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

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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.

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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/m^2, 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 cholesterols (LDL and VLDL) were determined by the following equations1 1-3:

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

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

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

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	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 µM

Eq/L) compared to control (3.27±1.46 H2O2 µM Eq/L) and adherent obese group (3.84±1.28 H2O2 µM 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±20.26a	165.25±29.92b	160.90±25.36b	0.005
TGs (mg/dL)	89.85±33.74a	163.40±55.55b	124.95±54.88c	<0.001
HDL (mg/dL)	42.85±3.31a	39.53±6.41b	38.65±6.45b	0.003
VLDL (mg/dL)	17.97±6.75a	32.68±11.11b	24.99±10.98c	<0.001
LDL (mg/dL)	86.28±22.75	93.05±25.87	97.26±21.52	0.112
Trp (µmol/L)	35.22±11.84a	27.71±7.54b	29.78±8.81b	0.002
Kynurenine (ng/L)	247.02±91.68a	307.45±144.10b	210.32±78.94a	<0.001
5-OHT (ng/mL)	49.33±13.30a/b	44.01±11.49a	53.10±18.44b	0.024
TOS (H2O2 µM Eq/L)	3.27±1.46a	4.65±2.28b	3.84±1.28a	0.002
TAC (Vit. C mM Eq/L)	1.65±0.38a	0.69±0.26b	1.07±0.40c	<0.001
OSI	2.22±1.57a	7.60±5.05b	4.08±1.88c	<0.001
8-OHdG (ng/mL)	9.23±4.11a	13.02±5.84b	11.40±3.23b	0.001

Mean±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-	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
WHpR	-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
WHtR	-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
Cholesterol	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
Kynurenine	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.

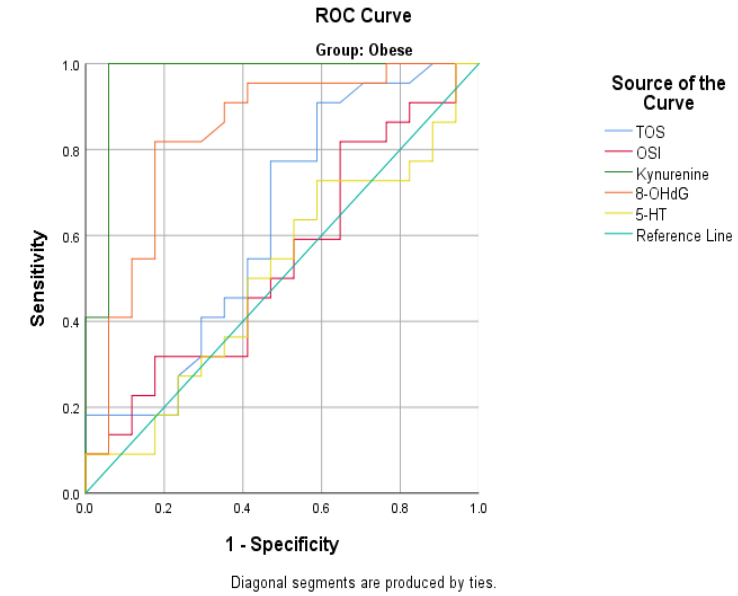
Table 7. ROC analysis for the diagnosis of hypertension in non-adherent obese subjects

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%

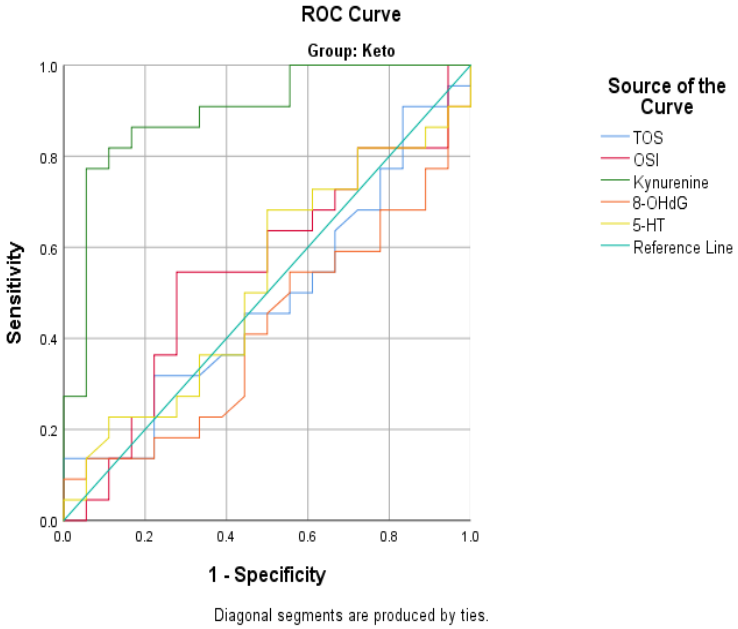
Table 8.ROC analysis for the diagnosis of hypertension in obese diet.

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.



(a)



(b)

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.

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