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Impact of Different Dietary Components on Some Adipocytokines in Association with Obesity Related Metabolic Disorders Induced in Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAS designed the study and wrote the protocol. Authors SFD, AAER and HMI managed and performed the biological experiment and analyses of the study. Author HMI managed the literature searches and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study was designed to investigate the effect of low calorie and antioxidant vitamins (A & E) diets on some metabolic risk factors associated with obesity in rats.
Methodology: Obesity was induced in healthy rats using high fat-high sucrose diet. The animals were divided into 5 groups (12 rats/group); group 1 served as normal control, group 2 served as obese control and the other 3 groups fed the low calorie and/or high antioxidant vitamins (A & E) diets. The study involved measurement of some nutritional and anthropometric parameters, apparent digestibility through fecal characteristics, serum biochemical measurements as leptin, adiponectin, blood lipids profile, insulin, glucose, glycated hemoglobin (HbA1c) quantitative insulin sensitivity check index (QUICKI) and homeostatic model assessment of insulin resistance (HOMA-IR).
Results: Dietary induction of obesity resulted in significant ($P<0.05$) increase in body weight and BMI by 40.9% and 40.7% compared with normal rats respectively. Serum leptin resistance,

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lipotoxicity and insulin resistance were manifested by induction of obesity. Obesity resulted in significant (P<0.05) increase in leptin serum level by 129.8% and decrement in adiponectin serum level by 60.7% compared with normal rats. However, treatment of obese rats with high fiber and antioxidant vitamins diet resulted in significant (P<0.05) reduction in body weight and BMI by 22.5% and 21.7% respectively. Also significant (P<0.05) reduction in serum levels of leptin by 30.3% with increase in adiponectin serum level by 99.1% was found compared with obese rats. Blood lipids profile, atherogenic indices and insulin resistance (HOMA-IR) condition were improved by high fiber and/or high antioxidant vitamins diets significantly (P<0.05) compared with obese animals. HDL-C and insulin sensitivity index levels were increased.

Conclusion: Nutritional management can be useful tools in the improvement of obesity condition and its related risk conditions and prevention of developing other diseases as diabetes mellitus and cardiovascular diseases.

Keywords: Obesity; leptin resistance; QUICKI; lipotoxicity; anthropometric measures.

1. INTRODUCTION

Obesity is the major component of the metabolic syndrome. The prevalence of metabolic syndrome is associated with the severity of obesity; its pathophysiology is related to both genetics and food intake habits, especially the consumption of a high caloric, high-fat and high-carbohydrate diet [1]. The excess intra-abdominal fat in obesity is a marker of the inability of subcutaneous adipose tissue to store the excess energy known as ectopic fat deposition. This results in the excess fat being stored at undesired sites such as the liver, the skeletal muscle and the heart, as well as in pancreatic β cells. The increased fat mass leads to difficulties in locomotion and pain in back, hip, knee, ankle, or foot [2].

Adipose tissue functions as an endocrine and paracrine tissue, producing an array of adipocytokines, such as leptin and adiponectin. Adiponectin is an adipocyte-derived hormone that acts as an anti-diabetic, anti-atherogenic and anti-inflammatory adipocytokine [3]. Adiponectin has an important insulin sensitizing effect and is inversely related to fat mass [4]. Leptin, a 167-amino acid protein, is a signal of adiposity, which decreases appetite and reduces body weight [4]. Its secretion can be positively regulated by insulin [5]. Leptin plays important roles in modulating satiety and energy homeostasis. Specifically, circulating leptin acts as a trophic factor for the development of hypothalamic circuits that control energy homeostasis and food-seeking and reward behaviors [3]. Regulation of hunger and satiety is a complex mechanism that is influenced by the appetite related hormones, such as leptin and adiponectin which regulate the energy intake in the long term [6].

In the modern society, obesity induced by high-caloric/high-fat diet (HFD) and reduced physical activity results in a serious health threats. Skeletal muscle plays an important role in regulating whole-body homeostasis. For example, skeletal muscle is responsible for approximately 80% of the postprandial clearance of glucose. Thus development of obesity and type II diabetes were associated with: (1) impaired insulin secretion from beta cell; (2) increased hepatic glucose production; and (3) decreased peripheral glucose utilization in muscle. In particular, obesity-induced insulin resistance in skeletal muscle is a multi-factorial process [7].

