & WHpR, kynurenine & WHtR, kynurenine & 8-OHdG, and 8-OHdG & BMI. Moreover, a negative correlation was observed between TAC & age, TAC & OSI, Trp & TGs, and Trp & VLDL-C (Table 3). Data analyzed using Pearson's correlation coefficient.

Table 3. Correlation of oxidative stress indicators and Trp metabolic markers in non-adherent obese subjects.

Parameters	TOS		TAC		OSI		Trp		Kynurenine		8-OHdG		5-HT	
	r	p	r	p	r	p	r	p	R	p	r	p	r	p
Age	-	0.90	-	0.00	0.277	0.08	-	0.4	0.130	0.42	-	0.9	-	0.7
BMI	0.431	0.00	-	0.13	0.423	0.00	0.10	0.5	0.893	<0.0	0.521	0.0	-	0.7
WC	0.258	0.10	-	0.17	0.235	0.15	0.20	0.2	0.446	0.00	0.190	0.2	-	0.4
HC	0.233	0.14	-	0.59	0.121	0.46	0.23	0.1	0.208	0.19	0.051	0.7	-	0.4
WHpR	0.141	0.38	-	0.09	0.238	0.14	0.05	0.7	0.467	0.00	0.251	0.1	-	0.6
WHtR	0.254	0.11	-	0.14	0.251	0.12	0.21	0.1	0.500	0.00	0.246	0.1	-	0.3
Cholest	0.124	0.44	0.067	0.68	-	0.65	-	0.1	0.306	0.05	0.278	0.0	-	0.1
TGs	-	0.70	-	0.80	-	0.65	-	0.0	0.204	0.20	0.085	0.6	-	0.9
HDL	-	0.76	-	0.07	0.085	0.60	-	0.4	0.264	0.09	0.114	0.4	-	0.0
VLDL	-	0.70	-	0.80	-	0.65	-	0.0	0.204	0.20	0.085	0.6	-	0.9
LDL	0.182	0.26	0.165	0.31	-	0.64	-	0.8	0.201	0.21	0.257	0.1	-	0.1
TOS	1	-	-	0.20	0.765	<0.0	0.16	0.3	0.529	<0.0	0.301	0.0	0.01	0.9
TAC	-	0.20	1	-	-	<0.0	-	0.7	-	0.15	-	0.4	0.02	0.9
OSI	0.765	<0.0	-	<0.0	1	-	0.20	0.2	0.487	0.00	0.268	0.1	0.09	0.5
Trp	0.163	0.31	-	0.78	0.209	0.20	1	-	0.125	0.44	0.184	0.2	-	0.4
Kynure	0.529	<0.0	-	0.15	0.487	0.00	0.12	0.4	1	-	0.502	0.0	-	0.6
8-OHdG	0.301	0.05	-	0.49	0.268	0.10	0.18	0.2	0.502	0.00	1	-	-	0.1
5-HT	0.016	0.92	0.020	0.90	0.093	0.57	-	0.4	-	0.61	-	0.1	1	-

Adherent obese subjects showed a positive correlation between TOS & TGs, TOS & OSI, TOS, & 8-OHdG, TOS & 5-HT, Trp & 8-OHdG, kynurenine & BMI, 8-OHdG, & 5-HT, 5-HT & TGs, and 5-HT & VLDL-C. Moreover, a negative correlation was observed between TAC & age, TAC & OSI, Trp & age, 5-HT & BMI, 5-HT & WC, 5-HT & WHpR, and 5-HT & WHtR (Table 4). Data analyzed using Pearson's correlation coefficient.

Table 4. Correlation of oxidative stress indicators and Trp metabolic markers in adherent obese subjects.

