



## Research Article

# Immune system response to lifestyle intervention in obese subjects with non-alcoholic Steatohepatitis

Rowaid M. Qahwaji <sup>2</sup>

<sup>1</sup> Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, P.O. Box 80324, Jeddah, 21589, Saudi Arabia.

\* Correspondence: rgahwaji@kau.edu.sa (R.M.Q)

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**Abstract:** It has recently been estimated that non-alcoholic steatohepatitis (NASH) affects 10–24% of people worldwide. Prior research shown that individuals with chronic NASH frequently have inadequate immune system response. Nonetheless, for NASH patients, obesity is strongly linked to compromised immune function. The purpose of this study was to determine how obese NASH patients' responses to a weight-loss program were affected by specific immunological characteristics. In this study, 80 obese Saudi NASH patients with body mass indices (BMIs) ranging from 31 to 36 kg/m<sup>2</sup> and ages ranging from 45 to 59 years were included. Every participant was divided into two equal groups: Group (A) underwent a weight-loss program consisting of aerobic workouts and food management, whereas Group (B) did not get any diet control or training. Immune system parameters and BMI were measured both before and after the three-month trial period. Immunological parameters (white blood cells, total neutrophil count, monocytes, CD3, CD4, and CD8) and BMI mean values significantly decreased as a result of group (A)'s weight reduction program. However, there were no appreciable changes in the aforementioned parameters in the control group (B). Furthermore, at the conclusion of the study, a comparison of the two groups showed notable disparities. In obese patients with nonalcoholic steatohepatitis, weight loss alters immune markers.

**Keywords:** Immune system; Lifestyle intervention; Nonalcoholic steatohepatitis; obese

## 1. Introduction

A disorder known as nonalcoholic fatty liver disease (NAFLD) causes fat to accumulate in the liver. NAFLD includes nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver (NAFL). Inflammation, liver damage, and liver fat are all present in people with NASH. About 3% to 5% of people worldwide suffer with NASH, a major health issue[1–3]. NAFLD is a condition that rarely or never shows any symptoms. Obesity, metabolic syndrome, and type 2 diabetes are among the illnesses and health factors that increase your risk of developing non-alcoholic fatty liver disease (NAFLD). To diagnose NAFLD, physicians look at your medical history, perform a physical examination, and run testing. To diagnose NAFLD and distinguish it from NAFL or NASH, doctors may employ imaging studies, liver biopsies, and blood testing. In 15% to 20% of cases, NASH can develop to hepatic cirrhosis, which can result in hepatocellular cancer and death [4-6]. Immune system alterations have been seen in obese people, and the degree of immune system degradation is associated with the obesity grade[7,8]. Furthermore, earlier studies found that obese participants had a higher incidence and severity of some infections compared to non-obese individuals[9]. Furthermore, obese individuals are more likely to get infections after trauma[10–12], and obese critically sick trauma patients are twice as likely to get infections[10]. Furthermore, Renehan et al. discovered a link between obesity and the incidence of some malignancies [13].

One of the most prevalent liver diseases in the world is nonalcoholic fatty liver disease (NAFLD). When hepatic steatosis, or the macrovesicular buildup of triglycerides in hepatocytes, occurs without secondary reasons (such as drugs, excessive alcohol use, or specific genetic disorders), it is referred to as nonalcoholic fatty liver disease (NAFLD). Steatosis, hepatocyte damage (ballooning), inflammation, and fibrosis are all present in NASH, the inflammatory subtype of NAFLD. NASH can eventually lead to cirrhosis, end-stage liver disease, or the requirement for a liver transplant, despite the fact that it is frequently clinically silent. More than 20% of people with NASH will eventually acquire cirrhosis, despite the fact that simple steatosis progresses more slowly—only 4% of patients get cirrhosis. NASH caused a 114% increase in liver transplant waitlist registration for males and an 80% increase for women between 2004

and 2016. NASH is currently the most common reason for liver transplant listings for women, and in the next years, it is anticipated to surpass alcoholic liver disease as the most common reason for liver transplants for all patients. NASH patients are more likely to develop hepatocellular cancer. In 2017, the anticipated lifetime direct medical costs for NASH patients in the United States were \$222 billion. This estimate will only go up when the prevalence of NASH increases and excludes indirect medical or social expenditures. For doctors, NASH might provide diagnostic and treatment challenges. The epidemiology of NASH, its aftereffects, and current diagnostic and therapeutic methods will all be covered in this review, along with upcoming diagnostic technologies and treatments.

