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Research Article

Bovine whey improved the myocardial and lung damage of mother rats fed on a high fat diet

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Abstract

Back ground: High fat diet associated obesity associating losing of body organs structure and function is of important public health problem. The heart and lungs represent the main organs of supplying oxygen, nutrients and nutritive molecules necessary for the body function. Little of work is concerned with higher fat diet associated myocardial and lung damage. Also, the bovine whey is rich in micronutrients with biological and medicinal activity. The present study aimed to illustrate the role of whey in ameliorating the damaged effects of higher fat diet on both heart and lung.

Methods: In the present study, one hundred and twenty fertile male and virgin female rat (Rattus norvegicus) weighing approximately 100-110g. body weight at ratio of 1 male/3 females. The experimental group fed on a high fat diet (15% fat) was carried out for 4months prior to mating. After allowing feeding on either standard or a higher fat diet for 4months, mating of virgin females were s carried out at evening and examining the sperm in vaginal sperm in the next morning and determined the onset of gestation. The pregnant categorized into four groups; control, whey supplemented group (Orally administered 1mL^3), a high fat diet and a combined high fat diet and whey supplementation. At 21days-post-partum, the pregnant were sacrificed and their lung and heart were separated and fixed in 10 percent neutral buffered formalin. Histological sections stained with hematoxylin and eosin as well as immunohistochemically with p53, caspase, COX and iNOS were carried out.

Results: The present findings revealed that high fat diet induced myocardial damage with apparent fragility of the myocardial fibers, hyalinization and necrosis of myocardial fibers. Over expression of caspase 3 immunostaing and increased collagen deposition in between the myocardium was observed after masson-trichrome staining. Also, the lung tissues explained interstitial inflammatory cell infiltration with apparent fibrosis and losing alveolar spaces. The inflamed lung tissues possessed over expression of the immunostaining of COX-2, INOS and caspase 3. However, whey supplementation to the inflamed lung exhibited marked improvement and decreased expression of the assessed immunostaing.

Conclusion: Finally the authors concluded that whey contains several bioactive nutrients which facilitated reduction of the oxidative stress and supplied antioxidant components which scavenge the free radicals and ameliorated the damage associated with dietary supplementation of fat diet.

Introduction

The heart required 60%–80% of their demand of energy for pumping blood and transmission of gases and nutrients from the oxidation of fatty acids (FAs) with glucose, lactate, and ketones. Also, it used this energy in the generation of ATP [1]. Although, fat is the most calorically dense of macronutrients, the development of metabolic syndrome including obesity and type 2 diabetes is associated with intake of a higher fat diet. According to Mendoza et al. [2], dietary fat predicted obesity, elevated fasting insulin levels, and the related disorders. The incidence of obesity attained to 1.6billion overweight adults worldwide (BMI >25kg/m2) [3,4]. The WHO further predicts that, by 2015, around 2.3billion adults will be overweight and more than 700million will be obese. High fat diet associated obesity was found to alter myocardial function [5-7] and both lung stem cells and functional activity [8,9].

On the same time, bovine whey is a liquid residue of cheese,

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casein and yoghurt production with s a pH of 5.9-6.6. Bovine whey proteins contain important dairy ingredients rich in their amino acid content, digestibility and antioxidant activity. Consumption of whey products can modulate redox biomarkers to reduce oxidative stress. However, whey proteins themselves are targets of oxidation during processing particularly when exposed to high thermal loads. Oxidative damage of whey proteins can be associated with the degree of protein unfolding, with a-Lactalbumin more susceptible than b-Lactoglobulin [10].

Whey protein is composed of several bioactive fractions including glycomacropeptide, β-lactoglobulin, α-lactalbumin and lactoferrin, with multiple health benefits against cancer, infection and inflammation [11].

Whey protein supplementation significantly accelerated the closure of diabetic wounds by impairing inflammation and restoration the normal level of normal IL-10, TNF-α, IL-1β and IL-6 levels [12].

There is no available work illustrated the myocardial and lung damage associated intake of a higher fat diet. The present study aimed for clarification of the histopathological abnormalities and how to ameliorate by whey supplementation.

Material and methods

The study was approved by the Ethical Committee for Animal Experimentation at Faculty of Science, Mansoura University, Egypt.