Parameters	TOS		TAC		OSI		Trp		Kynurenine		8-OHdG		5-HT	
	r	P	r	p	r	P	r	p	r	p	r	p	r	p
Age	0.032	0.844	-0.324*	0.042	0.233	0.147	-0.450**	0.004	-0.035	0.832	-0.197	0.222	-0.021	0.899
BMI	-0.034	0.837	0.033	0.842	-0.050	0.761	-0.031	0.847	0.590*	<0.001	-0.011	0.947	-0.323*	0.042
WC	-0.038	0.817	0.130	0.423	-0.047	0.773	-0.128	0.430	0.029	0.861	-0.263	0.101	-0.523**	0.001
HC	0.025	0.876	0.044	0.789	0.097	0.554	0.044	0.786	0.293	0.067	0.022	0.893	-0.207	0.200
Uric acid	-0.047	0.773	0.093	0.568	-0.102	0.530	-0.157	0.334	-0.178	0.272	-0.271	0.091	-0.356*	0.024
Uric acid	-0.036	0.823	0.093	0.569	-0.042	0.796	-0.227	0.158	0.066	0.685	-0.255	0.113	-0.551**	<0.001
Chole sterol	0.223	0.167	0.176	0.278	-0.085	0.604	0.150	0.356	0.236	0.142	0.165	0.308	0.058	0.722
TGs	0.383*	0.015	0.099	0.545	0.105	0.520	0.237	0.140	0.279	0.081	0.255	0.113	0.345*	0.029
HDL	0.064	0.693	0.157	0.332	-0.126	0.440	0.185	0.253	-0.185	0.253	0.221	0.171	0.004	0.979
VLDL	0.383*	0.015	0.099	0.545	0.105	0.520	0.237	0.140	0.279	0.081	0.255	0.113	0.345*	0.029
LDL	0.048	0.768	0.110	0.500	-0.115	0.478	0.001	0.999	0.191	0.237	-0.001	0.995	-0.109	0.503
TOS	1		0.229	0.154	0.391*	0.013	0.256	0.110	0.088	0.587	0.557*	<0.001	0.355*	0.024
TAC	0.229	0.154	1		-0.727**	<0.001	0.225	0.163	-0.182	0.262	0.105	0.521	0.005	0.978
OSI	0.391*	0.013	-0.727**	<0.001	1		-0.003	0.986	0.264	0.100	0.190	0.241	0.108	0.507
Trp	0.256	0.110	0.225	0.163	-0.003	0.986	1		0.060	0.712	0.459**	0.003	0.217	0.178
Kynure nine	0.088	0.587	-0.182	0.262	0.264	0.100	0.060	0.712	1		-0.070	0.667	-0.266	0.098
8-OHdG	0.557**	0.000	0.105	0.521	0.190	0.241	0.459**	0.003	-0.070	0.667	1		0.416**	0.008
5-HT	0.355*	0.024	0.005	0.978	0.108	0.507	0.217	0.178	-0.266	0.098	0.416**	0.008	1	

The increase of TOS level causes an increase in the risk of hypertension by 23% (95% CI 0.937-1.614), but non-significantly ($p>0.05$), Table 5(Data analyzed using univariate logistic regression analysis). A weight adjustment indicated a 29-fold increase in the risk of hypertension by the increase of TOS level in non-adherent obese subjects significantly ($p<0.05$), and a 16-fold increase in the risk of hypertension in adherent obese subjects, with significant ($p<0.05$) indication, Table 6(Data analyzed using multinomial logistic regression adjusted for weight). TAC was a significant ($p<0.05$) protective factor (OR=0.251; 95% CI 0.114-0.554) against hypertension, Table 5. The reduction of TAC level indicated a 34-fold increased risk of hypertension in non-adherent obese subjects, while in adherent obese subjects, the reduction of TAC level increases the risk of hypertension by 27-fold (Table 6). Moreover, OSI was a non-significant ($p>0.05$) risk factor for hypertension (OR=1.048, 95% CI 0.927-1.185), Table 5. Nevertheless, OSI risk increased by 19-fold in the non-adherent obese group significantly, and increased by 21-fold in the adherent obese group significantly, Table 6. The increase in the level of 8-OHdG caused an increase in the risk of hypertension by 13.7% (95% CI 1.018-1.270), significantly, Table 5. While the risk of 9-OHdG increased in non-adherent obese subjects by 19-fold, and in adherent obese subjects by 20-fold significantly, Table 6.

Moreover, kynurenine increased the risk of hypertension by 3.9% (95% CI 1.022-1.056) significantly, Table 5. Kynurenine risk was increased by 310-fold in non-adherent obese subjects, and 8723-fold in adherent obese subjects, significantly, Table 6. 5-HT was not related to hypertension risk (OR=1.008, 95% CI 0.980-1.037), Table 5. But the increase of 5-HT increases the risk for hypertension in non-adherent obese subjects by 27-fold, and in adherent obese subjects by 22-fold significantly, Table 6.

Table 5. Non-adjusted risk estimates for hypertension.

Parameters	OR	95% CI	p-value
TOS	1.230	0.937-1.614	0.135
TAC	0.251	0.114-0.554	0.001
OSI	1.048	0.927-1.185	0.451
8-OHdG	1.137	1.018-1.270	0.023
Kynurenine	1.039	1.022-1.056	<0.001
5-HT	1.008	0.980-1.037	0.565

Table 6. Weight adjusted risk estimates for hypertension.

