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Elevated blood apelin levels in type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Aims: Apelin is a circulatory blood peptide acting as a ligand for the orphan G protein-coupled receptor known as APJ. Whether apelin blood levels can affect the pathogenesis of type 2 diabetes mellitus is an open question. In the present study, we aimed to assess the levels of circulatory apelin peptide in the type 2 diabetic subjects using systematic review and meta-analysis under random-effects model and standardized mean difference (SMD) as the effect size. For heterogeneity testing, Q and I^2% statistic indices as well as meta-regression were applied.

Methods: Using specialized biomedical online databases of Pubmed, Pubmed Central, Medline, Google scholar, Scopus and Embase databases without the beginning date restriction until July 2018, the systematic review retrieved nine studies for meta-analysis after fulfilling the inclusion and exclusion criteria.

Results: Analysis of Q and I^2% statistic indices as well as meta-regression showed a high heterogeneity in the 16 selected studies (737.578 and 96.475, respectively), thus, the random-effects model was chosen. The primary analysis for the main hypothesis on a total number of 1102 cases and 1078 healthy control subjects found that the weighted pooled SMD for the impact of apelin blood concentration in type 2 diabetes mellitus was as follows: SMD = 2.136 (95% confidence interval, 1.580–2.693). The P-value for the significance of the combined SMD examined by the z-test was 0.000 and thus, it was clearly significant.

Conclusions: This meta-analysis presents evidence that apelin circulatory levels are higher in type 2 diabetic subjects than normal controls.

1. Introduction

The apelin encoding gene has been localized on X chromosome at Xq25-q26.3. Apelin precursor is produced as a pre-proprotein polypeptide containing a total of 77 amino acids and finally secreted after cellular processing into mature apelin peptide. Apelin peptide acts as a ligand for the orphan G protein-coupled receptor also known as APJ. It is called "apelin," for APJ Endogenous Ligand [1]. The ligand part of the APJ receptor is located at the C-terminal segment of mature apelin peptide. However, apelin is found in several forms according to its mature peptide sequence length in

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the body. Indeed, apelin is found in several active forms such as apelin-36, apelin-17, apelin-13, and the pyroglutamated form of apelin-13 [2,3]. Apelin is a ubiquitous peptide and its receptor is expressed in many parts of the body, including central nervous system, particularly in the hypothalamus and many peripheral tissues. From the functional aspects, it has been shown that apelin plays important physiological roles in the regulations of cardiovascular and fluid homeostasis, angiogenesis, cell proliferation, food intake, and immune responses [4–7]. Besides, it is secreted as an adipokine by adipocytes resident in the adipose tissues. Furthermore, apelin biochemical roles and associated signaling pathways both in lipid and glucose metabolisms have been amply investigated in recent years [8–13]. This led to an entirely new field of study establishing the links among apelin peptide and obesity with type 2 diabetes mellitus. Recent investigations emphasize that apelin peptide appears as a beneficial adipokine in metabolic disorders and a promising therapeutic target with anti-obesity and anti-diabetic properties. Notwithstanding, whether apelin blood levels can affect the pathogenesis of type 2 diabetes mellitus is an open question. The majority, but not all, of the studies have reported increased circulatory apelin levels in humans and different animal models of metabolic pathologies. In the present study, we aimed to assess the levels of circulatory apelin peptide in type 2 diabetes subjects using systematic review and meta-analysis under random-effects model and SMD as the effect size.

2. Methods

2.1. Protocol of the systematic review and meta-analysis

The PRISMA Checklist 2009 was applied to conduct this systematic review and meta-analysis [14].

2.2. Information sources and search strategies

A systematic literature search was independently carried out by three of authors (A. N., S. B., and S. K.) using specialized biomedical databases of Medline, Pubmed, Pubmed Central, Google scholar, Scopus and Embase databases without the beginning date restriction until July 2018. Publications using the MeSH and non-MeSH terms “apelin” in combination with “type 2 diabetes”, “type 2 diabetes mellitus” and “T2DM” with additional keywords such as “blood samples”, “plasma”, “serum” and “case-control study” were identified. The harvested references from publications were scrutinized to identify any additional relevant aplein blood level studies. Then, the search results were restricted to English language and the review possesses were limited to case-control studies by three authors independently, which fulfilled our inclusion and exclusion criteria.

2.3. Eligibility criteria

Studies were pre-included if they used standardized methods such as chemiluminescent technique and enzyme-linked immunosorbent assay (ELISA) for all kinds of apelin blood level detection. Limitation was applied to the subtypes of diabetes mellitus and publications investigating only type 1 diabetes were excluded. However, no limitation was applied to the severity of diabetes, race, or sex of the study participants. Moreover, studies were excluded if they enrolled populations other than diabetes as well as reports describing diabetes interventional therapies. Only publications describing apelin blood levels in the case and control groups considered for the pooled effect size calculation.

2.4. Study selection

Only the case-control studies providing enough information about their results in such a way to compute an estimate of the effect size (such as mean and standard deviation or standardized error of the mean, etc.) for apelin blood levels were included. Due to the different protocol definitions used for circulatory apelin level assessments, only studies which determined the levels of apelin in comparison with healthy subjects were considered to be included in the current meta-analysis. Two authors selected the studies (A. N. and S. K) and disagreements have been solved by another author (K. H.).

