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REVIEW

The relationship between adipose tissue RAAS activity and the risk factors of prediabetes: a systematic review and meta-analysis

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ABSTRACT

The exponential increase in the prevalence of prediabetes has become a global concern due to the comorbidities and mortality rates that are positively associated with it. The incidence of prediabetes is directly proportional to the prevalence of comorbidities with risk factors such as insulin resistance, adiposity, lipotoxicity, obesity and the alteration of the renin-angiotensin-aldosterone system. Hence, the current study systematically reviewed and performed a meta-analysis of these risk factors, their clinical indicators and the RAAS components.

Methods: This systematic review was developed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-2020) standards. This was accomplished by searching clinical MeSH categories in MEDLINE with full texts, EMBASE, Web of Science, PubMed, Cochrane Library, Academic Search Complete, ICTRP and ClinicalTrial.gov. Reviewers examined all the findings and selected the studies that satisfied the inclusion criteria. The Downs and Black Checklist was used to assess for bias, followed by a Review Manager v5. A Forrest plot was used for the meta-analysis and sensitivity analysis. The protocol for this review was registered with PROSPERO CRD42022320252.

Results: The clinical studies ($n = 2$) comprised 1065 patients with prediabetes and 1103 normal controls. The RAAS measurements were completed in the adipose tissue. The RAAS components, renin and aldosterone were higher in the prediabetic (PD) compared to the control [mean difference (MD) = 0.16, 95% CI 0.16 (−0.13, 0.45), $p = 0.25$]. Furthermore, the PD group demonstrated higher triglycerides mean difference [MD = 7.84, 95% CI 7.84 (−9.84, 25.51), $p = 0.38$] and increased BMI [MD = 0.13, 95% CI 0.13 (−0.74, 0.99), $p = 0.77$] compared to the control. The overall quality of the studies was fair with a median score and range of 17 (16–18).

Conclusion: The current study highlights the relationship between increased BMI, RAAS and insulin resistance which is a predictor of prediabetes. The renin is slightly higher in the prediabetes group without any statistical significance, aldosterone is rather negatively associated with prediabetes which may be attributed to the use of anti-hypertensive treatment.

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KEYWORDS
prediabetes; renin angiotensin aldosterone system; obesity; adiposity; body mass index (BMI)

Introduction

The adipose tissue does not only serve as the principal fat storage site but is a group of connective tissue that serves as an endocrine organ that secretes hormones which regulate several metabolic processes, including glucose homoeostasis [1]. The adipose tissue maintains glucose homoeostasis through the interactions of several anti-hyperglycaemic hormones, namely, omentin, leptin and adiponectin [2–4]. Omentin is an insulin-sensitizing adipokine that exerts anti-inflammatory, anti-atherogenic and anti-diabetic properties through the activation of protein kinase AKT/protein kinase B in the insulin signalling pathway [5,6]. Thus, promoting insulin-stimulated glucose uptake irrespective of the presence of insulin [7,8]. In addition to omentin, adiponectin is also an insulin sensitizing adipokine that exerts pleiotropic effects such as anti-inflammatory, anti-apoptotic and improves glucose handling [9]. Adiponectin is crucial in glucose homoeostasis as it reduces gluconeogenesis, conversely promoting the utilization of glucose and free fatty acids by other tissues such as the skeletal muscle, thus regulating the blood glucose levels [9,10]. Furthermore, adiponectin has protective effects on the pancreatic β-cells, which are the chief producers of insulin [11]. However, in type 2 diabetes (T2D), due to a high caloric diet, the adiponectin and omentin levels have been found to be inversely proportional to the glucose levels and insulin sensitivity, consequently promoting adiposity [12]. Leptin is an appetite-suppressing adipokine stimulated by insulin that regulates food intake [13]. However, type 2 diabetics have been reported to be resistant to leptin, promoting constant food intake beyond the fed state resulting in

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overnutrition, adiposity, lipotoxicity and increased body mass index (BMI) [14,15]. Interestingly, studies have evidenced a bi-directional relationship between overnutrition, the risk factors of prediabetes such as, insulin resistance, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), increased body mass index (BMI), adiposity, lipotoxicity and the upregulation of adipose tissue renin angiotensin aldosterone system (RAAS) [16]. Prediabetes (PD) is a state of moderate hyperglycaemia associated with impaired fasting glucose and impaired glucose tolerance [17]. In 2019, 373.9 million people were estimated to have IGT and projected to progress from 453.8 million in 2030 to 548.4 million in 2045 in middle-income countries. In 2017, the most attributable fatalities of diabetes were caused by prediabetes risk factors such as elevated triglycerides (TGs), free fatty acids (FFA), high BMI and behavioural factors, namely, high caloric diet and sedentary lifestyle. Additionally, in 2017 high BMI was responsible for 30.8% of deaths and dietary risk was responsible for 24.7% of deaths [18]. Furthermore, animal studies have evidenced adipose RAAS activity in a prediabetic state. In prediabetes, RAAS components such as renin, angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (AT1R), aldosterone and angiotensin II were elevated in animal studies. Local RAAS is required for adipocyte development and triglyceride regulation [17]. Mature adipocytes generate angiotensin II type 2 receptors (AT2R), which promote mature insulin-sensitive adipocyte proliferation and preadipocyte differentiation, hence capacitating the insulin signalling pathway as well as triglyceride metabolism and control [19]. However, in mild hyperglycaemia, the Ang II/AT1R signalling is upregulated, increasing NADPH oxidase, and the downstream effects result in insulin resistance, as seen in prediabetes and T2D [17]. Consequently, further contributing to impaired glucose tolerance and increase blood glucose [20]. The hyperglycaemia and insulin resistance cause a decrease in anti-hyperglycaemic hormones such as omentin, leptin and adiponectin [21].

Therefore, due to positive correlation between adipose RAAS activity and overt hyperglycaemia risk factors, the current study seeks to evaluate adipose RAAS activity in prediabetes by systematically evaluating RAAS components and the biochemical/clinical markers of the risk factors of prediabetes that are associated with the adipose tissue.

