Apelin and its ratio to lipid factors are associated with cardiovascular diseases: A systematic review and meta-analysis

Hamed Akbari¹,², Mahnaz Hosseini-Bensenjan³, Sarvenaz Salahi⁴, Fatemeh Moazzen⁵, Hamid Aria⁶, Alireza Manafi⁷, Saeed Hosseini⁸,⁹, Maryam Niknam¹⁰*, Gholamreza Asadikaram¹,¹¹

¹ Department of Biochemistry, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran, ² Student Research Committee, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran, ³ Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran, ⁴ Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran, ⁵ Department of Hematology, Faculty of Allied Medicine, Bushehr University of Medical Sciences, Bushehr, Iran, ⁶ Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, ⁷ Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, ⁸ Center for Healthcare Data Modeling, Department of Biostatistics and Epidemiology, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, ⁹ Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran, ¹⁰ Department of Biochemistry, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, ¹¹ Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

* niknam8892@gmail.com

Abstract

Background
The present systematic review and meta-analysis aimed to ascertain if the circulating levels of apelin, as an important regulator of the cardiovascular homeostasis, differ in patients with cardiovascular diseases (CVDs) and controls.

Methods
A comprehensive search was performed in electronic databases including PubMed, Scopus, EMBASE, and Web of Science to identify the studies addressing apelin in CVD up to April 5, 2021. Due to the presence of different units to measure the circulating levels of apelin across the included studies, they expressed the standardized mean difference (SMD) and their 95% confidence interval (CI) as summary effect size. A random-effects model comprising DerSimonian and Laird method was used to pool SMDs.

Results
Twenty-four articles (30 studies) comprised of 1793 cases and 1416 controls were included. Pooled results obtained through random-effects model indicated that apelin concentrations in the cases’ blood samples were significantly lower than those of the control groups (SMD = -0.72, 95% CI: -1.25, -0.18, P = 0.009; I² = 97.3%, P<0.001). New combined biomarkers showed a significant decrease in SMD of apelin/high-density lipoprotein cholesterol (apelin/
HDL-C) ratio [-5.17; 95% CI, -8.72, -1.63, P = 0.000; I² = 99.0%], apelin/low-density lipoprotein cholesterol (apelin/LDL-C) ratio [-4.31; 95% CI, -6.08, -2.55, P = 0.000; I² = 98.0%] and apelin/total cholesterol (apelin/TC) ratio [-17.30; 95% CI, -22.85, -11.76, P = 0.000; I² = 99.1%]. However, no significant differences were found in the SMD of apelin/triacylglycerol (apelin/TG) ratio in cases with CVDs compared to the control group [-2.96; 95% CI, -7.41, 1.49, P = 0.000; I² = 99.2%].

Conclusion
The association of apelin with CVDs is different based on the region and disease subtypes. These findings account for the possible usefulness of apelin as an additional biomarker in the diagnosis of CVD in diabetic patients and in the diagnosis of patients with CAD. Moreover, apelin/HDL-c, apelin/LDL-c, and apelin/TC ratios could be offered as diagnostic markers for CVD.

Introduction
Cardiovascular diseases (CVDs) are one of the main life-threatening diseases with high prevalence [1, 2]. Globally, CVDs are responsible for 31% of mortality, the majority of this in the form of coronary heart disease (CHD) and cerebrovascular accident. It has been recommended that improvement of the disease risk factors, including dyslipidemia, smoking, hypertension, diabetes, and abdominal obesity is important in CVD prevention [3–5]. As an active endocrine organ, white adipose tissue plays crucial roles in obesity-related CVD including the secretion of adipokines that affect the whole-body homeostasis [6]. One of these adipokines, apelin, is one of the most potent endogenous positive inotropic compounds yet identified [7]. It is widely distributed in the heart and may act as an important regulator of the cardiovascular homeostasis [8].

Although previous reports confirm that apelin is involved in cardiovascular function, there is controversy about its causative association with CVDs [9]. In addition, the acceleration of CVD prevention via early diagnosis and treatment of risk factors is still a critical issue [10]. It has been revealed that the role of apelin in the cardiovascular field is widespread. Although it remains to be seen whether apelin will translate into a therapeutic target in the future, the results of previous studies confirm the importance of further investigation. More functional studies are required to determine the exact role of apelin/APJ in cardiovascular regulation. The present systematic review and meta-analysis aimed to summarize the available data about the circulating levels of apelin as a possible regulator of the cardiovascular homeostasis in patients with CVDs. Considering the acute influences of apelin on lipid metabolism and its correlation with total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), and high-density lipoprotein cholesterol (HDL-C), as crucial factors for the development of atherosclerotic plaque, we also calculated the ratios of apelin to lipid profile levels for cases and controls. This comprehensive data would further enhance our knowledge of the function of apelin and its receptor in CVDs and help us to assess this receptor system as a future drug target.