Abnormalities in lipid and lipoproteins in metabolic syndrome can be explained by increased adiposity, insulin resistance and alterations in transcription factors related to lipogenesis and lipolysis, in the liver and adipose tissue. Most of these conditions are a result of the amount and the quality of the alimentary fat. Saturated fatty acids (SFAs) have been associated with deleterious effects regarding several parameters related to metabolic syndrome, due to their influence on plasma triacylglycerols (TAG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations [1].

Dietary fiber is not digested in the human intestine and it entraps the organic molecules (e.g. glucose), which play a critical role in controlling obesity and diabetes. After entering the large intestine, it is fermented and produces short chain fatty acids that help to maintain the colonic health. Besides, plant-derived dietary fibers were also enriched in phytochemicals which can be considered as dietary antioxidants. Thus, the consumption of diet rich in dietary fiber

helps to reduce the risks of common diseases such as diabetes, obesity and colon cancer [8].

Furthermore, natural protection against oxidative stress can be provided by endogenous enzymes that capture free radicals such as superoxide dismutase or catalase and by nonenzymatic dietary compounds such as vitamins A, E and C [9]. Vitamin A and E supplementation was found to normalize the changes induced in lipid profiles suggesting an improvement in insulin sensitivity. All together shows the importance of vitamin A and E as nutrient molecules which help in preventing the body from biohazards related to obesity through their regulation of carbohydrates and lipids metabolism together with their anti-oxidant activities [10]. Retinoic Acid (RA) was found to reduce body weight and adipose depot mass independent of the changes in food intake, and improves glucose tolerance and insulin sensitivity through adipocytokines regulation. It increases thermogenic potential in brown adipose tissue and muscle and reduces body fat content, and partly opposes the development of obesity [11].

The present study aimed to investigate the impact of different dietary treatments, including low and high calorie diets, as well as high antioxidant vitamins (A & E) diets on some nutritional and anthropometric parameters, leptin resistance, insulin resistance and dyslipidemia conditions related to obesity in rats.

2. MATERIALS AND METHODS

2.1 Animals

The experimental animals used in the present study were normal adult male Spargue-Dawley albino rats weighing 200 ± 10 g and supplied by the Breading Unit of the Egyptian Organization for Biological Products and Vaccines (Helwan, Egypt).

2.2 Diets

The diets used in the study were the following: (1) balanced diet prepared according to American Institute of Nutrition (AIN-93) and adjusted by Reeves et al. [12], (2) the high fat-high sucrose diet, used for induction of obesity, prepared according to Yang et al. [13], (3) high fiber/low calorie diet (containing 20% fiber) according to Bragado et al. [14], (4) High antioxidant vitamins (A & E) diet (containing 782 mg vitamin A /kg diet and 2.19 g vitamin E /kg diet) according to Soliman et al. [10] and (5) high fiber and high antioxidant vitamins (A & E) diet (containing 20% fiber and 782 mg vitamin A /kg diet and 2.19 g vitamin E /kg diet). The composition of each diet presented I the following Table 1.

Table 1. Composition of the balanced diet and the tested diets used throughout the study

Ingredients	Balanced diet g/kg diet	High fat- high sucrose diet g/kg diet	High fiber low calorie diet g/kg diet	High antioxidant vitamins diet g/kg diet	High fiber & high antioxidant diet g/kg diet
Corn starch	620.69	180.69	470.69	620.69	470.69
Casein	140.00	140.00	140.00	140.00	140.00
Sucrose	100.00	370.00	100.00	100.00	100.00
Corn oil*	40.00	40.00	40.00	40.00	40.00
Fiber	50.00	50.00	200.00	50.00	200.00
Minerals mixture	35.00	35.00	35.00	35.00	35.00
Vitamins mixture**	10.00	10.00	10.00	10.00	10.00
L. Cystine	1.80	1.80	1.80	1.80	1.80
Choline chloride	2.50	2.50	2.50	2.50	2.50
Tert-Butylhydr-oquinone	0.008	0.008	0.008	0.008	0.008
Supplemented ingredients					
Vitamin A (mg)**	-	-	-	782	782
Vitamin E (g)**	-	-	-	2.19	2.19
Beef tallow (g)*	-	170.00	-	-	-

