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THE ASSOCIATION OF CARDIOVASCULAR DISEASE AND TYPE 2 DIABETES IN ADULTS WITH ATOPIC DERMATITIS: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *Atopic dermatitis (AD) is one of the most common inflammatory diseases in medicine, associated with a broad patient burden of skin lesions, pruritus, and both allergic and non-allergic comorbidities.*

The aim: *This study aims to show about the association of cardiovascular disease and type 2 diabetes in adults with atopic dermatitis.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 169 articles, whereas the results of our search on SagePub brought up 60 articles. The results of the search conducted for the last year of 2014 yielded a total 41 articles for PubMed and 46 articles for SagePub. The result from title screening, a total 5 articles for PubMed and 20 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *The link between AD and other allergic diseases such as food allergies, allergic rhinitis, and asthma is well known. Recently, in addition to allergic diseases, research has been conducted on the relationship between AD and other diseases such as depression, alopecia areata, inflammatory bowel disease, and cardiovascular disease (CVD) and metabolic syndrome like type 2 diabetes.*

Keyword: *Atopic dermatitis, cardiovascular disease, type 2 diabetes.*

INTRODUCTION

Chronic inflammation is an important risk factor for cardiovascular disease (CVD). Chronic inflammatory diseases, such as systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease, may be associated with an increased risk of CVD. Eczema, which is also a chronic inflammatory disorder, appears to affect adults as well as children. Some studies associate eczema with CVD risk, probably through inflammation. However, several studies have reported null findings about eczema and CVD, so the association is still controversial. In addition, existing reports using population-based cohort studies are mainly from Western countries; no Japanese cohort study has investigated the association between eczema and risk of CVD.[1,2]

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with a heterogeneous and often variable constellation of symptoms and signs. The symptoms of AD include cutaneous itch and pain, sleep disturbance and fatigue, and mental health symptoms. The cutaneous signs of AD include erythema (redness), lichenification (accentuation of the skin lines from chronic rubbing), scaling, oozing or weeping, and prurigo (pickers) nodules. Together, these contribute toward profound functional disturbances that limit the ability to perform activities of daily living and cause psychosocial distress and stigma.[3,4]

However, AD appears to have effects that are not just “skin deep”. Many patients have comorbid infectious, autoimmune, respiratory, neuropsychiatric, musculoskeletal, and potentially even cardiovascular disorders. Some authors have wondered whether AD is a systemic disease, i.e. with global impact beyond the immediate skin signs and symptoms. This review will summarize recent developments in the understanding of the comorbid health disorders associated with AD.[3]

Atopic eczema, AD is a complex chronic inflammatory skin disease with diverse clinical manifestations and symptoms suffered by approximately 20% of children and 3% of adults worldwide, with the incidence still increasing. AD was proved to be a potential risk factor for several autoimmune diseases (OR = 1.97; 95% CI, 1.93–2.01) including T1D (OR = 1.08; 95% CI, 1.03–1.14). Wu et al. showed that the prevalence of T1D was significantly higher in patients with AD. In addition, AD directly increased the risk of metabolic diseases especially T2D after adjusting for age, sex, metabolic disorders and other CVD (HR = 2.96; 95% CI, 2.56–3.41, $P < 0.001$). In multivariate models controlling for socio-demographic characteristics, smoking history, drinking history and strenuous activity, AD was still associated with a higher risk of diabetes (OR, 1.37; 95% CI, 1.16–1.63). However, the causal relationship between AD and diabetes remains controversial, which makes it indispensable and significant to verify the relationship between AD and diabetes.[5,6]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast the association of cardiovascular disease and type 2 diabetes in adults with atopic dermatitis. It is possible to accomplish this by researching or investigating the association of cardiovascular disease and type 2 diabetes in adults with atopic dermatitis. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the association of cardiovascular disease and type 2 diabetes in adults with atopic dermatitis. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " the association of cardiovascular disease and type 2 diabetes in adults with atopic dermatitis.” as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((*"Cardiovascular disease*"[MeSH Subheading] OR "*risk factor of cardiovascular disease*"[All Fields] OR "*type 2 diabetes*" [All Fields]) AND (*"risk factor of type 2 diabetes*"[All Fields] OR "* Atopic dermatitis *"[All Fields]) AND (*"Mechanism of atopic dermatitis*"[All Fields]) OR (*"Complications of atopic dermatitis” *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