Methods

This meta-analysis was prepared in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA 2020) guidelines which was created to aid systematic reviewers in reporting why the review was conducted, what the authors did and what they discovered in a transparent manner [22]. The protocol used to conduct this systematic review and meta-analysis is registered on PROSPERO (reg. no. CRD42022320252).

This systematic review and meta-analysis was performed in order to address the following questions:

(1) Is adipose RAAS activated in prediabetes?
(2) What is the relationship between adipose RAAS activity and prediabetes risk factors?

Selection criteria

Inclusion criteria

Randomized controlled clinical trials, observational studies and case–control studies from the year 2000–2022 written in English published in peer-reviewed journals were eligible for review.

Participants who are 18 years and older that satisfy all or some of the American Diabetes Association (ADA) criteria for prediabetes diagnosis were considered for this study. The fasting blood glucose (FBG): 5.6 -7.0 mmol/L; 2 h postprandial blood glucose (2 h - OGTT): 7.8 -11.0 mmol/L with Glycated haemoglobin (HbA1c): 5.7-6.4% as per the ADA criteria

Exposure

Randomized control trials, observational studies and case–control studies that report on the risk factors of prediabetes, namely, obesity, adiposity, lipotoxicity and insulin resistance in association to changes in the RAAS components in a prediabetic state, were eligible for the systematic review. Studies that inform on the clinical markers of any of the mentioned risk factors (obesity, adiposity, lipotoxicity and insulin resistance) in a prediabetic state and its relation to alteration of the RAAS components were considered for this review.

Comparators

Prediabetic patients defined by the ADA criteria, fasting blood glucose (FBG): 5.6 -7.0 mmol/L; 2 h postprandial blood glucose (2 h - OGTT): 7.8 -11.0 mmol/L with Glycated haemoglobin (HbA1c): 5.7-6.4% and control group (non-prediabetic) patients were compared in this review.

Outcomes

(1) Primary Outcomes

- Activity of the RAAS components, viz., renin, angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (AT1R), angiotensin II (Ang II), angiotensin 1–7 (Ang 1–7), angiotensin-converting enzyme 2 (ACE 2) and the AT1R receptor expression.
- Comorbidities are regarded as risk factors for prediabetes and type 2 diabetes, namely, insulin resistance, lipotoxicity, adiposity and obesity (reported as OR)

(2) Surrogate outcomes

- Obesity risk markers such as adipokines/adipocytokines expression/triglycerides/cholesterol concentration

Data sources and searches

Databases such as MEDLINE, Web of Science, Cochrane Library, Academic Search Complete, ICTRP and ClinicalTrial.gov were implored with the assistance of an experienced subject librarian from inception to 12 May 2022. Medical Subject Headings (MeSH) with the keywords such as the renin angiotensin aldosterone system OR Ang II AND 'Prediabetes' or 'impaired glucose tolerance' or 'impaired fasting glucose' AND 'adipose' or 'adiposity' or 'body mass index' or 'bmi' or 'obese' or 'obesity' or 'overweight' or 'weight' were implored to identify published studies highlighting the relationship between prediabetes and the mentioned comorbidities.

Study selection

Endnote X20 reference manager database was used to exclude duplicates. All titles and abstracts were separately reviewed by two reviewers (B.C.M. and P.M.) for potential relevance, and full texts were obtained for those judged pertinent. Conflicts were settled by a third independent reviewer (PSN)

Data collection process

BCM and PM independently screened the titles, abstracts and the selected full-text articles against the eligibility criteria to extract data.

All pertinent publications were carefully chosen after being subjected to impartial evaluation by two researchers, BCM and PM. A third investigator, PSN, was consulted in order to explain anomalies. An independent researcher retrieved pertinent data from each article, including the name and year of publication, the nation where the study was conducted, the fasting blood glucose/glycated haemoglobin and impaired fasting glucose, in order to satisfy the aims and objectives (AK).

Assessment of risk of bias and quality of evidence

BCM and PM assessed the risk of bias using the modified Downs and Black checklist, which is suitable for both randomized and nonrandomized research [23,24]. Furthermore, the Downs and Black Checklist takes into account the methodological quality of each study, regardless of the quantity and kind of outcomes measured [25]. The third investigator, PSN, was consulted to settle any disputes. The overall total scores of each study were rated poor if the score was (≤13 points), fair if (14–18 points), good if (19–23 points) and excellent if the score was (24–27). However, the overall quality of the studies included in this meta-analysis was fair, with a median score and range of 17 [16–18] overall agreement 93%, kappa = 0.87. Here, most studies had a low reporting bias, with a median of 12 [11,12] out of a possible score of 13 ($k = 0.86$). The included studies had poor external validity and selection bias, with a median score of 1 (0–3) out of possible 3 scores ($k = 0.92$) and a median of 4 [3,4] out of the possible score of 4 ($k = 0.58$), respectively.

Data synthesis and analysis

To determine whether there is a relationship between the condition (prediabetes) and the risk variables, the statistical heterogeneity in the chosen studies was evaluated using a RevMan 5.4 forest plot and the I^2 and Chi-squared statistical tests [26]. Low heterogeneity is defined as an I^2 of less than 25%, moderate heterogeneity as between 25% and 50%, and high heterogeneity as greater than 50%. A forest plot displays the effect estimates and confidence intervals of individual studies and their meta-analysis, therefore, to quantify the size of the connection, the forest provided an odds ratio and confidence interval, with solid lines denoting the 95% confidence interval [27]. Studies with an I^2 greater than 50 were evaluated for potential sources of heterogeneity using a sensitive analysis, and studies judged to be at high risk of bias were excluded. Furthermore, a significant overlap in the confidence intervals indicated significant homogeneity.

