Running title: dietary intake and apelin

Is Apelin Gene Expression and Concentration Affected by Dietary Intakes? A Systematic Review

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Abstract

Background: Overproduction of apelin in obesity could be one of the last protective defenses before type 2 diabetes develops.

Objective: To summarize the existing evidence on the association between dietary intake and apelin gene expression and concentration.

Methods: We systematically searched MEDLINE, EMBASE, and google scholar and hand-searched bibliographies, including peer-reviewed articles with English abstracts, without restriction in publication date, updated until 21 February 2016 that reported the association between dietary intake and apelin gene expression or concentration.

Results: From a total of 1075 articles, we identified 12 relevant studies. There were 6 clinical trials in human and 6 studies in animals. Overall, two of three studies conducted in humans showed that calorie-restriction diet in obese subjects decreases apelin concentration. Five animal studies reported that higher intake of fatty acids and eicosapentaenoic acid (EPA) increased apelin expression and concentration. Given the paucity of data available, the heterogeneity of study designs used, and exposures tested, no quantitative meta-analysis was justified.

Conclusion: Based on human studies, hypocaloric diet can reduce apelin concentration in obese individuals. In addition, higher intakes of total fatty acids and EPA may increase apelin gene expression and concentration.

Key words: fatty acids, hypocaloric diet, eicosapentaenoic acid, adipose tissue

Introduction:

Not only is adipose tissue the largest repository of lipids, it also represents a major endocrine organ producing a variety of factors (adipokines) such as leptin, apelin, adiponectin, resistin, visfatin, estrogen, retinol binding protein-4, omentin, and tumor necrosis factor-alpha (TNF-α) (Wozniak et al. 2009). Alteration in adipokine levels in obesity due to excess adipose tissue is known to affect insulin sensitivity and regulate whole body energy homeostasis (Wozniak et al. 2009; McGown, Birerdinc, and Younossi 2014; Hauner 2005). Among these adipokines, apelin is one of the most potent molecules, described as a beneficial adipokine related to obesity (Lv, Li, and Chen 2013).

Apelin, a bioactive peptide, is a ligand of the G protein-coupled APJ receptor, that are synthesized and secreted by mature adipocytes in both humans and mice (Boucher et al. 2005; Kleinz and Davenport 2005). Apelin is a key regulator in glucose and lipid metabolism (Dray et al. 2008) and plays an important role in pathogenesis of insulin resistance and type 2 diabetes (Przewlocka-Kosmala et al. 2011; Li et al. 2006; Chong et al. 2006). Administered in a physiological range apelin in vivo, improved glucose metabolism in normal and insulin-resistant high-fat fed mice by increasing glucose utilization in insulin-sensitive tissues (Dray et al. 2008); in human adipose tissue in vitro as well, apelin was found to stimulate glucose uptake (Attane et al. 2011). Consequently, it has been suggested that over-production of apelin could be one of the last protective defenses before the development of obesity-related disorders (Castan-Laurell et al. 2005; Dray et al. 2010; Wei, Hou, and Tatemoto 2005).

The capability of fatty acids to stimulate apelin mRNA expression and secretion in 3T3-L1 rat adipocytes has been reported (Lorente-Cebrian et al. 2010; Fernandez-Galilea et al. 2011). Treatment with EPA increased both apelin gene expression and secretion (Lorente-Cebrian et al. 2010); however, lipoic acid increased only apelin secretion but not apelin gene expression in 3T3-L1 adipocytes (Fernandez-Galilea et al. 2011). In addition, treatment with vitamin C increased apelin gene expression in primary adipocyte with (Garcia-Diaz et al. 2011). Interestingly, human and animal studies have also been shown that patterns of gene expression and level of apelin concentration in response to dietary intakes may be changed (Krist et al. 2013; Tasci et al. 2009; Bertrand et al. 2013; Perez-Echarri et al. 2009).

It seems that dietary factors may contribute to adipocyte metabolism, and then change apelin gene expression and secretion as has been shown in vitro, in vivo, and human studies. Since apelin is the beneficial adipokine, which encounters glucose intolerance and insulin resistance, it is important to understand the contribution of dietary intakes to apelin gene expression. No previous comprehensive systematic review focusing on dietary factors and apelin has been conducted to systematically summarize the existing evidence. Thus, we carried out a systematic review to determine whether micro- and macro-nutrients and dietary patterns are associated with adipocyte gene expression and serum levels of apelin in humans and animals.

