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ORIGINAL CONTRIBUTIONS

A Population-based Study of the Prevalence of Abdominal Aortic Aneurysms in Relation to Bone Mineral Density

The Tromsø Study

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In a population-based study of 2,586 men and 2,806 postmenopausal women aged 55–74 years in Tromsø, Norway, in 1994–1995, associations between the prevalence of abdominal aortic aneurysms and bone mineral density were examined. The presence of an abdominal aortic aneurysm was assessed by ultrasonography. The bone mineral density of the forearm was measured by single X-ray absorptiometry. In postmenopausal women aged 55–64 years (nine cases of aneurysm), the adjusted odds ratio for abdominal aortic aneurysm was 0.42 (95% confidence interval: 0.19, 0.95) for each standard-deviation increase in bone mineral density. In other age groups (65–69 years and 70–74 years) including a total of 50 cases, the corresponding odds ratios for abdominal aortic aneurysm were 1.17 and 0.70, respectively. In men aged 55–59 years, based on 45 cases, the odds ratio for abdominal aortic aneurysm was 0.72 (95% confidence interval: 0.50, 1.03). In other age groups (60–64, 65–69, and 70–74 years) including a total of 206 cases, the odds ratios ranged from 1.00 to 1.10. The associations among men (in any age group) and among women older than 64 years were not statistically significant. The authors' main conclusion is that abdominal aortic aneurysms and bone mineral density are not related. However, an association in younger subjects cannot be ruled out.

aortic aneurysm, abdominal; bone density

Abbreviations: CI, confidence interval; SD, standard deviation.

Atherosclerosis and abdominal aortic aneurysms frequently coexist. Calcified plaques are often found in the walls of aneurysms, and traditionally atherosclerosis has been thought to be the cause of abdominal aortic aneurysms (1). Several studies (2–8), though not all (9–13), have shown that arterial calcification is associated with low bone mineral density. Similarities in some of the predisposing risk factors for abdominal aortic aneurysm, atherosclerosis, and osteoporosis, such as smoking, low serum levels of high density lipoprotein cholesterol, high serum levels of low density lipoprotein cholesterol, and hypertension, may link the diseases (14–17).

Vascular calcification is increasingly seen as an active, organized process similar to that of osteogenesis, and expressions of factors such as matrix Gla protein, osteocalcin, and collagen type I have been found in human atherosclerotic lesions (16). These factors are also involved in the regulation of bone metabolism and may underlie the pathogenesis of osteoporosis, atherosclerosis, and abdominal aortic aneurysm. Studies on relations between bone mineral density and abdominal aortic aneurysm are sparse, but it has been shown that mice that lack matrix Gla protein develop osteoporosis, exhibit arterial calcification, and die prematurely because of rupture of the thoracic or abdominal aorta

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(18). To our knowledge, the question of whether humans with low bone mineral density are at increased risk of abdominal aortic aneurysm has not been examined. Thus, in this population-based study, we examined the relation between bone mineral density and the prevalence of abdominal aortic aneurysms.

MATERIALS AND METHODS

The Tromsø Study is an ongoing population-based study of inhabitants of the municipality of Tromsø, Norway. The study has been approved by the Regional Committee for Medical Research Ethics, and all subjects have given informed consent. In the fourth Tromsø Study survey, conducted in 1994–1995, all inhabitants aged 25 years or above were invited to a screening. The protocol was similar to that of the previous surveys carried out in this population (19). It included standardized measurements of a number of characteristics, including height, body weight, blood pressure, and nonfasting serum lipid levels. Height and weight were measured while the participant stood in light clothing without shoes. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Blood pressure was recorded before blood sampling in a separate, quiet room by a specially trained nurse using an automatic blood pressure device (Dinamap Vital Signs Monitor 1846; Criticon, Inc., Tampa, Florida). Serum total cholesterol was analyzed by enzymatic colorimetric methods with a commercial kit (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany), and serum high density lipoprotein cholesterol was measured after the precipitation of low density lipoprotein with manganese chloride (20). In connection with the screening, the participants completed self-administered questionnaires including questions about smoking habits, prevalent diabetes mellitus or angina pectoris, previous myocardial infarction or stroke (all yes/no), treatment for hypertension (never/previous/current), and physical activity. We defined persons as physically inactive if they reported that they were never so active during their leisure time that they were sweating or out or breath and that they had been lightly active only (not sweating or out of breath) for less than 3 hours per week during the past year.

