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Orlistat Modulates Caspase-4, Interleukin-15, and Pancreatic Lipase Activity in Obese Females: A Cohort Study.

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ABSTRACT: Caspase-4 is a pro-inflammatory mediator involved in activation of non-canonical inflammasomes and has been strongly associated with obesity-related inflammation and metabolic dysfunction. Interleukin-15 (IL-15) plays an important role in body weight regulation and reduction of adipose tissue mass, while pancreatic lipase is a key enzyme responsible for lipid digestion and absorption, making it essential for lipid metabolism and energy balance. This study aimed to evaluate the effect of orlistat treatment on serum levels of IL-15, Caspase-4, and lipase activity in obese women and to compare the therapeutic outcomes between single-dose and double-dose orlistat regimens. This case–control study was conducted on women attending the Nutrition Clinic at Marjan Teaching Hospital, Babylon, Iraq. A total of 300 women aged between 21 and 42 years were enrolled, including 60 obese women, 90 obese women treated with one dose of orlistat for two weeks, 90 obese women treated with two doses of orlistat for two weeks, and 60 non-obese healthy controls classified according to body mass index (BMI). Women with endocrine, autoimmune, renal, or cardiovascular diseases were excluded. Serum IL-15 and Caspase-4 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits supplied by BT Lab, China, while serum lipase activity was estimated spectrophotometrically using the kinetic method (Biolabo, France). Obese women receiving two doses of orlistat showed significantly better improvement in inflammatory and metabolic biomarkers than those receiving a single dose. The two-dose regimen produced the most favorable therapeutic outcomes, while untreated obese women exhibited the poorest metabolic status.

INTRODUCTION:

Obesity is a medical disorder, and some people think of it as a sickness, in which too much body fat has built up to the point that it might be bad for health (1). If a person's body mass index (BMI), which is their weight divided by the square of their height, is above 30 kg/m², they are considered obese. If their BMI is between 25 and 30 kg/m², they are considered overweight (2). Obesity is a significant source of impairment and is linked to many illnesses and ailments, including type 2 diabetes, obstructive sleep apnea, several forms of cancer, and osteoarthritis (3).

The US Food and Drug Administration (FDA) has authorized Orlistat (tetrahydrolipstatin) as a drug to help people lose weight. This drug is a saturated derivative of the natural lipstatin discovered in the bacteria *Streptomyces toxytricini* (4). Orlistat helps

people lose weight by temporarily blocking gastric and pancreatic lipases in the intestines. These lipases are very important for breaking down triglycerides into free fatty acids and monoglycerides that the body may use. Orlistat attaches to the serine residues of the active sites of these lipases in a covalent way, making them inactive. This stops lipase from breaking down triglycerides, which makes it harder for free fatty acids to be absorbed (5).

Caspase-4 is pro-inflammatory in obesity, especially because it helps activate non-canonical inflammasomes. It finds lipopolysaccharides within cells and causes the release of IL-1 β and IL-18, two inflammatory cytokines that are important in metabolic inflammation. Most research on obesity-related inflammation and insulin resistance has looked at caspase-1, -3, and -8 (6). However, new data shows that caspase-4 may also play a role in the long-term low-grade inflammation that occurs in obesity, notably in fat tissue and maybe even in the brain. This swelling is connected to metabolic problems and insulin resistance (7).

Interleukin-15 (IL-15) is a cytokine that is well recognized for controlling the immune system, especially the formation of natural killer cells (8). However, more and more data shows that it has a big role in metabolism, particularly when it comes to obesity. People who are overweight tend to have lower amounts of IL-15 in their blood than people who are not overweight (9). IL-15 levels in the blood are inversely connected to trunk fat mass and the percentage of body fat generally (10).

IL-15 causes weight reduction and fat cell shrinking even in mice that don't have lymphocytes. This shows that its impacts on obesity aren't only caused by immune cells like NK or T cells (11). This may happen by speeding up lipolysis and fatty acid oxidation in organs like the liver and muscles. IL-15 lowers body fat and weight, and research in both animals and people suggest that it may help people lose weight (12,13).

