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CLINICAL REPORT

A Population- and Hospital-based Cross-sectional Study of Renal Function in Hidradenitis Suppurativa

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The chronic inflammatory skin diseases hidradenitis suppurativa (HS) and psoriasis have been linked to cardiovascular risk factors and the latter has also been linked to possible renal dysfunction. Since basement membrane thinning in the skin of HS patients has been described, we speculated whether similar basement membrane defects might occur in renal tissue. Our objective was to investigate a possible association between HS and renal dysfunction. We performed a hospital and population-based cross-sectional study using estimated Glomerular-Filtration-Rate (eGFR) to assess renal function. Thirty-two hospital individuals with HS, 430 population individuals with HS, and 20,780 population individuals without HS (controls) were identified. The age-, sex-, smoking-, BMI-, hypertension- and diabetes-adjusted analysis revealed a statistically significant higher eGFR for the hospital group with HS and a mean difference in eGFR of 6.81 (1.27–12.35) ml/min/1.73 m^2 between the hospital group with HS and the population group without HS. The observed higher eGFR in the hospital group with HS indicates a possible association of HS and renal dysfunction.
Key words: co-morbidities; epidemiology; estimated glomerular filtration rate (eGFR); hidradenitis suppurativa (HS); hyperfiltration; inflammation.

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During the last decade evidence that chronic inflammatory skin diseases may be linked to systemic disorders has accumulated. For example, psoriasis has been linked to metabolic syndrome and cardiovascular disease, and recently also to renal dysfunction (1–4).

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder, which manifests itself as recurrent painful deep-seated boils and fistulae in apocrine gland-bearing skin, i.e. axillae and groin with subsequent scarring (5, 6). A population-based prevalence of 2.1% has been reported (7), and an association to metabolic syndrome has been described (8–10). Furthermore, basement membrane thinning in the skin of HS patients has been suggested (11). It may be speculated that a similar defect can occur in other tissues, e.g. renal tissue, where a disturbance of the glomerular basement membrane may promote hyperfiltration.

We therefore hypothesised that HS may be associated with renal dysfunction independent of traditional risk factors, i.e. overweight, hypertension and diabetes, and have therefore investigated a possible association between HS and renal dysfunction taking advantage of the Danish General Suburban Population Study (GESUS), a cross-sectional study of the adult Danish general suburban population in Naestved Municipality (70 km south of Copenhagen) (12), and a hospital HS group recruited from the outpatient clinic at the Department of Dermatology at Roskilde Hospital in Denmark (serving the region of Zealand which includes Naestved).

MATERIALS AND METHODS (Appendix S1[1])

RESULTS

The data used from GESUS were within the period January 1, 2010 to October 10, 2013. A total of 32 individuals in the hospital HS group, 430 individuals in the population HS group, and 20,780 individuals in the population non-HS group (controls) were identified. The background factors and characteristics of the HS group and the non-HS group showed that the HS groups were predominately younger, female and smokers (Table SI[1]).

Renal function assessed by estimated glomerular filtration rate

The unadjusted analysis revealed a statistically significant mean difference (MD) of 17.61 ml/min/1.73 m^2 (95% CI 11.10–24.13) ($p < 0.0001$) for the hospital HS group vs. non-HS group, and a statistically significant MD of 6.42 ml/min/1.73 m^2 (95% CI 4.63–8.22) ($p < 0.0001$) for the population HS group vs. the non-HS group (Tables SII and SIII[1]).

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The age-, sex- and smoke-adjusted analysis revealed a mean eGFR of 94.63 ml/min/1.73 m^2 (95% CI 89.99–99.27) for the hospital HS group, 88.00 ml/min/1.73 m^2 (95% CI 86.72–89.29) for the population HS group, and 88.41 ml/min/1.73 m^2 (95% CI 88.10–88.71) for the population non-HS group. Thus, yielding a statistically significant age-, sex- and smoke-adjusted MD of 6.22 ml/min/1.73 m^2 (95% CI 0.92–11.53) ($p > 0.0172$) for the hospital HS group vs. the non-HS group, and a statistically non-significant age-, sex- and smoke-adjusted MD of –0.40 ml/min/1.73 m^2 (95% CI –1.87–1.06) ($p = 0.7866$) for the population HS group vs. the non-HS group (Tables SII and SIII[1]).

