Impact of niacin combined with ubiquinone on inhibition of lipoprotein lipase as a mechanism of anti-obesity and antiatherogenic agents in rats fed on high-fat diet

Fatma A. Eissa,[1] Taha A. Kumosani,[1,2,3] Elie K. Barbour,[3] Soonham S. Yaghmoor,[2,3] Khalid M. El-Say,[4] May M.M. Tadros,[5] Said S. Moselhy[5]

[1]Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia; [2]Production of Bio-products for Industrial Applications Research, King Abdulaziz University, Jeddah, Saudi Arabia; [3]Experimental Biochemistry Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [4]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia; [5]Department of Biochemistry, Faculty of Science, Ain Shams University, Cairo, Egypt

Correspondence: Said S. Moselhy, Department of Biochemistry, Faculty of Science, Ain Shams University, Cairo, Egypt.
E-mail: moselhy6@hotmail.com

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Abstract

Niacin is one of the B-complex vitamins that play an important role in metabolic pathways, while ubiquinone (Coenz-Q) is a component of the electron transport chain required for energy production. This study evaluated the role of niacin combined with ubiquinone in the inhibition of lipoprotein lipase as a mechanism of anti-obesity and antiatherogenic agents in rats fed on a High-Fat Diet (HFD). To achieve this purpose, sixty male albino rats (100–150 g) were used in this study and divided into six groups (10 each). Group I (control): rats fed on a normal diet. Group II: Rats fed on HFD. Group III: Rats fed HFD and were given Niacin at 10 mg/kg body weight (b.w)/day orally by stomach tube. Group IV: Rats fed HFD and were given Coenz-Q (10 mg /kg b.w/day) orally. Group V: Rats fed HFD were given Niacin (10 mg/kg b.w/day) and Coenz-Q (10 mg /kg b.w/day). Group VI: Rats were given a hypocholesterolemic agent (cholerose) orally (10 mg/kg b.w/day) as positive control. The obtained results showed that treatment with Niacin or Coenz-Q or combined increased the activity of lipoprotein lipase ($p < 0.001$) and reduced the atherogenic effect and obesity index ($p<0.001$). The combined treatment is more effective than individual one or cholerose. In conclusion, Niacin combined with Coenz-Q increased lipid clearance and prevented its accumulation in blood. This combination is promising as antiatherogenic agent. Further investigation is required to identify the pathways regulated by these supplements that help in weight management.

Introduction

Dyslipidemia and obesity are the major risk factors for cardiovascular diseases. Accumulation of excess fats in the body is due to imbalance between energy intake and expenditure.[1] The etiological factors contributing in obesity include the lifestyles, high fat and carbohydrate diet, low fibers intake, low exercise, psychological stress, and genetic factors.[2] Flavonoids and saponin showed promising effects to reduce body weight by different mechanisms.[3] Dietary triacylglycerol needs emulsification with bile acids and co lipase before hydrolyzed with pancreatic lipase. This enzyme hydrolyzes triacylglycerol with release of monoacylglycerol and free fatty acids that are then absorbed as mixed micelles and transported to circulation via lymph nodes as chylomicrons. However,

lipoprotein lipase (clearing factor) plays an important role in hydrolysis of blood lipoproteins, (chylomicrons and Very Low Density Lipoproteins (VLDL-c).