Pancreatic lipase is very important for breaking down and absorbing lipids. This makes it a key player in lipid metabolism and energy balance. Pancreatic lipase is very important for digestion because it changes dietary lipids into monoacylglycerols and fatty acids in the duodenum (14). The lipid metabolism route, which comprises both the exogenous and endogenous processes, depends on this enzyme's functioning (15). It is well known that blocking PL with drugs may help lower the amount of fat that the body absorbs from food. Orlistat is a well-known PL inhibitor that has been licensed to treat obesity (16). It works by lowering the amount of fat that the body absorbs and helping people lose weight (17).

The study aimed to assess the effect of orlistat on levels of IL-15, caspase 4 and lipase in obese women comparing one dose orlistat with two dose orlistat.

2-PATIENTS AND METHODS:

Study Design:

Blood samples were obtained from women who were registered Nutrition Clinic at Marjan Teaching Hospital- Babylon, Iraq, to conduct this cohort study. The ages of the women and controls who participated in the study ranged from (21- 42 years). A total of 300 cases were categorized into four groups: 60 obese control (OCG), 90 obese persons with one dose orlistat (two weeks) (ODOG), 90 obese with two Doses orlistat (2 weeks) (TDOG) and 60 Non-obese controls (HG), all clinical data were documented. Women with a history of endocrine, autoimmune kidney diseases, and cardiovascular diseases were excluded.

The collection of blood samples

The 3 millilitres of blood were collected in a gel tube. The gel tube was subsequently transferred to the laboratory for immediate centrifugation at 3000 rpm Following this procedure, serum was separated into distinct tubes, in accordance with standard laboratory protocols.

The IL-15 and Caspase 4 were estimated by Enzyme Linked Immune Sorbent Assay (ELISA) by BT Lab. Kits/ China. serum lipase was estimated by spectrophotometry by kinetic method (Biolabo / French).

Ethical Approval

Approval of scientific committee in chemistry Department of College of science. The objectives and methodology of this study were explained to all participants in the current study to gain their verbal acceptance. The objectives and methodology of this study were explained to all participants in the current study to gain their verbal acceptance. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 129 in 7/1/2025 to get this approval

Statistical study: -

The SPSS-26.0 version of the Software Package for Social Science was used in data analysis. The mean and standard deviation (SD) presentations of the data Using ANOVA and linear regression analysis—which helped to find noteworthy variations between the groups—the normalcy of continuous variables was evaluated. P. values were considered highly significant if less than 0.001 and significant if less than 0.05.

RESULTS

Table 1 and table 2 show that among the four groups under investigation, there were extremely significant variations in serum pancreatic lipase, IL-15, and caspase-4 ($P < 0.01$). The non-obese group (NOBG; 35.2 ± 7.64 IU/L) had the greatest mean lipase activity, while the obese group (OBG; 29.06 ± 5.61 IU/L) had the lowest. The one-dose (ODG; 31.1 ± 7.04 IU/L) and two-dose (TDG; 33.52 ± 8.27 IU/L). Similarly, IL-15 concentrations were significantly lower in OBG (121.77 ± 52.36 ng/mL) and increased with increasing orlistat dose in ODG (136.82 ± 35.55 ng/mL) and TDG (214.45 ± 74.19 ng/mL). The highest levels were found in NOBG (246.38 ± 99.18 ng/mL), indicating improvement in IL-15-related metabolic status and weight. On the other hand, caspase-4 activity was highest in OBG (2.39 ± 0.67 IU/L), gradually decreased in ODG (1.98 ± 0.53 IU/L) and TDG (1.69 ± 0.48 IU/L), and reached its lowest values in NOBG (1.40 ± 0.39 IU/L). This indicates that orlistat therapy attenuates inflammatory caspase activation linked to obesity. All of these results point to a strong connection between obesity, orlistat treatment, and changes in the digestive (lipase), metabolic (IL-15), and inflammatory (caspase-4) pathways.