2.5. Data collection process

The first author of the selected articles, publication date, the apelin levels in patients and healthy controls, evaluated criteria for the diabetes and the total number of cases and controls, and other related information were extracted from the studies that have been provided for systematic review of the meta-analysis process.

2.6. Summary measures and synthesis of results

Stata version 14.0 (Stata Corporation, College Station, TX, USA) was employed for data analysis of the systematic review and meta-analysis. Between-study heterogeneity was assessed using the χ^2 based Q-test and I^2 statistics. The Q test and I^2 statistics were applied to evaluate the inconsistencies and heterogeneities among the studies. A significant Q suggests the existence of heterogeneities. Moreover, I^2 statistic estimates the magnitude of the inconsistencies among the studies [15]. Moreover, for further assessment of heterogeneity among studies, the meta-regression was applied as well. The commercial apelin blood level detection kits which have been reported by the included studies were assessed for the type of apelin fragment detection and numerical codes (as 1, 2, etc.) donated to them according to the similarity of the detections. For analysis of an estimated pooled effect size, the random-effects model and SMD were used. Data were shown as the estimated SMD with 95% confidence interval (CI) for each study and pooled studies as well. The significance of the total SMD was examined by the z-test and $P < 0.05$ was considered statistically significant. The data extracted from each study for calculation of overall effect size, have been presented in Tables 1 and 2. For meta-regression analysis, the moderator variable was the type of the commercial apelin blood level assessment kit (Table 3) and it was plotted against the SMD.

Table 1 – Studies which have been included in this meta-analysis and the demographic data and clinical characteristics extracted from them for apelin blood levels.

Study	Subgroups*	Age in Diabetes (years)	BMI (kg/m^2) in Diabetes	Diabetes gender male/female	Controls gender male/female	BMI (kg/m^2) in controls	Age in controls (year)
Ling Li [19]	–†	56 ± 10	23.5 ± 2.4	13/17	13/23	23 ± 3.2	51 ± 9
Maria Gisella Cavallo [20]	–	61 ± 10	30.4 ± 4.5	75/43	65/72	27.4 ± 5.6	49 ± 11
Marana Habchi [21]	–	60 ± 9	34.5 ± 7	51/47	98/64	24. 4 ± 3.6	47 ± 15
Bulent Bilir [22]	a	56.91 ± 7.44	31.99 ± 6.14	23/23	24/29	28.04 ± 3.28	57.31 ± 8.41
Bulent Bilir [22]	b	58.85 ± 9.04	33.07 ± 5.33	24/29	24/29	28.04 ± 3.28	57.31 ± 8.41
Atif E. Abd-Elbaky [23]	a	42 ± 3	32.4 ± 1.4	80/0	80/0	21 ± 1.7	38.6 ± 4.2
Atif E. Abd-Elbaky [23]	b	40.3 ± 2.5	32.6 ± 1.6	80/0	80/0	21 ± 1.7	38.6 ± 4.2
Tarek M. K. Motawi [24]	–	55.3 ± 6	32.5 ± 1.8	11/34	14/16	21.8 ± 1.3	54.6 ± 3.1
Sanaa Sayed Gazareen [25]	a	–	–	5/15	5/5	–	–
Sanaa Sayed Gazareen [25]	b	–	–	7/8	5/5	–	–
Sanaa Sayed Gazareen [25]	c	–	–	8/7	5/5	–	–
Ashraf T. Abd Elmouttaleb [26]	–	58.9 ± 15.3	27.1 ± 4.6	19/11	22/8	26.4 ± 4.2	58.1 ± 13.2
G. Erdem [27]	–	52.03 ± 8.9	29.9 ± 3.1	17/23	21/19	28.9 ± 3.3	49.33 ± 8.0
Federico Soriguer [28]	–	43.4 ± 7.8	53.9 ± 7.5	5/11	4/8	24.9 ± 3.1	39.3 ± 6.2
YU Shan [29]	a	–	28.9 ± 1.9	22/19	44/35	21.6 ± 1.7	–
YU Shan [29]	b	–	28.7 ± 2.6	20/20	44/35	21.6 ± 1.7	–
Yong Tao [30]	–	52.2 ± 9.8	24.6 ± 2.8	28/27	13/21	23.8 ± 2.9	62.1 ± 10.4
Mehmet Guney Senol [31]	–	57.4 ± 7.9	28.4 ± 3.4	20/20	13/9	27.1 ± 2.6	54.9 ± 6.2
Hala O. El-Mesallamy [32]	a	63.40 ± 0.53	35.16 ± 0.63	0/20	0/20	26.10 ± 0.21	62.35 ± 0.46
Hala O. El-Mesallamy [32]	b	63.35 ± 0.54	26.73 ± 0.29	0/20	0/20	26.10 ± 0.21	62.35 ± 0.46
Hala O. El-Mesallamy [32]	c	64.70 ± 0.45	37.66 ± 0.40	0/20	0/20	26.10 ± 0.21	62.35 ± 0.46
Qutaiba A Qasim [33]	a	39.0 ± 8.8	27 ± 1.8	18/17	13/12	27 ± 2.1	36.4 ± 10.9
Qutaiba A Qasim [33]	b	40.2 ± 7.3	36.7 ± 3.4	17/18	13/12	27 ± 2.1	36.4 ± 10.9
Qutaiba A Qasim [33]	c	39.0 ± 8.8	27 ± 1.8	18/17	13/12	37.4 ± 3.4	38.4 ± 8.5
Qutaiba A Qasim [33]	d	40.2 ± 7.3	36.7 ± 3.4	17/18	13/12	37.4 ± 3.4	38.4 ± 8.5
Waleed Mahdy Nada [34]	a	55.4 ± 9.4	–	7/13	13/7	–	55.2 ± 8.1
Waleed Mahdy Nada [34]	b	59.7 ± 8.2	–	6/14	13/7	–	55.2 ± 8.1