It was reported that flavonoids from citrus fruits exert anti-obesity effects through regulation of lipid metabolism, energy intake and expenditure, and adipogenesis.[4] *In vitro* and *in vivo* studies showed that citrus fruits are considered as a good source for developing novel anti-obesity therapies.[4] The first choice for treatment of hyperlipidemia and hypercholesterolemia is statin derivatives as cholerose that acts via inhibition of Hydroxymethylglutaryl Coenzyme -A Reductase (HMGCoA-Rase). Statin reduces cholesterol synthesis and fat absorption from the Gastrointestinal Tract (GIT) to avoid weight gain.[5] Statins, as a class, are generally safe, but in some cases they may be associated with an increased risk of diabetes mellitus and hepatic transaminase elevations, as well as incidence of cataracts or cognitive dysfunction.[6] For these reasons, scientists are looking for alternative safe agent. Niacin (vitamin B3) is one of B complex vitamins. In the body it is converted to the active coenzyme forms Nicotinamide Adenine Dinucleotide or Nicotinamide Adenine Dinucleotide Phosphate (NAD^+ or $NADP^+$) that are important for dehydrogenases reactions during carbohydrates, proteins and lipid metabolism.[7] The foods rich in niacin or its derivatives may be an effective way to control lipid profiles. However, it was reported in Korea that the daily intake of niacin has been declining over the past 10 years. Consumption of foods with high niacin levels may help prevent or delay the onset of dyslipidemia.[7] These coenzymes participate in redox signaling pathways.[8] Niacin can be synthesized in the body from tryptophan which is used to reduce blood lipid level. The antioxidant effect of niacin showed to prevent the formation of oxidized Low Density Lipoprotein Cholesterol (LDL-c).[9] Niacin is used to minimize the risk of heart attacks, atherosclerotic diseases, and for the detoxification of xenobiotics.[10] Ubiquinone (Coenz-Q) is one of the main components of the respiratory chain that is important for oxidative phosphorylation and ATP synthesis. It was reported that Coenz-Q administration improves glucose tolerance in experimental diabetic animals.[11] The metabolic role of Coenz-Q may be attributed to its role in improving insulin action. This study investigated the role of combined Niacin and Coenz-Q in dyslipidemia and obesity in rats fed on High Fat Diet (HFD).

Materials and Methods

Animals

This study was carried out on sixty male albino rats (100–150g) obtained from King Fahad Medical Research Center (KFMRC), maintained at a 12/12-hour dark/light cycle, at a temperature of 18°C with 30-40% humidity. Food and water were given *ad libitum*. The experimental protocol was approved by the Animal Ethics Committee and proceeded according to the guidelines of the Committee at King Abdulaziz University (KAU.SCI-5-130-43:1/2/2023). Rats were divided into six groups (10 each). Group I (control): rats fed on a normal diet. Group II: Rats fed on HFD, namely 55% of the basal diet, containing 25% beef tallow and 5% sesame oil.[12] Group III: Rats fed on HFD and given Niacin 10 mg/kg body weight (b.w.)/day orally. Group IV: Rats fed HFD and given Coenz-Q (10 mg/kg b.w./day) orally. Group V: Rats fed HFD and given Niacin and Coenz-Q (10 mg /kg b.w./day). Group VI: Rats fed on HFD and given cholerose (10 mg/kg b.w./day) as positive control. The doses of Niacin and Coenz-Q were given according to Abdullah *et al.*[13] and Elkenawy *et al.*[14]

Biochemical analysis

At the end of experiment (10 weeks), rats were anesthetized with thiopental and blood was collected for serum separation. Sera were subjected for estimation of Fasting Blood Glucose (FBG), lipid profile (triglycerides, total cholesterol, LDL-c, HDL-C) and liver function markers Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP) and Gamma Glutamyltranspeptidase (GGT) were measured by kits from BIO-RAD, Hertfordshire, UK. Lipoprotein lipase enzyme activity was measured using a commercially available assay kit (Biorad, Hertfordshire, UK). Atherogenic index was calculated as: log (triglycerides/HDL-c).

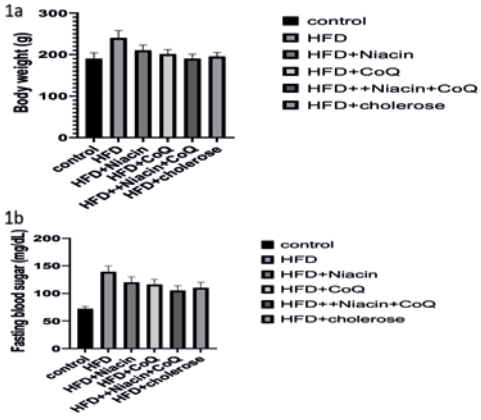
Obesity index was calculated as weight in kg divided by height in meter square: Body Mass Index (BMI) = kg/m^2.