**Beef tallow was added plus the corn oil in the high fat-high sucrose diet.*

***The supplemented doses of vitamins A and E were added to the vitamins mixture in the high antioxidant vitamins diets*

2.3 Experimental Trial

All rats were randomly housed individually in stainless steel cages with constant controlled environments; temperature 25ºC ± 5ºC, air humidity 55% ± 10% and 12/12 hrs light /dark cycle were held. A number of 12 animals served as normal control group. A sufficient number of animals (60 animals) consumed the high fat and sucrose diet for 7.5 weeks for induction of obesity. Weekly monitoring of body mass index (BMI) until measurement of obesity by BMI reached 0.82±0.01 g/cm2 as indicated by Novelli et al. [15]. It was calculated by the following equation [15];

$$\text{BMI (g/cm}^2\text{)} = \text{Body weight (g)} / \text{Nose to anus length}^2\ (\text{cm}^2)$$

The obese rats then divided into 4 groups each contain 12 rats. The whole groups were as follows;

- Group (1): Normal control rats consumed the balanced diet,
- Group (2): Obese control rats consumed the high fat-high sucrose diet,
- Group (3): Obese rats consumed the high fiber diet,
- Group (4): Obese rats consumed the high antioxidant vitamins (A & E) diet,
- Group (5): Obese rats consumed the high fiber and high antioxidant vitamins (A & E) diet.

The experimental period was 4 weeks after induction of obesity during which constant weight of diets were given for each animal while water was provided ad libitum. Food intake was measured every day by subtracting the residual and refusal diets from supplied diet. The length in cm (from nose to anus) and body weight in grams were measured weekly to monitor the body weight changes and measurement of BMI [15]. All the measurements were done in anaesthetized rats by inhalation of diethyl ether [16]. Feces were collected at the last week for fecal measurements. At the end of experimental period all rats were scarified under ether anesthesia after 12 hrs fasting with water ad libitum. The experiment was done in the animals' house of the faculty of Women for Arts, Science and Education at Ain Shams University.

2.4 Serum Biochemical Measurements

2.4.1 Quantitative immunoassay measurements

Serum leptin was measured using the ELISA kit (CAT. No. MBS264924) [17], adiponectin measurement was performed using the ELISA kit (CAT. No. MBS261106) [18] and insulin was measured following the quantitative immunoassay techniques [19].

2.4.2 Colorimetric measurements

Glycated hemoglobin (HBA1c) was measured in whole blood by using the assay kit (CAT. No. CA92807) [20] and serum glucose levels were measured following the colorimetric method using the assay kit (CAT. No. GL1320) [21]. Quantitative insulin sensitivity check index (QUICKI) and homeostatic model assessment of insulin resistance (HOMA-IR) were calculated using the following equations [22,23];

$$\text{QUICKI} = 1/\log \text{fasting insulin}\ (\mu\text{U/ml}) + \log \text{fasting glucose}\ (\text{mgdl})$$

$$\text{HOMA-IR} = \text{fasting insulin}\ (\mu\text{U/ml})\ \text{X}\ \text{fasting glucose}\ (\text{mg/dl})/405$$

Serum total cholesterol (TC) and triacylglycerols (TAG) were measured according to the colorimetric methods and using the assay kits (CAT. No. CH1220) [24] and (CAT. No. TR2030) [25] respectively. Also high density lipoprotein cholesterol (HDL-C) measurement in serum followed the instructions of the assay kit (CAT. No. CH1230) [26]. Serum low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) were calculated by the following equations [27]:

$$\text{LDL-C (mg/dl)} = \text{TC} - (\text{VLDL-C} + \text{HDL-C})$$

$$\text{VLDL-C (mg/dl)} = \text{TAG concentration}/5$$

Atherogenic indices were calculated using the following equations [28,29]:

$$\text{Atherogenic coefficient} = \frac{\text{TC}-\text{HDL}-\text{C}}{\text{HDL}-\text{C}} \qquad \text{Atherogenic index} = \frac{\text{LDL}-\text{C}}{\text{HDL}-\text{C}}$$

$$\text{Cardiac risk ratio} = \frac{\text{TC}}{\text{HDL}-\text{C}} \qquad \text{Atherogenic index of plasma} = \frac{\text{TAG}}{\text{HDL}-\text{C}}$$