In table 3 and table 4 there are serum pancreatic lipase, IL-15 and caspase-4 showed clear and highly significant differences across the BMI-based subgroups ($P < 0.01$). In untreated obese patients, those with BMI $30\text{--}35$ kg/m² had moderately raised lipase levels, whereas individuals with higher BMI ($36\text{--}47$ kg/m²) tended to have slightly lower values. With orlistat therapy, lipase increased gradually in both BMI categories, with the highest means observed in the second-dose treated groups, suggesting a progressive treatment-related shift in digestive enzyme activity. IL-15 followed a BMI-sensitive pattern: it was relatively higher in patients with BMI $30\text{--}35$ kg/m² and noticeably lower in those with BMI $36\text{--}47$ kg/m², while treatment with orlistat brought IL-15 levels in both ranges closer together and then higher, particularly after the second dose, indicating a possible recovery or enhancement of this metabolically active cytokine in more obese patients. Caspase-4 activity started higher in mildly obese subjects and slightly lower in those with more severe obesity, but it fell consistently with orlistat use in both BMI groups, reaching its lowest values after the second dose, which points to a gradual reduction in obesity-related inflammatory activation under treatment.

In the table 5 and figures 1,2, and 3. A moderate yet statistically significant correlation exists between lipase, IL-15, and caspase-4. Lipase exhibits a modest positive connection with IL-15 ($r = 0.166$, $P = 0.010$), suggesting that elevated lipase levels are marginally related with increased IL-15 concentrations. Conversely, lipase has a modest yet significant negative correlation with caspase-4 ($r = -0.162$, $P = 0.012$), indicating that elevations in lipase are associated with minor reductions in caspase-4 activity. IL-15 exhibits a notable negative connection with caspase-4 ($r = -0.241$, $P < 0.01$), indicating that elevated levels of IL-15 are associated with reduced caspase-4, which aligns with a transition towards a more advantageous metabolic and less inflammatory profile. Despite the minor effect sizes, the data suggests that increased digestive and metabolic activity (lipase and IL-15) is moderately correlated with diminished caspase-4-related inflammatory signaling.

Figure 4 and Table 6 illustrate that the ROC curve analysis revealed caspase-4 had an AUC of 0.785 (SE = 0.029, 95% CI: 0.728–0.842, $P < 0.01$), signifying a robust capacity to differentiate between obese patients and controls. With an ideal cut-off value of 1.8550 IU/L, caspase-4 demonstrated a sensitivity of 86.7% and a specificity of 63.3%, yielding a Youden index of 0.50, indicating a satisfactory equilibrium between accurately identifying afflicted persons and reducing false positives. These data endorse caspase-4 as a potentially valuable inflammatory biomarker for obesity-related changes, with moderate to strong diagnostic efficacy.

Table 1: The Mean and Std of IL-15, Lipase and Caspase 4

Parameter	Groups	No.	Mean $\pm$ Std.	P. value
Lipase (IU/L)	OBG	60	35.2 ± 7.64	<0.01

	ODG	90	33.52 ±8.27	
	TDG	90	31.1 ±7.04	
	NOBG	60	29.06 ±5.61	
IL15 ng/mL	OBG	60	121.77 ± 52.36	<0.01
	ODG	90	136.82 ± 35.55	
	TDG	90	214.45 ± 74.19	
	NOBG	60	246.38 ± 99.18	
Caspase4 (IU/L)	OBG	60	2.39 ± 0.67	<0.01
	ODG	90	1.98 ± 0.53	
	TDG	90	1.69 ± 0.48	
	NOBG	60	1.40 ± 0.39	

Abbreviations: OBG = obese group; ODG = one dose group; TDG = two dose group; NOBG = non obese group.

Table 2: Multiple Comparison (Tukey's test) Among Groups According Parameters.

