

THE ROLE OF INTERLEUKIN - 1 IN POSTPRANDIAL SOMNOLENCE IN DUHOK CITY, KURDISTAN REGION OF IRAQ

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ABSTRACT

Background: Many research studies have been conducted to understand the role of different interleukins in pathogenesis and/or treatment of diseases, majority of results are promising. Interleukin 1 plays a master role in inflammatory processes and innate immune mechanisms. Feeling drowsy or somnolence has been linked to IL-1. The current study aimed to examine the role of IL-1 in postprandial somnolence in both lean and obese individuals.

Methods: This is a cross-sectional study investigating the role of IL-1 level on postprandial somnolence. A sample of 88 healthy male and female participants recruited in the study, age between 18 and 65 years old and usually had breakfast at least three hours before being tested. The Stanford Sleepiness Scale (SSS) used as a validated method to measure subjective sleepiness.

Results: The result showed statistically significant correlation between IL-1 level and postprandial somnolence. Around 72% had postprandial somnolence (rated 4 and above in SSS), 16% had dozing (rated 3 in SSS) and only 12% were normal (rated 1 and 2 in SSS). Subjects with postprandial somnolence and dozing (78 out of 88 subjects) counted as 88% of the sample, 67% had high level of IL-1 and 67% were obese and 33% were lean.

Conclusions: It was found that IL-1 is correlated with postprandial somnolence and dozing, further in-depth research studies to understand the role of interleukins especially IL-1 are necessary.

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Keywords: Interleukin-1, Postprandial Somnolence, Inflammation, Stanford Sleepiness Scale.

Interleukin-1 (IL-1) is a 17 kDa cytokine protein that plays a master role in inflammatory processes and innate immune mechanisms^{1,2}. Several biological functions are attributed to IL-1 such as leukocytic pyrogen, acute-phase response and lymphocyte-activating factor, macrophage-derived immune mediator, and a role in tumor microenvironment^{2,3}. Since first described about 35 years ago, three forms of structurally related and biologically undistinguished functions of IL-1 are there, IL-1 α , IL-1 β and interleukin-1 receptor antagonist^{3,4}. Currently, there are 11 cytokines in IL-1 family: IL-1 α , IL-1 β , IL-1Ra, IL-18, IL-33, IL-36 α , IL-36 β , IL-36 γ , IL-36Ra IL-

37, and IL-382. Some IL-1 are receptor agonist (IL-1 α and β , IL-18, IL-33, IL-36 α , β , γ), others are receptor antagonists (IL-1Ra, IL-36Ra, and IL-38) while IL-37 is an anti-inflammatory cytokine⁵. The α and β forms of IL-1 characterize by the ability to induce fever, sleep, anorexia, hypotension, release of pituitary hormones⁴. Feeling fatigue or drowsy has been linked to IL-1 and it's a common finding in conditions with inflammatory component such as multiple sclerosis, rheumatic arthritis, neoplasms, diabetes mellitus, metabolic syndrome etc. in which there is increased level of proinflammatory cytokines such as IL-1^{6,7}.

The pathophysiology and the effects on the

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brain (central nervous system) causing perception of fatigue or somnolence is not clearly understood because cytokines are primarily secreted in the periphery^{6,8,9} reaffirmed that IL-1 β substance involve in sleep induction (increases non-rapid eye movement sleep) and promotion after exogenous administration of IL-1 β . Meanwhile, Wells et al. (1998) concluded that postprandial fatigue and somnolence can be induced by food particularly in obese people¹⁰. Opp and Krueger (1991) examine the role of IL-1 receptor antagonist to blocks IL-1 induced sleep in rabbits and found that non-rapid eye movement sleep was completely blocked¹¹.

Recently, the association between IL-1 and cancer in pathogenesis and is being tested in developing novel IL-1 blockers cancer treatment¹². Apart from inflammatory diseases, the role of IL-1 has been studied in other common diseases such as heart diseases¹³, infectious diseases¹⁴, and Alzheimer disease¹⁵. Somnolence which is a state of drowsiness or desire to fall asleep or commonly followed by sleep which can be dangerous in some instances such as driving¹⁶. IL1 β play an important physiological role in sleep regulation¹⁷.