Statistical analysis

Results were analyzed by using SPSS, version 20. The data were expressed as the mean ± standard deviation. Biochemical data were evaluated by one-way Analysis of Variance (ANOVA). In all experiments, a p value < 0.05 was considered as significant

Results

The changes in body weight of rats fed with HFD and treated with Niacin or Coenz-Q or combined for 10 weeks are presented in Figure 1a. At the end of the experiment, there was a significant increase (p=0.00067) in body weight in rats fed HFD compared with the normal control. However, HFD-fed rats treated with niacin, ubiquinone, or combined showed a significant reduction (p=0.0008) in body weight versus untreated. A slight significant elevation in the level of FBG (Figure 1b) was observed in rats fed HFD compared with normal control. Treatment with Niacin or Coenz-Q or combined prevented this elevation compared with untreated. The liver enzymes ALT (Figure 2a), AST (Figure 2b), ALP (fig. 2c), and GGT (Figure 2d) were significantly elevated in rats fed on HFD (p=0.00055, p=0.00061, p=0.00078, p=0.00083), respectively, compared with the normal control group. Treatment with Niacin or Coenz-Q or combined showed a normalization of



HFD, high fat diet; CoQ, ubiquinone.

Figure 1. a) Body weight changes in all groups; b) fasting blood sugar levels in all studied groups.

these enzymes compared with untreated HFD. However, the combined treatment showed similar effect of cholerose. Data obtained showed that rats fed on HFD revealed a significant elevation in the levels of total cholesterol (p=0.00057) (Figure 3a) and LDL-c (p=0.00075) (Figure 3b) and a significant decrease in the level of HDL-c (p=0.00085) (Figure 3c) compared with the control group. However, HFD rats treated with either Niacin or Coenz-Q or combined were protected against these alterations. The combined effect was similar to the effect of cholerose. It was found that rats fed on HFD resulted in a marked elevation in the activity of serum lipoprotein lipase (Figure 3d) (p=0.00084), atherogenic index (Figure 3d) and obesity index (Figure 3e) (p=0.00091) as compared with control rats receiving the normal diet. However, the treatment with Niacin or Coenz-Q or combined showed a significant reduction in the activity of lipoprotein lipase (p=0.00088) and a reduction of the atherogenic index and obesity index. The combined effect showed to be more effective than cholerose or individual treatment.

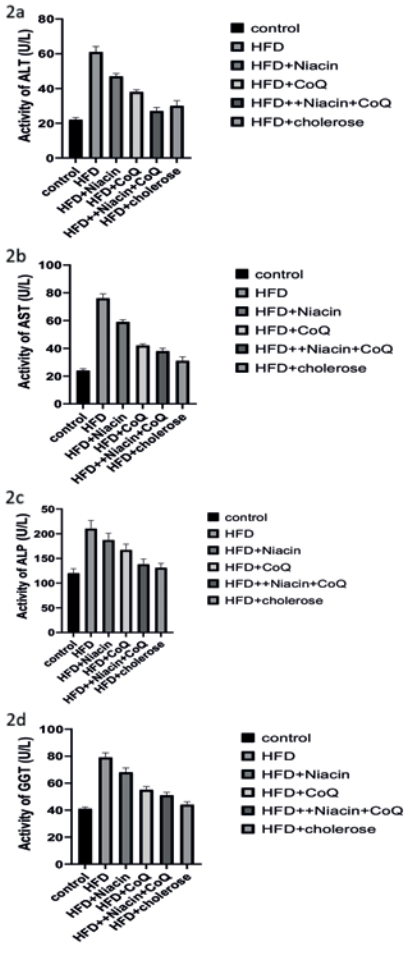


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Figure 2. a) Activity of alanine transaminase (ALT) in all groups; b) activity of aspartate transaminase (AST) in all groups; c) activity of alkaline phosphatase (ALP) in the different groups; d) activity of gamma glutamyltranspeptidase (GGT) in the different groups.

