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NO ASSOCIATION BETWEEN METABOLIC SYNDROME AND RADIOGRAPHIC HAND OSTEOARTHRITIS: DATA FROM THE FRAMINGHAM STUDY

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Abstract

Objective—To explore whether metabolic syndrome (MetS) and its components are associated with hand OA using longitudinal data from the Framingham study.

Methods—In our cross-sectional analyses we included 1089 persons (age 50–75 years), of whom 785 had 7-year longitudinal radiographs. Of these, 586 with no hand OA at baseline were included in analyses on hand OA incidence. We explored associations between and MetS and its components (central obesity, hypertension, diabetes, triglyceridemia, low high-density lipoprotein) and radiographic hand OA (defined as ≥2 interphalangeal joints with Kellgren-Lawrence grade≥2) using logistic regression analyses with adjustment for age, sex and body mass index (BMI). In longitudinal analyses, MetS was used as predictor for change in Kellgren-Lawrence sum score and incident hand OA.

Results—MetS was not associated with hand OA presence (OR=1.11, 95% CI 0.78–1.59), change in Kellgren-Lawrence sum score (OR=0.83, 95% CI 0.59–1.17) or hand OA incidence (OR=0.91, 95% CI 0.58–1.44). Hypertension was borderline statistically significantly associated with hand OA presence (OR=1.25, 95% CI 0.90–1.74), and a statistically significant association was found for change in Kellgren-Lawrence sum score (OR=1.47, 95% CI 1.08–1.99). Consistent dose-response relationships were not demonstrated (data not shown). Furthermore, hypertension

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was not statistically significantly associated with hand OA incidence (OR=1.23, 95% CI 0.82–1.83). No statistically significant associations were found between MetS and erosive hand OA.

Conclusion—We found no association between MetS and hand OA. The role of hypertension in hand OA pathogenesis warrants further investigation.

INTRODUCTION

Hand osteoarthritis (OA) is a common disease in the general population with symptomatic interphalangeal (20.4%) and thumb base OA (22.4%) being the most frequent phenotypes in persons above 50 year of age.[1] Persons with hand OA, and in particular those with erosive disease, may experience considerable pain and disability.[1] As no disease-modifying treatment exist, increased knowledge about modifiable risk factors for OA is needed in order to prevent disease development and progression. Although metabolic OA has been proposed as a phenotype of OA, the association between MetS and OA is controversial. The observed associations between MetS and knee OA may be explained by higher weight in persons with MetS, leading to an increased risk of OA due to unfavourable biomechanical loading. Alternatively, MetS may affect the joint through several systemic pathways.[2] Theoretically MetS can contribute to OA development and progression through chronic, low-grade systemic inflammation, release of adipokines and cytokines that act as pro-inflammatory and pro-catabolic factors, enzymatic glycation of collagen fibres and formation of advanced glycation end-products and altered blood flow to the subchondral bone.[2]

Hand OA, and especially erosive hand OA,[1] may be more strongly related to systemic risk factors than OA in lower limbs, which is large driven by biomechanical factors. Hence, our aim was to investigate whether MetS and its components were associated with hand OA in a longitudinal community-based cohort.

METHODS

Participants

The Offspring cohort included children of the original Framingham Heart Study participants and the spouses of these children. Participants were contacted as part of a family study of OA, and n=1800 (28–82 years) attended an OA examination in 1992–1995 (examination cycle 5). For our cross-sectional analyses, the inclusion criteria were available hand radiographs, available clinical data on MetS, no rheumatoid arthritis, and age 50–75 years at examination cycle 5, and n=1089 fulfilled the inclusion criteria.

In 2002–2005 (examination cycle 7), 1293/1800 (71.5%) returned, of whom n=785 fulfilled the inclusion criteria as listed above and had longitudinal hand radiographs. In total, n=586 had no hand OA at examination cycle 5, and were included in analyses on incident hand OA.

The study was approved by the ethical board, and all patients signed the informed consent.