Materials and methods

Eligibility criteria

Types of studies

We considered all types of published studies describing the association of micro- and macro-nutrients, food items, food groups, and dietary pattern with apelin concentration and expression including interventional trials (animal and human), observational (longitudinal and cross-sectional) design, and excluding narrative, nonsystematic reviews and conference abstracts.

Types of measures

Studies included were those that reported findings related to any features of diet such as high-fat diet, changes in the apelin concentration and regulation of adipose tissue gene expression among human and animals; we excluded in vitro studies as well as human or animal cell lines.

Search strategy

The three electronic databases MEDLINE (http://www.nlm.nih.gov), EMBASE (http://www.elsevier.com/online-tools/embase), and Google scholar (https://scholar.google.com) were searched 7 November 2015, and the entire search was re-run 21 February 2016 by another reviewer to ensure that all relevant articles had been retrieve complete update was done for newly published articles using the following keywords: apelin, APLN, APJ, gene expression, nutrition, nutrient, diet(ary), and food. A literature search was performed for studies involving both humans and animals and was restricted to articles published in English. Additional citations were identified by hand-searching reference lists of all selected articles. Citations were stored and managed with the reference software EndNote X5.

Study selection

The process of study selection was as follows: (i) exact duplicate articles was removed by EndNote tools. (ii) Two groups of authors were selected as reviewers; (iii) there 2 groups screened all titles identified through the electronic database search to detect irrelevant studies; (iv) They also read abstracts and full text of the citations selected in the first screening by applying all inclusion and exclusion criteria. Reviewers were not blinded to the journal or author names. If the results of a study were reported in more than one publication, only the publications with the most complete results were retained. Lastly, to identify other potentially relevant articles, E.Y. examined the reference lists of selected articles. By consensus, disagreements between the two reviewer author groups were resolved; when consensus could not be reached, another author not in either of the two groups made the final decision.

Results

Overview of studies identified

Flowchart of the studies throughout the selection process is illustrated in Figure 1 (Liberati et al. 2009). From the 672 citations identified from three electronic databases and the other searches, 12 articles met all inclusion criteria. A summary of details and findings of the included studies has been presented in Tables 1 and 2, categorized in to human and animal studies. Briefly, of the selected articles, six studies were conducted in animals (Perez-Echarri et al. 2009; Bertrand et al. 2013; Lasa et al. 2009; Fernandez-Galilea et al. 2011; Yang et al. 2015; Garcia-Diaz et al. 2007) and six in humans (Yavuz et al. 2014; Heinonen et al. 2009; Tasci et al. 2009; Celik et al. 2014; Krist et al. 2013; Castan-Laurell et al. 2008). Since the studies included located homogeneity in study design (duration, population, and intervention), no meta-analysis was performed.

All the studies selected in humans were non-randomized clinical trials and were conducted in subjects with different conditions including healthy, obese, dialysis patient and non-obese with hypercholesterolemia. Five of the six studies included adults, whereas only one study included children. In the human studies retrieved, the types of intervention were restricted-calorie (Krist et al. 2013; Heinonen et al. 2009; Castan-Laurell et al. 2008), Ramadan fasting (Celik et al. 2014), and modification diet (Yavuz et al. 2014; Tasci et al. 2009). The durations of the interventions ranged from four weeks (1 month) in the Cekik et al (Celik et al. 2014) to 24 weeks (6 months) in the Krist et al and Yavuz et al (Yavuz et al. 2014; Krist et al. 2013) studies. In some parts of two studies, anti-hyperlipidemic or anti-obesity drugs had been used; however we used data from the duration before drug treatment (Heinonen et al. 2009; Tasci et al. 2009).

Most animal studies conducted on rodents (rats, mice, and hamsters) assessed the effects of specific feeding patterns influencing insulin sensitivity, including high-fat diets on the apelin gene expression and concentration.

The effect of diet on apelin in humans

Yavuz et al in an interventional study (Yavuz et al. 2014), investigated whether apelin concentration could reflect the nutritional status of children on peritoneal dialysis and hemodialysis. Thirty patients received a dietary prescription for six months according to the caloric (100% of the estimated energy requirements (EER)) and protein requirements based on age and body size. After six months, results showed that modifications in nutritional status did not affect apelin concentration (1.48 vs. 1.19 ng/ml for peritoneal dialysis and 1.15 vs. 1.16 for hemodialysis ng/ml). It was a non-randomized intervention trial that did not describe information

about dietary intakes of participants at the beginning and end of intervention. Despite of this limitation, it contributed much evidence to our systematic review because it was the only study available that had been conducted among children.