Induction of a high fat diet

Experimental a high fat diet fed groups were carried out by feeding on a high fat diet composed of 15% soft animal fat mixed with stand diet contained all the standard nutritional components of protein, carbohydrate, fibers, vitamins and minerals. Virgin females were fed on a high fat diet for four months before undergoing pregnancy.

Whey syrup supplementation

Fresh bovine whey supplied from Dairy product Lab, Faculty of Agriculture, Mansoura Univ., Egypt and orally administered daily doses of 1mL[3] for two months by stomach tube.

Experimental work

Forty eight virgin female rats weighing approximately 100g body weight, obtained from Hellwan Breeding Farm, Ministry of Health were used for experimentation. Free access of standard diet was supplied. Free excess of water was allowed *ad-libitum.* One hundred and twenty fertile male and virgin female rat (Rattus norvegicus) weighing approximately 100-110g. Body weight obtained from Hellwan Breeding Farm, Ministry of Health, Egypt and used for this work. They were housed in good ventilation with 12hour light and dark cycle. Females were mated in a special cage (1 male/3 females) during overnight and conception was determined in the next morning by the presence of sperm in a vaginal smear. The day of conception was considered to be the first day of pregnancy. The pregnant were arranged into four groups (n-20); controls, whey supplemented group, a high fat diet -group, a high fat diet & whey syrup supplementation. The pregnant of the studied groups were sacrificed after 21days post-partum. The heart and lung of mother rats were dissected and immediately, fixed in 10% phosphate-buffered formalin (pH 7.4) and processed for histological investigations. Serial 5µm thick sections were cut and stained with hematoxylin and eosin. Also, the myocardial tissue sections were stained with mason trichrome stain [13], for collagen and immunohistochemically with the antibody of p53 (3 (Thermo fisher scientific, fremont, CA, USA). In case of lung, the tissue sections were incubated with antibodies against caspase 3 (Thermo fisher scientific, Fremont, CA, USA; Cat. No. Al-70007) and stained with hematoxylin for staining of the background of tissues. The specimens were investigated with a light microscope and photographed.

Results

Myocardium

Compared with the control and whey supplementation (Figure 1A), mother rat fed on a high-fat diet exhibited eosinophilic and hyalinized necrotic muscle fibers.

Other specimens of Other specimens of myocardial tissues displayed round cell infiltration between muscle fibers (Figure 1A2). Following Masson trichrome stain, there was a detected dense collagen deposition in between the myocardial muscle fibers manifesting fibrotic change (Figure 1B2). Also, the myocardium of mother fed on a high fat diet exhibited overexpression of p53 manifesting decreased myocardial function (Figure 1C2).

On the other hand, the supplementation of whey to mother rat fed at high-fat diet showed improved histopathological picture, but the muscle fibers appeared to be slightly widening (Figure 1A3). Following masson trichrome stain, there was a marked reduction in collagen deposition between my fibers (Figure 1B3. Also, there was a detected reduction of p53 immunohistochemically but was still increased from the control (Figure 1C3). Image analysis revealed dense collagen deposition and overexpression of p53 in myocardium of mother fed on a high fat diet compared to the other experimental groups (Figure 2).

Lung

In both control and whey supplemented mother, the lung is composed of alveoli of different sizes that acquire spongy-shaped architecture.

Two groups of pneumocytes, type I & II, lined the alveolar wall which become thin and straight.

Type I cells are squamous and cover the basal lamina and the alveolar lining surface. (Figure 3A,B).

In mother fed on a high fat diet, there was a detected dense inflammation of the lung. The inflammatory cells were densely aggregated through the peri-and inner of the alveolar space losing their luminal space. In some specimens, the lung

