Impact of Nutritional Intervention on Serum Level of Interferon Gamma and Insulin Resistance in Obese Women: Considerations during the COVID-19 Crisis

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Abstract

BACKGROUND: Obesity represents a major epidemic worldwide; it is accompanied by increased oxidative stress and reduction in immune efficacy.

AIM: The objective was to assess the impact of a healthy balanced hypocaloric diet with two dietary supplements on obesity related metabolic disorders and interferon gamma production.

SUBJECTS AND METHODS: Sixty obese women participated in the study that lasted for 8 weeks. They were divided into two groups, 30 subjects in each group, one group consumed a daily supplement in the form of cookies prepared mainly from corn flour, wheat germ and thyme, and the other consumed a blend composed mainly of barley flour, cocoa powder and ginger powder. All participants have followed a low caloric balanced regimen (1000-1200 KCal/day). Follow-up was performed with anthropometric measurements, dietary recall, and biochemical parameters.

RESULTS: After intervention, the results showed a significant reduction in the anthropometric parameters, the obesity related metabolic disorders criteria with significant elevation in total antioxidant and interferon gamma. Positive significant correlations were detected between total antioxidant and interferon gamma and negative significant correlations were detected between interferon gamma with triglycerides, body mass index, percent body fat mass, and hip circumferences.

CONCLUSION: All these issues have a very important role in decreasing the infection with covid-19.

Introduction

Obesity has been tripled in the last 50 years around the world. Obese or overweight increased to be more than 1.9 billion adults in 2016 [1].

White adipose tissues are associated with metabolic complications, as insulin resistance, and generation of systemic oxidative stress and inflammation. Obesity predispose by in direct way for the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of diseases like cardiovascular disease, dyslipidemia, also increase the risk of developing a number of

Obesity is accompanied with reduction in immune efficacy and impairment in the activity of immune cells with reduction in interferon gamma and antibodies production [4] that mean increased susceptibility of obese individuals to viral and bacterial infection [5] and reduction in response to vaccination when compared to healthy weight individuals [4,5].

Interferon gamma (INFγ), is an important immune activator cytokine, where it has an important role in innate and adaptive immunity against viral and some bacterial infection. INFγ has a critical role in the process of antibodies and antiviral immunity [6].

Whole wheat is widely consumed as edible grain in many countries worldwide, where wheat germ is an abundant natural source of antioxidants and anti-inflammatory compounds like vitamin E, it is also a rich source of amino acids especially lysine, methionine, and threonine [7].

Maize is an important source of many bioactive compounds like carotenoids, where there is a negative correlation between the consumption of these phytochemicals and the risk of development of chronic diseases [8].
Barley is considered as a major food in some nations worldwide, it is also one of the richest sources in nutritional functional ingredients such as fiber, phenolic compounds, folate, and other anti-obesity, antioxidants, and anti-inflammatory bioactive compounds such as beta glucan [9].

Thyme or Avishane shirazi, is well known in many countries as a spice and a medicinal plant. Many studies demonstrated its antioxidant, anti-inflammatory, and anti-diabetic capacity with its ability in enhancing immunity and insulin sensitivity [10]. Many studies demonstrated the beneficial effects of ginger and cocoa such as anti-obesity and anti-inflammatory properties [11], [12].

Recently, it has been characterized by WHO that both COVID-19 outbreak and obesity (epidemic) as international community health crises. Global clinical and epidemiological observations confirmed that COVID-19 can cause more severe symptoms and complications in people with obesity-related conditions. Indeed, Wu et al. [13] established the correlation between obesity-induced immune deficiency and COVID-19 adverse outcomes.

The aim of this study was to highlight the bad effects of obesity on immune function and to assess the impact of healthy balanced hypocaloric diet with two dietary supplements on obesity related metabolic disorders and interferon gamma production as an immune activator cytokine in immune function which could be associated with obesity.

### Subjects and Methods

#### Methods

The first supplement (Corn cookies) was prepared from corn flour, wheat flour (72% extraction), and wheat germ, milk, corn oil, and thyme in a ratio presented in Table 1. All the ingredients were mixed with each other and kneaded with suitable amount of water and yeast were added and then left to ferment, then formed as cookies that were baked at 180°C for about 20 min [14]. The second supplement (Talbina) was prepared by mixing, barley flour with cocoa powder, ginger powder, and Arabic gum in a ratio presented in Table 1. The Talbina was cooked with water until it exhibited the suitable thickness.

| Ingredients | Corn flour | Wheat flour (72%) | Wheat germ | Milk | Corn oil | Thyme | Yeast |
|-------------|------------|-------------------|------------|------|----------|-------|-------|
| %           | 40         | 30                | 5          | 10   | 10       | 3     | 2     |

### Study Design and Interventions

The first group consumed the corn cookies, two with breakfast and two with dinner (each weighed 20 g), the second group consumed Talbina 30 g of the Talbina at breakfast and 15 g at dinner.