Results

Selected studies

The search strategy yielded 18,646 studies, of which only 21 were assessed for eligibility. A total of 12,780 were removed by automation tools, and 1485 were duplicates. A total of 4357 did not satisfy the inclusion criteria, leaving 21 to be evaluated for eligibility. Among the assessed 21, 11 did not measure any RAAS components, 3 did not have full texts, 4 were review articles and 1 did not measure glucose levels as seen in Figure 1 [20]. Therefore [28–46], only two articles satisfied the inclusion in the current study [47,48].

Study characteristics

All included studies were published in peer-reviewed journals between 2000 and 2022, and their characteristics are shown in Table 1. In total, the included studies comprised 361 participants of which 168 (49.8%) were living with prediabetic and 193 (50.6%) were normal individuals. The mean age of the study population was 40.6 ± 10.4 and 57.1 ± 11.1 (48.85 ± 10.75) (Table 1).

Data synthesis

Reported glucose metabolic profiles

A. Fasting blood glucose levels

The pooled effect estimates of fasting blood glucose were significantly increased in individuals with PD when compared to controls [Mean difference (MD) = 13.40, 95% CI 13.40 (7.94, 18.85), $p < 0.00001$]. Notably as seen in Figure 2A, there was substantial statistical heterogeneity in these studies ($x^2 = 3.49$, $I^2 = 81\%$, $p = 0.06$).

B. Glycated haemoglobin

The pooled effect estimates in Figure 2B showed significantly increased levels of HbA1c in individuals with PD when compared to controls [MD = 0.49, 95% CI 0.49 (0.41, 0.56), $p < 0.00001$]. There was no heterogeneity in the studies ($x^2 = 0.86$, $I^2 = 0\%$, $p = 0.35$).

C. HOMA-IR

The pooled effect estimates of HOMA-IR were significantly increased in the PD compared to the controls in Figure 2C [MD = 0.64, 95% CI 0.64 (0.30, 0.99), $p = 0.0003$]. There was no heterogeneity in the included studies ($x^2 = 0.65$, $I^2 = 0\%$, $p = 0.42$).

D. Plasma renin activity

The pooled effect estimates showed that there was no statistical difference between the control and the PD groups in Figure 3A. However, there was an observational difference in favour of the PD compared to the control [MD = 0.16, 95% CI 0.16 (−0.13, 0.45), $p = 0.25$]. However, there was no heterogeneity in the selected research ($x^2 = 0.04$, $I^2 = 0\%$, $p = 0.85$).

E. Plasma aldosterone

There was no statistical significance between the PD and the control. Interestingly, the included studies demonstrated contradicting pooled estimates in Figure 3B. However, the overall estimates favoured the control compared to the PD [MD = −0.51, 95% CI −0.51 (−2.15, 1.12), $p = 0.54$]. The studies demonstrated moderate heterogeneity ($x^2 = 1.78$, $I^2 = 44\%$, $p = 0.18$).

F. Triglycerides

There was no statistical significance between the PD and the control. However, the selected studies displayed conflicting pooled estimates in Figure 4A. However, the overall estimates favoured the PD compared to the

Table 1. Overview characteristics of the included studies.

Authors, year	Study design Country	Population	Age (Years)	Glucose metabolism parameters	RAAS component reported	Link to the adipose	Main findings
La Sala et al. (2021) [47]	Original research Italy	205	40.6 ± 10.4	FPG (mg/dl) 107.6 ± 18.1 HbA1c (%) 6.2 ± 0.7, 2 HOMA-IR 4.9 ± 2.9	Upright PRA (ng/ml/h) 3.5 ± 5.2 Upright ALD (ng/dl) 7.2 ± 5.0	BMI (kg/m^2) 44.2 ± 5.7, Triglycerides (mg/dl) 144.9 ± 67.5	A significant increase in FPG was directly proportional to the upregulation of RAAS components, BMI and TGs
S.H. Min et al. (2017) [48]	Cross-sectional study Korea	156	57.1 ± 11.1	FPG (mg/dL) 109.1 ± 13.2 HbA1c (%) 6.0 ± 0.3 HOMA-IR 2.8 ± 1.2	PRA (ng/mL/h) 1.52 ± 1.0 ALD (ng/dL) 17.5 ± 5.8	BMI (kg/m^2) 24.3 ± 3.0 Triglycerides (mg/dL) 155.2 ± 89.7	The FPG, HbAlc and HOMA-IR were significantly increased in the prediabetic compared to the non-prediabetic group. Furthermore, the prediabetic group had significantly higher BMI and TGs when compared to the non-prediabetic group.