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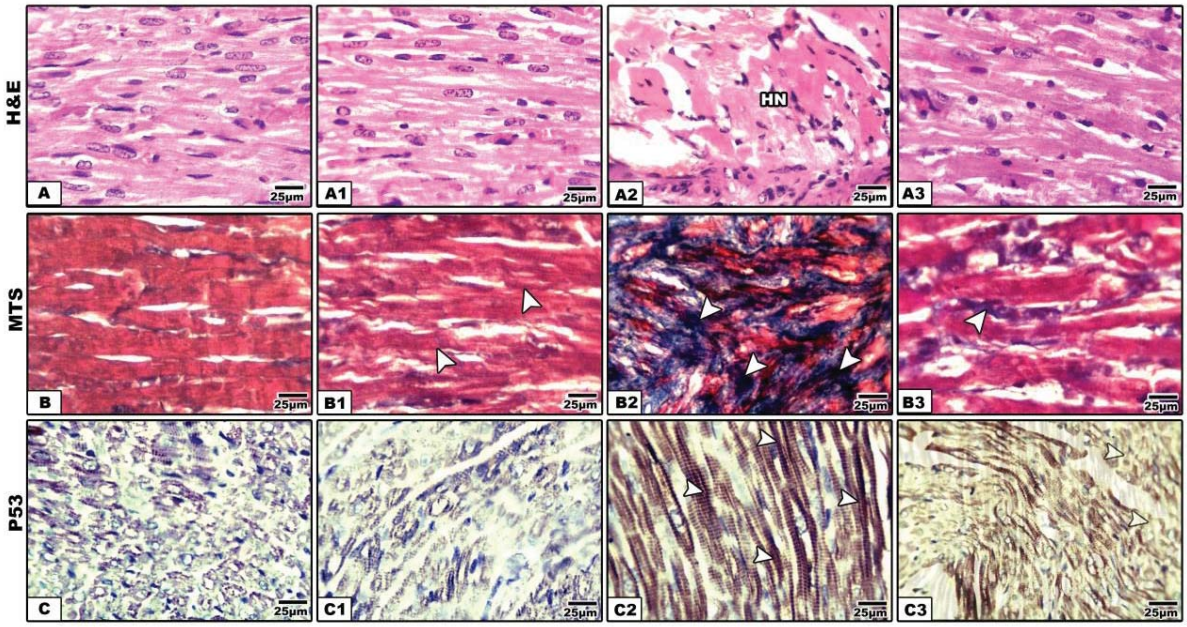

Figure 1: Photomicrographs of histological sections of heart ventricle in mother rat. A-A3. Hematoxylin eosin stained myocardium. A & A1. Control and whey supplementation showing regular arranged muscle fibers. A2. High fat diet supplementation showing hyaline necrosis. D. High fat diet plus whey supplementation showing improvement. Abbreviations: HN, hyaline necrosis.
B-B3. Masson trichrome-stained myocardium. B & B1. Control & whey supplementation showing missing of collagen fibers. C. High fat diet supplementation showing dense collection of collagen fibers in between myocardial muscle fibers. D. High fat diet plus whey supplementation showing decreasing collagen fibers in between muscle fibers. Arrow head showing dense collagen fiber deposition in between muscle fiber of mother fed on a high at diet.
C-C3. Formalin fixed histological sections immunohistochemical stained with P53. A & B. Control and whey supplemented mother rat showing missing of immunohistochemical reaction. C. High fat diet supplementation showing increased dark brown immunohistochemical reaction in muscle fibers manifesting cell death. D. High fat diet plus whey supplementation showing decreased immunohistochemical reaction . Arrow head indicating increase immunohistochemical reaction of P53.

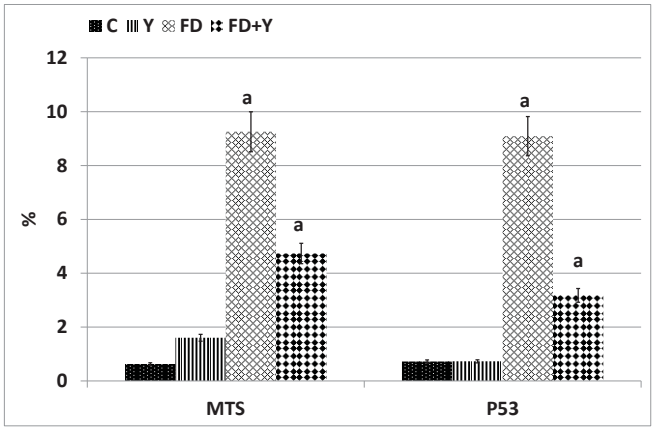

Figure 2: Histogram illustrating myocardial collagen fibers in mother rat fed on a high fat diet with or without whey supplementation. Note that the percentage of collagen fibers was increased in mothers fed on a high fat diet and improved in that supplemented whey plus fat diet and illustrating the percentages of immunohistochemical reaction of P53 in myocardium of mother rat fed on a high fat diet with or without whey supplementation. Note over expression of P53 of myocardium of mother rat fed on a high fat diet and improved in experimental group supplemented whey plus a high fat diet. Each result represents the mean± SE. a means significant at P<0.05.

tissues possessed wide spots of interstitial fibrosis associated with hyperplasia of type II pneumocyte. Many of the type II cells become foamy, eosinophil and infiltrated throughout the alveoli. Also, fibrosis of the alveoli associated with dense collagenous deposition and surrounded by dense distributions of inflammatory cells were also detected (Figure 3C-E). On the other hand whey supplementation to mother fed on a high fat diet improved the histological picture of the alveoli (Figure 3F).