Parameters	Non-adherent obese			Dietary adherent obese		
	OR	95% CI	p-value	OR	95% CI	p-value
TOS	29.284	5.453-157.270	<0.001	16.550	3.384-80.944	0.001
TAC*	34.730	4.646-259.60	0.001	27.923	4.882-159.705	<0.001
OSI	19.222	3.596-102.749	0.001	21.337	4.452-102.273	<0.001
8-OHdG	19.363	3.974-94.346	<0.001	20.393	4.225-98.432	<0.001
Kynurenine	310.331	16.489-5840.603	<0.001	8723.325	163.143-466439.350	<0.001
5-HT	27.030	5.643-129.464	<0.001	22.657	4.787-107.242	<0.001

* Reduction. OR: odds ratio, CI: confidence interval.

Kynurenine has shown excellent sensitivity (AUC=0.967) for the diagnosis of hypertension in non-adherent obese subjects with a cut-off value of 265.42 ng/L in 100% sensitivity and 94.1% specificity. Moreover, kynurenine has shown good sensitivity (AUC=0.894) in the diagnosis of hypertension in adherent obese subjects, where the cut-off value was 169.98 ng/mL in 86.4% sensitivity and 83.3% specificity. Moreover, 8-OHdG has shown good sensitivity (AUC=0.835) in the diagnosis of hypertension in non-adherent obese subjects with a cut-off value of 11.31 mg/mL in 82.6% sensitivity and 82.4% specificity, but not in adherent obese subjects, as shown in Table 7. Table 8, and Figure 1. Data analyzed using receiver operating characteristic (ROC) curve analysis. Kynurenine had superior diagnostic efficacy for hypertension among all evaluated biomarkers in both obese populations. In non-adherent obese individuals, kynurenine had an impressive AUC of 0.967, demonstrating 100% sensitivity and 94.1% specificity at a threshold of 265.42 ng/L. In obese individuals, kynurenine exhibited strong diagnostic accuracy, with an AUC of 0.894, 86.4% sensitivity, and 83.3% specificity at a threshold of 169.98 ng/mL.

The elevated AUC signifies kynurenine is a dependable biomarker for forecasting hypertension in obese women, particularly in those not following dietary treatments. This shows that increased kynurenine levels may act as a preliminary warning sign for hypertension risk, perhaps because of its established involvement in promoting oxidative stress and vascular impairment.

Table 7. ROC analysis for the diagnosis of hypertension in non-adherent obese subjects

Parameters	AUC	SE	p-value	Cut-off value	Sensitivity	Specificity
Kynurenine	0.967	0.033	<0.001	265.42 ng/L	100%	94.1%
5-OHTrp	0.506	0.094	0.945	-	-	-
TOS	0.646	0.091	0.119	-	-	-
OSI	0.540	0.095	0.671	-	-	-
8-OHdG	0.835	0.070	<0.001	11.31 ng/mL	82.6%	82.4%

Table 8. ROC analysis for the diagnosis of hypertension in obese diet.

Parameters	AUC	SE	p-value	Cut-off value	Sensitivity	Specificity
Kynurenine	0.894	0.053	<0.001	169.98	86.4%	83.3%
5-OHTrp	0.524	0.093	0.796	-	-	-
TOS	0.485	0.093	0.870	-	-	-
OSI	0.551	0.094	0.587	-	-	-
8-OHdG	0.419	0.091	0.384	-	-	-

AUC: area under the curve, SE: standard error.