The data presented as mean ± standard deviation.

* a, b, c and d letters show the subgrouping within that study.

† The data not provided by the authors.

Table 2 – The extracted data from each study which were used to calculate the overall effect sizes.

First author, year of publication	Apelin detection kit type	Mean apelin blood level in diabetic cases (ng/ml)	Standard deviation of apelin blood level in diabetic cases	Mean apelin blood level in healthy controls (ng/ml)	Standard deviation of apelin blood level in healthy controls
Qutaiba A Qasim [33]	Type 1	0.134	0.04	0.094	0.028
Qutaiba A Qasim [33]	Type 1	0.134	0.04	0.109	0.03
Qutaiba A Qasim, [33]	Type 1	0.036	0.017	0.094	0.028
Qutaiba A Qasim [33]	Type 1	0.036	0.017	0.109	0.03
Federico Soriguer [28]	Type 2	1.87	1.22	1.12	0.51
G. Erdem [27]	Type 2	0.44	0.38	0.75	0.42
Hala O. El-Mesallamy [32]	Type 2	33.12	0.78	35.28	0.94
Hala O. El-Mesallamy [32]	Type 2	28.95	0.89	35.28	0.94
Hala O. El-Mesallamy Mesallamy [32]	Type 2	1.66	1.06	35.28	0.94
Ling Li [19]	Type 2	0.498	0.035	0.459	0.032
Marana Habchi [21]	Type 2	0.59	0.35	0.43	0.29
Maria Gisella Cavallo [20]	Type 2	1.23	1.1	0.91	0.7
Mehmet Guney Senol [31]	Type 2	1.6	1.4	1	0.6
YU Shan, 2012a	Type 2	0.445	0.049	0.386	0.056
YU Shan [29]	Type 2	0.445	0.049	0.421	0.052
Bulent Bilir [22]	Type 3	0.093	0.18	0.055	0.187
Bulent Bilir [22]	Type 3	0.076	0.112	0.055	0.187
Atif E. Abd-Elbaky [23]	Type 4	1.79	0.17	0.79	0.07
Atif E. Abd-Elbaky [23]	Type 4	1.99	0.49	0.79	0.07
Sanaa Sayed Gazareen [25]	Type 5	4.65	2	0.6	0.35
Sanaa Sayed Gazareen [25]	Type 5	3.67	0.95	0.6	0.35
Sanaa Sayed Gazareen [25]	Type 5	5.85	2.29	0.6	0.35
Tarek M. K. Motawi [24]	Type 5	3.8	0.36	0.96	0.48
Ashraf T. Abd Elmouttaleb [26]	Type 6	1.21	0.72	2.67	0.8
Yong Tao [30]	Type 7	12.5	9.7	7.4	4.9
Waleed Mahdy Nada [34]	Type 8	0.97	0.3	0.98	0.42
Waleed Mahdy Nada [34]	Type 8	1.6	0.5	0.98	0.42

The studies were categorized according to the commercial apelin detection kit type.

Table 3 – The aplein blood level assessment kit types, which have been used by the included studies in this meta-analysis.

Apelin detection kit type*	Apelin commercial kit type and company
Type 1	Not reported by the authors
Type 2	Phoenix Pharmaceuticals
Type 3	Sunred Biological Technology Co
Type 4	MyBioSource
Type 5	Raybiotech
Type 6	Glory Science
Type 7	Uscnlife Science
Type 8	MyBioSource

* The kits were categorized for both apelin isoform similarity detection and company of production. For more information, please study the text of the included studies, which have been cited in this meta-analysis reference part.

2.7. *Risk of bias across studies*

For the risk of bias across studies, papers were scrutinized for method validation and data processing. From the effect size estimation of each and overall selected studies, the funnel plot was developed. For interpretation of any publication bias among studies, visual inspections of the generated funnel plot were employed to evaluate the plot symmetry. In this plot, the X and Y axes represent the standard deviation and Log of the effect sizes (Log of odds ratio), respectively.