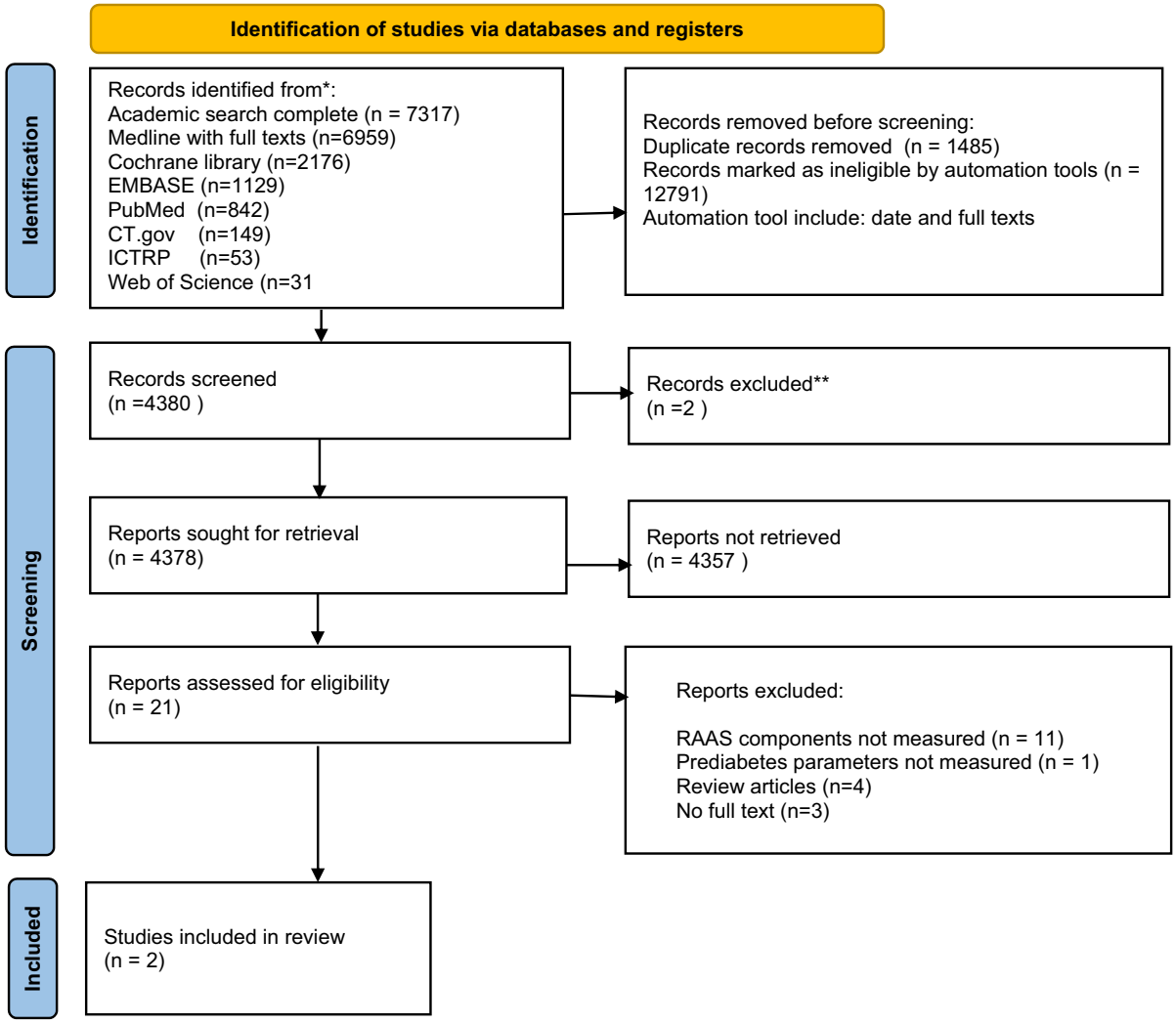


Figure 1. Preferred reporting items for systematic review and meta-analysis flow diagram of included studies.

control [MD = 7.84, 95% CI 7.84 (−9.84, 25.51), p = 0.38]. The studies demonstrated low heterogeneity (x^2 = 1.23, I^2 = 19%, p = 0.27).

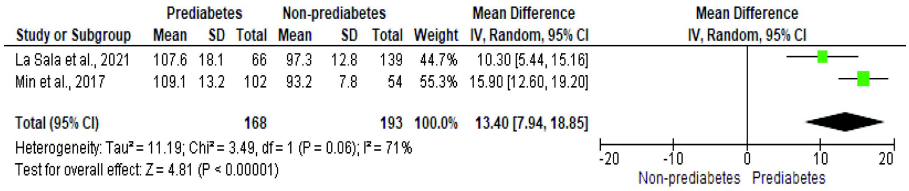
G. Body mass index (BMI)

There was no statistical significance between the PD and the control. However, the included studies demonstrated contradicting pooled estimates in Figure 4B. However, the overall estimates favoured the PD compared to the control [MD = 0.13, 95% CI 0.13 (−0.74, 0.99), p = 0.77]. The studies demonstrated no heterogeneity (x^2 = 0.01, I^2 = 0%, p = 0.92).

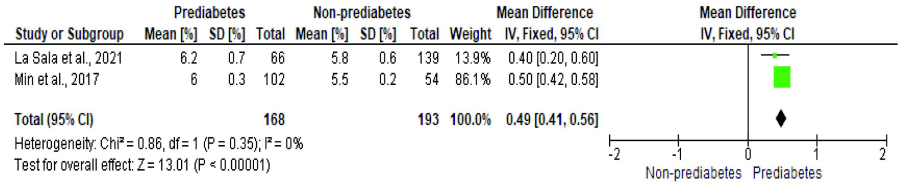
Discussion

The current study aims to systematically review the relationship between the renin-angiotensin-aldosterone system in prediabetes and the associated risk factors such as, insulin resistance, lipotoxicity, adiposity and obesity. The aim was achieved by conducting a meta-analysis of the markers, namely, fasting plasma glucose, plasma insulin, glycated haemoglobin, plasma renin, aldosterone, high-density lipoproteins, triglycerides and body mass index (BMI). The synthesized results of the current study showed that the PD had significantly higher levels of fasting plasma glucose compared to the control group. Furthermore, the plasma insulin and glycated haemoglobin of the PD were statistically significant in the PD compared to the control group. Elevated glycated haemoglobin and plasma glucose levels are associated with the upregulation of local RAAS and numerous comorbidities that are noted in type 2 diabetes (T2D) [49].

The RAAS is a well-known water and electrolyte balance system responsible for the long-term control of blood pressure [50]. Several studies have proven the relationship between T2D and RAAS [26]. More recent research has highlighted that this system is also locally



A) FPG



B) Glycated haemoglobin

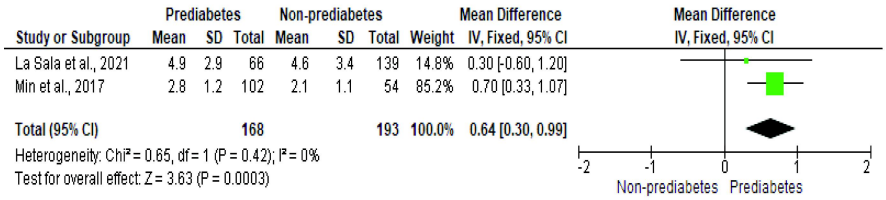


Figure 2. Glycaemic parameters. A) Fasting plasma glucose (FPG), B) glycated haemoglobin (HbAlc) and C) homeostatic model assessment of insulin resistance (HOMA-IR).