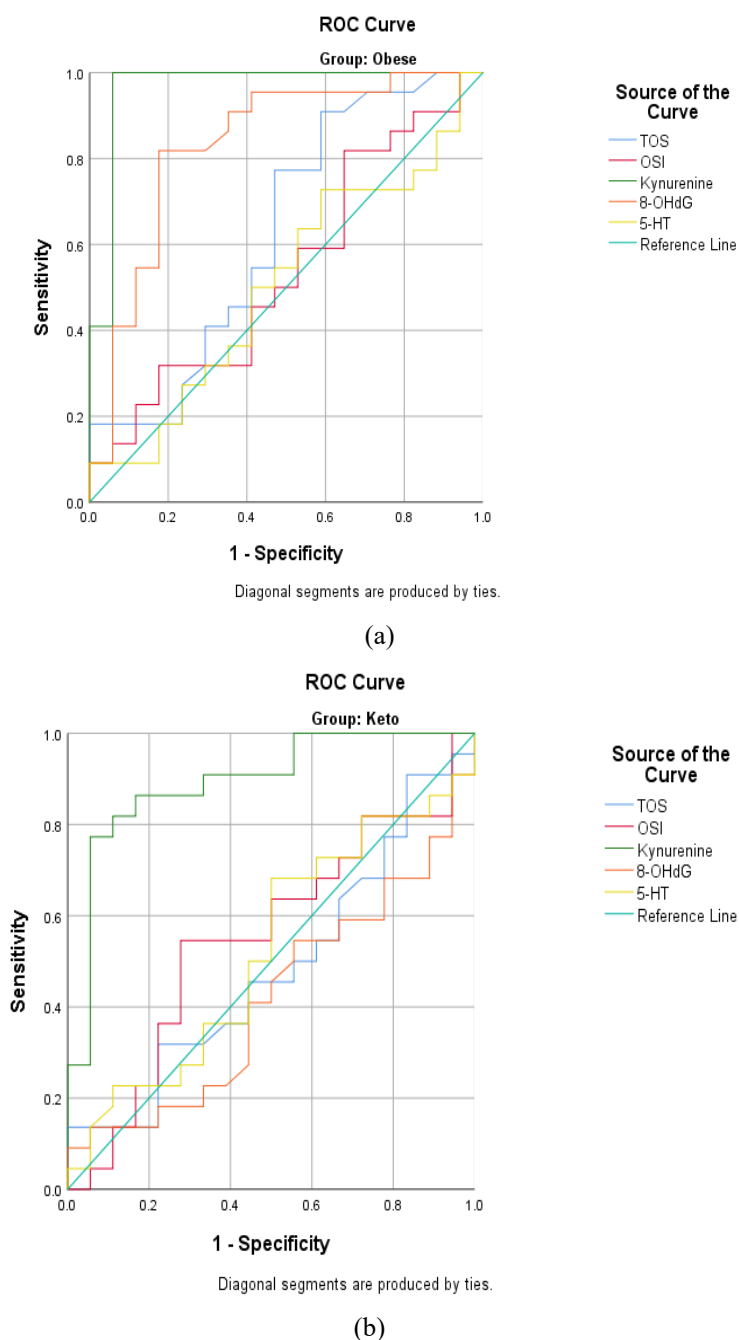


Figure 1. ROC curves for TOS, OSI, kynurenine, 8-OHdG, and 5-HT for the diagnoses of hypertension in non-adherent obese (left) and adherent obese (right)

Obesity is a major risk factor for hypertension [28] and increased oxidative stress [29]. Dyslipidemia is one way to increase blood pressure in obese subjects [30]. This study found that obese subjects exhibited markedly elevated levels of cholesterol, triglycerides, LDL-C, and VLDL-C (Table 2), corroborating the observations made by Taay et al., who reported analogous trends in both normotensive and hypertensive obese women [31]. It frequently coexists with dyslipidemia, which elevates blood pressure by raising free fatty acids that provoke inflammation and vascular dysfunction [32] and [33]. Conversely, triglycerides were markedly decreased in those adhering to low-carbohydrate intermittent fasting, signifying improved lipid management. Yancy et al. showed similar results with low-carbohydrate diets, demonstrating reduced triglycerides and elevated HDL cholesterol, exceeding the effects of low-fat diets [34]. Markers of oxidative stress were heightened in obese individuals. TOS rose in the non-adherent group, TAC decreased in both obese groups, and 8-OHdG was high in both (Table 2). The findings correspond with research conducted by Amani et al. and Amirkhizi et al., which indicated less total antioxidant capacity and elevated malondialdehyde levels in obese people [35] and [36]. Cejvanovic et al. also identified increased urine 8-OHdG associated with RNA oxidative damage in obese males [37]. Conversely, Himmetoglu et al. and Kocael et al. observed reduced 8-OHdG in blood of morbidly obese individuals, negatively correlated with insulin resistance [38] and [39], divergent from existing findings.

Elevated levels of 8-OHdG are frequently observed in obesity associated with diabetes [40,41], and cancer associated obesity [42,43]. Anthropometric measurements (WC, WHpR) validated central obesity (Table 1), which correlates with insulin resistance [44]. The latter is known as inducer of inflammatory cytokines [45] which are strongly associated with ROS and oxidative stress [29]. A study reported that low-carb diet improved liver health and oxidative stress status in rat models, in which a 6 weeks of low-carb diet caused significant improvements in the activities of superoxide dismutase and catalase, and the levels of malondialdehyde, nitric oxide, and glutathione [46]. Moreover, Sharsher *et al.* reported that IF reduced BMI, TGs, and malondialdehyde in rats, and it had increased the level of TAC significantly, which can contribute to a reduction in the risk of cardiovascular diseases [47].