Dependent Variable	Main group	Sub-group	P. value
Lipase (IU/L)	OBG	ODG	0.342
		TDG	0.002
		NOBG	<0.01
	ODG	TDG	0.119
		NOBG	0.005
	TDG	NOBG	0.515
IL15 (ng/mL)	OBG	ODG	0.539
		TDG	<0.01
		NOBG	<0.01
	ODG	TDG	<0.01
		NOBG	<0.01
	TDG	NOBG	0.025
Caspase4 (IU/L)	OBG	ODG	<0.01
		TDG	<0.01
		NOBG	<0.01
	ODG	TDG	0.002
		NOBG	<0.01
	TDG	NOBG	0.005

Table 3: The Mean and Std of IL-15, Lipase and Caspase 4 according BMI.

Parameter	BMI groups	N	Mean	Std. Deviation	P. value
Lipase (IU/L)	30-35	28	30.7143	4.32784	<0.01
	36-47	32	27.6250	6.25145	

	30-35 treated	46	29.0435	5.80022	
	36-47 treated	45	33.1111	7.57154	
	30-35 treated 2	50	33.1200	8.58009	
	36-47 treated 2	39	34.2051	8.00388	
	Total	240	31.5000	7.40462	
IL15 (ng/mL)	30-35	28	143.2888	44.84964	<0.01
	36-47	32	102.9443	52.36608	
	30-35 treated	46	141.1295	32.63770	
	36-47 treated	45	141.8387	57.37323	
	30-35 treated 2	50	175.3122	59.65435	
	36-47 treated 2	39	255.7485	62.82069	
Caspase4 (IU/mL)	30-35	28	2.5536	0.81764	<0.01
	36-47	32	2.2606	0.47722	
	30-35 treated	46	2.1135	0.44311	
	36-47 treated	45	1.8739	0.58161	
	30-35 treated 2	50	1.7856	0.58170	
	36-47 treated 2	39	1.5477	0.24705	

Table 4 : Multiple Comparison (Tukey's test)Among Groups According BMI .

Dependent Variable	Main GROUP	Subgroup	Sig.
Lipase	30-35 Obese	36-47 Obese	0.545
		30-35 treated	0.923
		36-47 treated	0.726
		30-35 treated 2	0.705
		36-47 treated 2	0.354
	36-47 Obese	30-35 treated	0.954
		36-47 treated	0.012
		30-35 treated 2	0.010
		36-47 treated 2	0.002
	30-35 treated	36-47 treated	0.073
		30-35 treated 2	0.059
		36-47 treated 2	0.012
	36-47 treated	30-35 treated 2	1.000
		36-47 treated 2	0.981

	30-35 treated 2	36-47 treated 2	0.980
IL15	30-35 Obese	36-47 Obese	0.041
		30-35 treated	1.000
		36-47 treated	1.000
		30-35 treated 2	0.111
		36-47 treated 2	0.000
	36-47	36-47 treated	0.021
		30-35 treated 2	0.000
		36-47 treated 2	0.000
	30-35 treated	36-47 treated	1.000
		30-35 treated 2	0.022
		36-47 treated 2	0.000
	36-47 treated	30-35 treated 2	0.028
		36-47 treated 2	0.000
	30-35 treated 2	36-47 treated 2	0.000
Caspase4	30-35 Obese	36-47 Obese	0.289
		30-35 treated	0.010
		36-47 treated	<0.01
		30-35 treated 2	<0.01
		36-47 treated 2	<0.01
	36-47	30-35 treated	0.842
		36-47 treated	0.025
		30-35 treated 2	0.002
		36-47 treated 2	<0.01
	30-35 treated	36-47 treated	0.279
		30-35 treated 2	0.037
		36-47 treated 2	<0.01
	36-47 treated	30-35 treated 2	0.967
		36-47 treated 2	0.066
	30-35 treated 2	36-47 treated 2	0.307

Table 5: Correlation of IL -15, Caspase 4 and Lipase

Correlation				
		Lipase	IL15	Caspase4
Lipase	Pearson Correlation	1	-.163*	0.160*
	Sig. (2-tailed)		.011	0.013
IL15	Pearson Correlation	-0.163*	1	-0.254**

	Sig. (2-tailed)	0.011		<0.0
Caspase4	Pearson Correlation	0.160*	-0.254**	1
	Sig. (2-tailed)	0.013	<0.01	
*. Correlation is significant at the 0.05 level (2-tailed).				
**. Correlation is significant at the 0.01 level (2-tailed).				