Immunohistochemistry of cysteine-aspartic acid protease 3 (caspase-3), cyclooxygenase-2COX-2) and induced nitric oxide synthase (INOS)

Concerning cysteine-aspartic acid protease 3 (caspase-3), the activity of caspase-3 was highly detected in the alveolar tissues of mother rats fed on a high fat diet (Figure 4A2). Mother rats fed on a high fat diet and whey supplementation possessed a moderate amelioration of the apoptic immune marker caspase-3 (Figure 4A3). Regard mild caspase 3 immunohistochemical reaction in the control and whey supplemented mothers (Figure 4A,A1). Image analysis revealed the increased intensity of the caspase-3 in a high fat diet fed mothers compared to mother fed on a high fat diet and whey supplementation (Figure 5).

In control and whey supplemented mother rats, the lung tissue possessed mild immunohistochemical reaction of COX (Figures 4B,B1). In experimental mother fed on a high fat diet, there was a marked increase of dark brown-deposits in the interstitial and alveolar wall (Figure 4B2). On the other hand whey supplementation to mother fed on a high fat diet showed a decreased immunohistochemical reaction (Figure 4B3). Image analysis revealed a marked increase of the immunostaining reaction in a high fat diet mother compared to the other studied groups (Figure 5).

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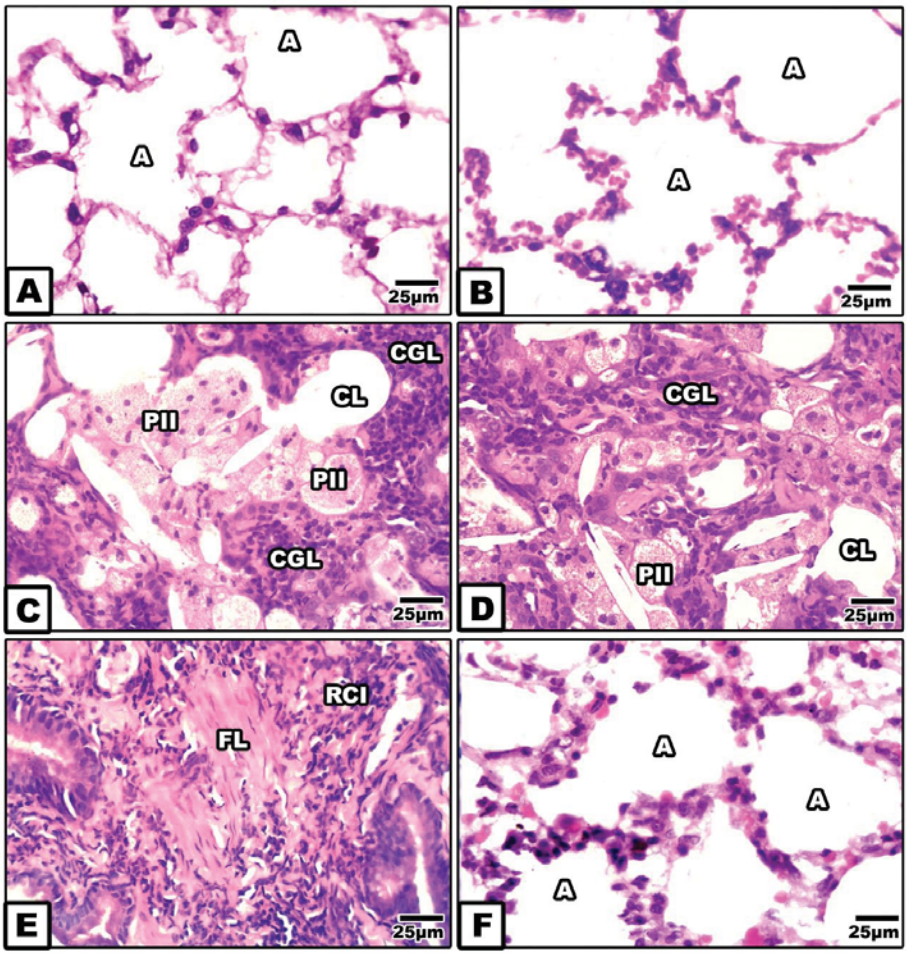