All subjects aged 55–74 years who attended the screening were invited to engage in a second visit 4–12 weeks after the first visit. At the second visit, more extensive examinations were carried out, including measurement of bone mineral density and ultrasonography of the abdominal aorta. Personnel performing the ultrasound assessments and personnel measuring bone mineral density had no knowledge of the results of other measurements, the questionnaires, or laboratory data. Among the subjects aged 55–74 years, 5,465 (79 percent of the Tromsø population in this age group) had valid bone mineral density measurements and successful ultrasonography of the abdominal aorta.

In the present cross-sectional analysis, we included all male subjects and all postmenopausal women aged 55–74 years (n = 5,392). Women were defined as postmenopausal if they were aged ≥60 years or if they were aged 55–59 years and reported that they had stopped menstruating. Among the 840 women in the age group 55–59 years, we thereby excluded 10 women who reported that they were still menstruating and 63 women who had not answered the question regarding postmenopausal status.

Bone densitometry

Bone mineral density was assessed by one of two single X-ray absorptiometry devices (DTX-100; Osteometer MediTech, Inc., Hawthorne, California) as previously described (21). In 99 percent of the subjects, bone mineral density at the distal and ultradistal sites of the nondominant forearm was measured, whereas, in 1 percent of the subjects, the dominant forearm was measured because of the presence of a plaster cast, wound, and so forth, on the nondominant arm. A total of 111 subjects had repeated measurements. The median coefficients of variation for two scans performed 1 week apart by two different operators were 0.79 percent and 0.98 percent at the distal and ultradistal sites, respectively (22). We reviewed all scans to detect and correct possible artifacts, and systematic differences in bone mineral density between the two densitometers were adjusted before analysis (21).

Ultrasonography of the abdominal aorta

Ultrasonography of the abdominal aorta was performed as described previously (17, 23). Briefly, the examination was carried out with a 3.5-MHz sector probe (Acuson 128-XP; Acuson Corporation, Mountain View, California). An abdominal aortic aneurysm was defined as present if one or more of the following criteria were met: 1) the aortic diameter at the renal level was ≥35 mm in either the anterior-posterior or the transverse plane; 2) the infrarenal aortic diameter was ≥5 mm larger than the renal aortic diameter in either plane; and/or 3) a localized dilation of the aorta was present.

Reproducibility was assessed by repeated ultrasound measurements in 112 subjects. For the maximal infrarenal aortic diameter in the anterior-posterior plane, the absolute intra- and interobserver difference was ≤4 mm in 97 percent and 96 percent of the cases, respectively. Furthermore, 93 percent and 88 percent of these measurements differed by ≤3 mm, respectively. The variability was similar for measurements in the transverse plane (23).

Statistical analysis

Analysis of covariance was used to compare age-adjusted mean bone mineral densities in subjects without or with an abdominal aortic aneurysm. We estimated the odds ratios for abdominal aortic aneurysm for each sex-specific one-standard-deviation (1-SD) increase in bone mineral density by the use of logistic regression analysis with adjustment for potential confounders. A 1-SD change in bone mineral density was 66.5 mg/cm^2 in men and 66.2 mg/cm^2 in women. Terms for interaction with age were included in the models in separate analyses.

The data were analyzed using the Windows 11.0 version of SPSS (SPSS, Inc., Chicago, Illinois).

TABLE 1. Age-adjusted characteristics of subjects without and with abdominal aortic aneurysm, Tromsø, Norway, 1994–1995