Equation	Model Summary					Parameter Estimates	
	R Square	F	df1	df2	Sig.	Constant	b1
Linear	0.026	6.239	1	238	.013	29.127	1.936

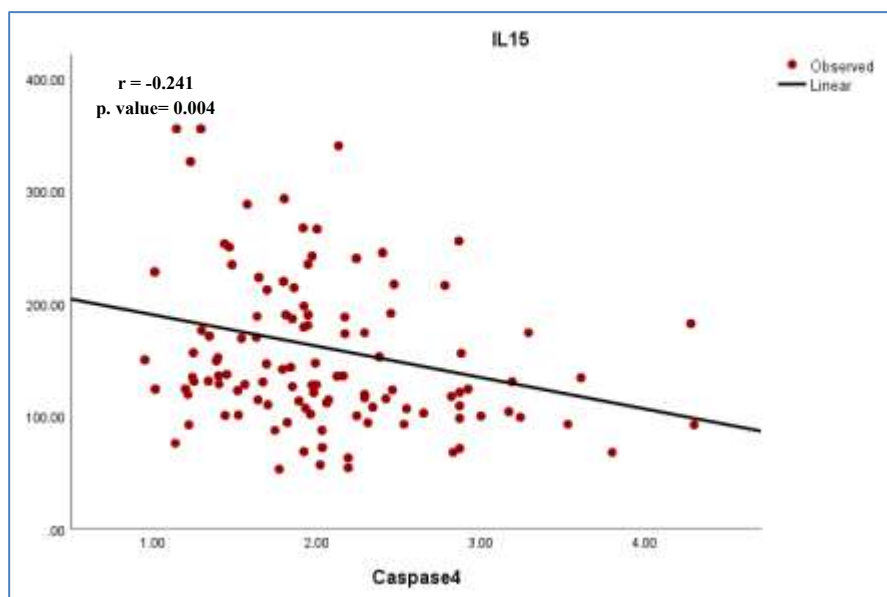


Figure 1: Correlation of IL-15 and Caspase 4

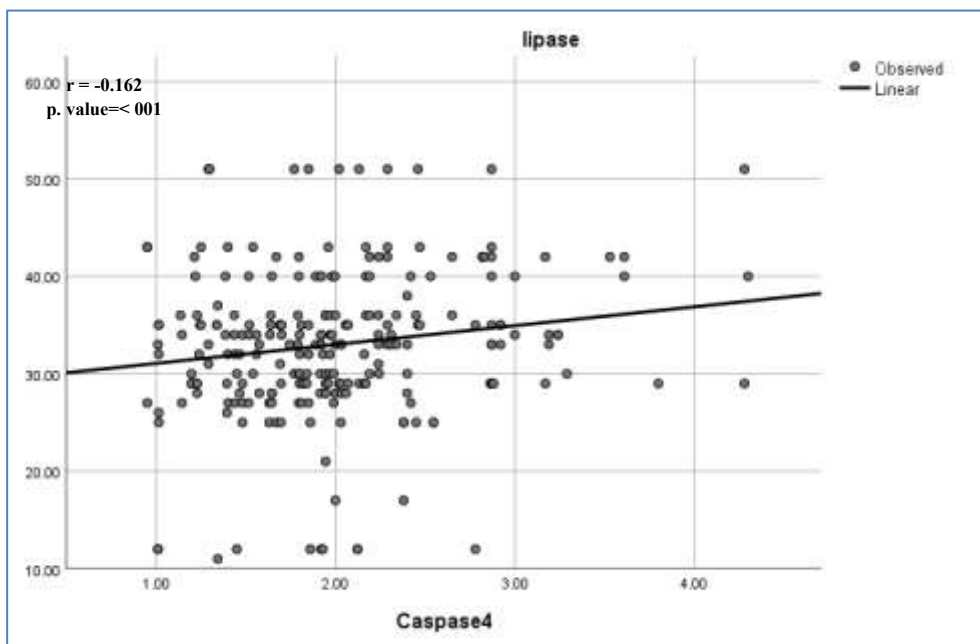