Figure 3: Photomicrographs of histological sections of lung tissue in mother rat. A & B. Control and whey supplementation showing thin alveolar wall with normal alveoli space. C,D & E. High fat diet supplementation showing thick alveolar wall with narrowing alveoli space associated with dense round cell infiltration (E) and cellular granulomatous lesions (C) & (E). F. Fat diet plus whey supplementation showing improvement. H & E. Abbreviations: Al, alveoli; CGL, cellular granulomatous lesions; FL, fibrotic lung; LC, lung cavity; PI, pneumocyte type I; PII, pneumocyte type II; RCI, round cell infiltration.

Concerning inducible nitric oxide synthase immunohistochemistry, compared to the control and whey supplemented mother rats (Figure 4C,C1), the lung tissue of mother fed on a high fat diet have a comparative increase of dark brown-deposits in the interstitial tissue of the alveoli (Figure 4C2. Experimentally mother fed on a high fat diet and received whey supplementation, possessed a decreased and improved immunohistochemical reaction (Figure 4C3). Image analysis revealed a marked increase of the immunostaining reaction in a high fat diet mother compared to the other studied groups (Figure 5).

Discussion

Heart

From the present work, mother rats fed on a higher fat diet for four month as well as throughout pregnancy and lactation period exhibited fragility of the myocardial muscle fibers, hyalinization and focal collection of inflammatory cells in the necrotic zones. Masson trichrome stain possessed dense collagenous formation in between muscle fibers predicting myocardial fibrosis.

These findings were consistent with who reported myocardial hypertrophy and inflammation of mice [14], rats [15] and pigs atrophied [16] fed on a high fat diet.

The induced myocardial damage was attributed to the increased lipid burden in the myocardial tissues [17] and sarcolemma [18], which enhanced cell death and myocardial fibrosis [19, 20]. These complications influenced on left ventricular wall thickness, hypertrophy [21] and fibrosis [22].

The dramatic effects of long term ingestion of fat diet on myocardial muscle may be attributed to the fatty acid oxidation and liberation of free radicals [23], or the formation of Fatty acyl-coal from the triglyceride which increased lipid accumulation and exerted lipotoxicity

Myocardial damage reflected pulmonary fibrosis. The inflamed lung tissues facilitated accumulation of extracellular matrix components, particularly collagen, at the site of injury [24]. At the same time acute and chronic lung inflammation is influenced in the development of cardiovascular disease [25].

The observed myocardial damage was reflected by increased p53 immunostaining.