According to a recent meta-analysis, over 25% of people globally have NAFLD. With the lowest rates in Africa (13%), and the greatest rates in the Middle East and South America (>30%), there is a notable geographic variation. According to earlier demographic research, between 20% and 30% of Americans in the 2010s satisfied the criteria for non-alcoholic fatty liver disease. According to estimates, the prevalence is rising, with 3.6 million new cases reported each year. Males are more likely to have NAFLD and NASH. There are racial and ethnic differences in NAFLD and NASH; in the United States, the prevalence of NAFLD is lowest among Black inhabitants and greatest among Hispanic ones.

Obese people have been found to have impaired immune system function and changed numbers of some immune cells, including higher total white blood cell, neutrophil, leukocyte, and monocyte counts[14–18, 19]. Furthermore, systemic inflammation has been linked to obesity[20–23]. Additionally, Kintscher et al. discovered that obese participants had higher CD3 and CD4 values, which were linked with the severity of obesity[24].

In order to cure NAFLD, which can be either NAFL or NASH, doctors advise losing weight. Losing weight can lessen liver fibrosis, inflammation, and fat. There are currently no approved medications to treat NASH or NAFLD. Maintaining a healthy weight and eating a balanced diet may help you avoid NAFLD, also known as NASH or NAFL. Your doctor could advise diet modifications and weight loss if you have non-alcoholic fatty liver disease.

Obesity has been linked to an increased risk of NASH[25]. The initial recommended course of treatment for patients with NASH is weight loss[26,27]. The influence of lifestyle interventions on immune system markers in patients with non-alcoholic steatohepatitis (NASH) in Saudi Arabia has not been well studied. The purpose of this study was to determine how certain immunological markers responded to a weight-loss program in patients with NASH.

## 2. Methods

**2.1. Subjects:** This study included 80 obese Saudi NASH patients with body mass indices (BMIs) ranging from 31 to 36 kg/m<sup>2</sup> and ages ranging from 45 to 59 years. Every participant was divided into two equal groups: Group (A) underwent a weight-loss program consisting of aerobic workouts and food management, whereas Group (B) did not get any diet control or training. Immune system parameters and BMI were measured both before and after the three-month trial period.

### 2.2. Measurements:

A. Analysis of peripheral blood cells: Beckman Coulter AcT 5diff hematology analyzer used to calculate the white blood cells, neutrophils, monocytes counts.

B. Flow cytometry analysis: Flow cytometry (FC 500 and CXP software, Beckman Coulter) used to measure CD3, CD4 and CD8.

C. Body mass index: A digital stadiometer (JENIX DS 102, Dongsang) used to measure weight and height to compute BMI (BMI= Body weight/Height<sup>2</sup>)[28]. All measurements done before the study and after three months at the end of the study.

### 2.3. Procedure:

**Group (A):** Participants involved into weight reducing program that consisted of aerobic treadmill exercise training for 12 weeks according to the standard recommendation of exercise training[29]. Training included warm up for 5 minutes, thirty minutes of 60-70% of maximum heart rate aerobic exercise training that followed by 10 minutes cooling down. Participants had three training sessions weekly for 3 months. In addition, a dietician supervised diet regimen that provided 1200 Kilocalories/day for 3 months[30-32].

**Group (B):** received no therapeutic intervention.

## 3. Results

**3.1. Comparative analysis between the two groups:** The two groups were homogenous as demographic and baseline criteria comparison revealed no significant differences as shown in Table 1.

**Table (1).** All participants' baseline criteria.

	Group (A)	Group (B)	Significance
Age (year)	46.18 ± 7.68	47.53 ± 6.94	p > 0.05

<b>BMI (kg/m<sup>2</sup>)</b>	32.93 ± 5.16	32.81 ± 5.21	p > 0.05
<b>Fat mass (kg)</b>	28.12 ± 3.16	26.85 ± 3.42	p > 0.05
<b>Albumin (gm/dl)</b>	3.74 ± 0.92	3.53 ± 0.87	p > 0.05
<b>Hb (gm/dl)</b>	12.26 ± 1.65	12.52 ± 1.74	p > 0.05
<b>Total Bilirubin (mg/dl)</b>	1.53 ± 0.61	1.42 ± 0.52	p > 0.05
<b>SBP (mm Hg)</b>	132.82 ± 9.34	130.11 ± 10.28	p > 0.05
<b>DBP (mm Hg)</b>	85.17 ± 7.23	83.45 ± 6.39	p > 0.05

BMI: Body Mass Index; Hb: Hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Weight reducing program of group (A) resulted in significant decrease in the mean values of BMI and immunological parameters (white blood cells, total neutrophil count, monocytes, CD3, CD4 and CD8) (Table 2). While, control group (B) experienced no significant changes in the above-mentioned parameters (Table 3). Moreover, comparison between both the groups revealed significant differences between them at the end of the study (Table 4).