2.5 Fecal Measurements

Some fecal characteristics were measured including; dry weight, volume, density and pH [30]. The collected feces were dried in the electrical oven at 110 ± 5ºC and weighted (grams). The volume of dry feces was estimated by using the substitution methods with sand. The dry feces were ground, and 1 g was mixed with 25 ml distilled water so that the pH was determined by using pH meter. The density of feces in g/cm^3 was counted as follows:

$$\text{Density of feces (g/cm}^3\text{)} = \frac{\text{weight of dry feces (g)}}{\text{Volume of feces(cm3)}}$$

2.6 Statistical Analysis

Data were statistically analyzed by Statistical Package for Social Science (SPSS) version 20.0 statistical packages. Values were presented as mean ± standard deviation (S.D.). Statistical differences between groups were performed using one way ANOVA, the mean difference was significant at the (P<0.05) level according to [31].

3. RESULTS

3.1 Nutritional and Anthropometric Parameters

Dietary induction of obesity by feeding the high fat-high sucrose diet in rats caused a statistically significant (P<0.05) increment in body weight (52.67±11.87 *vs.* 22.83±8.52), feed efficiency ratio (0.112±0.03 *vs.* 0.049±0.02) and BMI (0.83±0.05 *vs.* 0.59±0.03) in the obese rats *vs.* control normal group that consumed the balanced diet. However, treatment of obese rats by high fiber and antioxidant vitamins (A & E) diet resulted in significant (P<0.05) reduction in body weight (-51.25±16.20), FER-(0.11±0.04) and BMI (0.65±0.04) as compared with the control obese group. Whereas no significant (P>0.05) changes were observed in food intake and body length of all rat groups (Table 2).

3.2 Fecal Characteristics

Considering fecal characteristic measurements, the high fat-high sucrose diet increased fecal alkalinity, and significant decrement in fecal volume in obese rats 20.08±1.38 vs. 24.67±1.07 in the control normal rat group. Also obesity resulted in small reduction in fecal weight and increase in fecal density which were not significantly (P>0.05) different from those in normal rats. While treatment of obese rats with high fiber diet resulted in significant (P<0.05) increment in fecal weight (6.14±0.42 vs. 1.59±0.23) and volume (111.0±2.00 vs. 20.08±1.38) and significant (P<0.05) decrement in fecal density (0.39±0.03 vs. 0.56±0.09) and pH (6.38±0.06 vs. 7.83±0.07) to the acidic side compared with obese control group. Treatment of obese rats with high antioxidant vitamins diet caused similar results. Also combined treatment of obese rats with high fiber and antioxidant vitamins (A & E) diet resulted in significant (P<0.05) increment in fecal weight 5.25±0.88 and volume 112.5±2.84 and significant (P<0.05) decrement in fecal density 0.33±0.06 and pH 6.40±0.02 as compared with obese control group (Table 2).

Table 2. The effect of high fiber and/or antioxidant vitamins (A & E) diets on some nutritional and anthropometric measures, as well as some fecal characteristics in normal and obese adult male rats

Parameters	Group (1)	Group (2)	Group (3)	Group (4)	Group (5)
Change in body weight (g)	22.83±8.52	52.67±11.87*	-49.42±26.06	-33.42±11.87	-51.25±16.20**
BMI (g/cm^2)	0.59±0.03	0.83±0.05*	0.65±0.06	0.69±0.03	0.65±0.04**
Length (cm)	23.50±0.52	23.63±0.43	23.63±0.57	23.46±0.49	23.46±0.45
Food intake (g)	457.79±41.43	474.92±34.42	452.00±20.48	460.33±34.52	454.75±17.93
FER	0.049±0.02	0.112±0.03*	-0.11±0.06	-0.073±0.03	-0.11±0.04**
FCR	22.37±7.14	9.54±2.83*	-12.97±10.34	-15.8±6.70	-10.53±6.14**
Fecal weight (g/day)	1.87±0.20	1.59±0.23	6.14±0.42**	1.96±0.13	5.25±0.88**
Fecal volume (cm^3)	24.67±1.07	20.08±1.38	111.0±2.00**	27.92±2.11	112.5±2.84**
Fecal density (g/cm^3)	0.54±0.07	0.56±0.09	0.39±0.03**	0.49±0.03	0.33±0.06**
Fecal pH	7.24±0.04	7.83±0.07*	6.38±0.06**	7.28±0.02	6.40±0.02**