Metabolic syndrome (MetS)

MetS was defined in line with the American Heart Association/National Heart, Lung, Blood Institute (AHA/NHLBI) as ≥3/5 elements present: 1) central obesity (men: ≥102 cm,

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women: ≥88 cm waist circumference); 2) hypertension (systolic ≥130 mmHg, diastolic ≥85 mmHg and/or anti-hypertensive treatment); 3) diabetes (fasting blood glucose ≥100 mg/dL and/or anti-diabetic treatment); 4) elevated triglycerides (≥150 mg/dL); and 5) low high-density lipoprotein (HDL) (men: <40 mg/dL, women: <50 mg/dL) and/or cholesterol-lowering treatment. We created an alternative definition based on clinical/laboratory measurements only (i.e., excluding treatment-related information), as persons with MetS who are adequately treated theoretically may lower their risk of OA.

Hand radiographs

Bilateral hand radiographs from examination cycle 5 were read by one musculoskeletal radiologist according to the Kellgren-Lawrence (KL) scale (grade 0–4). Hand OA was defined at a person level as ≥2 distal (DIP) or proximal interphalangeal (PIP) joints (2^{nd}–5^{th}) with KL grade ≥2. We chose 2 joints as cut-off as we anticipated that hand OA in one single joint could be caused by trauma.

Paired longitudinal radiographs were read by the same radiologist according to the KL scale and central erosions. Erosive hand OA was defined as ≥2 DIP/PIP joints with KL grade≥2, of which ≥1 joint(s) had a central erosion. Radiographic change during follow-up was defined as an increase in KL sum score of ≥2 in DIP/PIP joints.

The radiologist re-evaluated 42 randomly selected radiographs with good reliability for KL (weighted kappa=0.80, intraclass correlation coefficient (ICC)=0.93) and erosions (kappa=0.58, ICC=0.89).

Statistical analyses

In cross-sectional analyses, we examined the association between MetS and its components (independent variable) and presence of hand OA (dependent variable) using logistic regression analyses. Dose-response relationships between the number of MetS components and the severity of the individual components and hand OA were explored using logistic regression analyses. Persons within the lowest quartile were used as reference for waist circumference, blood pressure, glucose and triglycerides, whereas persons within the highest quartile were used as reference for HDL. Whether MetS and its components were more strongly associated with erosive hand OA than with no hand OA or non-erosive hand OA was examined using logistic regression analyses.

In all persons with/without hand OA at baseline and with longitudinal x-rays we explored whether MetS and its components (independent variables) at examination cycle 5 were associated with change in KL sum score during follow-up (dependent variable). In those with no hand OA at examination cycle 5, we examined the associations between MetS and its components (independent variable) and incident radiographic hand OA at examination cycle 7 (dependent variable). Analyses were repeated using incident erosive hand OA as the outcome in persons with no OA or non-erosive hand OA at examination cycle 5.

All analyses were adjusted for age and sex, and repeated with additional adjustment for BMI. Interactions with sex were explored, and stratified analyses were performed if $p \leq 0.10$. Analyses were performed used IBM SPSS Statistics version 22.

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RESULTS

Table 1 shows demographic and clinical characteristics of the participants.

Cross-sectional associations between MetS and hand OA

No relationship was found between MetS and hand OA presence (Table 2). There was no dose-response relationship between increasing number of MetS components and the odds of hand OA. Persons with presence of all five metabolic components had similar odds of hand OA as persons with no components (Online Supplementary Table S1).

Among the individual components of MetS, an association with hand OA was found only for elevated blood pressure (Table 2). There was no clear dose-response relationship between systolic blood pressure and the odds of hand OA. Persons with diastolic blood pressure of ≥81 mmHg (highest quartile) demonstrated statistically significantly higher odds of hand OA as compared to persons with diastolic blood pressure <69 mmHg (lowest quartile) (Online Supplementary Table S1).

There was a tendency that MetS and the majority of components were associated with lower odds of erosive hand OA with a statistically significant association for MetS (OR=0.42, 95% CI 0.20–0.90). The association between elevated blood pressure and erosive hand OA was not statistically significant (OR=1.20, 95% CI 0.64–2.23).