Tryptophan Metabolism non-adherent obese females had reduced Trp and 5-HT levels, alongside increased kynurenine, whereas adherent participants presented lower Trp and kynurenine levels but enhanced 5-HT (Table 2). Shestopalov *et al.* ascribed elevated kynurenine levels in obesity to the activation of inflammatory cytokines [48-49]. Huang *et al.* associated it with adipocyte-induced IDO1 activity and IL-6/STAT3 signaling that lead to oxidative stress and insulin resistance [50]. Kynurenine showed positive correlations with TOS, OSI, and 8-OHdG (Table 3), underscoring its role in oxidative stress. These relationships were not present in adherent individuals, indicating regulation by low-carbohydrate intermittent fasting. The reduced kynurenine and elevated 5-HT in adherent people suggest a metabolic alteration in tryptophan catabolism that may enhance general health [51] and [52]. 5-HT exhibited a negative correlation with BMI, WC, WHpR, and WHtR (Table 4), establishing a connection between weight reduction and serotonergic activity. Concurrently, kynurenine persisted as a hypertension risk factor in both cohorts (Table 5, Table 6), presumably due to its influence on nitric oxide inhibition through superoxide interaction, hence facilitating vasoconstriction.

4. CONCLUSION

The metabolism of Trp participates in the pathophysiology of obesity-related hypertension and oxidative stress. Low-carb-IF adherents showed a shifting behavior of Trp metabolism in obese subjects from kynurenine to 5-HT. "While kynurenine predominated as the major metabolic pathway in non-adherent obese subjects that showed a positive correlation with the BMI of both adherent and non-adherent obese subjects, 5-HT was correlated negatively with BMI, WHpR, and WHtR in adherent obese subjects indicating that this adherent that causes a reduction in the anthropometrics of obesity resulted in elevated 5-HT levels by promoting this metabolic pathway of Trp metabolism against the kynurenine pathway. Furthermore, kynurenine is a hypertensive risk factor in adherent and non-adherent obese subjects, and an oxidative stress-inducing factor in non-adherent obese subjects.

ACKNOWLEDGEMENTS

The authors appreciate the College of Education for Pure Sciences - University of Diyala - for using laboratories with the necessary equipment to carry out the experiment.







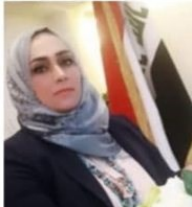


REFERENCES

- [1] I. Lingvay, R. V. Cohen, C. W. L. Roux, and P. Sumithran, "Obesity in adults," *The Lancet*, vol. 404, no. 10456, pp. 972–987, 2024, doi: 10.1016/S0140-6736(24)01210-8.
- [2] E. M. Eltayef, "Relationship of obesity to serum ferritin, lipid profile, uric acid and urea at Obesity Medical Center in Iraq," *Al-Mustansiriyah Journal of Science*, vol. 29, no. 1, pp. 87–96, 2018.
- [3] M. Safaei, E. A. Sundararajan, M. Driss, W. Boulila, and A. Shapi'i, "A systematic literature review on obesity: Understanding the causes and consequences of obesity and reviewing various machine learning approaches used to predict obesity," *Computers in Biology and Medicine*, vol. 136, p. 104754, 2021, doi: 10.1016/j.compbiomed.2021.104754.
- [4] World Health Organization, "Obesity and overweight," 2024. [Online]. Available: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed: Feb. 7, 2025.
- [5] X. Lin and H. Li, "Obesity: Epidemiology, pathophysiology, and therapeutics," *Frontiers in Endocrinology*, vol. 12, p. 706978, 2021, doi: 10.3389/fendo.2021.706978.
- [6] J. S. Volek, S. D. Phinney, and R. M. Krauss, "Alternative dietary patterns for Americans: Low-carbohydrate diets," *Nutrients*, vol. 13, no. 10, p. 3299, 2021, doi: 10.3390/nu13103299.
- [7] W. McGaugh and B. Barthel, "A review of ketogenic diet and lifestyle," *Missouri Medicine*, vol. 119, no. 1, pp. 84–88, Jan.–Feb. 2022.
- [8] K. A. Varady, S. Cienfuegos, M. Ezpeleta, and K. Gabel, "Clinical application of intermittent fasting for weight loss: Progress and future directions," *Nature Reviews Endocrinology*, vol. 18, no. 5, pp. 309–321, 2022, doi: 10.1038/s41574-022-00638-x.
- [9] R. Pojednic, E. Arpino, I. Halliday, and A. Bantham, "The benefits of physical activity for people with obesity, independent of weight loss: A systematic review," *International Journal of Environmental Research and Public Health*, vol. 19, no. 9, p. 4981, 2022, doi: 10.3390/ijerph19094981.
- [10] R. Oh, B. Gilani, and K. R. Uppaluri, "Low-carbohydrate diet," in *StatPearls*, Treasure Island, FL, USA: StatPearls Publishing, 2023. [Online]. Available: <https://www.ncbi.nlm.nih.gov/books/NBK537084/>
- [11] R. Huntriss, M. Campbell, and C. Bedwell, "The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials," *European Journal of Clinical Nutrition*, vol. 72, no. 3, pp. 311–325, 2018.
- [12] I. Shai, D. Schwarzfuchs, Y. Henkin, *et al.*, "Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet," *New England Journal of Medicine*, vol. 359, no. 3, pp. 229–241, 2008, doi: 10.1056/NEJMoa0708681.