3. Results

3.1. *Study selection*

The flowcharts of the study selections in the systematic review processes have been presented in Fig. 1. The initial search for apelin blood concentrations identified a total of 7311 potentially eligible studies and 5404 records removed being as duplicates. Of the 321 records, 302 publications were excluded after reading the titles or abstracts as being obviously irrelevant to the goal of this meta-analysis. Because of insufficient data presented by the authors of such publications for calculation of the SMD and 95% CI and because of poor quality, two papers were excluded [16,17]. Moreover, because of using therapeutics in the cases, one paper was excluded as well [18]. Finally, 16 studies (which have been detailed in Tables 1 and 2 and cited in the references part of the current study as [19–34]); were included in the meta-analytical processes for apelin blood concentrations (Fig. 1). Some of the selected studies include more than one case-control study within them (thereafter, known as within-article subgroups), which have been presented by letters (a, b, etc.), if applicable in further analyses and by adding them to the analysis, the systematic review process retrieved 27 case-control studies in overall (Tables 1 and 2).

3.2. *Study characteristics*

For each study, the epidemiological and disease characteristics data, reported by the authors, were extracted. The gender of type 2 diabetic cases, gender of healthy controls, type of the commercial kit, body mass index (BMI), mean age in cases and healthy controls have been presented in Table 1. Actually, this meta-analysis retrieved a total number of 1102 cases and 1078 control subjects until July 2018 for apelin blood levels.

3.3. *Risk of bias within studies*

The results showed that the selected studies were not homogenous and actually, they were inconsistent. The Q test was calculated as 737.578 for apelin concentrations across studies. As the Q statistic test is only applied for heterogeneity testing among the included studies, but not suitable for heterogeneity extent calculation, a tentative classification of I^2 values with the purpose to interpret heterogeneity magnitude is proposed. Thus, the percentages of nearly 25% ($I^2 = 25$), 50% ($I^2 = 50$), and 75% ($I^2 = 75$) would mean low, medium, and high heterogeneity, respectively [15]. The I^2% test for apelin blood concentrations was calculated as 96.475. As I^2 index and the between-studies variance, τ^2, are directly related: the higher the τ^2, the higher the I^2 index [15], therefore, the random-effects model of meta-analysis was applied for the presentation of apelin forest plot of the selected studies for type 2 diabetic subjects.

3.4. *Synthesis of results*

The forest plot for the included studies and their within-article subgroups in each study have been prepared and presented in Fig. 2. In this plot, the mean effect sizes and standard deviations and the SMDs with 95 percent of the confidence interval for each study and the overall effect size have been shown as well. The primary analysis for the main hypothesis found that the weighted average effect size for the impact of apelin concentration on the type 2 diabetes mellitus pathogenesis was as follows: SMD = 2.136 (95% confidence interval, 1.580–2.693), using the random-effects model in the meta-analysis as presented in Fig. 2 for the 16 included studies (including their corresponding within-article subgroups in each study). The P-value for the significance of the combined SMD examined by the z-test for apelin blood concentrations was 0.000 and it was clearly significant. In addition, according the type of the commercial apelin detection kit, the studies were categorized and subgrouped, then the overall effect size for each subgroup was calculated and shown in Fig. 3.