Methods
PRISMA guideline (the Preferred Reporting Items for Systematic Reviews and Meta-analysis) was used to design and perform the current meta-analysis (S1 Checklist) [11]. Moreover, no external board review was conducted before doing this study.
Search strategy

Two independent authors (MH-B and SS) performed a comprehensive search to identify the relevant published English language studies through inception up to April 5, 2021. The controversies were checked by a third expert person (MN). Electronic databases including PubMed, Scopus, EMBASE, and Web of Science were searched by using the following MeSH (Medical Subject Heading) terms and text keywords: (Apelin) AND (“Coronary Artery Disease” OR “Myocardial Ischemia” OR “Acute Coronary Syndrome” OR “Angina, Stable” OR “Angina, Unstable” OR “Coronary Disease” OR “Coronary Stenosis” OR “Myocardial Infarction” OR “Non-ST Elevated Myocardial Infarction” OR “ST Elevation Myocardial Infarction”). We also conducted a manual search in the reference list’s included articles and previous relevant reviews to increase the sensitivity of searches to find additional articles. Pubmed search strategy is presented in Supp 2. a in S1 File.

Study selection

English published articles that met the inclusion criteria were selected. Inclusion criteria were as follows: original observational studies including cross-sectional, case-control, and clinical cohort studies; and studies providing detailed information regarding blood circulating levels of apelin in patients diagnosed with heart diseases such as coronary artery disease (CAD), myocardial infarction (MI), congenital heart disease (CHD), congestive heart failure (CHF), heart failure (HF), atrial fibrillation (AF), ischemic heart disease (IHD), hypertensive heart disease (HHD) and controls (participants without heart diseases and other chronic/metabolic diseases). Studies were also excluded if they investigated animal models, using animal models, tissue-based cultures, cell cultures, and mRNA expression; and case reports, conference abstracts, comments, review articles, editorials, and articles without insufficient data. The title and the abstract of each article were reviewed by two independent investigators (FM and HA). Following this initial screening step, potential articles were included in our full-text review process. Any existing discrepancies were resolved by consensus or consultation with a third author (AM).

Data extraction and quality assessment

Following the identification of eligible studies, data extraction was done by three individual authors (HA, SH, and HA) using pre-designed data collection sheets in Excel. The first author’s name, publication year, geographical region, age, study design, study sample size, and apelin concentration in CVD patients and controls (means ± standard deviation (SD)) were collected. The quality of the study was evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS) [12], which involved evaluation of study design and analysis, selection bias, measurements of exposure and outcome, and generalizability of results. The NOS tool includes nine items with scores ranging from 0 to 9. Based on the type of study, quality scores ≥ 5 in cross-sectional designs and ≥ 7 in case-control or cohort designs represented good quality.

Statistical analysis

All meta-analyses were performed using STATA 11.0 (STATA Corp, College Station, TX). Given the different units of blood circulation levels of apelin across the included studies, they were expressed as standardized mean difference (SMD) and their 95% confidence interval (CI) was presented as summary effect size using Hedges and Olkin standard error. Moreover, with respect to the bias-correlation factor in effect size, an exact computation was used. For calculating the ratios of apelin to lipids, we used the following formula: To calculate the apelin/
HDL-c ratio: mean aplein / mean HDL-c in both groups (cases and controls). Then, the SD ratio using the following formula: $(\text{mean}_{\text{aplein}}^2 / \text{mean}_{\text{HDL}}^2) \times [(\text{SD}_{\text{aplein}}^2 / \text{mean}_{\text{aplein}}^2) - 2 (R \times \text{SD}_{\text{aplein}} \times \text{SD}_{\text{HDL}} / \text{mean}_{\text{aplein}} \times \text{mean}_{\text{HDL}}) + (\text{SD}_{\text{HDL}}^2 / \text{mean}_{\text{HDL}}^2)]$ [13, 14]. The correlation coefficients (Rs) for HDL-c, LDL-c, TC, and TG were included based on the studies conducted by Bilik et al. and Sun et al. [15, 16]. The selected studies were combined using the DerSimonian and Laird random effects model or the inverse variance fixed-effect model, depending on the existence of significant heterogeneity ($I^2 \geq 50\%$ with $P < 0.05$) [17]. Subgroup analyses were conducted on study design, comorbidities of diabetes/MetS, body fluid, type of heart disease, and continent to explore the source of heterogeneity. Sensitivity analyses were performed as additional analyses using the leave-one-out method to examine the influence one by one study on the validity of the pooled SMDs. Egger’s test and Funnel plot were also applied to assess the potential publication bias.

**Results**

**Literature search and study characteristics**

Fig 1 demonstrates the step by step process of identification and selection of relevant studies with more detail. The primary systematic search resulted in the retrieval of 4061 records. Of

![Fig 1. The flowchart of study identification and selection process.](https://doi.org/10.1371/journal.pone.0271899.g001)
these, 2670 were excluded as duplicates and 1391 remained as the screened records. Finally, 24 articles (30 studies) were included as the final records of the current meta-analysis [6, 15, 16, 18–38]. The included studies had been published between 2006 and 2020 and were comprised of 1793 cases and 1416 controls. The number of participants in each group varied from 8 to 202. Twelve studies reported data on CAD, and the remaining were based on other CVDs. Ten studies were performed in Asia, 13 in Europe, five in Africa, and two in America. Twenty-four, four, and two studies were conducted with case-control, cohort, cross-sectional design, respectively. The characteristics of selected studies are summarized in Table 1.