All the participants were examined at the beginning and at the end of the study with a weekly follow-up, for: Full medical history and medical examination, relevant anthropometric measurements (including height and weight using standard method [21]), Waist and hip circumferences in cm, BMI was calculated as weight in relation to height (weight in kg/height 2 in meter), basal metabolic rate, and body fat mass was measured using Geratherm Body Fitness (B-5010), German.

### Dietary History

Twenty-four hours dietary intake recall was recorded for all volunteers before and during the intervention. Nutrients intake was calculated before and during intervention using World Food Dietary Assessment System, “WFDAS), 1995, USA, University of California.
Blood samples were obtained on the day of clinical examination after an overnight fast. The blood samples were allowed to clot, centrifuged and sera separated and divided into aliquots and stored in Eppendorf tubes at –70°C until used for determination of the other biochemical parameters. Fasting blood glucose (FBG) was determined fresh sera using glucose oxidase method according to Trinder [22]. Serum total cholesterol was estimated according to Allain et al. [23], triglycerides was determined enzymatically according to Seidel et al. [24], and high-density lipoprotein (HDL-C) was estimated according to Wornick et al. [25]. All lipid profile were estimated using the kit supplied by Erba Lachema s.r.o., Karásek 1d, 621 00 Brno, CZ. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald et al. [26] equation and TGs/HDL-Ch ratio was calculated. Total antioxidant capacity as a marker of antioxidant capacity of the body was determined according to Koracevic et al. [27]. Fasting C-peptide level was measured by ELISA method (Monobind Inc. Lake Forest, CA 92630, USA). According to Bonser et al. [28], insulin resistance was expressed by modified homeostasis model assessment-insulin resistance according to Li et al. [29] (modified HOMA-IR = 1.5 × FBG (mg/dl) × fasting C-peptide (nanograms per milliliters)/2800), quantitative determination of interferon gamma concentration was assessed according to Boehm et al. [30] by human IFN gamma ELISA kit supplied by Wuhan EIAab Science Co. Ltd., catalog number E0079h.

Statistical Analysis

This is a comparison between two groups of obese cases who consumed two different supplements. Furthermore, the reported data were compared within each group before and after the dietary intervention. All values were expressed as mean value ± SE. Two-tailed student t-test was used to compare between data in the same group and between groups. Changes in different data were expressed as % change from baseline. Correlation coefficient (r) was calculated to find correlations between different variables. p < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS (10) software. SPSS window software version 17.0 (SPSS Inc. Chicago, IL, USA, 2008) was used.

Results

Table 2-4 illustrated the percentage of protein, fat, and crude fiber of the two prepared supplements. The supplement (1) is higher in percentage of protein and fat while the supplement (2) is higher in the percentage of ash and fiber. The supplement (1) is a good source of protein with higher percentage in essential, alkaline, and branched chain amino acid. However, the supplement (1) as presented in table (2) is higher in total phenols, total flavonoids content, and antioxidants activity, also this supplement contains a higher amount of iron and potassium and low in sodium. The supplement (2) contains a higher amount in zinc, magnesium, and calcium. Although the supplement 1 is higher in fat content, the supplement 2 contains higher percentage of omega-3 polysaturated fatty acids. The ratio between supplements I,2 of ω-6/ω-3 is 2:1 and 2.36:1 in two supplements, respectively. Table 3: Percent of amino acids and fatty acids in the two supplements

Table 5 demonstrated a comparison between the different macronutrients and the percent of the recommended dietary allowance (RDAs) of macronutrient intake of three types of dietary regimens daily consumed. The data showed the balanced and healthy distribution of the macronutrients in the two regimens compared to the habitual diet of the obese individuals.

Table 4: Levels of minerals (mg/100 g) in the two supplements
percentage of changes between the two groups, the second group showed more percentage reduction of all anthropometric measurements.