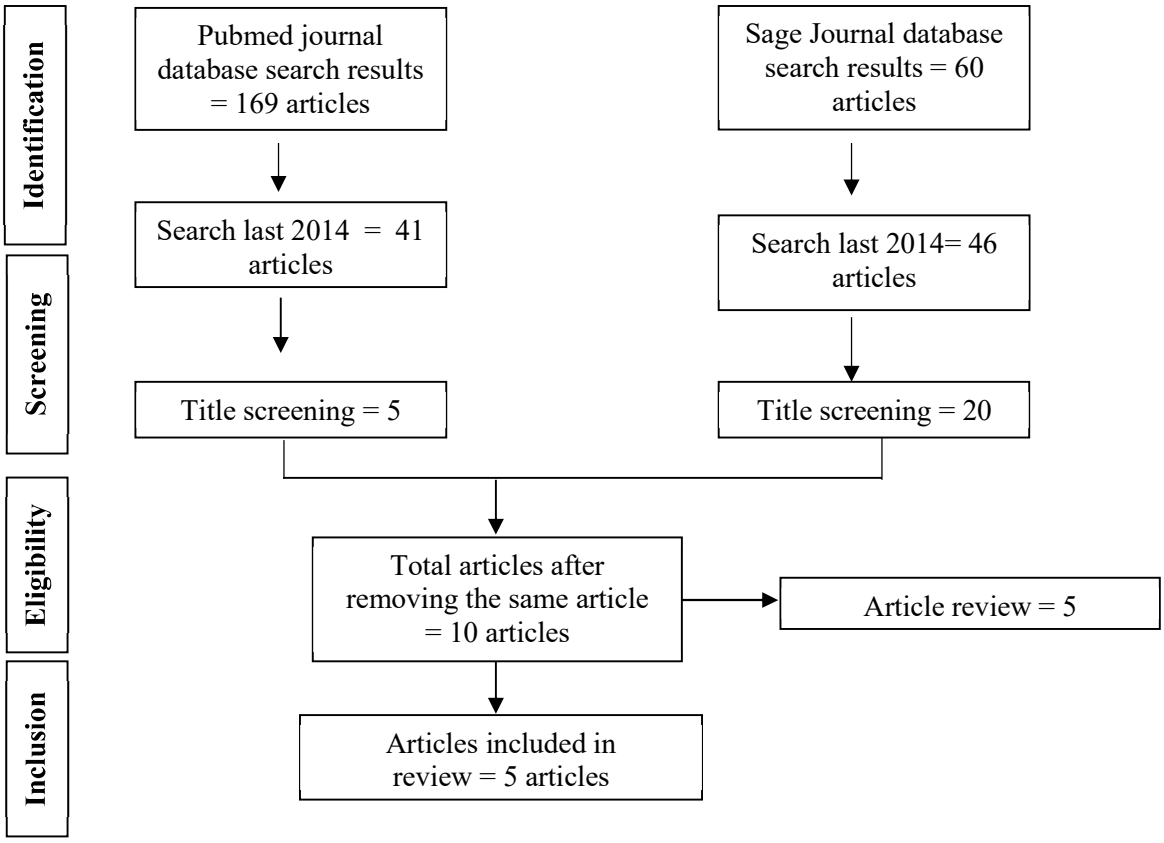

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 169 articles, whereas the results of our search on SagePub brought up 60 articles. The results of the search conducted for the last year of 2014 yielded a total 41 articles for PubMed and 46 articles for SagePub. The result from title screening, a total 5 articles for PubMed and 20 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Hedderson, MM *et al* (2022)[7] showed Among patients with moderate-to-severe AD in an integrated health care system, IRs per 1000 person-years were highest for MACE (2.6), followed by VTE (2.0), DVT (1.6), and PE (0.7). IRs were higher for older versus younger patients, patients with diabetes versus patients without, former smokers versus patients who had never smoked, and men versus women, except for PE, which was higher in women. Although patients with AD have been found to be at an increased risk for several CV safety events compared with patients without AD, prior studies

did not report IRs of the events among patients with moderate-to-severe AD. Therefore, the current data provided by this retrospective cohort study of patients enrolled in the KPNC health system fill a gap in the scientific literature about the incidence of CV events in patients with moderate-to-severe AD and provide valuable information for ongoing clinical trials as well as clinicians caring for patients with moderate-to-severe AD.