**Pooled effect of apelin and its ratios to lipid profile levels between cases and controls**

Based on the 30 selected studies, the meta-analysis finding indicated that the blood apelin concentrations among cases were significantly lower than those of the control groups (SMD = -0.72, 95% CI: -1.25, -0.18, \( P = 0.009; \) \( \chi^2 = 97.3\% \), \( P <0.001 \)). Findings of new combined markers demonstrated a significant decrease in SMD of apelin/HDL-c ratio [-5.17; 95% CI, -8.72, -1.63, \( P = 0.000; \) \( \chi^2 = 99.0\% \)], apelin/LDL-c ratio [-4.31; 95% CI, -6.08, -2.55, \( P = 0.000; \) \( \chi^2 = 98.0\% \)] and apelin/TC ratio [-17.30; 95% CI, -22.85, -11.76, \( P = 0.000; \) \( \chi^2 = 99.1\% \)]. However, no significant differences were found in the SMD of the apelin/TG ratio in cases with CVDs compared to the control group [-2.96; 95% CI, -7.41, 1.49, \( P = 0.000; \) \( \chi^2 = 99.2\% \)]. Forest plots that indicated the pooled SMD and each study on the apelin and new combined markers concentrations between cases and controls are shown in Fig 2A–2E.

Sensitivity analyses showed that the exclusion of each study did not change the pooled SMD for apelin levels. In addition, the lower and higher pooled effects for our outcomes, after the one-by-one exclusion of the studies, are shown in Fig 3.

**Additional analyses**

As observed in Table 2, the subgroup findings showed that the apelin levels in studies with a cohort or cross-sectional design, without medical comorbidities of diabetic/metabolic syndrome (MetS), plasma body fluid, patients with other diseases, and studies conducted in Europe or Asia were statistically significant when compared to other strata. Meanwhile, the findings of univariate meta-regression analyses based on total sample size, publication year, and quality score did not indicate any significant associations with apelin levels (\( P \geq 0.05 \) for all moderator variables).

**Publication bias**

Egger’s tests indicated no significant evidence of possible publication bias for apelin (Coef = -1.44, \( P = 0.556 \)) levels. The visual-filled funnel plots and Egger’s test were used to evaluate the potential publication bias across the included studies as shown in Supp 2. b in S1 File.