The age-, sex-, smoke-, BMI-, hypertension- and diabetes-adjusted analysis revealed a mean eGFR of 95.53 ml/min/1.73 m^2 (95% CI 90.66–100.40) for the hospital HS group, 90.25 ml/min/1.73 m^2 (95% CI 88.55–91.96) for the population HS group, and 88.72 ml/min/1.73 m^2 (95% CI 88.10–89.34) for the population non-HS group. Thus, yielding a statistically significant age-, sex-, smoke-, BMI-, hypertension- and diabetes-adjusted MD of 6.81 ml/min/1.73 m^2 ((95% CI 1.27–12.35) ($p = 0.0119$) for the hospital HS group vs. the non-HS group, and a statistically non-significant age-, sex-, smoke-, BMI-, hypertension- and diabetes-adjusted MD of 1.53 ml/min/1.73 m^2 (95% CI –0.35–3.41) ($p = 0.1322$) for the population HS group vs. non-HS group (Fig. 1, Tables SII and SIII[1]).

Stratifying eGFR levels according to chronic kidney disease (CKD) stages revealed a statistically higher frequency of eGFR>=90 ml/min/1.73 m^2 in HS groups compared to the non-HS group (Table SII[1]).

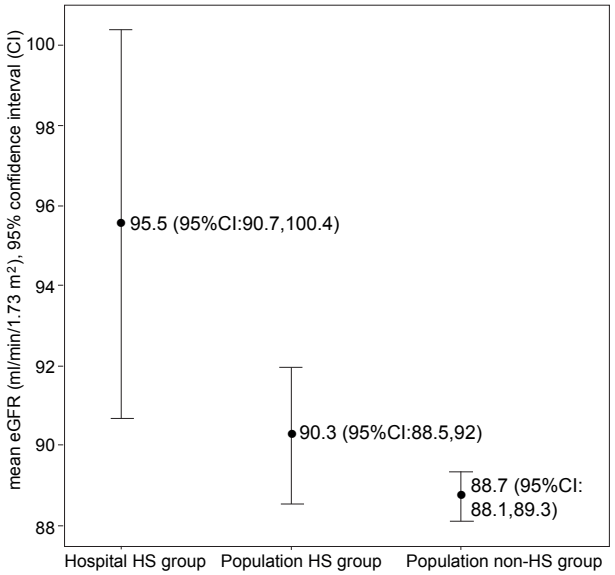

Fig. 1. Age-sex-smoking-BMI-hypertension-diabetes-adjusted eGFR mean values (95%CI) for the hospital HS- group, population HS- group, and population non-HS- group. The Mean Difference between the hospital HS group and non-HS group was 6.81 ml/min/1.73 m^2 ($p = 0.0119$), and the Mean Difference for the population HS group vs. the non-HS group was 1.53 ml/min/1.73 m^2 ($p = 0.1322$).

With regard to a possible association between HS severity degree and eGFR we found diverging results; a statistically significant association between the 3 HS severity degrees and eGFR; the more severe the HS was, the higher eGFR was (Table SIV[1]).

In contrast, the association between number of boils and eGFR was statistically non-significant ($p = 0.1307$). Similarly, the association between Sartorius score and eGFR was statistically non-significant ($p = 0.1996$).

Lastly, an age-, sex-, and smoking-adjusted subgroup analysis of severe population-based HS group ($n = 93$) only, revealed no difference in eGFR when compared to the non-HS group ($p = 0.598$).

DISCUSSION

The body of literature describing renal complications in chronic cutaneous inflammation is scarce, but renal dysfunction has been described in patients with psoriasis (4). To the best of our knowledge the association of HS and renal dysfunction is a hitherto unexplored topic.

We found that eGFR was higher for both the hospital and population-based HS groups when compared to the non-HS group (controls). When adjusting for background factors and possible confounders, the eGFR was only significantly higher in the hospital HS group vs. the non-HS group. Individuals recruited from a hospital outpatient clinic is more likely to represent severe skin disease than individuals recruited from the general population. This is supported by the distribution of severity observed in this study (Table SI[1]). According to Hills causal criteria in epidemiology a possible dose-response relationship favours causality. The fact that the hospital HS group (i.e. predominantly severe HS) has a higher eGFR when compared to the population HS group (ie. mild–severe HS) may thus suggest a causal relationship between HS and eGFR. Supportive of this we found a direct relationship between HS severity degree and eGFR. However, the results must be seen in light of a possible selection bias, i.e. the hospital and population HS groups may also represent certain subgroups or subtypes of HS and the inclusion criteria of the two HS groups varied.