The current study aims to examine the role of IL-1 (β subtype) in postprandial somnolence using a cohort of both lean and obese individuals in Duhok city, Kurdistan Region of Iraq.

METHODS

A sample of 88 healthy male and female participants recruited in the study, age between 18 and 65 years old and usually had breakfast at least three hours before being tested. Lean subjects are 34 (BMI less than 18 kg/m²) and the obese subjects are 54 (BMI more than 30 kg/m²). Exclusion criteria include smoking in the last 24 hours, increased alcohol consumption, person who had a nightshift work, existing sleep disorders or disturbances, subjects with a known

history or exhibit clinical signs of infection, hematologic, renal, hepatic, cardiac, pulmonary or inflammatory disease, history of carcinoma or tuberculosis were excluded, and subjects on any current treatment including vitamin supplementation were also excluded. As aforementioned, subjects with acute and chronic medical conditions were excluded, thus, any cause of somnolence was also excluded such as electrolyte disturbance, hypothermia, sleep-wake disorders, such as insomnia, sleep apnea, narcolepsy, restless leg syndrome, or delayed sleep phase disorder, medications such as antihistamines, benzodiazepines, hypnotics, opioids, antidepressants, anticonvulsants, and antipsychotics, and lifestyle factors, such as overworking, irregular work schedule, jet lag, and stress, may also lead to somnolence. Subjects enrolled in a cross-sectional study investigating the role of IL-1 concentration on postprandial somnolence in lean and obese but otherwise healthy subjects. The type of IL-1 used was β subtype and the reference laboratory to perform the test by high sensitivity ELISA and provided the normal range from 0.16 to 10 pg/mL with an incubation time of overnight (4°C), 1x1h, 1x15min, 1x30min, 1x10 min¹⁸. The study started in April 2023 until July 2023 at the Azadi Teaching Hospital in Duhok City, Kurdistan Region of Iraq after approval of Scientific Committee at College of Medicine, University of Duhok and Research Ethics Committee at Duhok Directorate General of Health. All subjects give oral and written consent prior to participation in the study. The Stanford Sleepiness Scale (SSS), developed by Hoddes et al. (1973), used as a validated method to measure subjective sleepiness¹⁹. The SSS consists of eight levels (Table: 01) and subjects asked to indicate which level described their current somnolence state, this scale evaluate the sleepiness at a specific point of time for the clinical and research purposes compare

to other scales such as Epworth Sleepiness Scale which is used to assess the sleepiness over the entire day²⁰. For the purpose of our study and according to SSS, the postprandial somnolence is defined as a score of above 3 based on the fact that score above 3 in SSS is considered sleepy, score of 1 and 2 considered normal while score of 3 is considered as high chance of dozing (going to sleep)²¹. Subjects with very high level of IL-1 had been referred to specialists for further follow up. Eligible subjects had a single interview and blood samples drawn and sent to biochemical analysis in the laboratory to measure IL-1

level. Results expressed as means \pm SEM, and significance accepted with $p < 0.05$. Student's paired t-test used to analyze SSS data in 2 groups (lean and obese subjects' groups). Limitation of the study was mainly related to the assessment of level of somnolence (not using one of the following scales: multiple sleep latency test or maintenance of wakefulness test or the Oxford Sleep Resistance Test) based upon the fact that the current study is not a clinical trial or interventional study, however, this could be considered as future potential research in Kurdistan region.

Table 01: The Stanford Sleepiness Scale

Degree of Sleepiness	Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

RESULTS

A total of 88 subjects enrolled in the study, none of them dropped, those who were ineligible according to the inclusion and exclusion criteria were excluded from the beginning. Thus, in total, a sample of 88 subjects went through the study methods. The age of the sample ranges from 18 to 60 years.

The characteristic of the sample with the most common age group being with a mean of 32 year (SD=11), BMI range from 15 (kg/m²) to 46 (kg/m²) with a mean of a 26 (kg/m²) (SD= 7.7), degree of sleepiness score range from 1 to 7 with a mean 4 (SD=2). The descriptive characteristics of the subjects are presented in (Table: 02).