**Discussion**

CVDs are the leading global cause of death worldwide. As highly prevalent diseases, the early detection and cure of CVDs is a critical issue [4, 6]. In obesity, as one of the important risk factors of CVD, dysregulation of adipokines such as apelin originating from adipose tissue may result in the association between obesity and CVD [6, 41, 42]. To the best of the author’s knowledge, this is the first systematic review and meta-analysis to summarize available data regarding the circulating levels of apelin and its ratio to lipid profile in patients with CVDs. Findings obtained from the present meta-analyses revealed the significantly lower circulating...
| Author            | Year | Total sample size | Study design | Country   | Mean age (control vs. case) | Gender male/female (control vs. case) | BMI (kg/m²) (control vs case) | Cases                  | Controls | Comorbidities of diabetes/MetS | Name of comorbidities | Body fluid | Quality scores |
|-------------------|------|-------------------|--------------|-----------|-----------------------------|-------------------------------------|-----------------------------------|-------------------------|----------|-----------------------------|-----------------------|------------|-----------------|
| Abdelaziz         | 2015 | 60                | Case-control | Egypt     | 56.05 ± 7.04                | NR, 30/10                           | NR, 25.3                            | CAD                     | Healthy subjects | With HT, DM                        | Plasma                 | High       |
| Abd-Elbaky        | 2016 | 160               | Case-control | Egypt     | 38.6±4.2, 40.3 ±2.5         | All men                             | 21, 32.6                           | CVD                     | Healthy, non-obese controls | With T2DM               | Serum      | Low              |
| Akcilar [21]      | 2015 | 276               | Case-control | Turkey    | 61.5 ± 10.75, 64.2 ± 11.94 | 64/54, 117/41                       | NR                                | CAD                     | Healthy subjects | Without -                            | Plasma                 | Low        |
| Basile [22]       | 2014 | 50                | Case-control | Italy     | 50 ± 7.8,                   | Sex matched controls, 16/14         | NR                                | CHF                     | Healthy subjects | Without -                            | Serum                  | Low        |
| Bilik [15]        | 2015 | 54                | Case-control | Turkey    | 51.6 ± 8.8, 53.6 ± 8.1     | 18/10, 19/7                         | 26.7, 28.1                        | CAE                     | Patients with normal coronary arteries | With HT, DM             | Plasma     | High             |
| Celik [23]        | 2016 | 76                | Case-control | Turkey    | 53.3±40.69, 60 ±32.6       | 9/11, 25/31                         | NR                                | Right ventricular dysfunction | Healthy subjects | NR Acute pulmonary embolism         | Plasma                 | High       |
| Chong [24]        | 2006 | 224               | Cohort       | United Kingdom | 51.3 ± 9.2, 51.7 ± 11.6 | 16/6, 157/45                       | 26.4, 28.8                        | CHF                     | No history of cardiac events | Without Left ventricular systolic dysfunction | Plasma                 | High       |
| El Amrousy [25]   | 2018 | 120               | Case-control | Egypt     | 15.9±7.8, 15.6 ±8.3        | 28/32, 28/32                        | NR                                | HF                      | Healthy children | Without Congenital heart disease | Serum                  | High       |
| Ellinor [26]      | 2006 | 146               | Cohort       | USA       | 54.3, 54.2                 | 58/15, 58/15                        | NR                                | AF                      | Healthy subjects | NR -                            | Plasma                 | High       |
| Francia [27]      | 2007 | 22                | Case-control | Italy     | 68±13                      | Sex matched controls, 9/5           | NR                                | CHF                     | Healthy subjects | Without -                            | Plasma                 | High       |
| Gurger#a [28]     | 2014 | 59                | Case-control | Turkey    | 40 ± 8, 45 ±7              | 43.3% Male, 39.5% Male               | NR                                | Lone AF                | Healthy subjects | With DM, HT                   | Plasma                 | High       |
| Gurger#b [28]     | 2014 | 59                | Case-control | Turkey    | 40±8, 42±9                | 43.3% Male, 44.4% Male              | NR                                | PSVT                    | Healthy subjects | With DM, HT                   | Plasma                 | High       |
| Hazbar [30]       | 2018 | 84                | Case-control | Iraq      | 55.38±10.35, 57.78±9.85   | 20/4, 32/28                         | 23.82, 26.56                      | CAD                     | Healthy subjects | Without -                            | Plasma                 | High       |
| Małyszko [39]     | 2006 | 81                | Cross-sectional | Poland | 56.10 ± 15.07, 63.42 ± 10.01 | NR                               | 24.2, 24.8                       | HD with CAD            | HD without CAD         | Without Renal failure             | Plasma                 | High       |
| Miettinen [30]    | 2007 | 79                | Case-control | Finland   | 61±11, 53±12               | 2/12, 50/15                        | NR                                | IDC                     | Healthy subjects | Without -                            | Plasma                 | High       |
| Motawi#a [6]      | 2018 | 60                | Case-control | Egypt     | 54.6±3.1, 53.7 ±7.6       | 14/16, 23/22                       | 21.8, 23.1                       | CAD                     | Healthy subjects | Without -                            | Serum                  | High       |
| Motawi#b [6]      | 2018 | 60                | Case-control | Egypt     | 54.6±3.1, 55.3 ±6          | 14/16, 11/34                       | 21.8, 32.5                       | CAD with diabetes and obesity | Healthy subjects | With T2DM                        | Serum                  | High       | (Continued)
| Author       | Year | Total sample size | Study design | Country | Mean age (control vs. case) | Gender male/female (control vs. case) | BMI (kg/m²) (control vs. case) | Cases | Controls | Comorbidities of diabetes/MetS | Name of comorbidities | Body fluid | Quality scores |
|--------------|------|-------------------|--------------|---------|-----------------------------|----------------------------------------|-------------------------------|-------|----------|--------------------------------|-----------------------|------------|------------------|
| Pang# [31]   | 2015 | 44                | Case-control | China   | 67.43 ± 7.43, 67.05 ± 12.51 | 19/21, 11/13                          | NR                           | HHD   | Healthy subjects               | With DM, Hyperlipidemia, Atrial fibrillation, Renal impairments | Plasma      | High            |
| Pang# [31]   | 2015 | 55                | Case-control | China   | 67.43 ± 7.43, 68.05 ± 11.47 | 19/21, 17/18                          | NR                           | HHD+CAD | Healthy subjects               | With DM, Hyperlipidemia, Atrial fibrillation, Renal impairments | Plasma      | High            |
| Rachwalk # [32] | 2011 | 33                | Case-control | Poland  | 51 ± 15.56, 52 ± 17.79      | 9/7, 11/6                            | 23.9, 28.2                    | CAD    | Healthy subjects               | With DM                      | Serum       | High            |
| Şimşek [33]  | 2019 | 120               | Cross-sectional | Turkey  | 38.6 ± 9.9, 39 ± 14         | 40/18, 45/17                        | 26.0, 26.5                    | BAV    | Healthy subjects               | Without                    | Serum       | High            |
| Sun# [16]    | 2020 | 75                | Case-control | China   | 58.06 ± 9.51, 62.08 ± 8.29  | 15/35, 29/21                        | 25.02, 25.5                    | CAD    | Patients without CAD          | With DM, HT                  | Serum       | High            |
| Sun# [16]    | 2020 | 65                | Case-control | China   | 58.06 ± 9.51, 61.28 ± 8.46  | 15/35, 26/14                        | 25.02, 25.17                   | CAE    | Patients without CAD          | With DM, HT                  | Serum       | High            |
| van Kimmenade [34] | 2006 | 599               | Cohort       | US      | 56.9 ± 16.3, 72.8 ± 13.6     | 51% male, 51% male                  | NR                            | Acute HF | No Acute HF                    | With DM, HT, Obstructive lung disease | Plasma      | High            |
| Velliou [35] | 2020 | 100               | Case-control | Greece  | 58.9 ± 10.7, 60.6 ± 12.1     | 28/22, 29/21                       | 28.3, 28                       | AF     | Non-AF                         | With Obesity, MetS, DM, Dyslipidemia, HT | NR         | High            |
| Wang [36]    | 2018 | 61                | Cohort       | China   | 53.81±15.84, 58.50±7.56      | 23/13, 13/9                        | 23.23, 23.1                    | ERAF   | No ERAF                        | With DM, HTN, AF               | Serum       | High            |
| Wilson [37]  | 2014 | 20                | Case-control | India   | 34 ± 10, 26 ± 6             | 7/3, 4/6                            | 22.8, 22.2                     | Mitral Stenosis patients | Healthy subjects | Without                    | Hypertension, Hyperlipidemia, Cerebrovascular disease | Plasma      | High            |
| Zhou# [40]   | 2014 | 122               | Case-control | China   | 56.9 ± 4.1, 55.7 ± 3.4       | 62.8% male, 63.1% male              | NR                            | STEMI patients | No coronary heart disease | Without                   | Plasma      | High            |
| Zhou# [40]   | 2014 | 119               | Case-control | China   | 56.9 ± 4.1, 57.2 ± 2.5       | 62.8% male, 64.5% male              | NR                            | Non-STEMI patients | No coronary heart disease | Without                   | Plasma      | High            |
| Author | Year | Total sample size | Study design | Country | Mean age (control vs. case) | Gender male/ female (control vs. case) | BMI (kg/m²) (control vs. case) | Cases | Controls | Comorbidities of diabetes/MetS | Name of comorbidities | Body fluid | Quality scores |
|--------|------|-------------------|--------------|---------|----------------------------|----------------------------------------|---------------------------------|-------|----------|-------------------------------|--------------------|------------|----------------|
| Zhou#c [40] | 2014 | 126 | Case-control | China | 56.9 ± 4.1, 56.3 ± 2.8 | 62.8% male, 61.8% male | NR | Stable angina patients | No coronary heart disease | Without | Hypertension, Hyperlipidemia, Cerebrovascular disease | Plasma | High |