**means ±SD are significant (P<0.05) compared with normal control group (1), **means ±SD are significant (P<0.05) compared with obese control group (2). FER; Feed efficiency ratio, FCR; Feed conversion ratio*

3.3 Appetite and Insulin Resistance Related Hormones

Serum levels of leptin hormone were found to be significantly (P<0.05) increased in obese rats fed the high fat-high sucrose diet (5.24±0.14) and serum adiponectin hormone levels (11.10±1.21) were significantly (P<0.05) reduced in comparison with the normal rats fed on the balanced diet. Whereas obese rats fed the high fiber and antioxidant vitamins (A & E) diet showed significant (P<0.05) improvement in the leptin resistance status with significant (P<0.05) reduction in serum leptin levels (3.65±0.08) and increment in serum adiponectin levels (22.10±0.42) as compared with the control obese group (Table 3).

3.4 Carbohydrates Metabolism Dysfunction Markers

Compared with the control normal rats, induction of obesity resulted significant (P<0.05) increase in the blood levels of insulin (112.67±5.31), fasting blood glucose (101.97±4.65) and HBA1c (6.58±0.34) and decrement in QUICK index (0.246±0.002). Treatment of obese rats with high fiber and/or antioxidant vitamins (A & E) diets resulted in reduction in the risk for developing diabetes mellitus in obese rats by significant (P<0.05) reduction in the blood levels of insulin, fasting blood glucose, HOMA-IR and HBA1c and increment in QUICK index as compared with the control obese rat group (Table 3).

3.5 Blood Lipids Profile and Atherogenic Indices

With respect to the blood lipids profile, obesity resulted in significant (P<0.05) increment in the serum levels of TC, TAG, LDL-C, VLDL-C and atherogenic indices as compared with the normal rat group consuming the balanced diet respectively. While significant (P<0.05) reduction was found in the level of HDL-C in obese rats 14.98±1.43 vs. 35.79±2.23 in normal rats. Whereas treatment of obese rats with the high fiber and antioxidant vitamins diet resulted in significant (P<0.05) increment in the blood level of HDL-C and reduction in the serum levels of TC, TAG, LDL-C, VLDL-C and atherogenic indices as compared with the control obese group (Table 3).

4. DISCUSSION

Lifestyle factors, such as overeating and physical inactivity, induce visceral fat accumulation, which can result in adipocyte dysfunction leading to a state known as adipotoxicity. Taken together, abdominal obesity, including dysfunctional visceral fat adipocytes, dysregulated production of adipocytokines and ectopic fat deposition, might be the major mechanisms of lifestyle-related diseases as obesity [32].

Table 3. The effect of high fiber and/or antioxidant vitamins (A & E) diets on blood levels of leptin and adiponectin hormones, some carbohydrates metabolism dysfunction markers, lipids profile and atherogenic indices in normal and obese adult male rats

Parameters	Group (1)	Group (2)	Group (3)	Group (4)	Group (5)
Leptin (ng/ml)	2.28±0.19	5.24±0.14*	3.69±0.22	3.74±0.13	3.65±0.08**
Adiponectin (ng/ml)	28.23±2.49	11.10±1.21*	20.17±0.89	21.06±1.38	22.10±0.42**
Insulin (µU/ml)	48.75±3.47	112.67±5.31*	75.58±4.01	80.17±3.49	74.17±4.26**
Glucose (mg/dl)	66.02±3.36	101.97±4.65*	76.65±3.25	81.67±5.12	76.21±4.78**
HbA1c (%)	3.98±0.15	6.58±0.34*	4.99±0.91	5.18±0.73	4.58±0.51**
HOMA-IR	7.94±0.54	28.39±2.26*	14.30±0.90	16.19±1.50	13.95±1.15**
QUICK index	0.286±0.002	0.246±0.002*	0.266±0.001	0.262±0.002	0.266±0.002**
TC (mg/dl)	184.8±8.49	439.59±20.96*	194.10±13.47	204.18±7.36	190.56±5.21**
TAG (mg/dl)	118.5±4.10	214.67±30.49*	144.78±4.59	172.08±7.62	139.65±5.62**
HDL-C (mg/dl)	35.79±2.23	14.98±1.43*	27.57±2.06	23.73±1.61	29.13±1.85**
LDL-C (mg/dl)	125.32±8.13	381.68±24.68*	137.58±14.19	146.03±7.23	133.50±5.98**
VLDL-C (mg/dl)	23.70±0.82	42.93±6.10*	28.96±0.92	34.42±1.52	27.93±1.12**
Cardiac risk ratio	5.18±0.35	29.66±3.71*	7.09±0.83	8.65±0.75	6.57±0.48**
Atherogenic coefficient	4.18±0.35	28.66±3.71*	6.09±0.83	7.65±0.75	5.57±0.48**
Atherogenic index of plasma	3.32±0.22	14.43±2.27*	5.28±0.42	7.28±0.65	4.81±0.35**
Atherogenic risk	3.51±0.32	25.77±3.59*	5.03±0.77	6.19±0.64	4.61±0.43**