Table 02: Descriptive statistics of the study sample characteristics (n = 88)

Characteristic	Minimum	Maximum	Mean	Standard Deviation
Age (years)	18	60	32	11
BMI (kg/m ²)	15.78	46.29	26.59	7.68
Degree of sleepiness	1	7	4	2
IL-1 (pg/dL)	0	234.57	22.24	35.23
MEAN (OD)	0.006	2.75	0.697	0.632

from 18 - 29 years old (45.5%), 61.4% of them were females and same were obese (Table: 03).

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Table 03. Frequency of the study sample characteristics

	Characteristic	No.	%
Age (years)	18 - 29	40	45.5
	30 - 44	32	36.4
	45 - 60	16	18.2
Sex	Male	34	38.6
	Female	54	61.4
BMI groups	Underweight	34	38.6
	Obese	54	61.4
Total		88	100.0

In order to investigate whether postprandial somnolence is driven by IL-1, we tested the serum level of IL-1. The result showed statistically significant relation between age and to identify any sleepiness level, subjects were asked about the degree of sleepiness using SSS and inclusion and exclusion criteria to avoid any bias in subjects' selection, then level

of somnolence is compared to the results of SSS. The result showed that out of 64 subjects who had somnolence counted as 72% of the sample, 25 subjects had high level of IL-1 level with high level being most common in the older age (45-60 years) while the normal level was most common in the young age group (Table: 04).

Table 04: Relation of IL-1 with age, sex and BMI

Characteristic	IL-1						P value*	
	High		Normal or low		Total			
	No.	%	No.	%	No.	%		
Age (years)	18 - 29	4	26.7	36	49.3	40	45.5	0.045
	30 - 44	5	33.3	27	37	32	36.4	
	45 - 60	6	40	10	13.7	16	18.1	
Sex	Male	5	33.3	29	39.7	34	38.6	0.643
	Female	10	66.7	44	60.3	54	61.4	
BMI (kg/m ²)	Underweight	5	33.3	29	39.7	34	38.6	0.643
	Obese	10	66.7	44	60.3	54	61.4	
Total		15	17	73	83	88	100.0	

* Based on Chi square test.

72% had postprandial somnolence (rated 4 and above in SSS), 16% had dozing (rated 3 in SSS) and only 12% were normal

(rated 1 and 2 in SSS). In total, 88% of subjects had postprandial degree of sleepiness rated 3 and above (Table: 05).

Table 05. Degree of postprandial sleepiness of the study sample characteristics

Grade	Frequency	%
Postprandial somnolence	64	72
Postprandial dozing	14	16
Normal	10	12
Total	88	100.0

IL-1 (39%) and 38 subjects had normal level of IL-1 (60%) and 1 subject had low level of IL-1 (1%) (Table: 06).

Table 06. IL-1 level of the somnolence subjects

IL-B level	No.	%	R with degree of sleepiness	P-value
High	25	39.1	0.031	0.805
Low	1	1.5		
Normal	38	59.4		
Total	64	100.0		

Those who had somnolence and high level of IL-1, 15 subjects were obese (60%) and 10 subjects were lean (40%). It was also noted that those who had dozing (14 subjects) counted as 16%, 10 subjects had normal level of IL-1 and 4 subjects had high level of IL-1.

There is a significant correlation between IL-1 and age but not with the degree of

sleepiness score even if we those with high level of IL-1, 3 subjects were obese and 1 subject were lean (Table: 07). Thus, among those who rated 3 and above in SSS (78 out of 88 subjects) counted as 88% of the sample, 67% had high level of IL-1 and 67% were obese and 33% were lean take the somnolence group only (Table: 08, Figures 01 and 02).