produced and active in multiple organs viz the adipose tissue [17,51]. In order for adipose tissue to mature properly and respond to caloric excess by expanding as intended, RAAS integrity is crucial [51]. The Ang II and AT2R interaction promotes preadipocyte differentiation and In humans, ATII generated by mature adipocytes has been demonstrated to suppress the differentiation of adipocyte precursors, lowering the fraction of tiny insulin-sensitive adipocytes [52]. This consequence might result in decreased adipose tissue capacity, a build-up of free fatty acids in other tissues and the development of insulin resistance [52]. This idea is reinforced by the fact that the expression of ATII-forming enzymes in adipose tissue is negatively associated with insulin sensitivity. Angiotensin II and aldosterone are the effector peptides of adipose RAAS that respond to overnutrition are upregulated in prediabetes [53]. The Ang II may directly induce adipocyte leptin release which is a satiety hormone that regulates food intake thus preventing overnutrition. Ang II has been found in rats to boost prostaglandin I2 synthesis in adipocytes, which encourages adipogenic differentiation of pre-adipocytes into mature adipocytes [54]. In humans, Ang II has been demonstrated to impede adipogenic development of primary cultured preadipocytes [55]. Ang II was found to boost the activity and transcription rate of glycerol-3-phosphate dehydrogenase and fatty acid synthase, two essential lipogenic enzymes, in both mouse 3T3 preadipocytes and human adipocytes [56]. Interstitial Ang II was also demonstrated to have tissue-specific effects on lipolysis in human adipose and tissue [57]. Aldosterone and mineralocorticoid receptor activation enhance the expression of proinflammatory adipokines, which decreases the expression of the insulin receptor and impairs insulin-induced glucose uptake [58,59]. Accordingly, the glucose parameters were statistically significant in this study. Interestingly there was no statistical difference between the control and the PD group of some parameters. These observations are inconclusive as a moderate heterogeneity was noted in the included studies. Renin which is the first protein of RAAS was assessed in the current study. The data revealed that there was no statistical difference between the 2 groups, however, there was an observational difference in favour of the PD. Additionally, there was no heterogeneity between the studies. Furthermore, the study that had a smaller sample size and weighed 4% had a large standard deviation consequently pulling the data to the left. Interestingly, the means of the included studies are indicative of increased renin activity when glucose levels and BMI are increased. The study by La Sala et al 2021 had increased renin activity in both the control and the PD group. The control group of that study had a BMI range of 44.0 ± 5.8 which fall in the obesity range. Obesity and hypertension are known risk factors for prediabetes and

T2D, due to insulin resistance and RAAS activity, which was demonstrated by La Sala et al 2021. Therefore, the data of the current study highlights the relationship between insulin resistance, and the risk factors of prediabetes such as obesity and increased triglycerides. Adipose RAAS as discussed affects the preadipocyte differentiation, hence the adipose tissue lipid buffering capacity resulting in increased triglycerides [51,60]. The data from the current study concurs with these reports as there was an observational difference in favour of the PD in comparison to the control group. Moreover, the study that pulled some of the data to the control had a sizable standard deviation, thus the study weighed 23.6% in contrast to the 73.6% of the study by La Sala et al. 2021 which indicated a significant increase in triglycerides in the PD compared to the control group. Research has outlined the positive correlation between overt hyperglycaemia, increased adipose and systemic RAAS activity and adipose tissue dysfunction which is evidenced by increased triglycerides [51,61]. Inherently, the same trend was noted in the current study. Triglycerides are directly proportional to BMI. Hence, in the current study the observational difference in favour of the PD that was noted with the triglycerides was also observed with the BMI. The observational differences noted in the current study are determined by the skewness of the forest plot and the Z-values which indicate the overall effect which indicate that some parameters are not statistically significant yet may have biological significance.

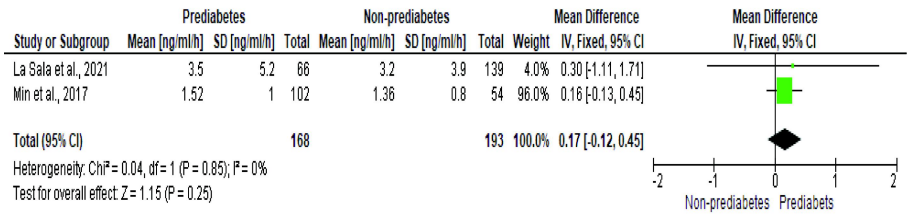
Study limitations

This systematic review and meta-analysis comprises only two studies; therefore, there was a paucity of data. Furthermore, due to the limited number of studies, where there was heterogeneity, subgroup analysis could not be conducted. Additionally, the included studies had a sizable standard deviation for some of the parameters which could be indicative of the inclusion of outliers by the authors.

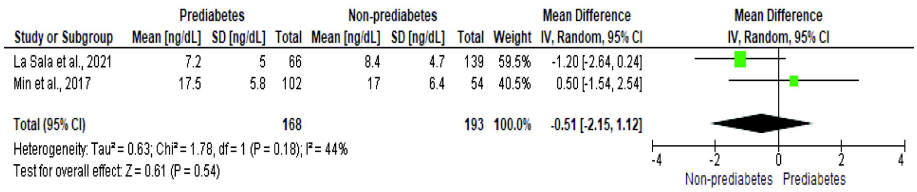
Conclusion

This systematic review and meta-analysis suggest a biological positive correlation between hyperglycaemia, insulin resistance, adipose tissue and the upregulation of RAAS in prediabetes and obesity, although there was no statistical difference between some of the parameters. In groups with a BMI in the obesity range, insulin resistance had increased renin activity. Furthermore, there was an observational difference in the renin activity in participants that had obesity and insulin resistance as evidenced by the mean values of renin exceeding the normal range. The renin, triglycerides, BMI and insulin resistance are directly proportional to each other which highlights that insulin resistance which is a predictor of PD and obesity is positively associated with RAAS. Additionally, studies which are not part of the quantitative instead inform of the qualitative aspect highlight significantly increased RAAS components, renin and aldosterone in the PD [29]. Furthermore, a study using the oral glucose tolerance test demonstrated a difference in RAAS activity between the participants who had normal glucose handling and impaired glucose tolerance and increased BMI [34].