**Abbreviations:** CAD: coronary artery disease, CVD: cardiovascular disease, CHD: congenital heart disease, CHF: congestive heart failure, CAE: coronary artery ectasia, HF: heart failure, AF: atrial fibrillation, MI: myocardial infarction, DM: diabetes mellitus, PSVT: paroxysmal supraventricular tachycardia, AMI: acute myocardial infarction, IHD: ischemic heart disease, HD: hemodialysis, SAP: stable angina pectoris, UAP: unstable angina pectoris, IDC: idiopathic dilated cardiomyopathy, ADHF: acute decompensated heart failure, HHD: hypertensive heart disease, BAV: bicuspid aortic valve, ERAF: early recurrence of atrial fibrillation, ACS: acute coronary syndrome, STEMI: ST elevation myocardial infarction, Non-STEMI: non ST elevation myocardial infarction, NR: not reported, MetS: metabolic syndrome, HT: hypertension.

https://doi.org/10.1371/journal.pone.0271899.t001
levels of apelin among patients with CVD in comparison to those of the controls. Moreover, apelin was significantly lower in patients without diabetes/MetS. Furthermore, apelin/HDL-c, apelin/LDL-c, and apelin/TC ratios were associated with risk of CVD development.

Apelin, an endogenous peptide ligand of the 7-transmembrane G-protein, coupled with its receptor (APJ), is a strong inotrope and vasodilator [9, 43]. Apelin is secreted by white adipose tissue and its expression has also been identified in other tissues, including the heart, kidney, and endothelium [44–46]. Increased apelin expression has been found in cardiovascular tissues such as cardiomyocytes, endothelial cells, and vascular smooth muscle cells [47]. The apelin–APJ axis plays an important role in the cardiovascular system [48, 49]. Additionally, apelin has recently been implicated in the physiology of cardiovascular system in regard to cardiac contractility, endothelium-dependent vasodilation, and the reduction of vascular wall inflammation [9]. As a regulating peptide of cardiovascular, gastrointestinal, hypothalamus-hypophysis, and immune systems, apelin appears to regulate lipid metabolism and adiposity since it increases uncoupling protein 1 (Ucp1) mRNA levels (a marker of peripheral energy...
expenditure) in brown adipose tissue and Uco3 mRNA levels (a regulator of fatty acid export) in skeletal muscle [50, 51].

The findings obtained from the present study showed that the circulating levels of apelin in patients with CVD were significantly lower than those in the controls. Subgroup analyses based on medical comorbidities of diabetes/MetS revealed that apelin levels were significantly lower in CVD patients without diabetes and MetS than in the controls. Apelin synthesis in adipocytes is stimulated by insulin and its plasma levels are demonstrated to increase in relation to diabetes mellitus, IR, and hyperinsulinemia [52]. Furthermore, it appears that in obese patients, such as those with diabetes or CVD, in addition to obesity, the type of disease also impacts the levels of inflammatory or anti-inflammatory mediators [53]. Moreover, subgroup
analyses based on the CVD type demonstrated that apelin levels were significantly lower in other CVD subgroups such as CHD, CHF, HF, AF, and AMI than in the controls. These findings account for the possible usefulness of apelin as an additional biomarker in the diagnosis of CVD in diabetic patients and in diagnosis of patients with CAD. The findings on new combined markers indicated a significant decrease in SMD of the apelin/HDL-c ratio, apelin/LDL-c ratio, and apelin/TC ratio. However, no significant differences were found in the SMD of the apelin/TG ratio in cases with CVDs compared to the control group. The effects of apelin on lipid metabolism have been described by previous studies; apelin was shown to inhibit lipolysis and increase the stability of lipid vacuoles by making them resistant to lipases. Accordingly, apelin is related to enhanced serum lipids and can be utilized as a predictor of premature atherosclerosis in T1DM patients [54, 55].

Despite a number of unresolved questions, it appears that apelin has significant therapeutic potential. The observed cardiovascular roles of apelin suggest that this peptide could be considered a potential candidate for addition to the standard therapy of CVDs.