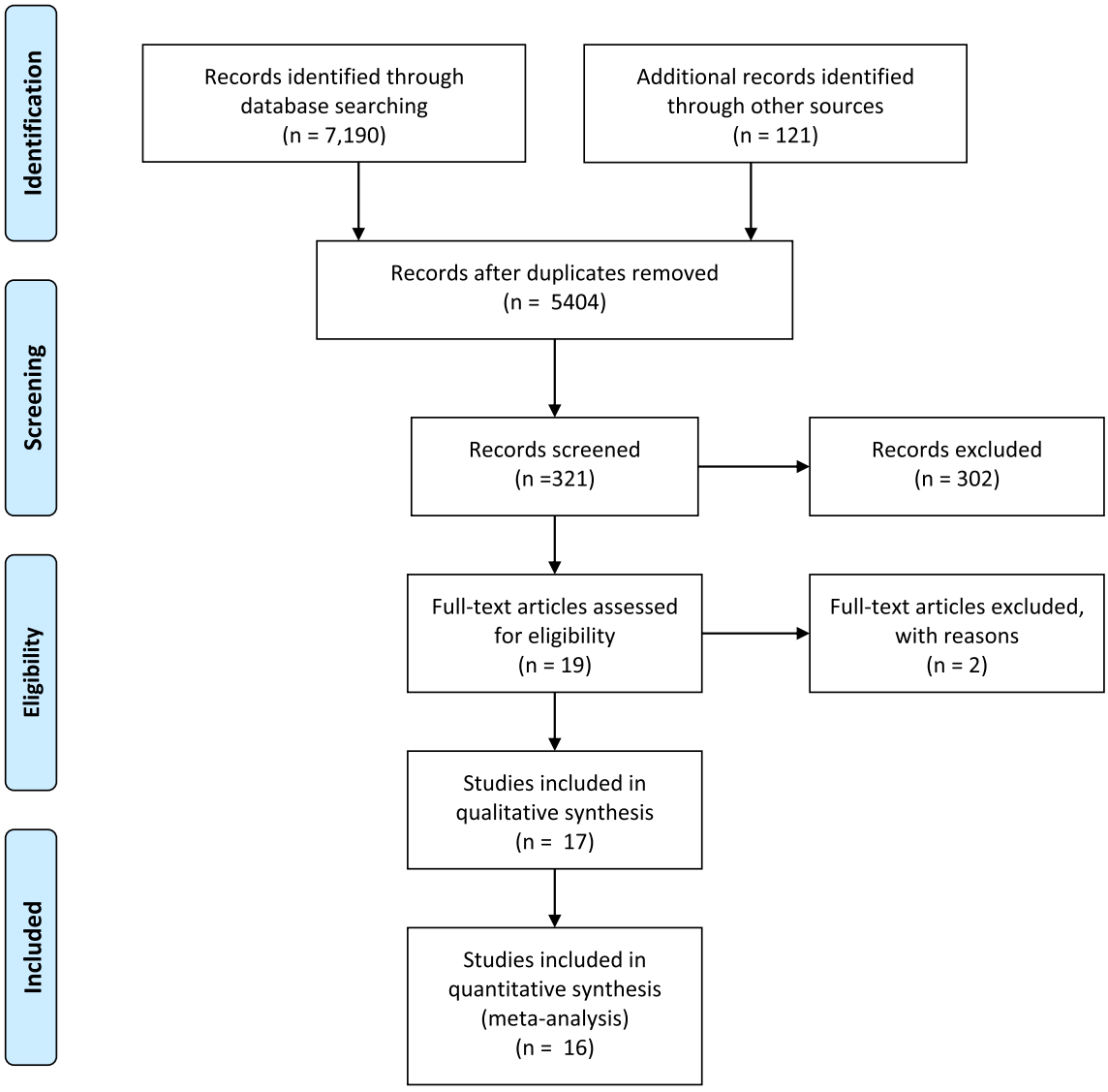

Fig. 1 – Searching strategy for systematic review. This flowchart illustrates the processes for identifying relevant studies to be included according to the exclusion and inclusion criteria. 16 included studies fulfilled the inclusion/exclusion criteria. These studies include within-article subgroups. Including these within-article subgroups, the systematic review process retrieved 27 case-control studies.

3.5. *Risk of bias across studies*

The generated funnel plot was considered to be moderately asymmetrical in shape confirming publication bias in the related published studies for apelin blood concentrations in type 2 diabetic patients. For apelin blood levels, this bias refers mainly to the right part of the plot that has been mainly occupied by the publications demonstrating the higher SMD scores for type 2 diabetic subjects as compared to healthy controls (Fig. 4). Moreover, the moderator variable was plotted (apelin commercial kit type that has been used for apelin blood detection in each study) against the SMD in meta-regression and it has been presented in Fig. 5. It showed that different apelin commercial kit types influence both accuracy and precision of the detections in each study. Studies which have been conducted by numbers 2 and 3 of apelin ELISA commercial kits had the lowest precision in comparison with other ELISA commercial kits (Fig. 5). Additionally, numbers 4 and 5 of apelin ELISA kits had the lowest accuracy as compared to others (Fig. 5).

4. Discussion

Even though there are many published papers and systematic reviews that considered apelin blood concentrations in association with type 2 diabetes mellitus pathophysiology, however, to the best of our knowledge, meta-analysis has not performed in this regard so far. In this investigation, the number of included studies for synthesizing meta-analysis data was proper and in a number of studies, there were some within-article subgroups that were also used for calculating pooled effect size. In the current study, the blood levels of