Table 7 showed the mean±SE of the biochemical parameters of the two groups at the two the visits. The levels of all lipid parameters were significantly improved in two supplements groups, with more relevant to supplement (2), except for triglycerides in Group 1 showed non-significant reduction, also fasting blood glucose showed non-significantly reduction in both groups. The level of cystatin-C showed a significant reduction in the mean concentrations of both groups. On the other hand, the concentrations of total antioxidant capacity and interferon gamma showed a significant reduction in the mean concentrations and nearly double reduction in % change in Group 2 than Group 1. While, supplement 2 Group showed significant reduction in total antioxidant capacity and non-significant reduction in interferon gamma.

**Pearson Correlation between Interferon Gamma and Different Variables in the Two Groups at the Baseline of the Study**

| Parameters                  | Cookies       | Talbina       |
|-----------------------------|---------------|---------------|
| Triglycerides               | -0.046        | -0.230        |
| Total antioxidant capacity  | 0.422**       | 0.406**       |
| Modified HOMA                | 0.037         | 0.213*        |
| Risk factor (triglycerides/ high-density lipoprotein C) | -0.185 | -0.194* |
| Body mass index             | -0.482**      | -0.210        |
| Fat mass                    | -0.395*       | -0.202        |
| Waist circumference         | -0.038        | -0.186        |
| Hip circumference           | -0.359*       | -0.268        |

*(Numbers presented in this table are the value of r =correlation coefficient), Correlation is significant at the 0.05 level (2-tailed).* Correlation is significant at the 0.01 level (2-tailed).

**Discussion**

In the present study, the obese participants were characterized by high BMI >30 kg/m² and visceral adipose tissue expansion, which was indicated by an increased in fat mass, waist circumference, hip circumferences, and dyslipidemia. Other related complications like insulin resistance, with low grade inflammation demonstrated by a reduction in the serum level of total antioxidant capacity that might be due to a reduction in the expression of antioxidant enzymes along with excessive generation of free radicals and inflammatory cytokines in adipose tissues [31].

In obese subjects, adipose tissue macrophages deviate toward M1 phenotype and secretion of inflammatory cytokines such as tumor necrosis factor which contribute to insulin resistance [32].

Improving body weight and its related metabolic syndrome can be obtained by healthy balanced diet, physical activity along with supplements by dietary functional foods that have a role in improving obesity and other diseases [33], where foods, plants, and herbal medicine contain a huge amount of natural phytochemicals and other bioactive components that have a positive role on many diseases without any side effects like medications [33]. In this context, the aim of this study was assessing the efficiency of two dietary supplements on obesity and obesity related metabolic disorders and interferon gamma production as an important immune activator cytokine in immune function.

The analytical data of this study showed that the two dietary supplements, cookies and Talbina, are enriched with anti-obesity elements and immune enhancer active compounds such as fiber, essential amino acids, phenolic compounds, Vitamins, and minerals.

Corn, wheat germ, and barley have a considerable amount of dietary fiber in which have role in regulating body weight, by increasing satiety. However, the fiber helps in modulating intestinal microbial populations by increasing the production of short chain fatty acids in large intestine along with reducing the level of cholesterol and promoting its fecal excretion [34].

Our results are in agreement with Jin et al. [35], who stated that Beta glucan of corn and parley have a beneficial effect on the improvement of the levels of blood cholesterol, HDL-C, and glucose with increasing in satiety feeling.

**Table 5: Daily intake of calories, macronutrient (as a % of calories), mean values, and % of the RDAs of macronutrient intake of three types of dietary regimens consumed by the obese volunteers**

| Macronutrients intake | Habitual diet | Regimen with formula 1 | Regimen with formula 2 | RDAs | p-value |
|-----------------------|---------------|------------------------|------------------------|------|---------|
| Mean±SE and % of the RDAs | 2459.33±33.92 | 1038.28±23.10 | 1035.47±20.48 | 2200 | 0.002**|
| Energy (kcal) | 41.37±4.26 | 50.12±5.08 | 48.97±4.12 | 50 | 0.002**|
| Protein (g) | 177.99 | 100.04 | 97.94 | 25 | 0.002*|
| Fiber (g) | 14.55±0.53 | 23.09±0.21 | 24.15±0.12 | 96.6 | 25 | 0.002*|
| Total carbohydrate (g) | 325.85±5.35 | 102.40±3.71 | 109.39±4.16 | 300 | 0.002**|
| Fat (g) | 108.62 | 34.13 | 36.46 | 77 | 0.003**|
| Saturated fatty acids (g) | 110.05±9.08 | 47.58±4.33 | 44.67±3.28 | 77 | 0.003**|
| Monounsaturated fatty acids (g) | 66.31±4.10 | 8.06±1.42 | 8.01±3.71 | No more than 7% | 0.003**|
| Polyunsaturated fatty acids (g) | 24.16 | 6.99 | 6.96 | 12%-14% of total Calories | 0.010*|
| Cholesterol (mg) | 15.23±1.40 | 9.67±2.46 | 9.74±2.11 | 220-40% of total Calories | 0.012*|
| 5.49 | 8.38 | 8.47 | 6-8% of total Calories | 300 | 0.002**|