Celik et al (Celik et al. 2014) investigated the effects of Ramadan fasting on concentrations of apelin in a non-randomized intervention among 42 healthy males. The subjects had fasted 15-16 hours per day throughout the month; findings demonstrated that Ramadan fasting did not affect the apelin concentration. Despite no changes in apelin concentration during Ramadan fasting, BMI significantly reduced at the end of investigation compared to baseline values. As far limitations of the study, since dietary intakes of participants had not been recorded, the effect of Ramadan fasting on usual dietary intakes was not shown. Moreover, other shortcomings of this study were lack of control groups to compare outcomes and non-matched allocation of participants in the study groups.

A weight-loss intervention study conducted by Krist et al (Krist et al. 2013) to assess the impact of six months caloric-restricted diet on the apelin concentration in 19 obese subjects, used a weight loss diet, providing a daily energy deficit of 1200 kcal/day; this non-randomized study showed that apelin concentrations declined six months following the energy-restricted diet(1.61 vs. 1.39 ng/ml). I addition, a significant reduction was observed in BMI (5.21%), insulin (29.2%), and hsCRP (33.3%) at the end of intervention. Participants' characteristics and dietary intakes were not clarified before and after intervention.

Another non-randomized intervention study conducted by Heinonen et al (Heinonen et al. 2009), to investigate the effect of very low calorie diet (800 kcal/day) over eight weeks on apelin

concentration among 35 obese (BMI between 30 and 45 kg/m^2) subjects with metabolic syndrome. Results showed that apelin concentration was not significantly changed from baseline to after eight weeks intervention (1.00 vs. 0.90 ng/ml); additional findings of this study demonstrated that adherence to a very low calorie diet led to significant reduction of BMI (14.2%), levels of insulin (47.1%), as leptin (61.8%), as well as increment of adiponectine (35.7%). However, the intervention had no effect on inflammatory biomarkers (IL-6 and TNF-α). The major bias of this study was the lack of a matched control group that could affect the results. Also, this study did not provide any information about dietary intakes of the subjects at baseline and after follow-up. Neither did it explain how adherence to the dietary intervention was evaluated.

Castan-Laurell in a well-designed study (Castan-Laurell et al. 2008), investigated the effect of hypocaloric diet on the apelin concentration and gene expression in adipose tissue among 20 obese women (mean BMI: 32.2 Kg/m^2) who were drug free and without any diagnosed disease; twelve healthy and lean women were chosen (mean BMI: 20.7 kg/m2) as the control group. The advised diet provided 600 kcal/day less than estimated energy requirement. After 12 weeks intervention, plasma apelin concentration significantly decreased (0.364 to 0.249 ng/ml). In addition, adipose tissue mRNA expression of apelin was significantly decreased. Furthermore, BMI (32.2 in baseline vs. 29.8 kg/m2 at the end of follow up), insulin concentration (8.1 in baseline vs. 6.1 mU/ml at the end of follow up), and TNF-α level (0.66 in baseline vs. 0.55 pg/ml at the end of follow up), like apelin, decrease at the end of the intervention. A major limitation was the lack of careful matching between case and control groups. This intervention study

because of considering the similarity of our research question, the results provided valuable evidence to the current systematic review.

Tasci et al, in their intervention study (Tasci et al. 2009) aimed to assessing the impact of 12 weeks therapeutic lifestyle change (TLC) recommended by NCEP ATP III ("Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)" 2001) on apelin concentration among 134 patients with high LDL-C levels and BMI <30 kg/m2, showed that apelin concentration increased at the end of the 12-week TLC intervention (0.181 vs. 0.826 ng/ml) among patients who achieved target LDL-cholesterol levels (LDL-C <160 mg/dl); there was no significant change in the body weight, although, plasma levels of insulin (12.3 vs. 8.1 μU/ml) and leptin (10.4 vs. 5.8 ng/ml for man and 14.4 vs. 8.31 ng/ml for women) decreased and plasma levels of adiponectin (3.1 vs. 7.0 ng/ml) increased. Furthermore, there was no significant change in TNF-α and hsCRP concentration to the baseline compared to the end of intervention. A methodological limitation of this well-conducted study was lack of a control group for comparing impacts of the TLC intervention. In addition, no information was provided about dietary advice within therapeutic lifestyle change and data on dietary intakes of participant before and after the intervention.