**Table 2.** Mean value and significance of body mass index and immunological parameters of group (A) before and at the end of the study.

	Mean + SD		T-value	Significance
	Pre	Post		
<b>BMI (kg/m<sup>2</sup>)</b>	32.93 ± 4.16	27.28 ± 3.11*	8.15	p < 0.05
<b>White blood cells count (10<sup>9</sup>/μL)</b>	9.13 ± 1.86	7.25 ± 1.78*	7.48	p < 0.05
<b>Total neutrophil count (10<sup>9</sup>/μL)</b>	5.72 ± 0.95	3.59 ± 0.83*	6.14	p < 0.05
<b>Monocytes (10<sup>9</sup>/μL)</b>	0.75 ± 0.24	0.51 ± 0.17*	5.28	p < 0.05
<b>CD3 count (10<sup>9</sup>/L)</b>	1.86 ± 0.95	1.42 ± 0.83*	6.31	p < 0.05
<b>CD4 count (10<sup>9</sup>/L)</b>	1.37 ± 0.64	0.98 ± 0.56*	6.14	p < 0.05
<b>CD8 count (10<sup>9</sup>/L)</b>	0.83 ± 0.22	0.51 ± 0.19*	5.69	p < 0.05

BMI= Body Mass Index; (\*) indicates a significant difference between the two groups, p < 0.05.

**Table 3.** Mean value and significance of body mass index and immunological parameters of group (B) before and at the end of the study.

	Mean +SD		T-value	Significance
	Pre	Post		
<b>BMI (kg/m<sup>2</sup>)</b>	32.81 ± 5.21	33.41 ± 4.36	0.82	p > 0.05
<b>White blood cells count (10<sup>9</sup>/μL)</b>	9.26 ± 1.97	8.86 ± 1.83	0.79	p > 0.05
<b>Total neutrophil count (10<sup>9</sup>/μL)</b>	5.58 ± 0.91	5.76 ± 0.94	0.71	p > 0.05
<b>Monocytes (10<sup>9</sup>/μL)</b>	0.71 ± 0.26	0.79 ± 0.28	0.53	p > 0.05
<b>CD3 count (10<sup>9</sup>/L)</b>	1.76 ± 0.69	1.84 ± 0.75	0.64	p > 0.05

<b>CD4 count (10<sup>9</sup>/L)</b>	1.28 ± 0.51	1.33 ± 0.54	0.58	p > 0.05
<b>CD8 count (10<sup>9</sup>/L)</b>	0.73 ± 0.25	0.76 ± 0.27	0.52	p > 0.05

BMI= Body Mass Index; (\*) indicates a significant difference between the two groups, p < 0.05.

**Table 4.** Mean value and significance of body mass index and immunological parameters of group (A) and group (B) at the end of the study.

	Mean +SD		T-value	Significance
	Group (A)	Group (B)		
<b>BMI (kg/m<sup>2</sup>)</b>	27.28 ± 3.11*	33.41 ± 4.36	6.37	p < 0.05
<b>White blood cells count (10<sup>9</sup>/μL)</b>	7.25 ± 1.78*	8.86 ± 1.83	5.41	p < 0.05
<b>Total neutrophil count (10<sup>9</sup>/μL)</b>	3.59 ± 0.83*	5.76 ± 0.94	5.25	p < 0.05
<b>Monocytes (10<sup>9</sup>/μL)</b>	0.51 ± 0.17*	0.79 ± 0.28	4.32	p < 0.05
<b>CD3 count (10<sup>9</sup>/L)</b>	1.42 ± 0.83*	1.84 ± 0.75	4.61	p < 0.05
<b>CD4 count (10<sup>9</sup>/L)</b>	0.98 ± 0.56*	1.33 ± 0.54	4.17	p < 0.05
<b>CD8 count (10<sup>9</sup>/L)</b>	0.51 ± 0.19*	0.76 ± 0.27	3.48	p < 0.05

BMI= Body Mass Index; (\*) indicates a significant difference between the two groups, p < 0.05.

**4. Discussion:** This study designed to detect the selected immune parameters response to weight reduction program among NASH patients. The main finding in the present study is that weight-reducing program resulted in improved immunological parameters of obese subjects with NASH that agreed with several related studies.