- [13] A. Bellavia, F. Stilling, and A. Wolk, "High red meat intake and all-cause cardiovascular and cancer mortality: Is the risk modified by fruit and vegetable intake?" *The American Journal of Clinical Nutrition*, vol. 104, no. 4, pp. 1137–1143, 2016, doi: 10.3945/ajcn.116.133348.
- [14] D. Aune, E. Giovannucci, P. Boffetta, *et al.*, "Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality: A systematic review and dose-response meta-analysis of prospective studies," *International Journal of Epidemiology*, vol. 46, no. 3, pp. 1029–1056, 2017, doi: 10.1093/ije/dyw319.
- [15] S. Akter, T. Mizoue, A. Nanri, *et al.*, "Low carbohydrate diet and all-cause and cause-specific mortality," *Clinical Nutrition*, vol. 40, no. 4, pp. 2016–2024, 2021, doi: 10.1016/j.clnu.2020.10.015.
- [16] I. Vasim, C. N. Majeed, and M. D. DeBoer, "Intermittent fasting and metabolic health," *Nutrients*, vol. 14, no. 3, p. 631, 2022, doi: 10.3390/nu14030631.
- [17] K. Nowosad and M. Sujka, "Effect of various types of intermittent fasting (IF) on weight loss and improvement of diabetic parameters in humans," *Current Nutrition Reports*, vol. 10, no. 2, pp. 146–154, 2021, doi: 10.1007/s13668-021-00353-9.
- [18] C. Xue, G. Li, Q. Zheng, *et al.*, "Tryptophan metabolism in health and disease," *Cell Metabolism*, vol. 35, no. 8, pp. 1304–1326, 2023, doi: 10.1016/j.cmet.2023.06.012.
- [19] C. Xue, X. Gu, Q. Zheng, *et al.*, "Effects of 3-HAA on HCC by regulating heterogeneous macrophages: A scRNA-seq analysis," *Advanced Science*, vol. 10, no. 16, p. 2207074, 2023, doi: 10.1002/advs.202207074.
- [20] Y. Zhao, "Auxin biosynthesis: A simple two-step pathway converts tryptophan to indole-3-acetic acid in plants," *Molecular Plant*, vol. 5, no. 2, pp. 334–338, 2012, doi: 10.1093/mp/ssr104.
- [21] S. K. Masenga, L. S. Kabwe, M. Chakulya, and A. Kirabo, "Mechanisms of oxidative stress in metabolic syndrome," *International Journal of Molecular Sciences*, vol. 24, no. 9, p. 7898, 2023, doi: 10.3390/ijms24097898.
- [22] R. A. Raheem, S. A. K. Essmat, and Y. M. Taay, "The role of advanced glycation end products and oxidative stress in the pathophysiology of thyroid disorders," *ALP Conference Proceedings*, vol. 3229, no. 1, 2024.
- [23] Y. Zhou, H. Li, and N. Xia, "The interplay between adipose tissue and vasculature: Role of oxidative stress in obesity," *Frontiers in Cardiovascular Medicine*, vol. 8, 2021, doi: 10.3389/fcvm.2021.650413.
- [24] M. K. Brahma, E. H. Gilgioni, L. Zhou, E. Trépo, P. Chen, and E. N. Gurzov, "Oxidative stress in obesity-associated hepatocellular carcinoma: Sources, signaling and therapeutic challenges," *Oncogene*, vol. 40, no. 33, pp. 5155–5167, 2021, doi: 10.1038/s41388-021-01950-y.
- [25] E. Çolak and D. Pap, "The role of oxidative stress in the development of obesity and obesity-related metabolic disorders," *Journal of Medical Biochemistry*, vol. 40, no. 1, pp. 1–9, 2021, doi: 10.5937/jomb0-27544.
- [26] S. M. Kadhim, S. M. Abbood, Y. M. Taay, and M. T. Mohammed, "Oxidative stress in multiple sclerosis disease," *Diyala Journal of Medicine*, vol. 21, no. 2, pp. 33–40, 2021.
- [27] K. S. Abod, M. T. Mohammed, and Y. M. Taay, "Evaluation of total oxidant status and antioxidant capacity in sera of acute and chronic renal failure patients," *Journal of Physics: Conference Series*, vol. 1853, no. 1, p. 012038, 2021, doi: 10.1088/1742-6596/1853/1/012038.
- [28] S. Z. Jiang, W. Lu, X. F. Zong, H. Y. Ruan, and Y. Liu, "Obesity and hypertension (Review)," *Experimental and Therapeutic Medicine*, vol. 12, no. 4, pp. 2395–2399, Oct. 2016, doi: 10.3892/etm.2016.3767.
- [29] A. Fernández-Sánchez, E. Madrigal-Santillán, M. Bautista, *et al.*, "Inflammation, oxidative stress, and obesity," *International Journal of Molecular Sciences*, vol. 12, no. 5, pp. 3117–3132, 2011, doi: 10.3390/ijms12053117.
- [30] N. Tang, J. Ma, R. Tao, *et al.*, "The effects of the interaction between BMI and dyslipidemia on hypertension in adults," *Scientific Reports*, vol. 12, no. 1, p. 927, 2022, doi: 10.1038/s41598-022-05110-2.
- [31] Y. M. Taay, M. T. Mohammed, R. Abbas, A. Ayad, and M. A. Mahdi, "Determination of some biochemical parameters in sera of normotensive and hypertensive obese female in Baghdad," *Journal of Physics: Conference Series*, vol. 1853, p. 012037, 2021, doi: 10.1088/1742-6596/1853/1/012037.
- [32] J. A. N. Dorresteyn, F. L. J. Visseren, and W. Spiering, "Mechanisms linking obesity to hypertension," *Obesity Reviews*, vol. 13, no. 1, pp. 17–26, 2012, doi: 10.1111/j.1467-789X.2011.00942.x.
- [33] V. Kotsis, S. Stabouli, S. Papakatsika, Z. Rizos, and G. Parati, "Mechanisms of obesity-induced hypertension," *Hypertension Research*, vol. 33, no. 5, pp. 386–393, 2010, doi: 10.1038/hr.2010.4.
- [34] W. S. Yancy, M. K. Olsen, R. P. Bakst, and E. C. Westman, "A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia," *Annals of Internal Medicine*, vol. 140, no. 10, pp. 769–777, 2004, doi: 10.7326/0003-4819-140-10-200405180-00006.
- [35] R. Amani, M. Parohan, N. Jomehzadeh, and M. H. Haghighizadeh, "Dietary and biochemical characteristics associated with normal-weight obesity," *Zeitschrift für Gesundheitswissenschaften*, vol. 89, pp. 331–336, 2019, doi: 10.1024/0300-9831/a000570.
- [36] F. Amirkhizi, F. Siassi, M. Djalali, and A. R. Foroushani, "Evaluation of oxidative stress and total antioxidant capacity in women with general and abdominal adiposity," *Obesity Research & Clinical Practice*, vol. 4, no. 3, pp. e209–e216, 2010, doi: 10.1016/j.orcp.2010.07.001.
- [37] V. Cejvanovic, C. Asferg, K. L. Kjær, *et al.*, "Markers of oxidative stress in obese men with and without hypertension," *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 76, no. 8, pp. 620–625, 2016, doi: 10.1080/00365513.2016.1230776.
- [38] S. Himmetoglu, S. Teksoz, K. Zengin, T. Yesim, M. Taskin, and Y. Dincer, "Serum levels of fetuin A and 8-hydroxydeoxyguanosine in morbidly obese subjects," *Experimental and Clinical Endocrinology & Diabetes*, vol. 121, no. 8, pp. 505–508, 2013, doi: 10.1055/s-0033-1352060.
- [39] A. Kocael, H. Erman, K. Zengin, *et al.*, "The effects on oxidative DNA damage of laparoscopic gastric band applications in morbidly obese patients," *Canadian Journal of Surgery*, vol. 57, no. 3, pp. 183–187, 2014, doi: 10.1503/cjs.014613.
- [40] H. A. Al-Aubaidy and H. F. Jelinek, "Oxidative DNA damage and obesity in type 2 diabetes mellitus," *European Journal of Endocrinology*, vol. 164, no. 6, pp. 899–904, 2011, doi: 10.1530/EJE-10-0890.