The observed higher eGFR in the hospital HS group remains after adjusting for potential confounders including elements of the metabolic syndrome, suggesting that the HS comorbidities may not entirely explain the higher eGFR.

A histology study of skin samples from 20 HS patients suggested a structural defect of the basement membrane zone in the folliculopilosebaceous unit (11). We speculated that a similar defect could occur in other tissues, e.g. renal tissue, where a similar thinning of glomerular basement membrane may promote glomerular hyperfiltration, and subsequent augmented eGFR and proteinuria.

An association between the metabolic syndrome (MetS) and CKD as well as HS has been demonstrated

(8–10, 15–18). MetS is a cluster of cardiovascular risk factors, i.e. insulin resistance/diabetes, dyslipidemia, hypertension, and obesity. Glomerular hypertension and hyperfiltration is a recognised early change in subjects with diabetes and hypertension (19, 20). Dyslipidemia seems to damage podocyte function leading to protein leakage (21) and accumulation of lipids in the glomerular capillary endothelial and mesangial cells may stimulate local inflammation leading to chronic nephropathy (22, 23). Obesity-related nephropathy appears to include an increased renal blood flow, augmentation of GFR, and proteinuria as well as vascular changes resulting from renal hyperfiltration and hyperperfusion (24–26).

The treatment regime of HS include systemic cyclosporine and rifampicin, both known to be associated with risk of kidney injury, although the latter very rarely (27–29).

Chronic inflammation may interlink atherosclerosis, MetS, CKD, and HS (26, 30–33). The inflammatory cytokine TNF-alpha, which has been linked to HS pathogenesis, induces mineralisation of vascular cells *in vitro* (34), appears to induce apoptosis of renal cells (35), and progression of diabetic nephropathy (36). Thus, chronic inflammation in HS may mediate renal vascular change and apoptosis of renal cells with subsequent alterations in renal function.

No commonly acknowledged definition of glomerular hyperfiltration exists (37). However, several studies set the threshold for hyperfiltration from 125 to 175 ml/min/1.73 m^2 (37). Glomerular hyperfiltration has been observed as a physiological response as well as a pathological sign (37).

Although the traditional perception of renal dysfunction reduced renal flow and low eGFR, an increased GFR can be an expression of early manifestations of a renal dysfunction.

Both the association of eGFR with cardiovascular risk and mortality appear U-shaped (38, 39), i.e. both low and high eGFR may be predictive of increased mortality and cardiovascular risk. The finding may be biased by muscle waisting in chronic disease/malnutrition/cachexia with subsequent low muscle mass, low creatinine and high eGFR. However, a recent study adjusting for muscle mass found renal hyperfiltration to be a possible novel marker for all-cause mortality (40). Additionally, a Hazard ratio for all-cause mortality of 1.29 (1.19–1.41) for patients with high eGFR (90–119 ml/min) and an odds ratio of 1.49 (1.05–2.09) for carotide intima media thickness in high eGFR (101.2–138.6 ml/min) have been reported (38, 39). Animal models indicate that loss of nephrons induce an adaptive response with increased intraglomerular pressure, glomerular hypertrophy, and compensary glomerular hyperfiltration in the spared nephrons with subsequent secondary glomerulosclerosis (35).The higher eGFR demonstrated in the hospital HS group may thus reflect the earliest signs of renal dysfunction. Our study may have identified early as opposed to end-stage HS-related kidney damage, only because the HS individuals are relatively young with a mean age of 42 years.

In aggregate, possible association between HS and renal dysfunction could in theory occur via one or several of the following mechanisms: 1) HS-basement membrane nephropathy, 2) co-morbidities (i.e. MetS), 3) treatment-associated nephrotoxicity, or 4) chronic inflammatory-associated nephropathy.

The major strengths of our study are the large number of population HS individuals and the broad inclusion of both hospital- and population HS individuals reducing selection bias and adding a broader range of disease severity aiding the generalisation. The HS diagnosis has previously been validated yielding a sensitivity of 90% and a specificity of 97% providing information on misclassification bias (7). As the self-reported questions used to identify the population HS group refer to symptoms (i.e. boils) rather than the actual diagnosis (i.e. do you suffer from HS?), possible undiagnosed HS subjects were included. The diagnosis of the hospital HS group was physician-verified, and possible confounders were explored.