As Figure 3A shows a trend of renin slightly higher in prediabetes group without any statistical significance, aldosterone is rather negatively associated with prediabetes. The data may suggest that adrenal

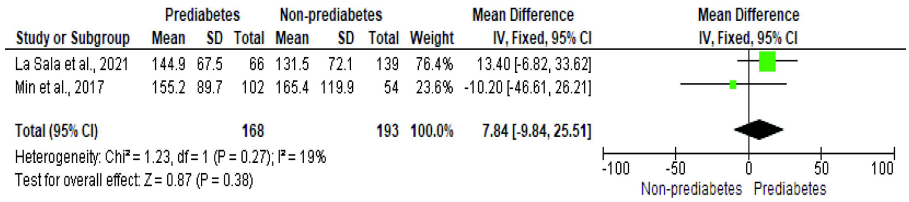


A) Renin

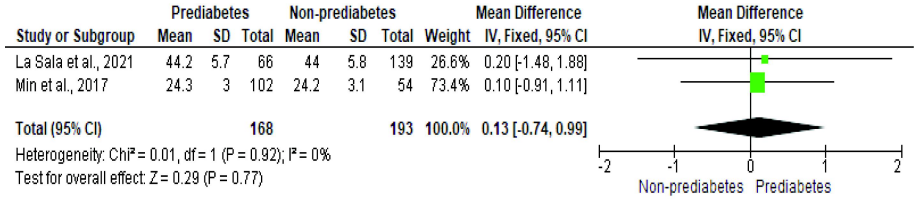


B) Aldosterone

Figure 3. Renin-angiotensin-aldosterone system (RAAS) components.



A) Triglycerides



B) Body mass index

Figure 4. Adipose tissue markers.

aldosterone production might be lower in prediabetes population. Therefore, renin might be higher in prediabetes, but there is no difference in aldosterone level between control and prediabetes populations. The observed aldosterone results might be attributed to the inclusion of patients undergoing anti-hypertensive therapy by the use of anti-hypertensive medication. The studies do not specify the type or mechanism of action of the RAAS blockers. However, the most common anti-hypertensive treatment is ACE blockers and therefore impairs the conversion of angiotensin I to Ang II. Additionally, other hypertensive medication includes angiotensin II type 1 receptor (AT1R) antagonists which target Ang II receptors, thus hindering the effects of Ang II which is a hormone that triggers aldosterone production.

Henceforth, the synthesized data suggests that adipose renin might be upregulated in impaired glucose handling, insulin resistance and obesity, resulting in the risk factors of prediabetes such as adiposity and lipotoxicity. The current study highlighted a paucity of clinical trials aimed at investigating adipose RAAS activity in prediabetes.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

All data relevant to the study are included in the article.

Ethics and dissemination

The systematic review and meta-analysis do not require ethics clearance since studies with non-identifiable data are used.

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References

[1] Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013;9(2):191. doi: 10.5114/aoms.2013.33181

[2] Moreno-Navarrete JM, Catalán V, Ortega F, et al. Circulating omentin concentration increases after weight loss. Nutr Metab (Lond). 2010;7(1):1–6. doi: 10.1186/1743-7075-7-27

[3] Wurm S, Neumeier M, Weigert J, et al. Plasma levels of leptin, omentin, collagenous repeat-containing sequence of 26-kDa protein (CORS-26) and adiponectin before and after oral glucose uptake in slim adults. Cardiovasc Diabetol. 2007;6(1):1–7. doi: 10.1186/1475-2840-6-7

[4] Zhou J-Y, Chan L, Zhou S-W. Omentin: linking metabolic syndrome and cardiovascular disease. Curr Vasc Pharmacol. 2014;12(1):136–143. doi: 10.2174/15701611129991402170950 38