- [41] J. Sun, X. Lou, H. Wang, et al., "Serum 8-hydroxy-2'-deoxyguanosine (8-oxo-dG) levels are elevated in diabetes patients," *International Journal of Diabetes in Developing Countries*, vol. 35, pp. 368–373, 2015, doi: 10.1007/s13410-015-0210-7.
- [42] T. Sato, H. Takeda, S. Otake, et al., "Increased plasma levels of 8-hydroxydeoxyguanosine are associated with development of colorectal tumors," *Journal of Clinical Biochemistry and Nutrition*, vol. 47, no. 1, pp. 59–63, 2010, doi: 10.3164/jcbrn.09-222.
- [43] A. Al-Taie, M. Sancar, and F. V. Izzettin, "8-Hydroxydeoxyguanosine: A valuable predictor of oxidative DNA damage in cancer and diabetes mellitus," *Cancer*, vol. 127, pp. 179–187, 2021, doi: 10.1002/cncr.33422.
- [44] Y. Tong, S. Xu, L. Huang, and C. Chen, "Obesity and insulin resistance: Pathophysiology and treatment," *Drug Discovery Today*, vol. 27, no. 3, pp. 822–830, 2022, doi: 10.1016/j.drudis.2021.11.007.
- [45] M. Shimobayashi, V. Albert, B. Woelnerhanssen, et al., "Insulin resistance causes inflammation in adipose tissue," *The Journal of Clinical Investigation*, vol. 128, no. 4, pp. 1538–1550, 2018, doi: 10.1172/JCI96202.
- [46] H. B. Jebur, "Therapeutic evaluation of the anti-inflammatory and anti-oxidative protective effects of the ketogenic diet on Wistar rats," *Egyptian Journal of Nutrition*, vol. 38, no. 3, pp. 34–43, 2023.
- [47] S. I. Sharsher, A. I. Ahmed, M. Metwally, A. H. Arisha, and K. E.-D. Ahmed, "Intermittent fasting decreases oxidative stress parameters and increases total antioxidant capacity," *Biointerface Research in Applied Chemistry*, vol. 12, no. 5, pp. 6763–6775, 2022, doi: 10.33263/BRIAC125.67636775.
- [48] A. Shestopalov, O. Shatova, M. Karbyshev, et al., "Kynurenine switch" and obesity," *Bulletin of Siberian Medicine*, vol. 20, no. 4, pp. 103–111, 2022.
- [49] T. Huang, J. Song, J. Gao, et al., "Adipocyte-derived kynurenine promotes obesity and insulin resistance by activating the AhR/STAT3/IL-6 signaling," *Nature Communications*, vol. 13, no. 1, p. 3489, 2022, doi: 10.1038/s41467-022-31232-6.
- [50] C.-W. Liu, T.-L. Lee, Y.-C. Chen, et al., "PM2.5-induced oxidative stress increases intercellular adhesion molecule-1 expression in lung epithelial cells through the IL-6/AKT/STAT3/NF-κB-dependent pathway," *Particle and Fibre Toxicology*, vol. 15, p. 16, 2018, doi: 10.1186/s12989-018-0254-y.
- [51] İ. Otrav and A. M. Günal, "Effects of 5-Hydroxytryptophan (5-HTP) nutritional supplement on health," *Journal of Innovative Healthcare Practices*, vol. 4, no. 1, pp. 1–8, 2023.
- [52] S. Sun, F. Hu, Y. Sang, et al., "Dysregulated tryptophan metabolism contributes to metabolic syndrome in Chinese community-dwelling older adults," *BMC Endocrine Disorders*, vol. 25, no. 1, p. 7, 2025, doi: 10.1186/s12902-024-01357-6.