**means ± SD are significant (P<0.05) compared with normal control (group 1),*
***means ± SD are significant (P<0.05) compared with obese control (group 2)*

Long term feeding with high-fat diet (HFD) has been found to be effective in promoting obesity, through increased adiposity index and higher body weight. The obese state may be due to a high feeding effectiveness ratio (FER) in the hyperlipidic diet as observed in our results. This favors the deposition of lipids such as triacylglycerols in adipose tissue, leading to an increase in body weight [33] which was indicated by the increase in BMI measurement in our study. Body mass index (BMI) has been stated to be a simple reliable estimate of body fat and obesity in rats as there are positive correlations between daily lipid intake and BMI as well as fat deposition [34]. Consumption of high fat diet has been positively related to BMI and linked to increased risk for type 2 diabetes, coronary heart disease and colon cancer [34]. Thus the observed increase in body weight and BMI in our study by feeding animals the high fat-high sucrose diet may be due to excessive energy intake and accumulation of adipose tissue [34]. Consumption of HFD causes increase of body fat mass with development of symptoms of metabolic diseases such as hyperlipidemia, impaired glucose tolerance and insulin resistance. It also reduced functions of the immune system and induced inflammatory pathways [35,36].

Our observations on rats consumed diet high in fat and sucrose showed significant elevation of plasma leptin and reduction of adiponectin levels in comparison with normal rats. The early increases in leptin may promote macrophage infiltration and M1 polarization. TNF-α produced by M1 macrophages and hypertrophied adipocytes induce systemic inflammation and insulin resistance [37]. The increased concentrations of serum leptin observed in obesity lead to the following effects: (1) desensitization of leptin receptors in the hypothalamus thus the individual does not exhibit a normal satiety response and thus keeps eating; (2) increased activation of T lymphocytes which release pro-inflammatory molecules such as IL-2, IL-6 and TNF-α, thus contributing to the chronic low-grade inflammation, and (3) during periods of excess energy intake, leptin receptors on adipose tissue decline and the adipose tissue develops a resistance to leptin, much like the hypothalamus [2].

However, the observed hypoadiponectinemia may be explained in part by the fact that in obesity, elevated T-cadherin in white adipose tissue (WAT) by fat reactive oxygen species (ROS) may capture free adiponectin from the blood stream and tether it in various tissues, thus affecting circulating adiponectin levels [38]. Decreased plasma adiponectin level may be one of the key factors for the elevation in plasma inflammatory mediators and worsened systemic oxidative stress after high fat diet treatment [39]. Also adiponectin activates AMP kinase in skeletal muscle and liver tissues, stimulating phosphorylation of acetyl coenzyme-A carboxylase, fatty acid oxidation and glucose uptake. By activating PPAR-α, adiponectin stimulated fatty acid oxidation and decreased TAGs in muscle and liver tissues. These actions tended to increase insulin sensitivity [40]. Binding of adiponectin to AdipoR1 elicits an increase in intracellular calcium levels that activates calmodulin-dependent protein kinase, AMP-activated protein kinase, and sirtuin-1, all of which play roles in increasing the cell's need for glucose and thus enhance skeletal muscle glucose uptake. These findings collectively support adiponectin's insulin sensitizing properties [41].