[5] Yin L, Huang D, Liu X, et al. Omentin-1 effects on mesenchymal stem cells: proliferation, apoptosis, and angiogenesis in vitro. Stem Cell Res Ther. 2017;8(1):1–14. doi: 10.1186/s13287-017-0676-1
[6] Xu F, Fu-Xing-Zi Li XL, Zhong J-Y, et al. Adipose tissue-derived omentin-1 attenuates arterial calcification via AMPK/Akt signaling pathway. Aging. 2019;11(20):8760. doi: 10.18632/aging.102251
[7] Daneshafrooz A, Yuzbashian E, Zarkesh M, et al. The relation of omentin gene expression and glucose homeostasis of visceral and subcutaneous adipose tissues in non-diabetic adults. Mol Biol Rep. 2022;49(1):163–169. doi: 10.1007/s11033-021-06854-4
[8] Greulich S, Chen WJ, Maxhera B, et al. Cardioprotective properties of omentin-1 in type 2 diabetes: evidence from clinical and in vitro studies. PLoS One. 2013;8(3):e59697. doi: 10.1371/journal.pone.0059697
[9] Yanai H, Yoshida H. Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: mechanisms and perspectives. Int J Mol Sci. 2019;20(5):1190. doi: 10.3390/ijms20051190
[10] Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002;8(11):1288–1295. doi: 10.1038/nm788
[11] Wang Y, Li Y, Qiao J, et al. AMPK α1 mediates the protective effect of adiponectin against insulin resistance in INS-1 pancreatic β cells. Cell Biochem Funct. 2019;37(8):625–632. doi: 10.1002/cbf.3440
[12] As A. the association between omentin and diabetes: a systematic review and meta-analysis of observational studies. Diabetes Metab Syndr Obes: Targets Ther. 2019;12:1277. doi: 10.2147/DMSO.S206981
[13] Fruhwürth S, Vogel H, Schürmann A, et al. Novel insights into how overnutrition disrupts the hypothalamic actions of leptin. Front Endocrinol. 2018;9:89. doi: 10.3389/fendo.2018.00089
[14] Amitani M, Asakawa A, Amitani H, et al. The role of leptin in the control of insulin-glucose axis. Front Neurosci. 2013;7:51. doi: 10.3389/fnins.2013.00051
[15] Moonishaa TM, Nanda SK, Shamraj M, et al. Evaluation of leptin as a marker of insulin resistance in type 2 diabetes mellitus. Int J App Basic Med Res. 2017;7(3):176. doi: 10.4103/ijabmr.IJABMR_278_16
[16] Izquierdo AG, Crujeiras AB, Casanueva FF, et al. Leptin, obesity, and leptin resistance: where are we 25 years later? Nutrients. 2019;11(11):2704.
[17] Mkhize BC, Mosili P, Ngubane PS, et al. Diet-induced prediabetes: effects on the activity of the renin–angiotensin–aldosterone system in selected organs. J of Diabetes Invest. 2022;13(5):768–780. doi: 10.1111/jdi.13690
[18] Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10(1):1–11. doi: 10.1038/s41598-020-71908-9
[19] Shum M, Pinard S, Guimond M-O, et al. Angiotensin II type 2 receptor promotes adipocyte differentiation and restores adipocyte size in high-fat/high-fructose diet-induced insulin resistance in rats. Am J Physiol Endocrinol Metab. 2013;304(2):E197–E210.
[20] López-Jaramillo P, Pradilla LP, Lahera V, et al. A randomized, double blind, cross-over, placebo-controlled clinical trial to assess the effects of Candesartan on the insulin sensitivity on non diabetic, non hypertense subjects with dysglyce mia and abdominal obesity."ARAMIA". Trials. 2006;7(1):1–12. doi: 10.1186/1745-6215-7-28
[21] As´ Habi A, Sadeghi M, Arab A, et al. the association between omentin and diabetes: a systematic review and meta-analysis of observational studies. Diabetes Metab Syndr Obes. 2019;Volume 12:1277–1286. doi: 10.2147/DMSO.S206981
[22] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):1–11. doi: 10.1186/s13643-021-01626-4
[23] Subramanian SK, Caramba SM, Hernandez OL, et al., editors. Is the Downs and black scale a better tool to appraise the quality of the studies using virtual rehabilitation for post-stroke upper limb rehabilitation? 2019 International Conference on Virtual Rehabilitation (ICVR); Tel Aviv University, Tel Aviv, Israel. IEEE; 2019.
[24] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377–384. doi: 10.1136/jech.52.6.377
[25] Büttner F, Winters M, Delahunt E, et al. Identifying the 'incredible'! Part 2: Spot the difference-a rigorous risk of bias assessment can alter the main findings of a systematic review. Br J Sports Med. 2020;54(13):801–808. doi: 10.1136/bjsports-2019-101675
[26] von Hippel PT. The heterogeneity statistic I2 can be biased in small meta-analyses. BMC Med Res Methodol. 2015;15(1):1–8. doi: 10.1186/s12874-015-0024-z
[27] Patole S. Forest plots in a meta-analysis. principles and practice of systematic reviews and meta-analysis. Springer; 2021. pp. 79–88. doi: 10.1007/978-3-030-71921-0_8
[28] Alaagib N, Sukkar M, Kardash M. The effects of salt and glucose intake on angiotensin ii and aldosterone in obese and nonobese patients with essential hypertension. Int J Hypertens. 2020;2020:1–9. doi: 10.1155/2020/6017105
[29] Alphan Z, Berberoglu Z, Gorar S, et al. Increased total renin levels but not angiotensin-converting enzyme activity in obese patients with polycystic ovary syndrome. Med Princ Pract. 2013;22(5):475–479. doi: 10.1159/000351572
[30] Barbieri DE, Ribeiro-Filho FF, Ribeiro AB, et al. Diuretic-induced potassium depletion and glucose intolerance are not related to hyperactivity of the renin-angiotensin-aldosterone system in hypertensive patients with the metabolic syndrome. J Clin Hypertens. 2009;11(10):549–554.
[31] Dorresteijn JA, Schrover IM, Visseren FL, et al. Differential effects of renin–angiotensin–aldosterone system inhibition, sympathoinhibition and diuretic therapy on endothelial function and blood pressure in

obesity-related hypertension: a double-blind, placebo-controlled cross-over trial. J Hypertens. 2013;31 (2):393–403. doi: 10.1097/HJH.0b013e32835b6c02

[32] Engeli S, May M, Nussberger J, et al. Systemic and tissue-specific effects of aliskiren on the RAAS and carbohydrate/lipid metabolism in obese patients with hypertension. J Am Soci Hypertens. 2017;11 (8):488–497. doi: 10.1016/j.jash.2017.06.002

[33] Joseph JJ, Echouffo Tcheugui JB, Effoe VS, et al. Renin-angiotensin-aldosterone system, glucose metabolism and incident type 2 diabetes mellitus: MESA. J Am Heart Assoc. 2018;7(17):e009890. doi: 10.1161/JAHA.118.009890

[34] Srinivasa S, Fitch KV, Wong K, et al. RAAS activation is associated with visceral adiposity and insulin resistance among HIV-infected patients. J Clin Endocrinol Metab. 2015;100(8):2873–2882. doi: 10.1210/jc.2015-1461

[35] Brook RD, Bard RL, Kehrer C, et al. Valsartan improves insulin sensitivity without altering vascular function in healthy overweight adults without the metabolic syndrome. Metab Syndr Relat Disord. 2007;5(3):255–261.