Potential limitations should be considered. First, it is crucial to recognise that as this study is cross-sectional, we cannot prove causality. Furthermore, the population is suburban, Caucasian and underrepresenting the age group 20–30, which may limit the generalisability. Additionally, background factors differered between the HS groups and non-HS group; however, statistical adjustments accordingly were made. The low participation rate of the hospital HS group reduced power, and may furthermore have resulted in selection bias, e.g. only the healthiest HS patients may have participated whereas the most mentally and physically burdened patients did not have the resources to participate in GESUS potentially excluding the HS patients with the most burdensome co-morbidities. We did not include information on HS medical treatment or known renal disease. Additionally, urine analysis for protein leakage was not performed. The method of estimating GFR should be questioned as the CKD-EPI equation (see Appendix S1[1]) expresses the kidney function as a body surface area indexed value (ml/min/1.73 m^2), which might underestimate eGFR in patients with extreme body sizes (12). As HS is associated with obesity, eGFR for HS subjects may be underestimated. However, we adjusted for BMI.We used CKD-EPI since it is the best validated method of estimating GFR. Furthermore, as the non-HS population (controls) has a relatively high mean age, this could indicate low muscle mass, low creatinine, overestimation of eGFR and subsequent underestimation of the difference in eGFR between the HS group and non-HS group. CKD-EPI is, however, validated up to 80 years. As with any questionnaire survey there is a risk of recall bias.

In conclusion, the observed higher eGFR amongst the hospital-based HS subjects indicates a possible association of HS and renal dysfunction. As this is the first study of its kind, it may be too speculative to suggest clinical implications such as routine renal screening i.e. eGFR and urine analysis.

Future studies are warranted to confirm or reject our results, preferably including a urine analysis for protein leakage and using a follow-up study design. Furthermore, experimental studies on the mechanisms promoting a possible renal dysfunction in HS are needed possibly using kidney biopsies.