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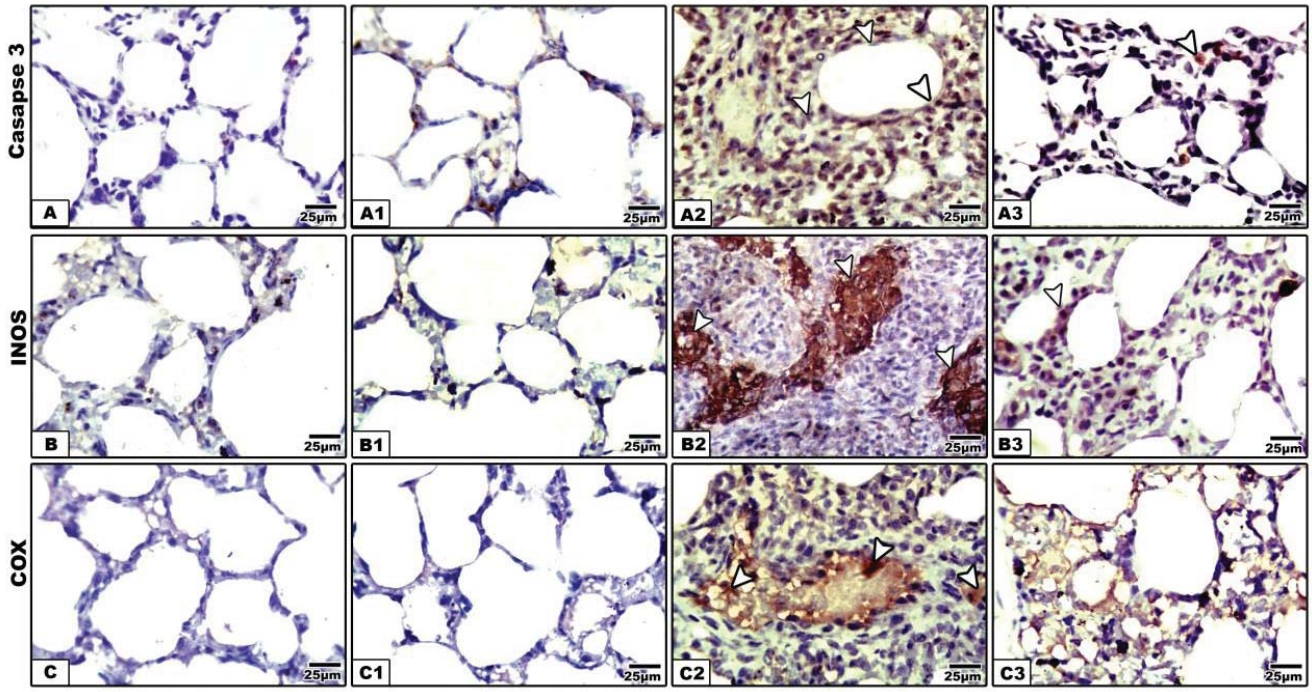

Figure 4: Photomicrographs of formalin fixed histological sections of lung tissue immunohistochemical stained with caspase3 (A-A3),INOS (B-B3) and COX (C-C3) of mother rat.
A &A1-B&B1-C&C1. Control and whey supplementation showing missing immunohistochemical reaction of caspase3, INOS and COX respectively.
A2, B2 and C2. Fat diet supplementation showing overexpression of casp 3, INOS and COX respectively.
A3,B3 &C3. High fat diet plus whey supplementation showing decreased immunohistochemical reaction of casp3. INOS and COX respectively.

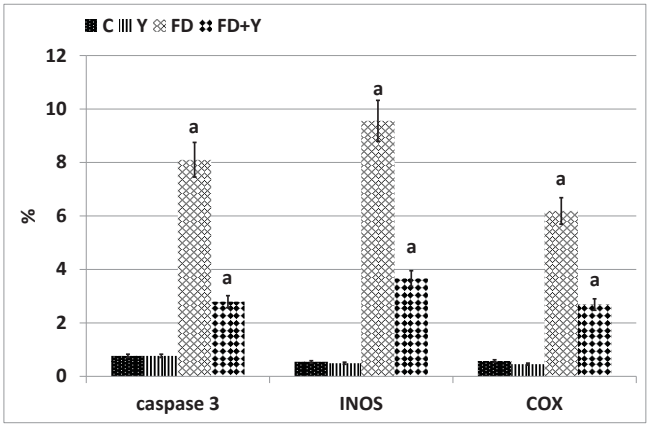

Figure 5: Histogram illustrating the percentages of immunohistochemical reaction of caspase 3, INOS and COX in lung tissue of mother rat fed on a high fat diet with or without whey supplementation. Note over expression of caspase 3, INOS and COX in lung tissue of mother rat fed on a high fat diet and improved in experimental group supplemented whey plus a high fat diet. Each result represents the mean± SE. a means significant at P<0.05

Similar findings were observed in patients with acute myocardial infarction [26].

Beside the mentioned, mother rat fed on a high fat diet enhanced the aggregation of inflammatory cells leading to the development of fibrosis through the peri-and inner of the alveoli losing their luminal space. Interstitial fibrosis characterized by dense collagen fibers and increased the average of type II pneumocyte within lung tissues having foamy and eosinophilic structure. The death of the alveolar epithelium explained by increased caspase 3 immunohistochemically.

Similar findings of damage [27] and fibrotic lung. Were reported in obese mice fed on a high fat diet ApoE(-/-) mice fed on a high fat diet developed inflammation of the lung associated with marked deposition of collagen and increased metalloproteinase-9 matrix [30].