[36] Choi GJ, Kim HM, Kang H, et al. Effects of telmisartan on fat distribution: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2016;32 (7):1303–1309. doi: 10.1185/03007995.2016.1171204

[37] Dadarlat A, Pop D, Procopciuc L, et al. Links between renin-angiotensin system genetic polymorphisms and leptin secretion in obese heart failure patients. Acta Endo (Buc). 2018;14(2):274. doi: 10.4183/aeb.2018.274

[38] Derosa G, Maffioli P, Ferrari I, et al. Different actions of losartan and ramipril on adipose tissue activity and vascular remodeling biomarkers in hypertensive patients. Hypertens Res. 2011;34(1):145–151. doi: 10.1038/hr.2010.205

[39] Moors CC, Blaak EE, van der Zijl NJ, et al. The effects of long-term valsartan treatment on skeletal muscle fatty acid handling in humans with impaired glucose metabolism. J Clin Endocrinol Metab. 2013;98(5): E891–E6. doi: 10.1210/jc.2012-4067

[40] Krikken J, Dallinga-Thie G, Navis G, et al. Short term dietary sodium restriction decreases HDL cholesterol, apolipoprotein AI and high molecular weight adiponectin in healthy young men: relationships with renal hemodynamics and RAAS activation. Nutr Metab Cardiovasc Dis. 2012;22(1):35–41. doi: 10.1016/j.numecd.2010.03.010

[41] Krum H, McMurray JJ, Horton E, et al. Baseline characteristics of the Nateglinide and Valsartan impaired glucose tolerance Outcomes Research (NAVIGATOR) trial population: comparison with other diabetes prevention trials. Cardiovasc Ther. 2010;28(2):124–132. doi: 10.1111/j.1755-5922.2010.00146.x

[42] Malmqvist K, Kahan T, Isaksson H, et al. Regression of left ventricular mass with captopril and metoprolol, and the effects on glucose and lipid metabolism. Blood Press. 2001;10(2):101–110.

[43] Morales E, Gutiérrez E, Caro J, et al. Beneficial long-term effect of aldosterone antagonist added to a traditional blockade of the renin–angiotensin–aldosterone system among patients with obesity and proteinuria. Nefrología (English Edition). 2015;35 (6):554–561.

[44] Quesada O, Claggett B, Rodriguez F, et al. Associations of insulin resistance with systolic and diastolic blood pressure: a study from the HCHS/SOL. Hypertension. 2021;78(3):716–725.

[45] Han SH, Lee S-J, Oh BC, et al. The additive beneficial effects of ramipril combined with candesartan in hypertensive patients on insulin resistance, plasma adiponectin. Korean Circ J. 2007;37(4):173–179. doi: 10.4070/kcj.2007.37.4.173

[46] van der Zijl NJ, Serné EH, Goossens GH, et al. Valsartan-induced improvement in insulin sensitivity is not paralleled by changes in microvascular function in individuals with impaired glucose metabolism. J Hypertens. 2011;29(10):1955–1962. doi: 10.1097/HJH.0b013e32834a7667

[47] La Sala L, Tagliabue E, Vieira E, et al. High plasma renin activity associates with obesity-related diabetes and arterial hypertension, and predicts persistent hypertension after bariatric surgery. Cardiovasc Diabetol. 2021;20(1):1–12. doi: 10.1186/s12933-021-01310-w

[48] Min SH, Kong SH, Lee J-E, et al. Association of angiotensin-II levels with albuminuria in subjects with normal glucose metabolism, prediabetes, and type 2 diabetes mellitus. J Diabetes Complications. 2017;31(10):1499–1505.

[49] Griffin T, Wall D, Browne G, et al. Associations between glycaemic control and activation of the renin-angiotensin-aldosterone system in participants with type 2 diabetes mellitus and hypertension. Ann Clin Biochem. 2018;55(3):373–384. doi: 10.1177/0004563217728964

[50] Remuzzi G, Perico N, Macia M, et al. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. Kidney Int. 2005;68: S57–S65.

[51] Marcus Y, Shefer G, Stern N. Adipose tissue renin–angiotensin–aldosterone system (RAAS) and progression of insulin resistance. Mol Cell Endocrinol. 2013;378(1–2):1–14.

[52] Cooper ME. The role of the renin-angiotensin-aldosterone system in diabetes and its vascular complications. Am J Hypertens. 2004;17(S2):16S–20S. doi: 10.1016/j.amjhyper.2004.08.004

[53] Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. Curr Hypertens Rep. 2013;15(1):59–70. doi: 10.1007/s11906-012-0323-2

[54] Thatcher S, Yiannikouris F, Gupte M, et al. The adipose renin–angiotensin system: role in cardiovascular disease. Mol Cell Endocrinol. 2009;302(2):111–117.

[55] Liang X, Sun J, Guan H, et al. Angiotensin II inhibits adipogenic differentiation and promotes mature adipocyte browning through the corepressor CtBP1. Biomedicines. 2022;10(12):3131.

[56] Kalupahana NS, Moustaid-Moussa N. The renin-angiotensin system: a link between obesity, inflammation and insulin resistance. Obesity Rev. 2012;13 (2):136–149.

[57] Goossens G, McQuaid S, Dennis A, et al. Angiotensin II: a major regulator of subcutaneous adipose tissue blood flow in humans. Journal Of Physiology. 2006;571(2):451–460.
[58] Tirosh A, Garg R, Adler GK. Mineralocorticoid receptor antagonists and the metabolic syndrome. Curr Hypertens Rep. 2010;12(4):252–257. doi: 10.1007/s11906-010-0126-2
[59] Igbekele AE, Jia G, Hill MA, et al. Mineralocorticoid receptor activation in vascular insulin resistance and dysfunction. Int J Mol Sci. 2022;23(16):8954. doi: 10.3390/ijms23168954
[60] Schütten MT, Houben AJ, de Leeuw PW, et al. The link between adipose tissue renin-angiotensin-aldosterone system signaling and obesity-associated hypertension. Physiology. 2017;32(3):197–209. doi: 10.1152/physiol.00037.2016
[61] Putnam K, Shoemaker R, Yiannikouris F, et al. The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. Am J Physiol Heart Circ Physiol. 2012;302(6):H1219–H30. doi: 10.1152/ajpheart.00796.2011