World Food Dietary Assessment System, (WFDAS), 1995, USA, University of California. Significant at *p<0.05, **p<0.01. RDAs: Recommended dietary allowance.
### Table 6: Mean ± SE of age and anthropometric parameters of obese women at the baseline and after the dietary intervention

| Parameters                   | 1st Group (Cookies) | 2nd Group (Tabina) |
|------------------------------|---------------------|--------------------|
|                             | n=30                | n=30               |
|                             | Baseline            | After intervention | % Change |
| Age (year)                   | 43.82 ± 1.01        | 46.70 ± 2.12       | 7.57 %   |
| Height (cm)                  | 161.25 ± 0.94       | 154.87 ± 0.88      | 4.51 %   |
| Body mass index (kg/m²)      | 36.54 ± 0.55        | 38.67 ± 1.49       | 6.37 %   |
| Body fat mass (kg)           | 42.13 ± 1.96        | 44.32 ± 1.89       | 5.37 %   |
| Waist circumference (cm)     | 91.18 ± 1.49        | 94.10 ± 2.81       | 3.07 %   |
| Hip circumference (cm)       | 118.30 ± 1.88       | 121.30 ± 2.32      | 2.51 %   |
| Basal metabolic rate (kcal)  | 2134.47 ± 36.11     | 2146.50 ± 36.53    | 0.54 %   |

**Significant at *p < 0.05 **p < 0.01.

### Table 7: MeantSE of the obesity-related metabolic disorders, total antioxidant capacity, and interferon gamma of obese women at the baseline and the end of the study

| Parameters                     | 1st Group (Cookies) | 2nd Group (Tabina) |
|--------------------------------|---------------------|--------------------|
|                               | (Consuming supplement 1) | (Consuming supplement 1) |
|                               | n=30                | n=30               |
|                               | Baseline            | After intervention | % Change |
| FBG (mg/dl)                   | 116.66 ± 7.8        | 107.81 ± 3.60      | -8.07 %  |
| Cholesterol (mg/dl)           | 204.80 ± 3.76       | 231.89 ± 4.03      | 13.17 %  |
| Triglycerides (mg/dl)         | 135.78 ± 2.22       | 150.62 ± 4.03      | 11.07 %  |
| High-density lipoprotein cholesterol (mg/dl) | 31.86 ± 1.00 | 32.13 ± 1.17      | 0.87 %   |
| Low-density lipoprotein cholesterol (mg/dl) | 145.79 ± 6.79 | 169.64 ± 6.51      | 16.12 %  |
| Risk factor (triglycerides/high-density lipoprotein cholesterol) | 4.39 ± 0.15 | 5.11 ± 0.32      | 18.67 %  |
| C-Peptide ng/ml               | 5.93 ± 0.24         | 6.05 ± 0.19        | 2.07 %   |
| Modified HOMA-IR              | 0.28 ± 0.03         | 0.25 ± 0.013       | -12.00 % |
| Total antioxidant capacity mg/dl | 1.03 ± 0.026 | 0.810 ± 0.023     | -24.81 % |
| Interferon Gamma pg/ml        | 165.69 ± 3.28       | 173.77 ± 7.88      | 4.87 %   |

FBG=Fasting blood sugar. HOMA-IR=homeostatic model assessment of insulin resistance. Significant at *p < 0.05 **p < 0.01.

In addition, several studies demonstrated the regulatory effects of beta glucan on immune response [36], [37], a clinical study showed their ability in the protection against infection and improvement of the immunogenicity of vaccines [38]. Our results are in agreement with Aoe et al. [39], who showed that beta glucan could decrease visceral obesity.

Redan et al. [40] declared that dietary supplements rich in phenolic compounds possess a safe inexpensive health therapeutic approach. On the other hand, Vernarelli and Lambert [41] established the anti-obesity effects of polyphenols rich diet, where high phenolic and flavonoids compounds improved BMI and anthropometric measurements such as waist and hip circumferences, also improved dyslipidemia, hypertension, and inflammatory status in addition to their huge power of antioxidant capacity. Another study by Shahidi and Ambigaipalan [42] showed the ability of polyphenols and their natural sources in modulating the immune response.