It should be noted that this meta-analysis had strengths and limitations that must be taken into account. As the first comprehensive meta-analysis, the present study ascertained the association between apelin and CVDs. Publication bias was not detected in our study. Subgroup analysis was performed to identify the possible sources of heterogeneity. The findings of the present study may have important implications for future research into whether apelin and its receptor could have a clinical value in the prevention and treatment of the diseases. The obtained results should be interpreted with caution due to the high heterogeneity of the selected studies. Therefore, further large-scale studies are required to confirm these findings.

Conclusion

The findings showed that the circulatory levels of apelin are significantly lower in CVD patients than in the controls. In addition, apelin levels were affected by the region and disease subtypes. Apelin could be considered an additional biomarker in the diagnosis of CVD in diabetic patients and patients with CAD. In addition, apelin/HDL-c, apelin/LDL-c, and apelin/TC ratios could be offered as diagnostic markers for CVD. However, as other factors, including smoking, dietary patterns, and coronary medication may also impact the plasma levels of apelin, further studies are required to define the risk factors affecting the levels of apelin and confirm these findings.

Supporting information

S1 Checklist. PRISMA_2020_checklist.

S1 File. PubMed search strategy (Supp 2. a) and the visual-filled funnel plots to evaluate the potential publication bias (Supp 2. b).

References

1. Akbari H, Asadikaram G, Jafari A, Nazari-Robati M, Ebrahimi G, Ebrahimi N, et al. Atorvastatin, losartan and captopril may upregulate IL-22 in hypertension and coronary artery disease; the role of gene polymorphism. Life sciences. 2018; 207:525–31. https://doi.org/10.1016/j.lfs.2018.07.005 PMID: 29981521

2. Akbari H, Asadikaram G, Aria H, Fooladi S, Vakili S, Masoumi M. Association of Klotho gene polymorphism with hypertension and coronary artery disease in an Iranian population. BMC cardiovascular disorders. 2018; 18(1):1–7.
3. Akbari H, Asadikaram G, Vakili S, Masoumi M. Atorvastatin and losartan may upregulate renalase activity in hypertension but not coronary artery diseases: The role of gene polymorphism. Journal of cellular biochemistry. 2019; 120(6):9159–71. https://doi.org/10.1002/jcb.28191 PMID: 30548657

4. Stewart J, Mannathan G, Wilkinson P. Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. JRSM cardiovascular disease. 2017; 6:2048004016687211. https://doi.org/10.1177/2048004016687211 PMID: 28286646

5. Kheirmand Parizi M, Akbari H, Malek-Mohamadi M, Kheirmand Parizi M, Kakoei S. Association of salivary levels of immunoglobulin-a and amylase with oral-dental manifestations in patients with controlled and non-controlled type 2 diabetes. BMC oral health. 2019; 19(1):175. Epub 2019/08/08. https://doi.org/10.1186/s12903-019-0868-4 PMID: 31387562.

6. Motawi TM, Mahdy SG, El-Sawalhi MM, Ali EN, El-Telbany RF. Serum levels of chemerin, apelin, vaspin, and omentin-1 in obese type 2 diabetic Egyptian patients with coronary artery stenosis. Canadian journal of physiology and pharmacology. 2018; 96(1):38–44. https://doi.org/10.1139/cjpp-2017-0272 PMID: 29857639

7. Szokodi I, Tavi P, Földes Gb, Voutilainen-Myllylä S, Ilves M, Tokola H, et al. Apelin, the novel endogenous ligand of the orphan receptor APJ, regulates cardiac contractility. Circulation research. 2002; 91 (5):434–40. https://doi.org/10.1161/01.res.0000033522.37861.69 PMID: 12215493

8. Földes G, Horkay F, Szokodi I, Vuoletseenaho O, Ilves M, Lindstedt KA, et al. Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. Biochem Biophys Res Commun. 2003; 308(3):480–5. Epub 2003/08/14. https://doi.org/10.1016/s0006-291x(03)01424-4 PMID: 12914775.

9. Kadoglu NP, Lampropoulos S, Kapelouzou A, Theofilogiannakos EK, Fotiadis G, et al. Serum levels of apelin and ghrelin in patients with acute coronary syndromes and established coronary artery disease—KOZANI STUDY. Translational Research. 2010; 155(5):238–46. https://doi.org/10.1016/j.trsl.2010.01.004 PMID: 20403579

10. Bamba V. Update on screening, etiology, and treatment of dyslipidemia in children. The Journal of Clinical Endocrinology & Metabolism. 2014; 99(9):3093–102.

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021; 372.

12. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. 2011:1–12.

13. Alan Stuart K. Kendall’s advanced theory of statistics. London: Wiley; p. 1998.

14. Elandt-Johnson RC, Johnson NL. Survival models and data analysis: John Wiley & Sons; 1980.

15. Bilk MZ, Kaplan I, Yıldız A, Akıl MA, Acet H, Yüksel M, et al. Apelin levels in isolated coronary artery ectasia. Korean circulation journal. 2015; 45(5):386–90. https://doi.org/10.4070/kcj.2015.45.5.386 PMID: 26413106

16. Sun X, Zhang Y, Qi X, Wei L. Impact of apelin-13 on the development of coronary artery ectasia. Acta Cardiologica Sinica. 2020; 36(3):216. https://doi.org/10.6515/ACS.202005_36(3).20190901A PMID: 32425436

17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002; 21(11):1539–58. https://doi.org/10.1002/sim.1186 PMID: 12111919

18. Abdelaziz AA, Daoud EM, El-Hussiny MAB, Mohamed SA. Plasma apelin level after percutaneous coronary intervention. The Egyptian Heart Journal. 2015; 67(1):63–8.