The damage of alveolar epithelium may result from the liberation of reactive oxygen species leading to oxidative damage to mitochondrial DNA which consequently induces cell death [31] and reflected the dietary administration of a high fat diet associated obesity [32].

The inflamed lung tissues led to fibroblast accumulation and damage of the alveolar epithelium associated the progress of idiopathic pulmonary fibrosis [33].

The observed increased inflammatory lesions were assessed by increased immunohistochemistry of cyclooxygenase-2COX-2) and induced nitric oxide synthase.

In mother rats maternal fed on a high fat diet, marked increase of COX-2 immunohistochemistry was detected within the cytoplasm of macrophages, alveolar epithelial cells, type-2 pneumocytes, and endothelial cells of blood vessels.

Similar findings of highly expressed cyclooxygenase-2 (COX-2) in AT [34].

The cyclooxygenase (COX) enzymes catalyze a key step in the conversion of arachidonate to PGH_2, the immediate substrate for a series of cell specific prostaglandin and thromboxane synthases.

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COX catalyzes the cyclooxygenation reaction through which arachidonic acid is enzymatically cleavage and generates the free radicals.

Inflammation of adipose tissue (AT) plays a major role in the development of many type 2 diabetes associated with obesity [35]. This inflammation is mediated by a large number of cytokines and chemokines, including TNF-α [36], IL-6 [37].

There is a direct correlation between consumption of a high fat diet and inflamed lung associated overexpression of immunostaining of cyclooxygenase 2.

The adipocyte tissues were found to enhanced expression of COX-2 inducing lung disease [38].

A high-fat diet (HFD) is known to shorten lifespan and to increase incidences of several metabolic diseases, including type-2 diabetes and various cardiovascular diseases [39].

The present findings agree with the work of Hegab et al. [8], Who reported increased number of lymphocytes and macrophages in the lung parenchyma.

Although a high fat diet does not have a direct correlation with lung cancer, the increased consumption of high fat diet increased the number of pulmonary metastases by 60% and tumor volume by 130% [40].

The overexpression of COX-2 is predicted of early diagnosed lung cancer associated with a high fat diet. The present findings supported the work of Zhu et al. [41].

Also, the observed lung inflammation of mother fed on a high fat diet exhibited increased immunohistochemical reaction of inducible nitric oxide synthase (iNOS). Inducible nitric oxide synthase (iNOS) was markedly upregulated and enhanced pulmonary disease. The overexpression of inducible nitric oxide synthase was associated with increased nitric oxide, the potent free radicle involved in damaging the alveolar epithelium and enhanced lung inflammation and fibrosis [42-44].

From the present findings, there was a detected increased collection of inflammatory cells in associated cell damage facilitated the release of free radicals associated overexpression of induced nitric oxide synthase especially in the interstitial of the alveoli.

The present findings agree with the work of whom reported increased expression of iNOS in aorta.

The present results are in consistent with the work of [45], who reported that the associated higher fat diet associated with obesity triggered macrophage increased iNOS gene expression [46]. This resulted from inducing inflammation associated type 2 diabetes [47].

From the observed findings, there were a detected improvement of fat associated the myocardium and lung tissue as well reduction of the immunostaining of p53 in heart and casp3, COX and iNOS in lung.

From the observed findings, there were a detected improvement of fat associated the myocardium and lung tissue as well reduction of the immunostaining of p53 in heart and casp3, COX and iNOS in lung.

These findings may be associated to increased whey content of sulfhydryl groups which enhanced glutathione production and reduced the in vitro production of interleukin (IL)-8 and consequently reduce the oxidative stress in cystic fibrosis [48] . The whey contents of bioactive molecules lysozyme, lactoferrin, immunoglobulins, growth factors and hormones [49], glycomacropeptide, β-lactoglobulin, α-lactalbumin and lactoferrin, with multiple health benefits against cancer, infection and inflammation [50]. These bio-components decreased creatinine kinase-MB, lactate dehydrogenase, homocysteine, triglycerides, low density lipoprotein and dyslipidemia [51], leading to myocardial and lung diseases. Supplementation of non-hydrolyzed milk protein (25g/day) for 8weeks improved vascular and endothelial function and hyperlipidemia associated diseases [52].

The authors finally concluded that whey contains bio-nutrients having antioxidant activity with therapeutic medicinal important in alleviating the dramatic changes of a higher fat diet in myocardial and lung tissues.

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