Table 07. Association of degree of sleeping to high level of IL-1 and BMI

Grade	Frequency (%)	High IL-1 (%)	BMI (%)
Postprandial somnolence	72%	39%	60% obese, 40 % lean
Postprandial dozing	16%	28%	75% obese, 25 % lean
Normal	12%	33%	--
Total	100.0	100.0	

Table 08. Correlation between IL-1 and age to degree of sleepiness

Characteristic		Age	Degree of Sleepiness
IL-1	Pearson Correlation	0.228	0.043
	P value	0.032	0.693
	No.	88	88

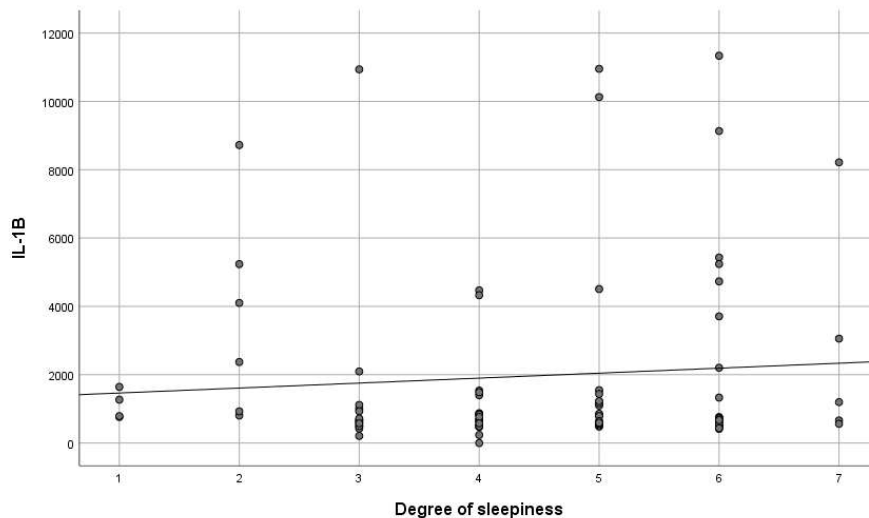


Figure 01: Scatter diagram for IL-1 with degree of sleepiness

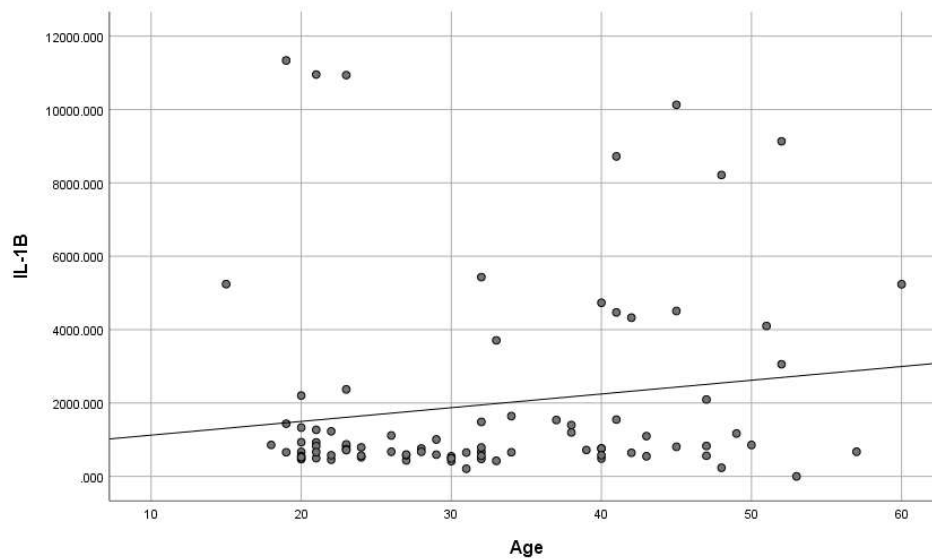


Figure 02: Scatter diagram for IL-1 with age

DISCUSSION

Beside the essential role that interleukin plays in immune system, they also have pro- and anti-inflammatory features²². The extensive studies on the role of IL-1 offers very interesting area of investigation that could help understanding more in-depth about IL-1 functions²³.

The aim of this study was to investigate the role of IL-1 in postprandial somnolence and whether it is more noticeable in obese or lean subjects. In total of 88 subjects enrolled in the study, the age ranges from 18 to 60 years, BMI range from 15 to 46, degree of sleepiness score range from 1 to 7, the most common age group being from 18 - 29 (45.5%), 61.4% of them were females and same were obese.

The result showed that 72% had postprandial somnolence (rated 4 and above in SSS), 16% had dozing (rated 3 in SSS) and only 12% were normal (rated 1 and 2 in SSS).