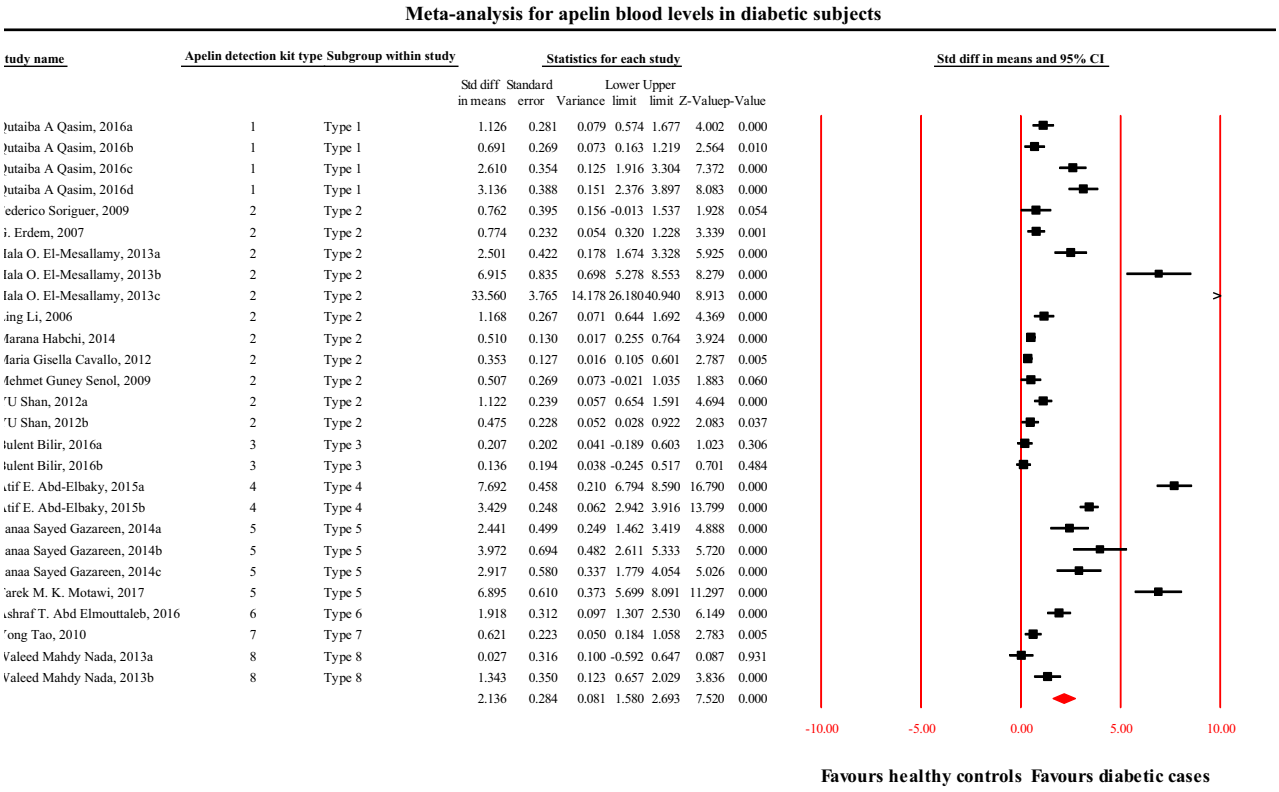

Fig. 2 – Forest plot of 16 included studies fulfilled the inclusion/exclusion criteria. These studies include within-article subgroups, which have been presented by letters (a, b, etc.), if applicable. Including these within-article subgroups, the systematic review process retrieved 27 case-control studies. In this presentation, pooled data evaluating the effects of apelin blood concentrations in type 2 diabetes mellitus compared to healthy controls have been demonstrated under random-effects model. The pooled estimate for standardized mean difference (SMD) was calculated as 2.136 (95% confidence interval, 1.580–2.693).

apelin were investigated using systematic review and meta-analysis in type 2 diabetes mellitus and under random-effects model the final combined SMD calculated as 2.136 (95% confidence interval, 1.580–2.693). Thus, the result confirms that apelin peptide circulatory levels are altered in the blood of type 2 diabetic subjects. On the other hand, the results also showed that heterogeneity level is high among the included studies. Meta-regression confirmed that the type of the commercial apelin detection kit affects the inaccuracy and imprecision of each study. This heterogeneity in the results may stem from the fact that in the body fluids such as plasma, apelin peptide is found in several active fragments such as apelin-36, apelin-17, apelin-13, and the pyroglutamated form of apelin-13. Recent investigation hypothesized that standard immunoassays such as ELISA cannot specifically detect and quantify each apelin peptide and liquid chromatography/tandem mass spectrometry can be adapted to quantify each form of it [35]. However, the main circulating fragments of apelin were not surprisingly detected in this study [35]. This discrepancy between the nature of peptide fragments and quantification using immunoassays and those detected by mass spectrometry raises questions and provides evidence that nature and concentrations of the immunoreactive circulating apelin fragments are very important topic that must be resolved in the future studies. It is interesting that apelin is degradable by a monocarboxypeptidase known as angiotensin-converting enzyme 2 (ACE2) [35]. It hydrolyses both apelin-36 and apelin-13 with a high catalytic efficiency to smaller fragments [35,36]. Since different studies have demonstrated that ACE2 is involved in diabetes pathogenesis [37], therefore, it is of intense interest to investigate ACE2 blood bioactivity in parallel and alongside with apelin blood levels. Even though, the current study only studied the blood concentrations of apelin, more investigations needed to further elucidate the role of apelin in type 2 diabetes mellitus pathophysiology. Several studies in apelin-APJ signaling gene knockout or obese/diabetic mice have already shown the beneficial effects of apelin [11,38–43]. The studies must pave the way to answer the question whether the higher level of apelin is beneficial or, in contrast, destructive and if beneficial, another question remains to be answered is the ineffectiveness of its higher levels to revert the pathogenesis to normal physiological conditions in this disease or maybe apelin actions depends on its fragment types. Notwithstanding,