Figure 2: Correlation of Caspase 4 and Lipase

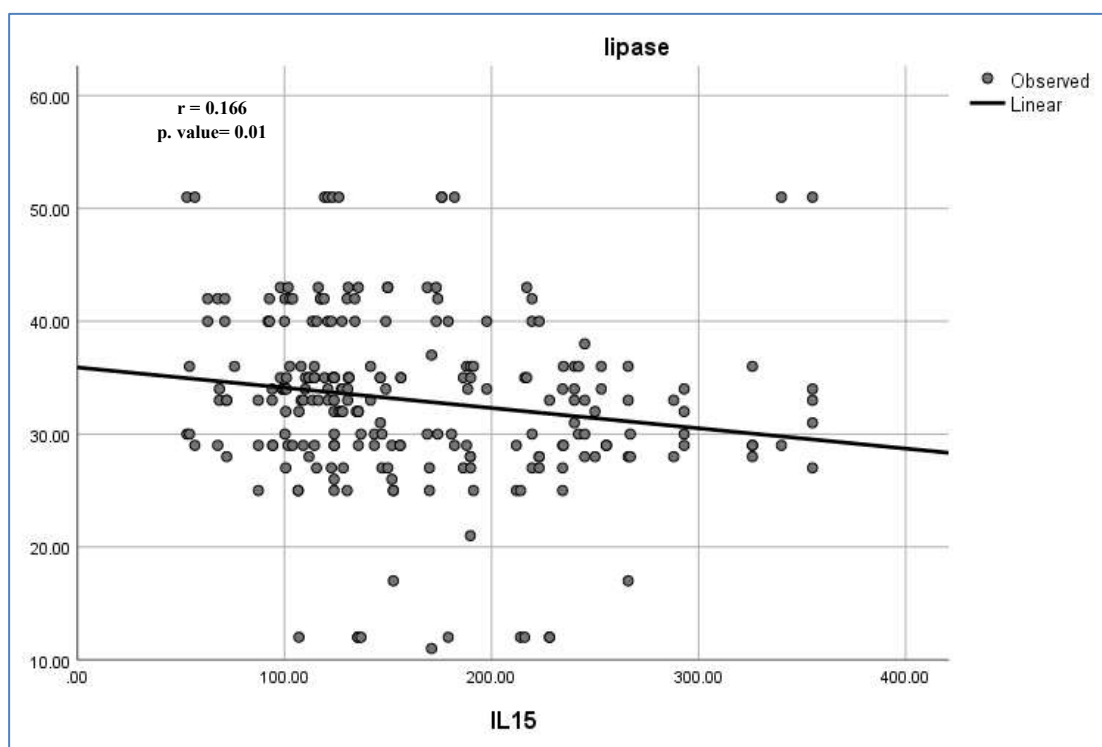


Figure 3: Correlation of IL -15 and Lipase

In figure 4 and table 6; the ROC curve analysis demonstrated that caspase-4 had an AUC of 0.785 (SE = 0.029, 95% CI: 0.728–0.842, $P < 0.01$).