In total, 88% of subjects had postprandial degree of sleepiness rated 3 and above. Postprandial sleepiness had been correlated with ingested food²⁴. Among those who had somnolence, 25 subjects had high level of IL-1 (39%) and 38

subjects had normal level of IL-1 (60%) and 1 subject had low level of IL-1 (1%). Fang et al. (1998) concluded that IL-1 is one of the best characterized sleep-promoting substances⁹. More insight about role of IL-1 has been described by Dinarello et al. (1986) to induces sleepiness in humans²⁵. Similar finding was brought by Krueger (2008) that IL-1 promote non-rapid eye movement sleep²⁶. Those who had somnolence and high level of IL-1, 15 subjects were obese (60%) and 10 subjects were lean (40%). It was also noted that those who had dozing, 4 subjects had high level of IL-1.

Thus, among those who rated 3 and above in SSS i.e. postprandial somnolence and dozing (78 out of 88 subjects) counted as 88% of the sample, 67% had high level of IL-1 and 67% were obese and 33% were lean. Ghanbari et al. (2021) refers to increase level of IL-1 in obese individuals²⁷. In recent study conducted by Frühbeck et al. (2022) IL-1 level is shown to be elevated in patients with high BMI especially in those with dysglycemia²⁸. Patel et al. (2009) concluded a relation between sleep duration to the increase in the level of inflammatory markers but not IL-129.

In conclusion, the result showed statistically significant correlation between IL-1 level and postprandial somnolence. Around 72% had postprandial somnolence (rated 4 and above in SSS), 16% had dozing (rated 3 in SSS) and only 12% were normal (rated 1 and 2 in SSS). Subjects with postprandial somnolence and dozing (78 out of 88 subjects) counted as 88% of the sample, 67% had high level of IL-1 and 67% were obese and 33% were lean. Since the study aimed to improve the understanding of IL-1 role, which could help develop strategies to treat postprandial somnolence more effectively, we found that IL-1 is correlated with postprandial somnolence and dozing especially in obese subjects but further in-depth research studies to understand the role of interleukins are recommended.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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پوخته

رولێ نینتەرلوکین -1 د خهوا پشتی خارنی دا ل پاریزگه‌ها دهوک/ههریما کوردستانی - عیراق

پیشهکی و نارمانج: د نوکه دا، چندين فهکولین ب شیوهکی بهرفره دهینه نه‌نجام دان بو تیگه‌هشتنا رولێ نینتەرلوکین جیاواز ل دروستبوونا نه‌خوشی یان دا یان چارسه‌رکرا وان بارا پتریا نه‌نجاما د ئومیدیه‌خشن. نینتەرلوکین-1 روله‌کی سه‌ره‌کی هه‌یه د پروسا هه‌ودانادا و میکانیزمێن به‌رگیا گشتی دا. هه‌ستکرن ب وه‌ستیانی یان خه‌وئ په‌یوه‌ندی ب نینتەرلوکین-1 فه‌هه‌ی، نارمانجا فه‌هه‌ی فه‌کولینی هه‌لسه‌نگاندنا رولێ نینتەرلوکین-1 د نه‌ستنا پشتی خوارنی دا ل ده‌ف که‌سین کیشاوان یا زیده و کیشاوان یا کیم ل پاریزگه‌ها دهوک/ههریما کوردستان - عیراق.

ریکن فه‌کولینی: نه‌ف فه‌کولینه دیزابنا کروس-سێکشن هاتیه بکارئینان کو هه‌لسه‌نگاندنا رولێ چر یا نینتەرلوکین -1 د نه‌ستنا پشتی خوارنی دا. نمونه ژ 88 که‌سین ساخه‌م ژ نافرمت و زه‌لامان هاتینه وه‌رگرتن. ژیی وان دناقه‌هرا 18 بو 65 سالیدا بوو پتریا وان سی ده‌مژمیر به‌ری پشکنینی خارنا سپندی خاربوو. پیه‌رین ستانفورد یین نه‌ستنی (SSS) کو وه‌کی ریکه‌کا پشتراستکرنی هاتینه بکارئینان بو پیه‌فانا بابه‌تین نه‌ستنی.