Characteristic	Men			Women		
	Without AAA* (n = 2,335)	With AAA (n = 251)	p value	Without AAA (n = 2,747)	With AAA (n = 59)	p value
Mean age (years)	63.2 (0.1)†	65.8 (0.4)	<0.001	63.9 (0.1)	68.7 (0.5)	<0.001
Mean body mass index‡	25.9 (0.07)	26.7 (2.1)	0.01	26.3 (0.1)	26.0 (0.6)	0.6
Mean blood pressure (mmHg)						
Systolic	142.9 (0.4)	143.5 (1.3)	0.6	142.9 (0.4)	150.1 (2.8)	0.01
Diastolic	82.8 (0.3)	84.8 (0.3)	0.01	79.6 (0.2)	82.0 (1.7)	0.1
Mean serum cholesterol level (mmol/liter)						
Total cholesterol	6.52 (0.02)	6.77 (0.07)	0.002	7.14 (0.02)	7.24 (0.16)	0.5
High density lipoprotein cholesterol	1.44 (0.01)	1.29 (0.03)	<0.001	1.68 (0.01)	1.53 (0.06)	0.007
Smoking						
Never smoking (%)	17	4	<0.001	45	15	<0.001
Current smoking (%)	31	52	<0.001	28	68	<0.001
Mean duration of smoking (years)	26.2 (0.4)	37.6 (1.1)	<0.001	15.1 (0.3)	32.6 (2.2)	<0.001
Physically inactive (%)	34	43	0.01	48	59	0.1
Cardiovascular diseases (%)						
Previous myocardial infarction	10	20	<0.001	3	14	0.001
Angina pectoris	11	25	<0.001	9	15	0.2
Previous stroke	4	3	0.7	2	6	0.1
Diabetes mellitus (%)	4	3	0.5	4	5	0.9
Use of medication for hypertension (%)						
Current use	15	24	<0.001	15	24	0.08
Never use	81	69	<0.001	80	65	0.009
Mean bone mineral density (mg/cm^2)						
Distal radius	538.2 (1.3)	536.7 (4.1)	0.6	391.4 (1.2)	378.3 (7.9)	0.09
Ultradistal radius	437.1 (1.4)	437.3 (4.3)	0.9	289.5 (1.1)	274.2 (7.6)	0.03

* AAA, abdominal aortic aneurysm.
† Numbers in parentheses, standard error.
‡ Weight (kg)/height (m)^2.

RESULTS

Selected characteristics of the study group are presented in table 1. There were 310 abdominal aortic aneurysms in total. In both men and women, age and age-adjusted mean levels of serum high density lipoprotein cholesterol, smoking, prevalence of myocardial infarction, and use of medication for hypertension were significantly associated with abdominal aortic aneurysm. Body mass index, diastolic blood pressure, serum total cholesterol level, physical inactivity, and prevalence of angina pectoris were significantly associated with abdominal aortic aneurysm in men, whereas systolic blood pressure was associated with the risk of abdominal aortic aneurysm in women. The bone mineral density values for the ultradistal site of the forearm also differed significantly in women.

Table 2 shows that no statistically significant adjusted relations between the bone mineral density of the distal forearm and the prevalence of abdominal aortic aneurysms were found before age stratification.

However, a significant interaction with age was found in women (p = 0.015) but not in men (p = 0.2). Table 2 also shows that in women aged 55–64 years, the adjusted odds ratio for an abdominal aortic aneurysm was 0.42 (95 percent confidence interval (CI): 0.19, 0.95) per 1-SD increase in bone mineral density. This finding was based on only nine cases, however. The results hardly changed when the 63 women with unknown postmenopausal status (of whom one had an abdominal aortic aneurysm) were included in the analyses; the odds ratio was 0.49 (95 percent CI: 0.23, 1.04) for each 1-SD increase in bone mineral density. Among women aged 65–69 and 70–74 years and among men in any of the 5-year age groups considered, no statistically significant association was found between bone mineral density and the prevalence of abdominal aortic aneurysm. However, a tendency toward a lower risk of abdominal aortic aneurysm in younger men may be suggested. The results in the seven age-sex strata presented in table 2 did not change notably when the 1,014 subjects with self-reported cardiovascular disease and/or diabetes (of whom 122 had an abdominal

TABLE 2. Adjusted odds ratios for abdominal aortic aneurysm per one-standard deviation* increase in bone mineral density of the distal forearm, by sex and age group, Tromsø, Norway, 1994–1995

Age group (years)	Men					Women				
	No. without AAA†	No. with AAA	Odds ratio‡	Odds ratio§	95% CI†	No. without AAA	No. with AAA	Odds ratio‡	Odds ratio§	95% CI
55–74 (all)	2,335	251	0.96	0.99	0.86, 1.15	2,747	59	0.79	0.81	0.60, 1.09
55–59	748	45	0.70	0.72	0.50, 1.03	766	1	0.36¶	0.42¶	0.19, 0.95
60–64	649	50	1.03	1.00	0.70, 1.41	687	8			
65–69	520	81	1.07	1.10	0.85, 1.41	734	25	0.97	1.17	0.73, 1,99
70–74	418	75	0.96	1.04	0.81, 1.34	560	25	0.86	0.70	0.43, 1.13

* A one-standard-deviation change in bone mineral density was 66.5 mg/cm^2 in men and 66.2 mg/cm^2 in women.