Brunner, PM *et al* (2017)[8] showed characterized a blood AD signature that is profoundly different from psoriasis. This profile helps to better understand cardiovascular risk in AD, and might also aid in identifying biomarkers to monitor therapeutic responses. Targeted therapeutic blockade of specific immune axes, e.g. Th17/IL-23 in psoriasis or Th2 in AD, is needed to assess the contribution of polar cytokine activation to overall systemic inflammation, and its effect on cardiovascular comorbidity and biomarkers. These studies should also assess whether biomarkers are modifiable risk factors responsive to treatment, as suggested by their decline with cyclosporine A treatment in severe chronic AD.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Hedderson, MM *et al*., 2022[7]	USA	A retrospective cohort study	8197	Among 8197 patients with moderate-to-severe atopic dermatitis, incidence rates per 1000 person-years (95% confidence interval) for major adverse cardiovascular events, venous thrombotic events, deep vein thrombosis, and pulmonary embolism were: 2.6 (2.1–3.2), 2.0 (1.5–2.5), 1.6 (1.2–2.1), and 0.7 (0.5–1.0), respectively. Incidence rates for all events were higher for older versus younger patients, patients with versus without diabetes, former smokers versus patients who had never smoked, and men versus women, except for pulmonary embolisms, which were higher in women. This study estimated the incidence of cardiovascular events in patients with moderate-to-severe atopic dermatitis and provides valuable information for clinicians.
Brunner, PM *et al*., 2017[8]	USA	A cohort study	59	We used an OLINK high-throughput proteomic assay to analyze moderate-to-severe AD (n = 59) compared to psoriasis (n = 22) and healthy controls (n = 18). Compared to controls, 10 proteins were increased in serum of both diseases, including Th1 (IFN-γ, CXCL9, TNF-β) and Th17 (CCL20) markers. 48 proteins each were uniquely upregulated in AD and psoriasis. Consistent with skin expression, AD serum showed up-regulation of Th2 (IL-13, CCL17, eotaxin-1/CCL11, CCL13, CCL4, IL-10), Th1 (CXCL10, CXCL11) and Th1/Th17/Th22 (IL-12/IL-23p40) responses. Surprisingly, some markers of

				atherosclerosis (fractalkine/CX3CL1, CCL8, M-CSF, HGF), T-cell development/activation (CD40L, IL-7, CCL25, IL-2RB, IL-15RA, CD6) and angiogenesis (VEGF-A) were significantly increased only in AD. Multiple inflammatory pathways showed stronger enrichment in AD than psoriasis. Several atherosclerosis mediators in serum (e.g. E-selectin, PI3/elafin, CCL7, IL-16) correlated with SCORAD, but not BMI. Also, AD inflammatory mediators (e.g. MMP12, IL-12/IL-23p40, CXCL9, CCL22, PI3/Elafin) correlated between blood and lesional as well as non-lesional skin.
Silverwood, RJ *et al*., 2018[9]	UK	Population based matched cohort study.	387439	387 439 patients with atopic eczema were matched to 1 528 477 patients without atopic eczema. The median age was 43 at cohort entry and 66% were female. Median follow-up was 5.1 years. Evidence of a 10% to 20% increased hazard for the non-fatal primary outcomes for patients with atopic eczema was found by using Cox regression stratified by matched set. There was a strong dose-response relation with severity of atopic eczema. Patients with severe atopic eczema had a 20% increase in the risk of stroke (hazard ratio 1.22, 99% confidence interval 1.01 to 1.48), 40% to 50% increase in the risk of myocardial infarction, unstable angina, atrial fibrillation, and cardiovascular death, and 70% increase in the risk of heart failure (hazard ratio 1.69, 99% confidence interval 1.38 to 2.06). Patients with the most active atopic eczema (active >50% of follow-up) were also at a greater risk of cardiovascular outcomes. Additional adjustment for cardiovascular risk factors as potential mediators partially attenuated the point estimates, though associations persisted for severe atopic eczema.
Smirnova, J *et al*., 2020[10]	Sweden	a population-based cross-sectional study	78004	AD was self-reported by 4,175 respondents, representing almost 14% of the study