Hypertrophied intra-abdominal adipocytes (visceral obesity) may undergo hyperlipolysis, leading to an increased flow of free fatty acids (FFA) to various organs, as liver, that may impair liver function, leading to increased hepatic glucose production and insulin resistance. The hepatic insulin resistance is associated with decreased apolipoprotein B degradation and an increased production of lipoproteins rich in triacylglycerols (TAG) [22]. Excess and pro-longed exposure to ROS overproduced in obesity suppresses insulin action and disrupts glucose metabolism [42]. Furthermore hypoadiponectinemia occurred in obesity may be another cause of insulin resistance due to its function in inducing insulin sensitivity. This may explain in part the observed insulin resistance and increased fasting glucose levels in obese rats in our study.

Our findings also indicated marked increase in serum levels of TC, TAGs, LDL-C and atherogenic indices with long time consumption of high fat-high sucrose diet, and this was in agreement with earlier studies [13,43]. However, low levels of circulating HDL-C have been recognized as a powerful predictor for atherosclerotic cardiovascular events [41]. HDL-C plays an important role in reverse cholesterol transport as an acceptor. Moreover, HDL-C has an anti-inflammatory function, which protects against the oxidative modification of LDL-C. This

may explain in part the association between decreased HDL-C levels and the increased risk for cardiovascular diseases [41].

Dietary fibers play an important role on hunger and satiety, through its intrinsic effects and hormonal responses. High-fiber food may promote satiation (lower meal energy content) and satiety (longer duration between meals) due to its bulk and relatively low energy density, leading to decreased energy intake [44]. It was indicated previously by Mirhashemi and coworkers that in animal models of metabolic syndrome, the normocaloric chow diet exerted an anti-adipogenic/anti-diabetogenic effects, which appear to be due to its lower caloric density and/or its higher fiber content [45,46]. Modulation of food intake by consuming foods rich in fiber of high satiety value may help to reduce obesity, as dietary fiber may cause earlier termination of a meal or reduce inter meal food intake [47]. Also a high fiber intake has been shown to delay the onset of hunger and thus enhance body weight loss over time [48,49]. Dietary fiber's ability to decrease body weight or attenuate weight gain may be attributed to decreased energy intake, decreased diet metabolizable energy (ME), decreased fat digestibility and decreased intake of fat and simple carbohydrates [50,51]. This may in part explain the observed reduction in body weight and BMI of obese rats treated with high fiber diets.

Our study showed a marked reduction in serum levels of leptin and increased serum adiponectin levels of obese rats after dietary calorie restriction. Our findings were supported by previous studies [52,53]. The low-calorie diet was found to result in reduced energy intake and weight loss that play a major role in the observed reduction in leptin levels and increment in adiponectin levels. Thus, lifestyle intervention is a useful therapeutic tool to increase adiponectin levels [54].

Calorie restriction in animals fed high dietary fiber was found to display significantly lower insulin concentration. The postprandial reduction in insulin with fiber feeding may be due either to a delay in gastric emptying or a slowed diffusion of glucose within the small intestine. These results suggest the role for calorie restriction in protecting against insulin resistance, through lowering adiposity and the up-regulation of adiponectin generation from adipose tissue [48,55]. Thus dietary strategies that limit hyperglycemia may be important in limiting complications of diabetes. In addition, numerous agencies from across the globe, including the British Diabetes Association (BDA), Canadian Diabetes Association (CDA), and European Association for the Study of Diabetes (EASD) and those from India, Japan and South Africa, have all recommended increasing dietary fiber intake in individuals with type 2 diabetes. Many of these agencies have also recommended the intake of low glycemic index (GI) diets. In general, most medium and low GI foods are those that are used as sources of fiber such as all-bran, oats and legumes [46].

Fibers was also found to play an important role in lowering plasma cholesterol by lowering absorption of intestinal bile acid, thus increasing fecal bile acid loss, and its synthesis in liver. This may alter hepatic cholesterol and lipoprotein metabolism, resulting in lower levels of plasma LDL-C. Fermentation of dietary fiber by the intestinal microflora could modify the short chain fatty acid production by increasing propionate synthesis, which reduces the endogenous synthesis of cholesterol, fatty acids and low density lipoproteins [56,57].