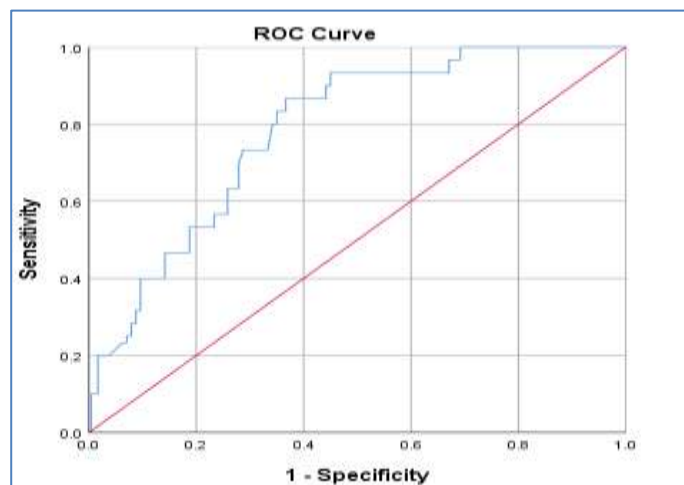


Figure 4: The Roc Curve of Caspase 4

Table 6: The Area Under Curve with Sensitivity and Specificity of Caspase 4

Area	Std. Error _a	P. value	Cut off value	Sensitivity	Specificity	Yoden index	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
0.785	0.029	<0.01	1.8550	0.867	0.633	0.5	0.728	0.842
a. Under the nonparametric assumption								
b. Null hypothesis: true area = 0.5								

DISCUSSION

In this study the levels of caspase were significantly elevated in obese persons in comparison with one Dose Orlistat, two Dose Orlistats and Non-obese persons, this may be due to that Caspase-4 is activated by fatty acids, which adds to the long-term low-grade inflammation that comes with obesity, this may be result from an inflammation is a major cause of metabolic problems including insulin resistance and type 2 diabetes. This agree with Nicolas J. Pilon *et al.* revealed that as a result of obesity, there is an increase in the levels of saturated fatty acids in the bloodstream, particularly palmitate (18).

These fatty acids have the ability to directly activate caspase-4 in human monocytes. This activation results in pyroptosis, which is an inflammatory form of cell death, and it also causes the release of pro-inflammatory cytokines, IL-1 β and IL-18 (19).Caspase-4, which activates pyroptosis and cytokine storms, disrupts gut motility, and exacerbates systemic inflammation, is a crucial link among dietary lipids, inflammation of the gut, and metabolic dysfunction in obesity (20). Targeting this pathway may provide new approaches for dealing with obesity-related gastrointestinal and metabolic diseases (21). The effect of orlistat on caspase 4 specifically is not directly detailed in the available search results (22). There is no direct evidence from current literature that orlistat affects caspase 4 specifically. Orlistat may modulate apoptosis differently depending on tissue context, reducing apoptosis in cardiac tissue under stress but promoting apoptosis in cancer and pancreatic cells (23).

Research indicates that orlistat reduces myocardial damage in obese rat models by inhibiting the NF- κ B pathway and caspase-dependent apoptosis pathways (caspase-3, caspase-8, and caspase-9), but not caspase-4 (24). Caspase-4 is associated with inflammation and immune responses instead of classical apoptosis pathways in myocardial injury models due to its role in non-canonical inflammasome activation, pyroptosis, and LPS responses (24). By increasing ROS and inflammatory signaling, it promotes vascular inflammation and oxidative stress in hyperlipidemia and chronic renal disease (25).

Orlistat helps heart tissue by reducing oxidative stress and inflammation, which may indirectly alter caspase-4-related inflammatory pathways (26). Also, the level of IL₁₅ was decreased in obese persons and in one dose Orlistat compared with

two Dose Orlistat and Non-obese persons, this consistent with LIBRIS S. Quinn and Barbara G. Anderson in that Circulating IL-15 is generally lower in obese individuals than in lean counterparts (27). The obese people tend to have reduced plasma IL-15 levels, which negatively correlate with body fat percentage and trunk fat mass (28). Interleukin-15 significantly influences obesity control via several mechanisms, including calorie consumption, fat mass reduction, and metabolic modification (29).

