Osteoporos Int (2006) 17: 426–432
DOI 10.1007/s00198-005-0003-z

ORIGINAL ARTICLE

Features of the metabolic syndrome and the risk of non-vertebral fractures: The Tromsø study

L. A. Ahmed · H. Schirmer · G. K. Berntsen · V. Fønnebø · R. M. Joakimsen

Received: 11 March 2005 / Accepted: 4 September 2005 / Published online: 31 December 2005

Abstract *Introduction:* We wanted to examine whether the features of the metabolic syndrome carried an increased risk of non-vertebral fracture. *Methods:* This is a population-based, 6-year follow-up of 27,159 subjects from the municipality of Tromsø, followed from 1994 until 2001. Age range was 25–98 years. Non-fasting serum levels of high-density lipoprotein (HDL), triglycerides and glucose, blood pressure (BP), weight and height were measured at baseline. All non-vertebral fractures were registered by computerised search in radiographic archives. *Results:* A total of 1,249 non-vertebral fractures were registered. Increasing number of metabolic syndrome features was associated with significantly reduced fracture risk in both men and women, p= 0.004 and p<0.0001, respectively. High BP was protective against fracture in men [relative risk (RR) 0.89; 95% confidence interval (CI) 0.8–0.99)] while increased body mass index (BMI) was protective in women (RR 0.91; 95% CI 0.84–0.98). Increasing non-fasting serum levels of HDL increased fracture risk in women (RR 1.12; 95% CI 1.05–1.21). BMI modified the effect of HDL in men. Accordingly, high HDL increased fracture risk in men with high BMI (RR 1.51; 95% CI 1.2–1.9). *Conclusions:* Increasing burden of metabolic syndrome features protects against non-vertebral fractures. Reduced non-vertebral fracture risk was associated with high BP in men and increased body mass in women. Lower non-fasting serum levels of HDL protect against fractures in women and obese men.

Keywords Blood pressure · Body mass index (BMI) · Diabetes mellitus · High-density lipoprotein (HDL) · Metabolic syndrome · Non-vertebral fractures · Triglycerides

L. A. Ahmed (✉) · H. Schirmer · G. K. Berntsen · V. Fønnebø
Institute of Community Medicine,
University of Tromsø,
9037 Tromsø, Norway
e-mail: Luai.Awad@ism.uit.no
Tel.: +47-77645511
Fax: +47-77644831

H. Schirmer
Department of Cardiology,
University Hospital of Tromsø,
Tromsø, Norway

R. M. Joakimsen
Department of Internal Medicine,
University Hospital of Tromsø,
Tromsø, Norway

Introduction

Apart from body mass index (BMI), little is known about the relationship between metabolic disturbances or features of the metabolic syndrome and the risk of non-vertebral fractures. No significant association has been found between diastolic/systolic blood pressure (BP), total cholesterol, triglycerides and glucose and the incidence of hip fracture [1]. Some studies have used the surrogate endpoint bone mass density with conflicting results. In one study, BP was associated with increased bone loss at the femoral neck [2]. Another study found that systolic and diastolic BP, serum triglycerides, blood glucose, BMI and waist-to-hip ratio were positively associated with bone density (p<0.001), and high-density lipoprotein (HDL) and serum cholesterol were negatively associated with bone density [3]. This indicates a possible protective effect of the metabolic syndrome on fracture risk, which is supported by one study showing that women with postmenopausal fractures had lower BMI and higher serum levels of HDL than those without fractures [4]. Although the metabolic syndrome is an important risk factor for diabetes [5], increased fracture risk among diabetics has been reported in some [1, 6, 7] but not all studies [8, 9]. We wanted to estimate the risk of non-vertebral fracture associated with the features of the metabolic syndrome in a large, population-based, follow-up of 27,159 people aged 25–98 years at baseline, independent of other known risk factors.

Material and methods

Study population

The Tromsø study is a population-based cohort study with five repeated health surveys since 1974. In the fourth Tromsø survey (1994/95), all residents of the Tromsø municipality born 1969 or earlier were invited to the first phase of the survey. Among the 37,559 persons invited, 2,139 persons died or moved before their scheduled phase I examination. The eligible population was therefore 35,420 persons, and 27,159 (77%) participants attended the phase I examination of the survey and answered the relevant questionnaires. All subjects aged 55–74 and random 5–10% samples of all other age groups were invited to a second visit for more extensive screening. A total of 7,694 subjects attended the second phase of the survey [10].