BIOGRAPHIES OF AUTHORS

	<p>Nabaa Jawad Kadhem is a Master's student in the Department of Chemistry, College of Science, Mustansiriyah University, Iraq. She received her B.Sc. degree in Chemistry from the same college. Her academic interests lie in the fields of biochemistry and clinical chemistry. She is currently conducting research related to obesity and low-carbohydrate dietary interventions. She can be contacted at: Email: nabaa.jawad99@uomustansiriyah.edu.iq</p> <p>Scopus®  </p>
	<p>Dr. Mustafa Taha Mohammed is a Professor at the College of Science, Mustansiriyah University, Iraq. He received his B.Sc. degree in Chemistry and his M.Sc. degree in Biochemistry from Mustansiriyah University, Iraq. He obtained his Ph.D. in Biochemistry from N.I. Lobachevsky State University of Nizhni Novgorod, Russia. His research interests include various topics in biochemistry. He has published numerous scientific papers in national and international conferences and journals. He can be contacted at: tahabiochem@yahoo.com.</p> <p>Scopus®  </p>
	<p>Dr. Rulla Sabah Naser Ali Assistant professor in the Department of Chemistry, College of Science, Mustansiriyah University, Iraq. She received her B.Sc. degree in Chemistry and her M.Sc. degree in Organic Chemistry from Mustansiriyah University (Iraq). She obtained her Ph.D. in Bioanalytical Chemistry from the same university in 2020. Her research interests focus on organic and bioanalytical chemistry. She has published several scientific papers in national and international conferences and journals. She can be contacted at: Email: rulla_sabah77@uomustansiriyah.edu.iq</p> <p>Scopus®  </p>