In humans, circulating IL-15 levels are typically diminished in obese individuals and exhibit a negative correlation with body fat percentage and trunk fat mass. Additionally, IL-15 may augment energy expenditure by stimulating brown adipose tissue function, thereby facilitating increased caloric expenditure and providing protection against obesity and type 2 diabetes (30). This indicates that IL-15 facilitates a metabolic condition that prioritizes fat burning over storage. There is no established impact of orlistat on IL-15 levels, as indicated by the current body of evidence. Orlistat's anti-inflammatory properties in obesity have been established for other cytokines; however, there is no specific research on IL-15 in conjunction with orlistat treatment (31). Pancreatic lipase is an exocrine enzyme released into the digestive system, not the bloodstream, hence fat people's levels are seldom boosted or diminished (32). Obesity increases pancreatic fat infiltration and function, which might affect lipase activity locally. Obesity increases triglyceride-rich intra-pancreatic fat. In pancreatitis, pancreatic lipase hydrolyzes this fat, generating free fatty acids that harm tissue (33).

Pancreatic lipase is essential for fat digestion and absorption; hence inhibitors are used to manage obesity and lose weight. In obesity, disruption of lipid metabolism and pancreatic enzyme activity may cause metabolic abnormalities, however circulating pancreatic lipase levels are more important in diagnosing pancreatitis than obesity (34). Obesity may modify pancreatic enzyme secretion or activity, however the precise alterations in pancreatic lipase levels in obese people under normal settings are unclear (35). Although metabolic problems in obesity may be caused by deregulation of lipid metabolism and pancreatic enzyme activity, the diagnosis of pancreatitis is more dependent on the direct measurement of circulating pancreatic lipase levels than obesity itself (36).

Orlistat blocks gut lipase activity by forming a Covalent Bond with the enzyme via the β -lactone ring, which is attacked by the serine residue's hydroxyl group. Orlistat and the enzyme form a stable covalent ester link when the lactone ring opens. The covalent bond physically inhibits the catalytic site, preventing the enzyme from binding and hydrolyzing triglycerides. Under gut physiological circumstances, this is irreversible (37). The results of correlation, there were negative correlation between IL-15 and caspase 4 also lipase and caspase 4, while positive significant correlation between IL-15 and Lipase. It seems that increased IL-15 levels reduce caspase-4 activity or expression (38). There is little direct evidence connecting IL-15 to caspase-4 regulation, which is implicated in non-canonical inflammasome activation and pyroptosis (39). IL-15 modulates inflammation and cell death, which may indirectly alter caspase pathways, however there is no clear evidence of a negative link with caspase-4 (40).

A negative connection may imply a metabolic-inflammatory balance between lipase activity and caspase-4 activity. The research does not show direct mechanistic linkages between lipase and caspase-4 (41). IL-15 promotes lipolysis and has a positive connection with lipase, according to multiple studies. IL-15 dose-dependently stimulates adipocyte lipolysis via protein kinase A and Janus kinase signaling pathways (42). This cytokine increases adipose tissue lipid mobilization, explaining its favorable connection with lipase activity (43).

ROC curve analysis demonstrated that caspase-4 had an AUC of 0.785 (SE = 0.029, 95% CI: 0.728–0.842, $P < 0.01$), reflecting acceptable diagnostic accuracy in obese subjects. At the optimal cut-off of 1.8550, sensitivity was 86.7% and specificity was 63.3% (Youden index = 0.50). These findings are consistent with Elkayam E. and coworkers in that the established role of caspase-4 as a noncanonical inflammasome effector in obesity-associated adipose tissue inflammation, and are comparable to AUC values reported for other inflammatory and metabolic biomarkers in obese populations (AUC range 0.70–0.80) (43).

Caspase4 is a noncanonical inflammasome effector that activates the NLRP3–IL1 β pathway and promotes pyroptosis through gasdermin-D pore formation [44]. Its elevated levels in inflammatory and metabolic conditions make it a biologically plausible diagnostic biomarker. The link between CASP4/11 and vascular inflammation, hyperlipidemia, and chronic kidney disease further supports its utility as a biomarker in metabolic/cardiovascular research contexts (45).

In conclusion, the comparison of results demonstrated that women who received two doses of Orlistat over a two-week period showed significantly better outcomes compared to those who received a single dose during the same period. Additionally, when

compared with obese women, the results indicated that the best outcomes were observed in the two-dose group, followed by the single-dose group, while the obese group showed the least improvement.

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