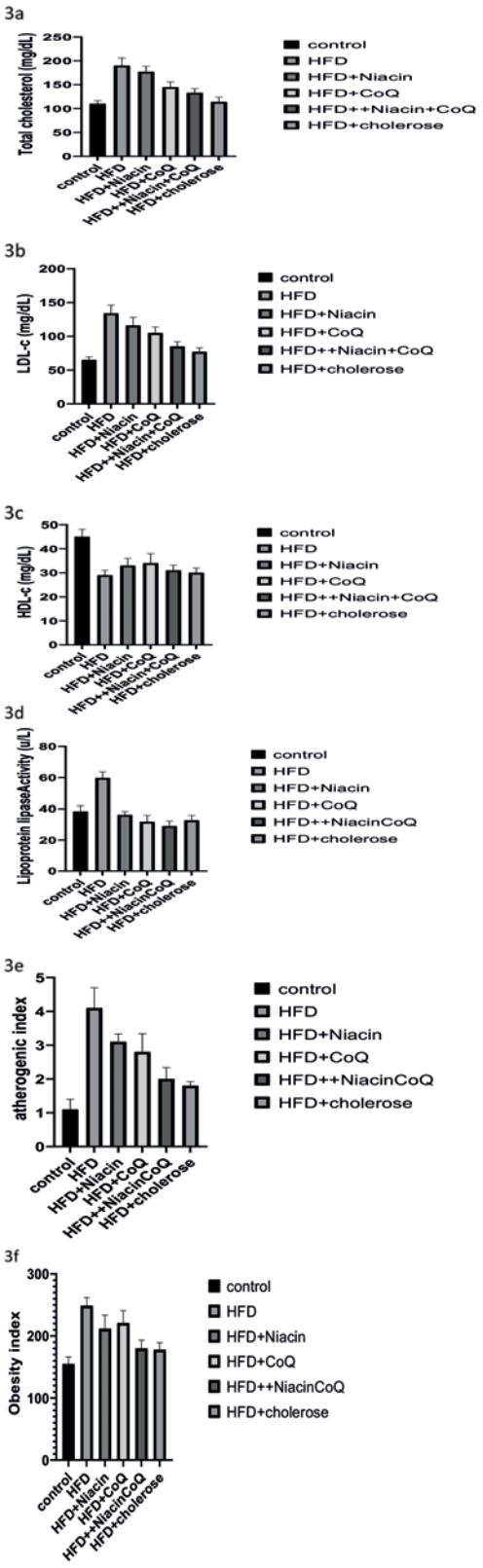

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Figure 3. a) Total cholesterol in all groups; b) level of LDL-c in all groups; c) level of HDL-c in the different groups; d) activity of lipoprotein lipase in the different groups; e) atherogenic index in the different groups; f) obesity index in the different groups.

Discussion

The incidence of obesity has increased to become epidemic in the last 40 years. It was associated with an increased risk of metabolic and cardiovascular diseases, leading to morbidity and mortality.[15] Dyslipidemia is caused by an imbalance between lipogenesis and lipolysis. Alternative and complementary supplements are useful due to the safety margin during use. It was reported that Niacin supplementation decreased body weight in young rats.[16] The NAD^+/NADH interconversion plays an important role in the regulation of lipid, carbohydrates and protein metabolism. In the current study, it was found that HFD-fed rats showed a significant increase in body weight and fasting blood glucose *versus* control. Supplementation of Niacin or Coenz-Q or combined reduced body weight and FBG compared with untreated rats fed HFD. The combined effect is better than the individual one. It was found that a lack of Niacin receptor G protein-coupled receptor 109A (GPR 109A) was associated with the amassing of fat in the liver and increased body weight.[17] In addition, it was suggested that supplementation of Niacin increased cellular NAD^+ in skeletal muscles and brown adipose tissues and decreased food intake and weight gain in obese rodent fed with HFD.[18] Niacin exerts antioxidant properties via scavenging reactive oxygen species and acting as a hydrogen donor. The administration of Niacin enhanced the activity of antioxidant enzymes, anti-inflammatory and oxidative status in dyslipidemic subjects.[19]