19. Abd-Elbaky AE, Abo-ElMatty DM, Mesbah NM, Ibrahim SM. Omentin and apelin concentrations in relation to obesity, diabetes mellitus type two, and cardiovascular diseases in Egyptian population. International Journal of Diabetes in Developing Countries. 2016; 36(1):52–8.

20. Abdullah MH, Sahab KS. The Use of Plasma Apelin Alteration in Diagnosis of Atherosclerosis. Journal of Biochemical Technology. 2018; 9(3):23.

21. Akcıl R, Yümmün G, Bayat Z, Donbaloğlu O, Erselcan K, Ece E, et al. Characterization of the apelin-1860T>C polymorphism in Turkish coronary artery disease patients and healthy individuals. International journal of physiology, pathophysiology and pharmacology. 2015; 7(4):165. PMID: 27073592

22. Basile G, Crucitti A, Cucinotta M, Lacquaniti A, Catalano A, Loddo S, et al. Serum levels of Apelin-36 are decreased in older hospitalized patients with heart failure. European Geriatric Medicine. 2014; 5(4):242–5.

23. Celik Y, Yardan T, Baydin A, Demircan S. The role of NT-proBNP and Apelin in the assessment of right ventricular dysfunction in acute pulmonary embolism. Age (years). 2016; 62:24–94. PMID: 26968282

24. Chong KS, Gardner RS, Morton JJ, Ashley EA, McDonagh TA. Plasma concentrations of the novel peptide apelin are decreased in patients with chronic heart failure. European journal of heart failure. 2006; 8(4):355–60. https://doi.org/10.1016/j.ejheart.2005.10.007 PMID: 16464638
25. El Amrousy D, El-Mahdy H. Prognostic value of serum apelin level in children with heart failure secondary to congenital heart disease. Pediatric cardiology. 2018; 39(6):1188–93. https://doi.org/10.1007/s00246-018-1879-7 PMID: 29632960

26. Ellinor PT, Low AF, MacRae CA. Reduced apelin levels in lone atrial fibrillation. European heart journal. 2006; 27(2):222–6. https://doi.org/10.1093/eurheartj/ehi48 PMID: 16278229

27. Francia P, Salvati A, Balla C, De Paolis P, Pagannoni E, Borro M, et al. Cardiac resynchronization therapy increases plasma levels of the endogenous isotope apelin. European journal of heart failure. 2007; 9(3):306–9. https://doi.org/10.1016/j.ejheart.2006.06.005 PMID: 16891152

28. Gurmer M, Celik A, Balin M, Gui E, Kobat MA, Bursali KB, et al. The association between apelin-12 levels and paroxysmal supraventricular tachycardia. Journal of Cardiovascular Medicine. 2014; 15(8):642–6. https://doi.org/10.2459/JCM.0000000000000010 PMID: 24933193

29. Małyszko J, Małyszko J, Pawlak K, Mysliwiec M. Visfatin and apelin, new adipocytokines, and their relation to endothelial function in patients with chronic renal failure. Advances in Medical Sciences (De Gruyter Open). 2008; 53(1).

30. Miettinen KH, Magga J, Vuoletenaho O, Vanninen EJ, Puntannen KR, Ylitalo K, et al. Utility of plasma adipokines in patients with obstructive sleep apnea syndrome. European journal of endocrinology. 2013; 216(1):T17. https://doi.org/10.1530/JOE-12-0232 PMID: 23160967

31. Pang H, Han B, Li Z, Fu Q. Identification of molecular markers in patients with hypertensive heart disease accompanied with coronary artery disease. Genet Mol Res. 2015; 14(1):93–100. https://doi.org/10.4238/2015.January.15.12 PMID: 25729940

32. Rachwałik M, Diakowska D, Kustrzycki W. Serum concentration of selected adipocytokines in patients with coronary artery disease suitable for surgical revascularization: a preliminary study. Kardiolochirurgia i Torakochirurgia Polska. 2011; 8(4):432–6.

33. Şimşek EÇ, Yakar Tülsüce S, Tülsüce K, Emre SV, Çuhadar S, Nazlı C. The relationship between serum apelin levels and aortic dilatation in bicuspid aortic valve patients. Congenital Heart Disease. 2019; 14(2):256–63. https://doi.org/10.1111/chd.12718 PMID: 30485657

34. van Kimmenade RR, Januzzi JL, Ellinor PT, Sharma UC, Bakker JA, Low AF, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. Journal of the American College of Cardiology. 2006; 48(6):1217–24. https://doi.org/10.1016/j.jacc.2006.03.061 PMID: 16879009

35. Veillicou M, Sanidas E, Papadopoulos D, Illopoulos D, Mantzourani M, Toutouzas K, et al. Adipokines and Atrial Fibrillation. The Important Role of Apelin. Hellenic journal of cardiology: HJC = Hellenike kardiologike epitheorese. 2020. https://doi.org/10.1016/j.hjc.2020.04.018 PMID: 32387519

36. Wang YZ, Fan J, Zhong B, Xu Q. Apelin: A novel prognostic predictor for atrial fibrillation recurrence after pulmonary vein isolation. Medicine. 2018; 97(39). https://doi.org/10.1097/MD.00000000000012580 PMID: 30278567

37. Wilson V, Gupta N, Prabhadkar P, Ramakrishnan L, Seth S, Maulik S. Effect of percutaneous transvenous mitral commissurotomy on plasma apelin level in mitral stenosis patients. J Clin Exp Cardiolog. 2014; 5(283):2.