Movement of materials through the colon is stimulated by the presence of residues in the lumen. A low-fiber diet may result in chronic insufficient bulk in the colon, thus the colon responds stronger to propel the smaller mass distally. Thus adequate intake of dietary fiber provides adequate bulk in the colon so that less forceful contractions are needed to propel it distally [58]. Dietary fat intake has a weak but significant correlation with fecal weight, suggesting that fat was not an integral dietary factor in this regard. Increased stool bulk associated with high fiber diet was important for intestinal motility as evidenced by more frequent bowel movements and shortened colonic transit time. Greater stool mass was found to reduce exposure of the colonic epithelium to potentially harmful agents in the fecal stream, including carcinogens [59]. The low fecal pH, produced by high fiber intake (due to short chain fatty acids), has been associated with a low colonic cancer incidence in obese patients [60]. Many fiber sources including cereal bran and mixed high-fiber diet increase stool weight, thereby promoting normal laxation. Stool weight continues to increase as fiber intake increases, but the added fiber tends to normalize defecation frequency to one bowel movement daily and gastrointestinal transit time to 2 to 4 days. The increase in stool weight is caused by the

presence of fiber, by the water that the fiber holds and by partial fermentation of dietary fiber, which increases the amount of bacteria in stool [61].

It has been found that dietary carotenoids were positively related with their plasma concentration in obese patients. Specifically, plasma concentrations of carotenoids were lower in adult participants with BMI ≥25 kg/m^2 compared to those who had BMI <25 kg/m^2. Also serum levels of β-carotene, retinol and α-tocopherol were negatively associated with all measures of obesity including body weight and BMI in central adiposity [62,63]. Retinol and α-tocopherol inhibited the production of pro-inflammatory cytokines in macrophages, and reduced inflammatory reactions in adipose tissue, as well as neutralized reactive oxygen species [63]. Vitamin E was found to inhibit NADPH oxidase activity. Oxidative stress increased in obese rats as a result of increased NADPH oxidase activity in adipose tissue may lead to decreased plasma adiponectin levels. Thus, vitamin E supplementation has the potential to increase plasma adiponectin levels and decrease leptin plasma levels in obese rats [64]. These findings can support our findings in the obese rats consumed the high antioxidant vitamins (A & E) diets.

Antioxidant vitamins supplementation of obese rats resulted in marked improvement in the insulin resistance condition and blood glucose levels deteriorated by the high fat-high sucrose diet. The mechanism of vitamin A-mediated amelioration of insulin resistance in obese rat may be that a significant increase in the ratio of phosphorylated insulin receptor (pIR) to insulin receptor (IR), associated with decrease in protein tyrosine phosphatase 1B (PTP1B) levels was observed in obese rats. PTP1B directly interacts with IR and attenuates the insulin signaling by dephosphorylating tyrosine phosphorylated proteins [65]. It has also been found that GLUT2 activation is increased after vitamin A and E administration which is a transmembrane carrier protein, which enables passive glucose movement across cell membranes (it transfers glucose between liver and blood). Thus vitamin A and E may ameliorate obesity through the increase in glycolysis and hepatic glucose uptake [10].

The observed reduction in blood cholesterol and improvement of HDL-C levels in obese animals fed the high antioxidant vitamins diets can be explained by the fact that vitamin A-enriched diet resulted in up regulation of hepatic scavenger receptor class B1 (SR-B1) levels in obesity, an authentic HDL receptor that brings about selective uptake of cholesterol esters from HDL particle by liver which is the final step in reverse cholesterol transport and its subsequent excretion as free cholesterol or bile acids through bile. Thus vitamin A can be involved in regulation of obesity-associated hypercholesterolemia in obese rats [65]. Vitamin A is involved in lipid metabolism and insulin responses through its ability to activate the nuclear receptors as retinoic acid receptors (RAR) and peroxisome proliferator-activated receptor β/δ (PPARβ/δ). Upon their activation, these receptors regulate the production of proteins that control adipocyte differentiation, lipolysis, energy dissipation, fatty acid oxidation, and glucose transport [66]. These may confirm the hypolipidemic action of vitamin A and E [10].

5. CONCLUSION

From the present study it was concluded that the nutritional factors as high fiber diet and antioxidant vitamins (A and E) can be useful tools in the improvement of obesity condition and its related risk conditions and thus in prevention of developing other diseases as diabetes mellitus and cardiovascular diseases. This can be obtained by the effect of these dietary factors on improving blood lipids profile, leptin resistance, adiponectin blood levels and enhancing insulin sensitivity conditions which were deteriorated by obesity.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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