It was reported that the insulin resistance induced in animals by a high-fat diet is due to increased visceral fat accumulation, or to diet composition.[15] The inhibition of digestive lipase enzyme is important to prevent fat absorption and accumulation in the body.[16,17] Previous studies showed that HFD can lead to visceral obesity in rodent animal models.[18,19] Dietary coenz-Q plays an important role in improving metabolic disorders and hyperglycemia by stimulating insulin action and oxidative phosphorylation for ATP production.[20] Coenz-Q improves insulin sensitivity, enhancing their affinity and its response in target tissues.[21] Dyslipidemia is a major risk factor for cardiovascular diseases (CVDs), including atherosclerosis.[23] In the present study, the levels of total cholesterol, LDL-c, and TG were significantly elevated while the level of HDL-c was significantly reduced in rats fed on HFD compared with control. On the other hand, rats fed HFD supplemented with Niacin or Coenz-Q or combined showed a reversed effect compared with HFD untreated. The combined treatment was more effective than cholerose. This is in accordance with previous studies that found, after treatment with Niacin, elevated serum HDL-c level and decreased levels of total cholesterol, LDL-c, TG and VLDL-c.[23,24] In addition, Niacin combined with Coenz-Q showed a potential effect in lowering total cholesterol.[25] Obesity index and atherogenic index were taken as markers for cardiovascular disorders; a high value correspond to an increased risk of developing CVD.[26] Rats fed on HFD resulted in increased obesity index and atherogenic index. The treatment with Niacin or Coenz-Q or combined significantly attenuated the obesity index and atherogenic index and thus acts as a cardioprotective agent. The reduction in obesity index and atherogenic index by Niacin or Coenz-Q or combined reflected its role in obesity and metabolic syndrome.

Elevated activities of liver enzymes (ALT, AST, ALP and GGT) in circulation reflect hepatic injury.[27] It was found that rats fed on HFD had a marked elevation of serum enzymes (ALT, AST, ALP and GGT) activities compared with control. However, the treatment with Niacin or Coenz-Q or combined reduced these elevations versus HFD untreated. It was demonstrated that Niacin exerts anti-inflammatory effect; additionally, treatment with Niacin reduces Tumor Necrosis Factor-alpha (TNF-α) gene expression and secretion of the proinflammatory chemokines Monocyte Chemoattractant Protein-1 (MCP-1) via suppression of the Nuclear Factor-Kappa B (NF-kB) signaling pathway.[28] Ozaydin *et al.*[22] reported that Niacin exerts an anti-inflammatory effect in brain injury in rats. It was demonstrated that Niacin inhibits vascular inflammation by decreasing endothelial reactive oxygen species and inflammatory cytokine production.[29] Lipoprotein lipase is a clearing factor that prevents the accumulation of chylomicrons and VLDL-c in blood.[30] Rats fed on HFD showed a reduction in the activity of lipoprotein lipase compared with control. Treatment with Niacin or Coenz-Q or combined enhanced the activity of lipoprotein lipase versus HFD untreated, but the combined treatment is more effective than the individual. The anti obesity effect may be due to the enhancement of lipoprotein lipase and activation of insulin secretion and action. The findings of this study indicated that the combination of supplements (Niacin and Coenz-Q) induced hypolipidemic, anti-inflammatory, and anti-atherogenic effects. It was suggested that the pleiotropic action of these supplements is effective in obesity-induced metabolic syndrome. The limitation of this study is lack of investigation of the epigenetic effects of these supplements that mediate its actions.

Conclusions

It was concluded that Niacin combined with Coenz-Q showed anti-inflammatory and hypolipidemic effects, so they are promising as complementary or alternative agents in the management of obesity and its complications.

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