No statistically significant interactions with sex were found (data not shown).

The associations between MetS and worsening and incident hand OA

The mean (SD) time of follow-up was 7.1 (0.9) years, and the median (IQR) change in KL sum score was 2 (0–6). Radiographic change occurred in 401/785 (51.1%) persons, whereas 151/586 (25.8%) developed incident hand OA. MetS was not associated with either change in KL sum score or incident hand OA (Table 3). Looking at the individual components of MetS, central obesity was associated with incident hand OA, but not with radiographic change. Hypertension was associated with change in KL sum score (Table 3), but no clear dose-response relationships were demonstrated (Online Supplementary Table S1). Weaker and statistically non-significant associations were found for incident hand OA (Table 3). Low HDL was associated with lower odds of change (borderline statistically significant) and incident hand OA (statistically significant) (Table 3).

In analyses of change in KL sum score, we found interactions with sex for hypertension (p=0.07). The association between baseline hypertension and change in KL sum score was statistically significant in women, whereas no statistically significant association was found for men. In analyses of incident hand OA, no interactions with sex were found (data not shown).

Incident erosive disease occurred in 56/736 (7.6%) persons. No statistically significant associations were found between MetS and its components and incident erosive hand OA, and no interactions with sex were found (data not shown).

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DISCUSSION

We found no evidence that MetS increases the risk of hand OA. Although metabolic OA has been suggested as a distinct phenotype, there is limited evidence from clinical studies that such a phenotype exists. We focused on hand OA because mechanical loading may be less salient as a risk factor than in knee OA, permitting a relationship of a systemic risk factor such as MetS to be more easily detected.

Previous studies have shown conflicting results regarding an association between MetS and OA (mainly knee OA). Conflicting results are likely due to different study designs (cross-sectional versus longitudinal studies), analyses with or without adjustment for BMI and varying definitions of OA and MetS. Importantly, associations do not prove causality. Cross-sectional studies are likely to show associations between MetS and knee OA due to more sedentary lifestyle in persons with knee OA leading to increased risk of MetS. Furthermore, MetS is strongly related to overweight/obesity, which is a well-known risk factor for knee OA. Hence, adjustment for BMI/weight in the analyses is crucial.

In the population-based ROAD study, significant associations were found between increasing number of MetS components and incident and progressive knee OA.[3] There was no adjustment for BMI, and the associations are likely confounded by higher weight in persons with MetS. Previous studies have demonstrated increased risk of knee arthroplasty in persons with MetS with inconsistent results after adjustment for BMI.[4,5] No associations have been found for hip arthroplasty, which may be explained by weaker relationships between BMI and hip OA.[4,5]

The association between MetS and hand OA has been explored in few studies, of which all have shown higher prevalence of MetS in persons with hand OA.[6–8] Importantly, none of these studies have been longitudinal, which prevents conclusions about causality. In the Rotterdam study, persons who were overweight and had both diabetes and hypertension had significantly higher odds of radiographic hand OA as compared with persons without these characteristics.[6] In line with these results, MetS was significantly associated with isolated clinical symptomatic hand OA in the Netherlands Epidemiology of Obesity (NEO) study, and the association remained statistically significant after additional adjustment for weight.[7] No such association was observed for persons with isolated clinical knee OA or a combination of clinical hand and knee OA, suggesting that the observed association was not confounded by less physical activity due to knee pain.[7] As the individual components of MetS were not analysed separately, it remains unknown whether the observed association was driven by one/few individual components. The definition of clinical hand OA requires the presence of hand pain, which is more likely to occur in diabetic patients due to neuropathy and cheiropathy, for example. In a smaller French study, higher frequency of radiographic hand OA was demonstrated in men with Human Immunodeficiency Virus-1 (HIV-1) infection as compared with men from the general population of Framingham. The higher prevalence of hand OA was especially observed in HIV-1 patients with MetS.[8] Radiographs from the two cohorts were scored by different readers, which may affect the results. Furthermore, the generalizability of results is limited as the study population consisted of HIV-1 patients.