38. Zhou Y, Wang Y, Qiao S. Apelin. International heart journal. 2014;13–234.

39. Małyszko J, Małyszko JS, Kożminski P, Myśliwiec M. Apelin and cardiac function in hemodialyzed patients: possible relations? American journal of nephrology. 2006; 26(2):121–6. https://doi.org/10.1159/000092122 PMID: 16549903

40. Zhou Y, Wang Y, Qiao S. Apelin: A potential marker of coronary artery stenosis and atherosclerotic plaque stability in ACS patients. International Heart Journal. 2014; 55(3):204–12. https://doi.org/10.1536/ihj.13-234 PMID: 24806385

41. Shah A, Mehta N, Reilly MP. Adipose inflammation, insulin resistance, and cardiovascular disease. JPEN Journal of parenteral and enteral nutrition. 2008; 32(6):638–44. Epub 2008/11/01. https://doi.org/10.1177/0148607108325251 PMID: 18974244.

42. Mattu HS, Randeva HS. Role of adipokines in cardiovascular disease. The Journal of endocrinology. 2013; 216(1):T17. https://doi.org/10.1530/JOE-12-0232 PMID: 23160967

43. Nowzari Z, Masoumi M, Nazari-Robati M, Akbari H, Shahrokhi N, Asadikaram G. Association of polymorphisms of leptin, leptin receptor and apelin receptor genes with susceptibility to coronary artery disease and hypertension. Life sciences. 2018; 207:166–71. https://doi.org/10.1016/j.lfs.2018.06.007 PMID: 29883719

44. Chandrasekaran B, Dar O, McDonagh T. The role of apelin in cardiovascular function and heart failure. European journal of heart failure. 2008; 10(8):725–32. https://doi.org/10.1016/j.ejheart.2008.06.002 PMID: 18583184
45. Hou X, Zeng H, He X, Chen JX. Sirt3 is essential for apelin-induced angiogenesis in post-myocardial infarction of diabetes. Journal of Cellular and Molecular Medicine. 2015; 19(1):53–61. https://doi.org/10.1111/jcmm.12453 PMID: 25311234

46. Li L, Zeng H, Hou X, He X, Chen J-X. Myocardial injection of apelin-overexpressing bone marrow cells improves cardiac repair via upregulation of Sirt3 after myocardial infarction. PloS one. 2013; 8(9): e71041. https://doi.org/10.1371/journal.pone.0071041 PMID: 24039710

47. Liu H-T, Chen M, Yu J, Li W-J, Tao L, Li Y, et al. Serum apelin level predicts the major adverse cardiac events in patients with ST elevation myocardial infarction receiving percutaneous coronary intervention. Medicine. 2015; 94(4). https://doi.org/10.1097/MD.0000000000000449 PMID: 25634182

48. Antushevich H, Wójcik M. Apelin in disease. Clinica chimica acta. 2018; 483:241–8.

49. Arababadi MK, Asadikaram P, Asadikaram G. APLN/APJ pathway: The key regulator of macrophage functions. Life sciences. 2019; 232:116645. https://doi.org/10.1016/j.lfs.2019.116645 PMID: 31299236

50. Sabry RN, El Wakeel MA, El-Kassas GM, Amer AF, El Batal WH, El-Zayat SR, et al. Serum apelin: a new marker of early atherosclerosis in children with type 1 diabetes mellitus. Open access Macedonian journal of medical sciences. 2018; 6(4):613. https://doi.org/10.3889/oamjms.2018.144 PMID: 29731925

51. Lago F, Gómez R, Gómez-Reino JJ, Dieguez C, Gualillo O. Adipokines as novel modulators of lipid metabolism. Trends in biochemical sciences. 2009; 34(10):500–10. https://doi.org/10.1016/j.tibs.2009.06.008 PMID: 19729309

52. Iwanaga Y, Kihara Y, Takenaka H, Kita T. Down-regulation of cardiac apelin system in hypertrophied and failing hearts: possible role of angiotensin II–angiotensin type 1 receptor system. Journal of molecular and cellular cardiology. 2006; 41(5):798–806. https://doi.org/10.1016/j.yjmcc.2006.07.004 PMID: 16919293

53. Japp A, Cruden N, Barnes G, Van Gemeren N, Mathews J, Adamson J, et al. Acute cardiovascular effects of apelin in humans. Circulation. 2010; 121(16):1818–27. https://doi.org/10.1161/CIRCULATIONAHA.109.911339 PMID: 20385929

54. Yue P, Jin H, Xu S, Aillaud M, Deng AC, Azuma J, et al. Apelin decreases lipolysis via Gq, Gi, and AMPK-dependent mechanisms. Endocrinology. 2011; 152(1):59–68. https://doi.org/10.1210/en.2010-0576 PMID: 21047945

55. Than A, Cheng Y, Foh L-C, Leow MK-S, Lim SC, Chuah YJ, et al. Apelin inhibits adipogenesis and lipolysis through distinct molecular pathways. Molecular and cellular endocrinology. 2012; 362(1–2):227–41. https://doi.org/10.1016/j.mce.2012.07.002 PMID: 22842084