				population of 34,313 adults. Our results showed positive associations between AD and chronic health disorders, including conditions of the oral cavity: chronic obstructive pulmonary disease (adjusted odds ratio [aOR] = 1.58, 95% confidence interval [CI]: 1.30 to 1.92), asthma (aOR = 2.13, 95% CI: 1.91 to 2.38), mild recurrent gastrointestinal symptoms (adjusted relative risk ratio [aRRR] = 1.78, 95% CI: 1.64 to 1.92), high blood pressure (aOR = 1.16, 95% CI: 1.06 to 1.26), obesity (aOR = 1.34, 95% CI: 1.23 to 1.47), mild joint pain (aRRR = 1.47, 95% CI: 1.35 to 1.61), mild headache or migraine (aRRR = 1.50, 95% CI: 1.38 to 1.64), caries (aOR = 1.25, 95% CI: 1.04 to 1.49), bleeding gums (aOR = 1.69, 95% CI: 1.38 to 2.08), periodontitis (aOR = 1.42, 95% CI: 1.13 to 1.77), sensitive teeth (aOR = 1.57, 95% CI: 1.35 to 1.82), and dry mouth (aOR = 1.52, 95% CI: 1.33 to 1.74). Adjustment for asthma and depression attenuated the magnitude of the associations between AD and the study outcomes. AD was also associated with poorer general psychological wellbeing.
Drucker, AM *et al*., 2017[11]	USA	A cross - sectional analysis	303270	AD was reported by 21,379 (8.4%) participants. A total of 52,787 cases of hypertension, 12,739 cases of T2D, 4,390 cases of MI and 2,235 cases of stroke were reported by participants at enrollment. In the multivariabl e -adjusted model, AD was associated with decreased odds (OR, 95% CI) of hypertension (0.87, 0.83 - 0.90), T2D (0.78, 0.71 -0.84), MI (0.87, 0.75 -1.00) and stroke (0.79, 0.66 -0.95) .

Silverwood, RJ *et al* (2018)[9] showed Severe and predominantly active atopic eczema are associated with an increased risk of cardiovascular outcomes. Targeting cardiovascular disease prevention strategies among these patients should be considered.

Smirnova, J *et al* (2020)[10] showed Adults reporting AD may be at increased risk of chronic disorders and decreased psychological wellbeing. Physicians should recognize that individuals with severe AD and those with comorbid asthma or depression may be especially vulnerable.

Driucker, AM *et al* (2017)[11] showed that they not find evidence of a positive association between AD and subsequent hypertension, T2D, MI or stroke ; AD was inversely associated with these outcomes in our study. Given our findings and the conflicting literature, AD is likely not a major risk factor for cardiovascular disease.

DISCUSSION

Atopic dermatitis (AD) is a common chronic relapsing inflammatory dermatosis with an estimated prevalence of up to 10%. The age distribution of AD shows a bimodal peak, with the first one in early childhood and the second one in middle-aged and older individuals. Recently, the systemic nature of AD has attracted interest, focusing on the comorbidities of patients with AD.[12,13]

Evidence has proven an association between AD and a variety of comorbidities, including asthma, hay fever, food allergies, anxiety, depression, suicidality, obesity, and cardiovascular disease. Recently, chronic inflammation in several skin diseases was associated with cardiovascular events. Therefore, it is necessary to determine the association between AD and cardiovascular disease. Among various cardiovascular disorders, myocardial infarction (MI) is a common cardiogenic emergency characterized by the necrosis of the myocardium due to the cessation of blood supply and is closely associated with significant mortality. A recent study by Thyssen *et al.* reported an increased risk of mortality in patients with AD due to cardiovascular disease compared to controls. Therefore, identifying risk factors and preventing MI and mortality is very important in patients with AD to reduce the disease burden.[12,14]

Atopic dermatitis (AD) is common and may affect 20% of the general population depending on age and geographical location and AD is not only a disease of childhood as previously thought. It is thought of as a systemic disease and is associated with various diseases including DM. The demarcation between type 1 and type 2 diabetes is currently hazy, type 2 diabetes is increasingly observed in the young age group, and more cases of type 1 diabetes are observed among adults. The association between AD and DM is a matter of controversy. Besides, it might be difficult to differentiate between the two most common types of DM at least during the early presentation.[15]

CONCLUSION

The link between AD and other allergic diseases such as food allergies, allergic rhinitis, and asthma is well known. Recently, in addition to allergic diseases, research has been conducted on the relationship between AD and other diseases such as depression, alopecia areata, inflammatory bowel disease, and cardiovascular disease (CVD) and metabolic syndrome like type 2 diabetes. Among them, the relationship between CVD, metabolic syndrome, and AD is interesting because it indicates that AD is an inflammatory disease beyond the skin and could threaten one's life.

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