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In contrast to previous studies, we did not find any association between MetS and development and change of hand OA, suggesting no causal relationships. Furthermore, we found no associations between MetS and erosive hand OA in neither cross-sectional nor longitudinal studies, refuting the hypothesis that erosive hand OA represents a more metabolically driven phenotype.[1] A possible protective effect of low HDL was found in longitudinal analyses. However, due to inconsistent results in cross-sectional and longitudinal analyses, these results should be treated with caution as they may be chance findings only.

We found a trend towards an association between hypertension and hand OA. Previous studies have shown conflicting results.[3,5,9–12] In line with our results, significant associations between hypertension and knee OA prevalence, incidence and progression have been found independent of BMI.[3,5,11,12] No associations were found between hypertension and hand OA in previous studies, which were hampered by constricted age groups (70-year old people)[9] and small sample sizes (n=70 with hand OA),[13] respectively. In the large Rotterdam study, a significant, but weak association was found between hypertension and radiographic hand OA in analyses adjusted for age, sex, smoking and overweight. This association disappeared after adjusting for overweight as a continuous variable.[6] Although persons with hypertension in our study demonstrated higher odds of hand OA in both cross-sectional and longitudinal analyses of change scores, the lack of a clear dose-response relationship and no association with incident hand OA indicate that our results should be treated with caution. Future large clinical studies are needed to replicate our findings.

Hypertension may potentially lead to OA as blood vessels are narrowed due to reduced production of nitric oxide by the endothelial cells,[2] leading to impaired nutrition supply to the overlying cartilage. An alternative hypothetic model is that hypertension leads to reduced bone mineral density at the subchondral plate, which will be more prone to micro-cracks at the osteochondral junction.[14]

We used a definition of hand OA based on involvement of the interphalangeal joints with the assumption that the MCP and thumb base joints are less related to systemic risk factors. As an example, subluxation of the carpometacarpal joint has been shown to be a predictor of OA development.[15] Dahaghin *et al.* found significant associations between MetS and OA in DIP, PIP and MCP joints, whereas no significant associations were found for thumb base OA. In our study, isolated MCP OA was uncommon. MCP OA (≥2 MCP joints with KL grade ≥2) was more common in persons with versus without DIP/PIP OA (10.6% and 1.9%, respectively). Hence, inclusion of MCP OA in our definition would likely not change the results.

Some study limitations must be mentioned. Analyses of radiographic change may be prone to null results due to the inclusion of persons who already have hand OA at baseline. To overcome this problem we also studied subjects without hand OA only in longitudinal analyses. Lack of significant associations may be due to type 2 errors, and particularly the analyses on incident hand OA. However, consistent results across both cross-sectional and longitudinal analyses and narrow confidence intervals strengthen the validity of the results. The odds ratios were also only trivially elevated in cross-sectional analyses, and a trend

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towards protective association was found in longitudinal analyses, suggesting that no such association exist between MetS and hand OA. Due to only two radiographic examinations 7 years apart, we do not have information about whether hand OA changes occurred early or late in this interval. Lastly, we did not account for competing risks. Persons with MetS may demonstrate increased mortality, and we observed a higher loss to follow-up in persons with MetS as compared to persons without MetS (35.0% vs. 22.9%). MetS was statistically significantly associated with loss to follow-up (OR=1.61, 95% CI 1.22–2.12) in age-and sex-adjusted analyses.

In conclusion, MetS does not increase the risk of hand OA. The association between hypertension and hand OA warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNNOVATIONS

- We found no evidence for a relationship between metabolic syndrome (MetS) and hand osteoarthritis (OA)
- In cross-sectional analyses, hypertension was borderline statistically significantly associated with the presence of hand OA. In longitudinal analyses, a statistically significant association was found with changes in radiographic findings, but not with incident hand OA. Consistent dose-response relationships were not found, and further research is needed.
- Erosive hand OA was not related to MetS or any of its components.