نه‌نجام: نه‌نجامان په‌یوه‌ندیا دناقه‌هرا نینتەرلوکین-1 د نه‌ستنا پشتی خوارنی دا نیشان دان. نیزیکی 72% پشتی خوارنی خه‌وا وان دهات (د پیه‌رین ستانفوردی دا ریژه 4 و سه‌ردا) 16% د نه‌ستن کیم (د پیه‌رین ستانفوردی دا ریزا 3) و بنتی 12% ناسایی بون (د ریزا 1 و 2 دهاتن د پیه‌رین ستانفوردی دا). نه‌و که‌سین د نه‌ستن و خه‌وا وان پشتی خوارنی دهات 78 ژ 88 که‌سان بون کو دببته 88%. 67% ریژا نینتەرلوکین-1 یا بلن‌دبوو 67% کیشان وان یا زیده‌بوو و 33% کیشا وان یا کیم بوو.

ده‌ر نه‌نجام: ده‌ر که‌ت کو نینتەرلوکین-1 په‌یوه‌ندی ب نه‌ستن و خه‌وا هاتنا پشتی خارنی فه‌هه‌یه ب تاییه‌تی د که‌سین کیشاوان زیده دا. ژ به‌ر رولێ گرنج یی نینتەرلوکینی، فه‌کولین به‌رفرتر و زیده‌تر به‌ینه کرن بو تیگه‌هشتنا رولێ نینتەرلوکینیا تاییه‌ت نینتەرلوکین-1.

الخلاصة

دور إنترلوكين - 1 في نعاس ما بعد الأكل

في محافظة دهوك، إقليم كردستان – العراق

الخلفية والأهداف: في الوقت الحاضر، يتم إجراء العديد من الأبحاث على نطاق واسع لفهم دور الإنترلوكينات المختلفة في التسبب في الأمراض و/أو علاج الأمراض، وغالبية النتائج واعدة. يلعب الإنترلوكين -1 دوراً رئيسياً في العمليات الالتهابية وآليات المناعة. تم ربط الشعور بالتعب أو النعاس ب الإنترلوكين -1 و تهدف الدراسة الحالية إلى فحص دور الإنترلوكين -1 في النعاس ما بعد الأكل باستخدام مجموعة من الأفراد النحيفين والبدناء في محافظة دهوك، إقليم كردستان العراق.

طرق البحث: هذه دراسة مقطعية تبحث في دور الإنترلوكين -1 على النعاس ما بعد الأكل. تم مشاركة عينة من 88 من الذكور والإناث الأصحاء في الدراسة، تتراوح أعمارهم بين 18 و 65 عاماً متناولين وجبة الإفطار قبل ثلاث ساعات على الأقل من الاختبار. استخدمت مقياس ستانفورد للنعاس (SSS) كطريقة لتحقيق من صحتها لقياس النعاس الذاتي.

النتائج: أظهرت النتائج وجود علاقة ذات دلالة إحصائية بين مستوى الإنترلوكين -1 والنعاس ما بعد الأكل. حوالي 72% لديهم نعاس ما بعد الأكل (تصنيف 4 وما فوق في مقياس ستانفورد للنعاس)، نسبة 16% لديهم غفوة (تصنيف 3 في مقياس ستانفورد للنعاس) و نسبة 12% فقط كانوا طبيعيين (تصنيف 1 و 2 في مقياس ستانفورد للنعاس)، الأشخاص الذين يعانون من النعاس بعد الأكل والنوم (78 من أصل 88 شخصاً) يمثلون 88% من العينة، و 67% لديهم مستوى عالٍ من الإنترلوكين -1 و 67% يعانون من السممة المفرطة و 33% كانوا نحيفين.

الاستنتاجات: وجد أن الإنترلوكين -1 يرتبط بالنعاس ما بعد الأكل والنوم خاصة في الأشخاص الذين يعانون من السممة المفرطة. بسبب الدور المهم الذي يلعبه الإنترلوكينات، مزيد من الدراسات البحثية المتعمقة لفهم دور الإنترلوكينات وخاصة الإنترلوكين -1 ضرورية.