Tzounis et al. [43] reported that consumption of food containing cocoa flavanol increases the amount of Lactobacilli and Bifidobacteria in humans, which have a protective effect on immune response as they were enhancing the differentiation of the regulatory T cells (Tregs) that produce anti-inflammatory cytokines.

The alterations in the metabolic environment associated with obesity can lead to loss of immune efficacy and impairment in the immune cells activity such as CD4+, CD8+, and B cells with reduction in antibodies and interferon gamma production [4] which explain why obese individuals are increase susceptibility to viral and bacterial infections as compared to healthy weight individuals [5].

The IFN-γ, considered as the central effector of cell mediated immunity, can manage a plenty of anti-microbial functions. It has a role in antigen presentation through antigen presenting cells by promoting antigen recognition through cognate T-cell interaction, increases the production of reactive oxygen species induce anti-viral responses [44].

Sheridan et al. [45] clarified the response of obese individuals and their immune systems, where the exposure of blood immune cells of obese, overweight, and healthy weight individuals to vaccine increased the number of IFN-production and CD8+ (65%) in healthy weight individuals followed by overweight (60%) and lastly obese individuals (40%). This is what was shown with the COVID 19 epidemic, where the seriousness of infection was found among obese individuals.

In this line, a report from France established that 85.7% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected obese subjects required mechanical ventilation when compared to 47.1% of infected healthy weight subjects [46].

Recent evidence indicates that CoVs have evolved to influence the features of the human IFN pathway to enhance their pathogenesis [47]. Analyses of single-cell RNA sequencing data showed that tissues that would potentially harbors SARS-CoV-2, in human airway epithelial cells, IFN-I, and to some extent IFN II, upregulate ACE2 expression [48]. Angiotensin-converting enzyme, a key component of the renin–angiotensin system cleaves angiotensin I to generate angiotensin II, whereas ACE2 inactivates angiotensin II and is a negative regulator of the system. The actions of angiotensin II drive acute lung injury through various mechanisms, including increased vascular permeability [49].

https://www.id-press.eu/mjms/index
A healthy, balanced diet with dietary supplements that can offer the necessary macro- and micronutrients, prebiotics, restore, and maintain immune cell function, our two dietary supplements contain a considerable amount of micro-immunoenhancer compounds such as essential amino acids and fatty acids (like omega 3) with vitamins (like A, E, D, C) and minerals (like Zn, mg).

Besides, the potent anti-inflammatory effect omega-3 fatty acids especially in the chronic state of inflammation like that found in obese individuals, it has an impact in modulating both innate, adaptive immunity which promotes B cells activation [50].

Fan et al. [51] documented that branched chain amino acids have a role in the regulation of immune functions, through increasing fuel sources for innate and adaptive immune response and pro-inflammatory cytokines.

Zinc is an important cofactor for many enzymes, where magnesium and zinc have a control role on immune function. Hasan et al. [52] stated that zinc deficiency could be accompanied by a reduction in INF gamma and antibodies production 116.

In accordance to vitamins such as C, E, and D that have a many role in several aspects of immunity, where they have a protective effects on influenza infection and in animal modules which was associated with improvement in Th1 responses as indicated by INF gamma and interleukin 2 production [53].

**Conclusion**

The reduction in the weight gain has several benefits toward improving many metabolic disorders associated with obesity such as dyslipidemia, insulin resistance, and inflammatory-immuno-disturbance. This study demonstrated that the dietary therapy with the two dietary functional foods supplemented rich in omega 3, vitamins, and minerals with a hypocaloric diet improved the metabolic disorders associated with obesity, also increased the total antioxidant capacity with improving the level of interferon gamma. All these issues have a very important role in decreasing the infection with covid-19.

**Ethical Approval**

The research was given ethical approval from Ethical Committee of National. Research Centre, (registration number is 19–180) and signed written informed consent was obtained from all subjects before enrollment.

**Authors’ Contributions**

HE and SS designed research, SS was responsible for clinical examination, MM anthropometrics measurements, HE had responsibility for biochemical analysis and laboratory investigations, HE wrote the manuscript, NH was responsible for preparation of the supplements and analysis of nutritional intake and dietary habit, HE and MM were responsible for statistical analysis. SS and ST were involved in consent signature by the subjects, have primary responsibility for final content. MS, had the responsibility for chemical analysis of the supplement;

All authors read and approved the final manuscript before submission.

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