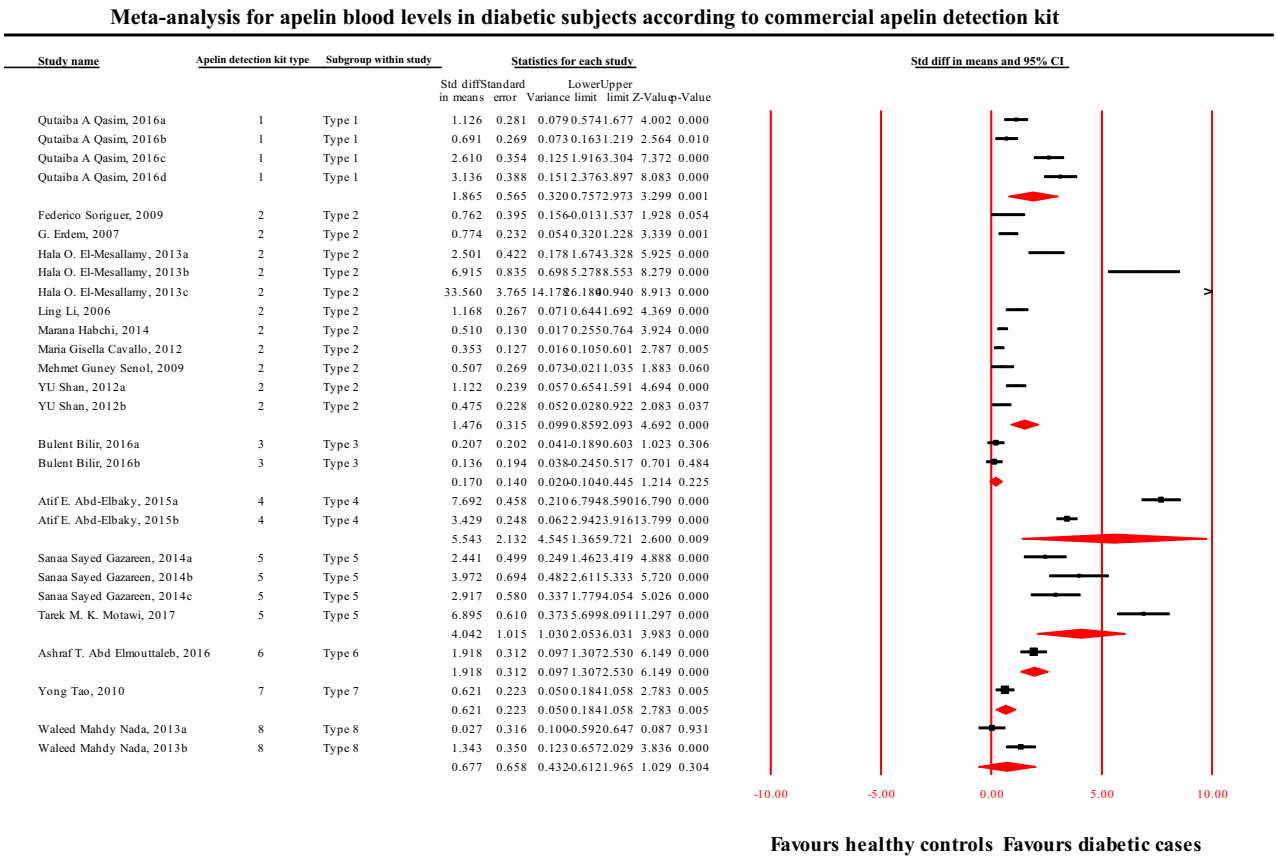

Fig. 3 – Forest plot for 27 case-control studies according to each type of apelin commercial detection kit. These studies include within-article subgroups, which have been presented by letters (a, b, etc.), if applicable. Including these within-article subgroups, the systematic review process retrieved 27 case-control studies. In this presentation, pooled data evaluating the effects of apelin blood concentrations in type 2 diabetes mellitus compared to healthy controls have been demonstrated for each type of apelin detection kit (as numbers) under random-effects model.

recent studies have shown that apelin exerts a pleiotropic effects on metabolism of numerous tissues and recent experimental investigations have enhanced the role of apelin on the whole body. Apelin is an adipokine and several studies have admitted apelin protective activities in the obesity-associated diseases in this regard [8,44,45]. It is well-known for decades that BMI in the diabetic subjects is significantly higher than that of controls [46–50] and a risk factor for those suffering from metabolic syndrome [51,52], and apelin are considered to be an adiopkine secreted from adipose tissue, which means the level of apelin might be influenced by BMI. In seems that body fat and apelin levels and insulin resistance are inter-connected. On the other hand, relationship between obesity, insulin resistance predisposes affected individuals to coronary heart disease. Interestingly, recent meta-analysis reported that circulating apelin was a prominent athero-protective marker against the development of coronary heart disease [53]. As apelin mimics the insulin effects on glucose metabolism, it can be considered as an insulin-sensitizing agent and hopeful and encouraging in the context of developing new therapeutics for treating type 2 diabetic patients. Therefore, studies in humans will be essential to confirm the role of apelin on carbohydrate metabolism and indeed recent study has shown that apelin improves insulin sensitivity in healthy volunteers [54]. In addition, a line of evidence suggests that apelin exerts regulatory effects on lipid metabolism by promoting fuel consumption and fat mass reduction, which is consistent with an insulin sensitivity improvement as well [11,13,55]. These findings highlight the protective and beneficial effects of apelin in obesity-associated diseases and hoist apelin peptide on the list of anti-diabetic therapies. Furthermore, since numerous clinical studies have reported a very wide range of apelin plasma levels, in both healthy controls and patients with different pathologies, it is notable that the bioavailability of apelin also deserves to be better defined, especially regarding the predominant isoforms circulating in the blood. Meanwhile, another apelin-related peptide known as Apela/Elabela also plays part in APJ receptor signaling and function [56,57] and it could be considered alongside to apelin blood concentrations as well. This meta-analysis paves the way to provides preliminary evidence that apelin blood concentration is asso-