The effect of diet on apelin in animal

Yang et al (Yang et al. 2015) evaluated insulin resistance induced by high-fat diet in rats and then measured the alteration of apelin gene expression and concentration. Rats were divided into three groups (n= 8 in each group) including (i) control group with normal diet, (ii) high-fat diet,

and (iii) high fat diet plus treadmill running. After 20-week intervention, a significant increase in apelin concentration (32.8 in control and 39.2 ng/mL in high fat diet rat groups) as well as mRNA expression in adipose tissues was observed in rats fed with a high fat diet. In addition, plasma levels insulin (15.5 vs. 22.3 µIU/ml) increased in high fat groups (Yang et al. 2015).

Bertrand et al (Bertrand et al. 2013) tested the beneficial effect of EPA on apelin concentration and gene expression. Mice were categorized to three groups as following: (i) normal diet, (ii) high-fat diet, (iii) and high-fat diet enriched with 36 g/kg EPA. After 10 weeks of intervention, apelin concentration and gene expression in adipose tissue was up-regulated in mice fed with a high-fat diet. In addition, there was no significant difference between mice fed with high-fat diet and those in high-fat diet plus EPA-treated group (0.70 vs. 0.67 ng/mL). Both high fat diet and high fat+EPA groups increased weight compared to normal diet, however high fat+EPA group gained weight less than high fat diet. Furthermore, high fat diet+EPA mice had lower plasma insulin compared to the high fat diet fed mice (496 vs. 1257 pg/mL). Leptin gene expression was increased and adiponectin gene expression was decreased in adipose tissue of high fat diet mice compared to control diet. In addition, leptin mRNA levels was decrease and adiponectin mRNA levels increased in adipose tissue of high fat diet+EPA mice compared to high fat diet mice.

An intervention study was conducted by Garcia-Diaz et al (Garcia-Diaz et al. 2012) to assess the impact of a 50-day high-fat diet on apelin mRNA expression and concentration. Rats were divided into two different dietary groups: (i) standard diet and (ii) high-fat diet. Apelin mRNA expression on the subcutaneous adipose tissue of the high-fat diet group increased, whereas apelin concentration did not change significantly (0.97 in standard vs. 0.87 ng/mL in high-fat

diet group). Furthermore, rats fed with a high fat diet gained more body weight and had higher levels of insulin and leptin compared to standard diet.

Fernandez-Galilea et al (Fernandez-Galilea et al. 2011) investigated the effect of lipoic acid on the regulation of apelin gene expression in adipose tissue. Rats were assigned into four groups: (i) standard diet; (ii) high fat diet in ad libitum; (iii) high fat diet supplemented with lipoic acid in a proportion of 0.25 g lipoic acid per 100 g diet, and (iv) pair-fed that fed with the same amount of food in lipoic acid group, but without adding lipoic acid (restricted group). After eight weeks intervention, apelin expression was increased in both high-fat diet and lipoic acid treated groups, compared with the standard group and a restricted group. In addition, body weight and insulin levels of both lipoic acid treated groups were lower than high fat diet mice.

Lasa et al (Lasa et al. 2009) investigated the effect of two different dietary patterns on apelin concentration and adipose tissue gene expression. At the beginning of the study, eight hamsters were fed a standard diet, and 24 were fed high-fat high-sucrose diet for seven weeks. Then, 16 hamsters fed high-fat high-sucrose diet were fed with standard diet with 25% reduction in food intake and were divided into two groups: (i) supplemented with 5 g/kg diet of linoleic acids and (ii) supplemented with 5 g/kg trans-10, cis-12 conjugated linoleic acid (CLA). After three weeks, although the weight reduced in the two restricted calorie groups, apelin concentration did not differ between groups. Similar results were observed for apelin gene expression. In addition, leptin serum levels and gene expression in adipose tissue were increased in high-fat high-sucrose diet groups and were decreased in both restricted calorie groups. Furthermore, adiponectin serum

levels were increased in high-fat high-sucrose diet and restricted calorie groups compared to the standard diet groups.

Perez-Echarri et al (Perez-Echarri et al. 2009) compared the effect of EPA supplementation in rats fed with high-fat diet with standard diet on apelin concentration and gene expression. Animals were divided into four groups: (i) standard diet, (ii) standard diet with EPA (1 g/kg), (iii) high-fat diet, and (iv) high-fat diet with EPA (1 g/kg). At the end of the five-week intervention, apelin gene expression increased in response to EPA administration and high-fat diet. Apelin gene expression in the high-fat diet with EPA-treated rats was higher than that in the high-fat diet group; however, no statistically significant change was observed for apelin concentration. Among both EPA treatment groups insulin levels were significantly decreased. In addition, visfatin gene expression in adipose tissue was decreased in high-fat diet diet mice and was increased in EPA-treated groups; however, visfatin concentration did not significantly change between groups.