NASH, which stands for chronic liver inflammation, was initially defined in 1980. In the absence of heavy alcohol consumption, a radiographic or histologic demonstration of more than 5% hepatic steatosis is required for a diagnosis of nonalcoholic fatty liver disease (NAFLD). On the other hand, a biopsy and histologic analysis showing hepatic steatosis of greater than 5%, hepatocyte ballooning degeneration, and hepatic lobular inflammation are necessary for a NASH diagnosis.

NASH is an advanced NAFLD stage that may lead to liver cirrhosis and hepatic cancer[33]. Annually about 9% of patients with NASH develop fibrosis that elevates the mortality rate to about 25 per 1,000 person[34]. The global prevalence on NASH is higher among obese individuals [35, 36]. About 25% of people globally are expected to have NAFLD, according to a recent meta-analysis. With the highest rates (>30%) in the Middle East and South America and the lowest rates (13%), there is a notable geographic variation. In the 2010s, 20% to 30% of Americans were estimated by earlier population surveys to have met the criteria for non-alcoholic fatty liver disease. The prevalence is thought to be rising, with an estimated 3.6 million new cases every year. The prevalence of NASH and NAFLD is higher in men. Both NAFLD and NASH exhibit racial and ethnic disparities; in the United States, the prevalence of NAFLD is lowest among Black inhabitants and greatest among Hispanic ones.

Because liver biopsies are rarely conducted for diagnosis, it is difficult to directly estimate the prevalence of NASH at the community level. NASH was discovered in 1.4% to 15% of individuals in a biopsy case series of clinic outpatients or living donors for liver transplants. Liver biopsy case series and voluntary or referred biopsies in NAFLD patient studies can be used to indirectly extrapolate estimates of the overall population prevalence. It is estimated that 20% of all NAFLD patients will exhibit NASH histology using these techniques. The majority of these indirect estimates indicate that between 3% and 6% of individuals have NASH at the population level. Over the next ten years, it is anticipated that the percentage of NAFLD patients with NASH would rise in accordance with present trends. A modeling study predicts that by 2030, the number of people with NAFLD will have increased by 18%. It is anticipated that the number of people with NASH will rise by 56%, reaching 27 million in the United States.

There are restrictions on liver biopsies. Despite being generally well tolerated, it can cause pain and carries risks of bleeding, infection, bile leakage, organ damage, and uncommon fatality (<0.01%). Diagnostic integrity is impacted by sampling error, pathologist experience, and biopsy adequacy. Additionally, pathologist concordance for NASH-defining criteria is suboptimal. In NASH clinical studies, differences in pathologic interpretation have been observed; after a central review of the enrollment biopsy material, 247 individuals (20.6%) who were included in one experiment based on an initial liver biopsy did not genuinely show hepatocellular ballooning (and hence NASH).

Shade et al. reported that natural killer cell (NK) cytotoxicity reduced significantly as result of greater than 10 pound of body weight loss following exercise training among obese postmenopausal women[37]. However, Wasinski et al. stated that CD4+and CD8+ T lymphocytes reduced significantly following six weeks of swimming training and diet restriction that led weight loss in overfeed mice[38]. Similarly, Carpenter et al. mentioned that immune profiles improved significantly following eight weeks of exercise training and diet restriction that led weight loss in overfeed mice [39]. While, Viardot et al. proved that inflammatory and immunological paramters improved among obese type 2 diabetics as a result of diet regimen for 6 months followed by gastric banding for 3 months that induced weight loss[40]. Moreover, Wing et al. and Tanaka et al. concluded that T cell counts and NK cell activity improved significantly following caloric restriction in obese individuals[41, 42]. Reduced adipose tissue mass affects secretion inflammatory cytokines, insulin sensitivity and leptin that completely activates the innate and adaptive immunity cells[43-46].

**5. Conclusions:** NASH has a broad and poorly understood pathophysiology that underlies its onset, progression, and interaction with other metabolic disease processes. Therefore, a wide range of mechanisms are being targeted by NASH treatments currently being investigated, including changes in the gut permeability and microbiome, oxidative stress, insulin resistance, apoptosis, lipotoxicity, inflammation, bile acid metabolism, and fibrogenesis. There are currently dozens of more medicines in phase 2 trials, and six substances under research have advanced to phase 3 after completing phase 2 clinical trials. Based on our entire study, we conclude that the weight loss modulates immunological parameters in nonalcoholic steatohepatitis obese patients.

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