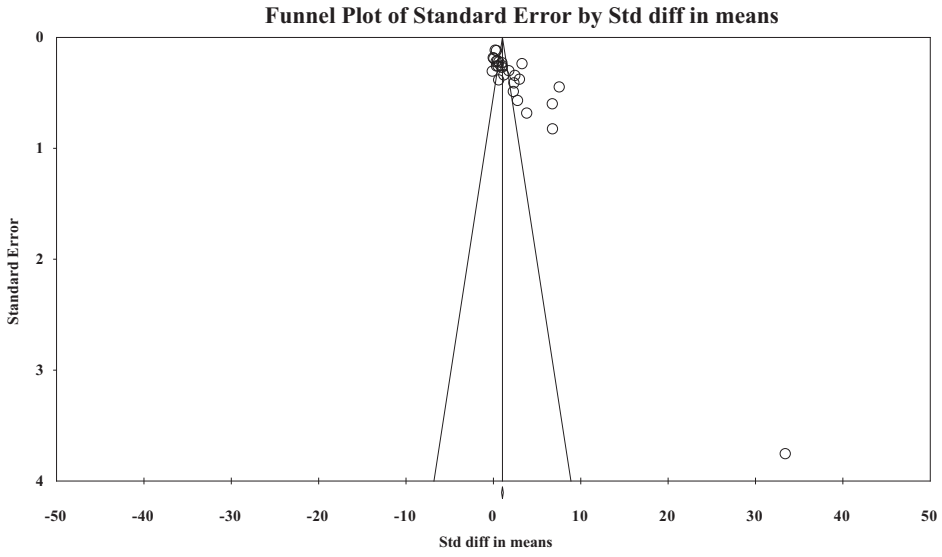

Fig. 4 – Funnel plot for 27 case-control studies. For interpretation of any publication bias among studies, visual inspection of the generated funnel plot under random-effects model employed to evaluate the asymmetry. The funnel plot appears asymmetrical and with publication bias toward studies reporting higher apelin blood levels in type 2 diabetic patients in comparison with healthy controls. In this plot, the X and Y axes represent the standardized mean differences (SMDs) and standard errors, respectively.

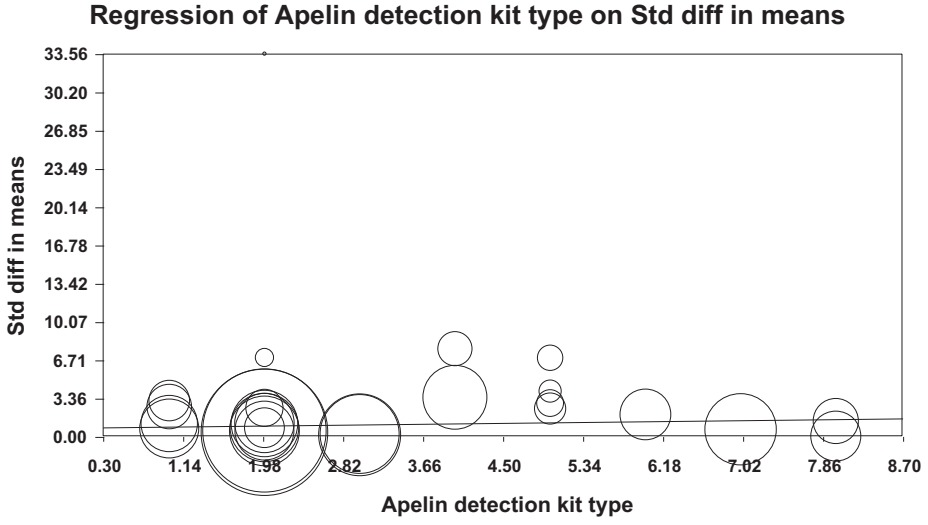

Fig. 5 – Meta-regression for commercial apelin ELISA kit type (as numbers) and standardized mean difference (SMD). As it is evident, studies which have been conducted by numbers 2 and 3 of commercial apelin ELISA kits have the lowest precision and numbers 4 and 5 of apelin ELISA kits have the lowest accuracy as compared to other commercial apelin ELISA kits. The X and Y axes represent the ELISA commercial kit type and SMD, respectively.

ciated with diabetes mellitus, however, more sophisticated laboratory methods needed to more specifically determine each apelin fragment type in the blood of diabetic patients.

5. Conclusions

This meta-analysis presents evidence that apelin circulatory levels are higher in type 2 diabetic subjects than normal controls.

Conflict of interest

The authors have no conflicts of interest.

Financial disclosures

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethics

The present study was approved by Ethics Committee of Ilam University of Medical Sciences.

Acknowledgments

None declared.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2018.12.012.

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