Summarizing the evidence

Of the studies conducted among obese human participants in weight loss programs, two studies showed that calorie restriction diet has the potential to reduce apelin concentration (Castan-Laurell et al. 2008; Krist et al. 2013) and adipose tissue gene expression (Castan-Laurell et al. 2008). Moreover, apelin concentration increased among hypercholesterolemic patients who decreased LDL-C by treated for three months with a TLC diet (Tasci et al. 2009). In the only non-randomized clinical trials among children under dialysis, after six months iso-caloric diet, no statistical change was observed in apelin concentration (Yavuz et al. 2014).

Two clinical trials evaluated EPA supplement in dosages of 1 g and 36 g/kg body weight (Perez-Echarri et al. 2009; Bertrand et al. 2013) on apelin concentration and gene expression. Other supplements were linoleic acids (Lasa et al. 2009), trans 10, Cis-12 conjugated linoleic acids (CLA) (Lasa et al. 2009), and lipoiec acids (Fernandez-Galilea et al. 2011). Higher fat intakes increased apelin concentration and gene expression in adipose tissue (Yang et al. 2015; Bertrand et al. 2013; Fernandez-Galilea et al. 2011; Perez-Echarri et al. 2009; Garcia-Diaz et al. 2012). In addition, EPA and lipoic acid supplementation, but not CLA and linoleic acid, up-regulated apelin gene expression in high-fat diet groups (Bertrand et al. 2013; Perez-Echarri et al. 2009; Fernandez-Galilea et al. 2011; Lasa et al. 2009).

Discussion

To the best of our knowledge, this was the first systematic review to focus on the association between diet and gene expression and concentration of apelin. Despite an extensive search strategy, our review identified only 12 relevant studies that met the inclusion criteria. The articles of human studies identified were very heterogeneous in their study designs, intervention, study population, and quality, an inherent variability that prevented any quantitative meta-analysis of their reported results, and also those of our systematic review. Most of the human studies identified were conducted without randomization and failed to include any control groups. In addition, all of the human studies had missing information about changes in dietary intakes before and after any intervention. Human studies showed that hypocaloric diet may decrease apelin concentration and animal studies revealed that high intake of fat can lead to increased apelin gene expression and concentration.

Although apelin has been considered as a beneficial adipokine (Beltowski 2006; Castan-Laurell et al. 2005), apelin induced by obesity in an effort to overcome insulin resistance or obesity-related cardiovascular diseases or other metabolic abnormalities such as apelin resistance is still a hypothesis. Thus, understanding the contribution of such an adipokine in obesity-associated disorder is important.

Overall, most of human studies which investigated the effect of dietary intake on apelin yielded controversial results with wide range of serum levels (from 0.249 to 4.64 ng/ml). Calorie-restricted diet for obese subjects reduced apelin concentration after weight loss (Castan-Laurell et al. 2008; Krist et al. 2013). Data from animal studies showed that apelin gene expression in adipose tissue may be increased by high-fat diets (Yang et al. 2015; Bertrand et al. 2013; Garcia-Diaz et al. 2012; Perez-Echarri et al. 2009; Fernandez-Galilea et al. 2011). Supplementation with EPA also may increase apelin concentration (Perez-Echarri et al. 2009; Bertrand et al. 2013; Garcia-Diaz et al. 2007). One study showed that intake of lipoiec acids may lead to increment of apelin gene expression (Fernandez-Galilea et al. 2011). Furthermore, linoleic acid and trance 10, Cis 12 CLA may not be able to alter the apelin mRNA expression and serum levels (Lasa et al. 2009).