† AAA, abdominal aortic aneurysm; CI, confidence interval.

‡ Adjusted for age (1 year).

§ Adjusted for age (1 year), body mass index (1 kg/m^2), systolic blood pressure (1 mmHg), medication for hypertension (current use (no vs. yes) and previous use (no vs. yes)), serum total cholesterol level (1 mmol/liter), serum high density lipoprotein cholesterol level (1 mmol/liter), duration of smoking (1 year), physical inactivity (no vs. yes), cardiovascular diseases (previous myocardial infarction (no vs. yes), angina pectoris (no vs. yes), or stroke (no vs. yes)), and diabetes mellitus (no vs. yes).

¶ Odds ratio for abdominal aortic aneurysm in the age group 55–64 years.

aortic aneurysm) were excluded from the analysis (results not shown).

The results of all analyses were similar when bone mineral density of the ultradistal site of the forearm was considered as the exposure variable. In women aged 55–64 years, the odds ratio for abdominal aortic aneurysm was 0.33 (95 percent CI: 0.13, 0.83) for each 1-SD increase in bone mineral density. In other age groups (65–69 years and 70–74 years) and in men in any of the age groups examined, no significant associations with bone mineral density at this site were found (results not shown).

DISCUSSION

The main finding of this study of the association between bone mineral density and the prevalence of abdominal aortic aneurysms in humans is that the two conditions are not related. However, although no relation was found in the older age groups, in which the majority of abdominal aortic aneurysms occur, an association in younger subjects cannot be ruled out.

The number of cases of abdominal aortic aneurysm among men (n = 251) was adequate for excluding any clinically significant relation between bone mineral density and risk of abdominal aortic aneurysm, since the 95 percent confidence interval was relatively narrow (95 percent CI: 0.86, 1.15). In women, the power of our study was more limited (with 59 cases included). This was particularly the situation in the small subgroup aged 55–64 years, comprising only nine cases.

The prevalence of abdominal aortic aneurysm was associated with well-known risk factors for cardiovascular disease, as shown in table 1 and described in detail elsewhere (17). Thus, we adjusted for these variables in our analyses, but this influenced the results of the logistic regression analyses only to a small extent. However, other confounding factors for which we failed to control may still have influenced our findings.

The present study had a high overall attendance rate: 79 percent of the eligible subjects had both their bone mineral density measured and ultrasonography of the abdominal aorta performed. Therefore, we find it unlikely that possible bias connected to a relatively small group of nonresponders would have had any major effects on our results. However, bias due to selective mortality in elderly subjects with cardiovascular diseases, an increased risk of abdominal aortic aneurysm, and osteoporosis may contribute to an explanation as to why low bone mass tended to be associated with abdominal aortic aneurysm only in the youngest men and women.

In the present study, we cannot rule out the possibility that a few subjects may have changed their living habits because of symptoms from or knowledge of osteoporosis or an abdominal aortic aneurysm and that this may have influenced our results. We were also concerned about a possible impact on the findings of the presence of cardiovascular diseases and diabetes, but we found that the point estimates were unchanged when we restricted the analysis to subjects who denied having these diseases.

The significant inverse relation between bone mineral density and the prevalence of abdominal aortic aneurysms found in relatively young women may reflect a causal relation, bias or confounding, or chance. Although chance is the most likely explanation, a tempting alternative hypothesis is that estrogen deficiency may play a role not only with respect to the development of osteoporosis but also in the pathogenesis of abdominal aortic aneurysms. Postmenopausal women lose more bone than men the same age. The fastest bone loss is found during the early postmenopausal years, and longitudinal studies clearly indicate that women showing the greatest magnitude of bone loss also have the greatest progressions in vascular calcification (4, 6). On the other hand, recent studies have failed to demonstrate beneficial effects of hormone replacement therapy in the prevention of cardiovascular disease (24, 25). The relevance of these findings for the development of abdominal aortic aneurysms remains to be shown.

In summary, the present study found no relation between bone mineral density and the prevalence of abdominal aortic aneurysms in the majority of elderly men and women. However, an association in younger subjects cannot be ruled out, and further studies are warranted.

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