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Table 1

Baseline characteristics of the participants

	Participants in cross-sectional analyses (n=1089)	Participants with longitudinal x-rays (n=785)	Participants with longitudinal x-rays and no hand OA at exam 5 (n=586)
Sex, n (%) women	564 (51.8)	432/785 (55.0)	300 (51.2)
Age, mean (SD) years	59.2 (6.4)	58.5 (6.0)	57.3 (5.6)
Body mass index, mean (SD) kg/m^2	27.7 (4.7)	27.5 (4.5)	27.4 (4.3)
Hand OA variables			
Presence of radiographic hand OA *, n (%)	245/1089 (22.5)	199/785 (25.4)	0 (0)
Erosive hand OA **, n (%)	49/786 (6.2)	49/785 (6.2)	0 (0)
KL sum score, median (IQR)	0 (0–5)	0 (0–4)	0 (0–1)
MetS (definition incl. treatment), * n (%)**	451/1089 (41.4)	293/785 (37.3)	210/586 (35.8)
MetS (clinical/laboratory definition), ** n (%)**	414/1089 (38.0)	270/785 (34.4)	194/586 (33.1)
Central obesity, n (%)	430/1088 (39.5)	296/785 (37.7)	219/586 (37.4)
Hypertension			
Elevated blood pressure and/or treatment, n (%)	610/1088 (56.1)	412/785 (52.5)	288/586 (49.1)
Elevated blood pressure, n (%)	525/1089 (48.2)	358/785 (45.6)	248/586 (42.3)
Diabetes			
Elevated fasting glucose and/or treatment, n (%)	411/1081 (38.0)	271/782 (34.7)	191/584 (32.7)
Elevated fasting glucose, n (%)	410/1081 (37.9)	271/782 (34.7)	191/584 (32.7)
Elevated triglycerides, n (%)	439 (40.3)	303/785 (38.6)	224/586 (38.2)
Low HDL/treatment			
Low HDL and/or treatment, n (%)	477/1088 (43.8)	333/784 (42.5)	251/585 (42.9)
Low HDL, n (%)	434/1087 (39.9)	305/783 (39.0)	232/585 (39.7)

OA=osteoarthritis; SD=standard deviation; MetS=metabolic syndrome; HDL=high-density lipoprotein.

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* 2 or more distal and proximal interphalangeal joints (2^{nd}–5^{th}) with Kellgren-Lawrence grade 2 or more;

** 2 or more distal and proximal interphalangeal joints (2^{nd}–5^{th}) with Kellgren-Lawrence grade 2 or more, of which at least one joint with central erosion;

*** MetS defined as 3 or more of the following: central obesity, elevated blood pressure and/or anti-hypertensive treatment, elevated fasting blood glucose and/or anti-diabetic treatment, elevated triglycerides, and low HDL and/or cholesterol-lowering treatment:

**** Alternative definition of MetS based on clinical/laboratory measurements only (central obesity, elevated blood pressure, elevated fasting glucose, elevated triglycerides and low HDL) excluding treatment-related information.

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Table 2

The cross-sectional associations between MetS and the presence of radiographic hand OA * at baseline (exam 5)

	OR (95% CI) of hand OA *	
	Adjusted for age and sex	**Adjusted for age, sex and BMI**
MetS (definition incl. treatment) **	1.24 (0.91–1.68)	1.11 (0.78–1.59)
MetS (clinical/laboratory definition) ***	1.21 (0.89–1.65)	1.08 (0.75–1.54)
Central obesity	1.13 (0.83–1.54)	0.90 (0.60–1.37)
Hypertension		
Elevated blood pressure and/or treatment	1.32 (0.95–1.82)	1.25 (0.90–1.74)
Elevated blood pressure	**1.40 (1.03–1.91)**	1.34 (0.98–1.84)
Diabetes		
Elevated fasting glucose and/or treatment	1.27 (0.92–1.74)	1.17 (0.84–1.64)
Elevated fasting glucose	1.25 (0.91–1.71)	1.15 (0.82–1.61)
Elevated triglycerides	1.21 (0.89–1.65)	1.15 (0.84–1.59)
Low HDL/treatment		
Low HDL and/or treatment	0.97 (0.71–1.32)	0.91 (0.66–1.25)
Low HDL	0.92 (0.67–1.26)	0.86 (0.62–1.19)