The effect of hypocaloric diet on reduction of apelin concentration is justified by weight reduction, in particular body fat mass (Krist et al. 2013; Castan-Laurell et al. 2008). At the end of the interventions, apelin concentration in obese subjects reached to the levels of lean ones (from 0.364 to 0.249 ng/ml) although BMI of obese subjects was still higher than those of normal weight ones (29.8 vs. 20.7 kg/m^2) (Heinonen et al. 2009). Decreased apelin concentration

induced by diet was accompanied with reduced apelin mRNA expression in adipose tissue (Castan-Laurell et al. 2008). However, evidence showed that neither in in Celik et al study by 1.12% reduction (Celik et al. 2014) nor in Heinonen et al study by 14.28% reduction of BMI (Heinonen et al. 2009), apelin concentrations did not change. It seems that the duration of intervention has an important role to changes in apelin concentrations. These discrepancies between studies may be beyond of weight reduction as in all studies weight decreased after intervention, similar to insulin levels. A more detailed look, the difference between studies that observed significant vs. no significant findings in apelin, the inflammatory marker changes in particular TNF-α may indicate apelin concentration changes. Interestingly, among the relevant studies, Heinonen et al found the most reduction in BMI (14.28%) and serum insulin (47.17%); while TNF-α and apelin concentrations did not significantly change over the course of the very low calorie diet (Heinonen et al. 2009). In contrast, when weight reduction was accompanied with inflammation marker reduction, apelin concentrations significantly changed (Krist et al. 2013; Castan-Laurell et al. 2005). Indeed, reduction of TNF-α may be more important than reduction of insulin and plasma glucose, a part from weight loss to apelin changes in response to the calorie-restricted diet. Therefore, longer intervention time when decreased inflammatory markers may affect apelin concentration. However, evidence reveals that the positive association between apelin and excessive weight gain induced high-fat diet may be due to increased insulin levels (Yang et al. 2015; Bertrand et al. 2013; Garcia-Diaz et al. 2012; Fernandez-Galilea et al. 2011; Perez-Echarri et al. 2009). Moreover, administration of apelin could alter the expression of brown adipose tissue uncoupling protein (UCP) 1 and energy expenditure in mice (Higuchi et al. 2007; Than et al. 2015).

Expression and concentration of apelin in response to EPA treatment increased (Lorente-Cebrian et al. 2010; Perez-Echarri et al. 2009), while EPA treatment led to decreased insulin concentrations, insulin resistance and adipose TNF-α expression (Perez-Matute et al. 2007). In addition, EPA treatment in mice fed with a high-fat diet decreased plasma glucose and insulin concentration and improved glucose tolerance via increased β oxidation in muscle and increased apelin and apelin receptor expression (Ma et al. 2014). However, in one study, no significant findings were observed in animals fed with high-fat diet compared with those fed with high-fat diet plus EPA treatment on apelin expression (Bertrand et al. 2013); this controversy may be explained by the composition of the diet and route of administration or dosage of EPA. Moreover, longer duration of intervention or higher dosage of EPA supplementation might be change apelin level and gene expression.

The potential mechanism of dietary intake on apelin is not well understood; however, some mediator pathways can be suggested. The relationship between apelin and insulin or TNF-α in obesity and obesity-associated disorders is dependent on the magnitude of insulin sensitivity. Therefore, insulin and TNF-α are potential candidates in the regulation of the diet-induced apelin levels (Wei, Hou, and Tatemoto 2005; Daviaud et al. 2006; Boucher et al. 2005; Castan-Laurell et al. 2011). Leptin is also another regulating factor for apelin production. Indeed, hypocalorie diet and EPA supplementation can affect apelin regulation through leptin (Izadi, Saraf-Bank, and Azadbakht 2014; Roberts, Berger, and Barnard 2002; Kratz et al. 2002); a high correlation has been described between apelin gene expression in subcutaneous adipose tissue and leptin serum or leptin mRNA levels (Garcia-Diaz et al. 2007). In addition, high LDL-C had negative effects on apelin synthesis and secretion (Tasci et al. 2007; Lv, Li, and Chen 2013). Therefore, dietary

interventions increase apelin concentrations in response to decline in cholesterol (Tasci et al. 2009).

Several potential limitations might have contributed to the effect of dietary intakes on apelin concentration and gene expression. First, it is possible that this review did not identify all relevant publications, although wide search terms, repeating our search in numerous relevant databases, and hand searching reference lists were used to minimize this possibility. Second, there are several factors that may have introduced bias in our findings, specifically the selection of English language publications.

Conclusion

This comprehensive systematic review showed that hypocaloric diet mediated by weight loss and decrease in plasma insulin level can reduce apelin concentration. In addition, higher intakes of fatty acids and especially EPA can increase apelin gene expression and concentration. Cross-sectional studies investigating the expression of apelin in visceral and subcutaneous fat in relation to metabolic indices are certainly warranted.