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REFERENCES

1. Miller IM, Jemec G. Maturation of an idea: a historical perspective on the association of psoriasis with the metabolic syndrome and cardiovascular disease. Arch Dermatol 2012; 148: 112.
2. Miller IM, Skaaby T, Ellervik C, Jemec GB. Quantifying cardiovascular disease risk factors in patients with psoriasis: a meta-analysis. Br J Dermatol 2013; 169: 1180–1187.
3. Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. J Am Acad Dermatol 2013; 69: 1014–1024.
4. Dervisoglu E, Akturk AS, Yildiz K, Kiran R, Yilmaz A. The spectrum of renal abnormalities in patients with psoriasis. Int Urol Nephrol 2012; 44: 509–514.
5. Jemec GB. Clinical practice. Hidradenitis suppurativa. N Engl J Med 2012; 366: 158–164.
6. Fimmel S, Zouboulis CC. Comorbidities of hidrdaenitis suppurativa (acne inversa). Dermatoendocrinol 2010; 2: 9–16.
7. Vinding GR, Miller IM, Zarchi K, Ibler KS, Ellervik C, Jemec GB. The prevalence of inverse recurrent suppuration: a population-based study of possible hidradenitis suppurativa. Br J Dermatol 2014; 170: 884–889.
8. Sabat R, Chanwangpong A, Schneider-Burrus S, Metternich D, Kokolakis G, Kurek A, et al. Increased prevalence of metabolic syndrome in patients with acne inversa. PloS One 2012; 7: e31810.
9. Gold DA, Reeder VJ, Mahan MG, Hamzavi IH. The prevalence of metabolic syndrome in patients with hidradenitis suppurativa. J Am Acad Dermatol 2014; 70: 699–703.
10. Miller IM, Ellervik C, Vinding GR, Zarchi K, Ibler KS, Knudsen KM et al. Association of metabolic syndrome and Hidradenitis Suppurativa. JAMA Dermatology. 2014; 150: 1273–1280.
11. Danby FW, Jemec GB, Marsch WC, von Laffert M. Preliminary findings suggest hidradenitis suppurativa may be due to defective follicular support. Br J Dermatol 2013; 168: 1034–1039.
12. Bergholdt HK, Bathum L, Kvetny J, Rasmussen DB, Moldow B, Hoeg T, et al. Study design, participation and characteristics of the Danish General Suburban Population Study. Dan Med J 2013; 60: A4693.
13. Redal-Baigorri B, Rasmussen K, Heaf JG. The use of absolute values improves performance of estimation formulae: a retrospective cross sectional study. BMC Nephrology 2013; 14: 271.
14. Sartorius K, Lapins J, Emtestam L, Jemec GB. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. Br J Dermatol 2003; 149: 211–213.
15. Singh AK, Kari JA. Metabolic syndrome and chronic kidney disease. Curr Opin Nephrol Hypertens 2013; 22: 198–203.
16. Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2011; 6: 2364–2373.
17. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 2005; 16: 2134–2140.
18. Yoon YS, Park HS, Yun KE, Kim SB. Obesity and metabolic syndrome-related chronic kidney disease in nondiabetic, nonhypertensive adults. Metabolism 2009; 58: 1737–1742.
19. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S. Glomerular hyperfiltration in prediabetes and prehypertension. Nephrol Dial Transplant 2012; 27: 1821–1825.
20. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int 1996; 49: 1774–1777.
21. Cases A, Coll E. Dyslipidemia and the progression of renal disease in chronic renal failure patients. Kidney Int Suppl 2005: S87–S93.
22. Gluba A, Mikhailidis DP, Lip GY, Hannam S, Rysz J, Banach M. Metabolic syndrome and renal disease. Int J Cardiol 2013; 164: 141–150.
23. Carrero JJ, Stenvinkel P. Persistent inflammation as a catalyst for other risk factors in chronic kidney disease: a hypothesis proposal. Clin J Am Soc Nephrol 2009; 4 Suppl 1: S49–S55.
24. Kasiske BL, Crosson JT. Renal disease in patients with massive obesity. Arch Int Med 1986; 146: 1105–1109.
25. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. Hypertension 1995; 26: 610–615.
26. Locatelli F, Pozzoni P, Del Vecchio L. Renal manifestations in the metabolic syndrome. J Am Soc Nephrol 2006; 17: S81–S85.
27. Markham T, Watson A, Rogers S. Adverse effects with long-term cyclosporin for severe psoriasis. Clin Exp Dermatol 2002; 27: 111–114.
28. Maza A, Montaudié H, Sbidian E, Gallini A, Aractingi S, Aubin F, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol 2011; 25 Suppl 2: 19–27.
29. De Vriese AS, Robbrecht DL, Vanholder RC, Vogelaers DP, Lameire NH. Rifampicin-associated acute renal failure: pathophysiologic, immunologic, and clinical features. Am J Kidney Dis 1998; 31: 108–115.
30. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415–1428.
31. Miyamoto T, Carrero JJ, Stenvinkel P. Inflammation as a risk factor and target for therapy in chronic kidney disease. Curr Opin Nephrol Hypertens 2011; 20: 662–668.
32. Shikata K, Makino H. Microinflammation in the pathogenesis of diabetic nephropathy. J Diabetes Investig 2013; 4: 142–149.
33. Anders HJ, Muruve DA. The inflammasomes in kidney disease. J Am Soc Nephrol 2011; 22: 1007–1018.
34. Tintut Y, Patel J, Parhami F, Demer LL. Tumor necrosis factor-alpha promotes in vitro calcification of vascular cells via the cAMP pathway. Circulation 2000; 102: 2636–2642.

35. Metcalfe W. How does early chronic kidney disease progress? A background paper prepared for the UK Consensus Conference on early chronic kidney disease. Nephrol Dial Transplant 2007; 22 Suppl 9: ix26–30.
36. Oh DJ, Kim HR, Lee MK, Woo YS. Profile of human β-defensins 1, 2 and proinflammatory cytokines (TNF-α, IL-6) in patients with chronic kidney diseas. Kidney Blood Press Res 2013; 37: 602–610.
37. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol 2012; 8: 293–300.
38. Cox HJ, Bhandari S, Rigby AS, Kilpatrick ES. Mortality at low and high estimated glomerular filtration rate values: a 'U' shaped curve. Nephron Clin Pract 2008; 110: c67–72.
39. Eriksen BO, Løchen ML, Arntzen KA, Bertelsen G, Eilertsen BA, von Hanno T, et al. Subclinical cardiovascular disease is associated with a high glomerular filtration rate in the nondiabetic general population. Kidney Int 2014; 86: 146–153.
40. Park M, Yoon E, Lim YH, Kim H, Choi J, Yoon HJ. Renal hyperfiltration as a novel marker of all-cause mortality. J Am Soc Nephrol 2015; 26: 1426–1433.