MetS=metabolic syndrome; OA=osteoarthritis; OR=odds ratio; CI=confidence interval; BMI=body mass index; HDL=high-density lipoprotein;

* 2 or more distal and proximal interphalangeal joints (2^{nd}–5^{th}) with Kellgren-Lawrence grade 2 or more;

** MetS defined as 3 or more of the following: central obesity, elevated blood pressure and/or anti-hypertensive treatment, elevated fasting blood glucose and/or anti-diabetic treatment, elevated triglycerides, and low HDL and/or cholesterol-lowering treatment:

*** Alternative definition of MetS based on clinical/laboratory measurements only (central obesity, elevated blood pressure, elevated fasting glucose, elevated triglycerides and low HDL) excluding treatment-related information.

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Table 3

The associations between baseline MetS and change in KL sum score as well as incidence of radiographic hand OA.

	OR (95% CI) of change in KL sum score* in persons with/without hand OA at baseline		OR (95% CI) of incident hand OA** in persons with no hand OA at baseline	
	Adjusted for age and sex	**Adjusted for age, sex and BMI**	**Adjusted for age and sex**	**Adjusted for age, sex and BMI**
MetS (definition incl. treatment)* **	0.87 (0.64–1.18)	0.83 (0.59–1.17)	0.98 (0.66–1.46)	0.91 (0.58–1.44)
MetS (clinical/laboratory definition)** **	0.85 (0.62–1.15)	0.80 (0.56–1.13)	1.00 (0.67–1.50)	0.92 (0.58–1.49)
Central obesity	1.00 (0.74–1.35)	0.98 (0.66–1.46)	1.42 (0.97–2.09)	1.68 (1.00–2.83)
Hypertension				
Elevated blood pressure and/or treatment	**1.43 (1.06–1.91)**	**1.47 (1.08–1.99)**	1.24 (0.85–1.82)	1.23 (0.82–1.83)
Elevated blood pressure	**1.34 (1.00–1.80)**	**1.36 (1.01–1.85)**	1.14 (0.78–1.67)	1.12 (0.75–1.67)
Diabetes				
Elevated fasting glucose and/or treatment	1.08 (0.79–1.48)	1.08 (0.79–1.50)	0.95 (0.63–1.44)	0.91 (0.59–1.41)
Elevated fasting glucose	1.08 (0.79–1.48)	1.08 (0.79–1.50)	0.95 (0.63–1.44)	0.91 (0.59–1.41)
Elevated triglycerides	1.06 (0.79–1.43)	1.06 (0.78–1.44)	1.01 (0.68–1.49)	0.98 (0.66–1.47)
Low HDL/treatment				
Low HDL and/or treatment	0.77 (0.57–1.03)	0.75 (0.56–1.02)	0.57 (0.38–0.84)	0.53 (0.35–0.80)
Low HDL	0.77 (0.55–1.01)	0.73 (0.54–0.99)	0.61 (0.41–0.91)	0.57 (0.37–0.86)

MetS=metabolic syndrome; KL=Kellgren-Lawrence; OA=osteoarthritis; OR=odds ratio; CI=confidence interval; BMI=body mass index; HDL=high-density lipoprotein;

*Change in Kellgren-Lawrence sum score in the distal and proximal interphalangeal joints (2^{nd}–5^{th}) of 2 or more from examination cycle 5 to 7;

**Development of 2 or more distal and proximal interphalangeal joints (2^{nd}–5^{th}) with Kellgren-Lawrence grade 2 or more at examination cycle 7 in persons with no hand osteoarthritis at examination cycle 5.

***MetS defined as 3 or more of the following: central obesity, elevated blood pressure and/or anti-hypertensive treatment, elevated fasting blood glucose and/or anti-diabetic treatment, elevated triglycerides, and low HDL and/or cholesterol-lowering treatment:

****Alternative definition of MetS based on clinical/laboratory measurements only (central obesity, elevated blood pressure, elevated fasting glucose, elevated triglycerides and low HDL) excluding treatment-related information.