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Table 1- Summary of the human studies that investigated to impact of dietary intake on apelin

Author	Subjects (age, n, gender)	Control	Intervention	Duration (week)	Outcome	Main results	Changes in other measurements
Yavuz (Yavuz et al. 2014)	<18 y, 30 dialysis, both	21 healthy	Set as an individual dietary prescription meeting caloric and protein requirement and control group same as intervention group	24	Serum apelin	Apelin not affected by nutritional intervention. Δ apelin in PD 19.59%↓ and in HD 4.34%↓	Δ z score BMI in PD 35%↑ and in HD 3.44%↑ Δ hsCRP in PD: 67.39↓ and in HD: 26.00↓
Celik(Celik et al. 2014)	Adults, 42 healthy, men		Ramadan fasting i.e. subjects fast for entire month of Ramadan	4	Serum apelin	Serum apelin not affected by Ramadan fasting Δ apelin: 9.69%↓	* Δ BMI: 1.12↓ Δ Insulin: 8.29↑
Krist (Krist et al. 2013)	Adults, 19 obese, both genders		As a caloric-restricted diet, daily energy deficit of 1200 kcal/d	24	Serum apelin	Apelin concentration was significantly reduced Δ apelin: 13.66%↓	* Δ BMI: 5.21↓ * Δ Insulin: 29.19↓ * Δ hsCRP: 33.33↓
Heinonen (Heinonen et al. 2009)	Adults, 35 obese, both genders		Participant consumed a very low caloric diet as 800 kcal/d	8	Serum apelin	No significant change in apelin level Δ apelin: 10.0%↓	* Δ BMI: 14.28↓ * Δ Insulin: 47.17↓ * Δ Leptin: 61.83↓ * Δ Adiponectin: 35.71↑

							Δ IL-6: 13.54↑ Δ TNF-α: 1.7↑
Castan-Laurell (Castan-Laurell et al. 2008)	Adults, 20 obese, women	12 healthy	Energy to provide 600 kcal/d less than the individually energy requirement.	12	Serum and gene expression of apelin	A significant decrease of concentration of apelin and mRNAs of apelin in adipose tissue Δ apelin: 31.59%↓	*Δ BMI: 7.45↓ *Δ TNF-α: 16.92↓ *Δ Insulin: 18.48↓
Tasci (Tasci et al. 2009)	Adults, 54 non-obese high LDL-C, both		A therapeutic life style change (TLC) intervention.	12	Serum apelin	Serum apelin level increased in patients in whom LDL-C level decreased Δ apelin: 356.3%↑	Δ BMI: 1.87↓ Δ TNF:1.80↓ Δ hsCRP: 23.12↓ *Δ Insulin: 32.83↓ *Δ Adiponectin: 127.33↑ *Δ leptin in male: 35.47↓ in female: 29.10

BMI, body mass index; PD, peritoneal dialysis; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; TNF-α, Tumor necrosis factor.

*$P<0.05$

Table 2- Summary of the animal studies that investigated to impact of dietary intake on apelin

Author	Sample	Intervention	Duration	Outcome	Main results	Changes in other measurements
Yang (Yang et al. 2015)	Rats	Standard and HFD	20 weeks	Gene expression and serum apelin	Serum and expression of apelin were significantly increased. Control vs. HFD (32.86 vs. 39.2 ng/mL,).	**Weight:** *control vs. HFD (551 vs. 616 g) **Insulin:** *control vs. HFD (15.48 vs. 22.32µIU/mL)
Bertrand (Bertrand et al. 2013)	Mice	Animal were distributed in three categories normal diet, HFD and HFD+EPA (36g/kg)	10 weeks	Gene expression and serum apelin	Apelin expression adipocytes and concentration were higher in both HFD group than control group, but did not differ between HFD and HFD+EPA groups. (0.70 in HFD, 0.67 in HFD+EPA).	**Weight:** *control vs. HFD (30.5 vs. 43.1 pg/mL) *Control vs. HFD+EPA (30.5 vs. 36.3 pg/mL) HFD vs. HFD+EPA (43.1 vs. 36.3 pg/mL) **Insulin:** *control vs. HFD (422 vs. 1257 pg/mL) Control vs. HFD+EPA (422 vs. 496 pg/mL) *HFD vs. HFD+EPA (1257 vs. 496 pg/mL)
Garcia-Diaz	Rats	Standard and HFD	8 days	Gene expressi	A significant increase in apelin	*__Weight:__ control vs.

(Garcia-Diaz et al. 2012)				on and serum apelin	expression in HFD group without any effect on apelin concentration. control vs. HFD (0.97 vs. 0.87 ng/ml)	HFD (381 vs. 445 g) *__Insulin:__ control vs. HFD (2.73 vs. 4.33 µg/L) *__Leptin:__ control vs. HFD (23.7 vs. 38.2 ng/mL)
Fernandez-Galilea (Fernandez-Galilea et al. 2011)	Rats	four group: control (standard diet), HFD ad libitum, HFD+lipoiec acid, restricted diet (same amount of food as HFD+lipoiec acid)	8 weeks	Apelin gene expression	Apelin expression was increased in those fed with a HFD and HFD with lipoic acid. Lipoic acid treated group had higher level expression than restricted diet and same level with HFD group.	__Weight:__ *control vs. HFD (386 vs. 481 g) Control vs. HFD+lipoic acid (386 vs. 378 g) Control vs. restricted diet (386 vs. 404 g) *HFD vs. HFD+lipoic acid (481 vs. 378) *HFD vs. restricted diet (481 vs. 404 g) HFD+lipoic acid vs. restricted diet (378 vs. 404 g) __Insulin:__ *control vs. HFD (1.12 vs. 2.04 ng/mL) Control vs. HFD+lipoic acid (1.12 vs.

						1.05 ng/mL) Control vs. restricted diet (1.12 vs. 1.47 ng/mL) *HFD vs. HFD+lipoic acid (2.04 vs. 1.05 ng/mL) *HFD vs. restricted diet (2.04 vs. 1.47 ng/mL) *HFD+lipoic acid vs. restricted diet (1.05 vs. 1.47 ng/mL)
Lasa (Lasa et al. 2009)	Hamsters	Standard and high fat high sucrose (HFHS) diet for 7 weeks and then, HFHS divided 2 groups, standard diet and 20% restricted energy+sunflower oil linoleic acids or trans10,Cis-12 CLA	7 weeks or 10 weeks	Gene expression and serum apelin	No significant difference was seen in any of intervention group Serum apelin in control: 6.13, HFHS: 4.55, standard diet: 4.64, and restricted diet: 4.39 ng/mL	*__Weight:__ control: 109 g, HFHS: 129g, standard: 110g, restricted diet: 107g. *__Insulin:__ control: 65.16 pmol/L, HFHS: 112.76 pmol/L, standard: 48.78 pmol/L, restricted diet: 40.21 pmol/L. *__Visfatin:__ control 21.25 ng/mL, HFHS: 20.08 ng/mL, standard:

						27.11 ng/mL, restricted diet: 26.72 ng/mL. *__Leptin:__ control: 0.12 ng/mL, HFHS: 0.56 ng/mL, standard: 0.11 ng/mL, restricted diet: 0.08 ng/mL. *__Adiponectin:__ control: 53.08 ng/mL, HFHS: 93.56 ng/mL, standard: 111.89 ng/mL, restricted diet: 161.05 ng/mL.
Perez-Echarri (Perez-Echarri et al. 2009)	Rats	Animal were distributed in four groups: control and control-EPA (standard pelleted diet+EPA ethyl ester 1g/kg) and overweight and overweight-EPA (cafeteria diet+EPA ethyl ester 1g/kg)	35 days	Gene expression and serum apelin	A significant increase in apelin expression in cafeteria and EPA-treated groups. No significant finding for serum apelin. Serum apelin: control: 1.47, control+EPA: 2.60, cafeteria: 3.73, and cafeteria+EPA:3.80).	__Weight:__ control vs. control+EPA (310 vs. 307 g) *Control vs. cafeteria diet (310 vs. 361 g) Control vs cafeteria+EPA (310 vs. 330g) __Insulin:__ *control vs. control+EPA (23.3 vs. 11.2 µIU/mL) Control vs.

						cafeteria diet (23.3 vs. 28.2μIU/mL) Control vs. cafeteria+EPA (23.3 vs. 19.9μIU/mL) **Visfatin:** control vs. control+EPA (0.90 vs. 0.89 ng/mL) Control vs. cafeteria (0.90 vs. 0.78 ng/mL) Control vs. cafeteria +EPA (0.90 vs. 1.01 ng/mL)

HFD, high-fat diet; EPA, eicosapentaenoic acid; CLA, Conjugated linoleic acid.

*$P<0.05$

Figure 1: Review flow-chart for effect of dietary intakes on apelin