Registration of exposure variables and confounding factors

The first questionnaire was printed on the reverse side of a letter of invitation. At the health examination, a trained nurse checked the questionnaire for inconsistency. The questionnaire included, among others, questions about having diabetes mellitus, myocardial infarction, angina pectoris, hypertension and use of drugs such as hypertension medications, lipid-lowering drugs (only for those younger than 70 years) and cortisone tablets, in addition to risk factors such as physical activity and smoking habits [11]. The examination included standardised measurements of BP, weight, height and non-fasting serum lipids. Height and weight were measured in light clothing without shoes to the nearest centimetre/kilogram. Among information collected in the second phase, non-fasting serum glucose levels and waist circumference in centimetres were measured and the time since last meal was reported. All levels of serum lipids and glucose were measured in millimoles per litre.

The metabolic syndrome criteria were defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III [12]. Accordingly, the criteria are:

1. Hypertension; BP ≥130/85 and/or medication
2. Hypertriglyceridemia; triglycerides >1.695 mmol/l
3. Low HDL cholesterol; <1.036 mmol/l (men), <1.295 mmol/l (women)
4. Central obesity; waist circumference >102 cm (men), >88 (women)
5. Fasting plasma glucose > 6.1 mmol/l

Measurements for the last two criteria were available only for participants attending the second phase. BMI was used instead of waist circumference, as both were possible alternatives in other studies [13, 14]. In this study, the cut-off values for BMI were calculated as the mean BMI values in men and women with waist circumference of 102 and 88 cm, respectively, among those who attended the second phase. Accordingly, BMI >28.3 for men and >27 for women was used. The last criterion was valued positive if non-fasting glucose level was ≥11, ≥10 or ≥6.1 mmol/l and the time since last meal was >1, >2 or >8 h, respectively. Mean BP was calculated using the formula (systolic BP+ diastolic BP*2)/3.

A complete validated register of cases of diabetes mellitus was available. Cases of diabetes mellitus were identified by review of medical records of all participants who:

1. Reported diabetes mellitus or age when diagnosed in the fourth survey
2. Reported use of anti-diabetic drugs in the fourth survey
3. Reported diabetes mellitus in the second, third and fifth surveys
4. Had elevated HbA1c (≥6.5) level in the fourth or fifth surveys
5. Were registered with a diabetes-related diagnosis in the medical records

Out of 756 possible cases of diabetes mellitus, 646 subjects were confirmed to have diabetes; of them, 455 subjects had the disease before the start of follow-up and the other 191 subjects developed the disease during the follow up.

Fracture registration

Our fracture registry is based on the radiographic archives at the University Hospital in Tromsø. The nearest alternative radiographic service or fracture treatment facility is located 250 km from Tromsø. The only fractures that would be missed are fractures occurring while inhabitants were travelling and no control radiographic examination was done after returning home as well as fractures not radiographically examined. The computerised records in the radiographic archives of the hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. All fracture-coded radiographic examinations performed on participants of the fourth survey were reviewed to ascertain fracture code, identify exact anatomical location of the fracture and distinguish consecutive fracture cases from one another. Similar registration for participants in the second and third surveys was performed, validated and described by Joakimsen et al. [15].

For our target population, the fracture registry covered the period between 1 January 1994 and 31 December 2000. Follow-up time was assigned for each participant from the date of phase I examination to the date of first fracture or to 31 December 2000.

Statistics and analysis

The relative risk (RR) of fracture was calculated using Cox proportional hazard model in the SAS statistical package [16]. All subjects with a missed value for any criteria of the metabolic syndrome were excluded (n=168). Data are

presented stratified by gender. Differences in means between groups were tested using age-adjusted general linear models. Subjects were given a score of 1 for each feature of the metabolic syndrome (based on the NCEP definition) and grouped according to number of features. All variables were included in one model to assess their independent effects on fracture risk. First, the variables were entered in continuous forms then in dichotomous forms based on cut-off points defined by the NCEP definition of the metabolic syndrome to assess linear trends and threshold effects. The metabolic features were ranked in quartiles, and linear trends of the risk of fractures assessed. Interaction terms between variables were tested. Models were stratified by statistically significant ($p<0.05$) interacting variables. Stratification was based on the cut-off point determined by the NCEP definition of the interacting variable. Risks associated with elevated non-fasting serum glucose adjusted for time since last meal were measured among those attending the second phase of the survey only. Multi-variate models of the continuous and dichotomous forms of variables were adjusted for age, diabetes mellitus, smoking and physical activity. Each model including quartiles of one metabolic feature was adjusted for the other features in their continuous forms in addition to age and diabetes mellitus.

Results

A total of 446 and 803 non-vertebral fractures were registered among 12,866 men and 14,293 women, respectively. After excluding all subjects with missed measurements of any metabolic syndrome criteria, 438 men out of 12,780 and 789 women out of 14,211 suffered non-vertebral fractures. Among 227 men and 228 women with validated diabetes mellitus, there were 51 and 30 type I diabetics, respectively. Table 1 show the characteristics of the total study population, non-diabetics and type II diabetics stratified by gender. Generally, there were significant age-adjusted differences at baseline between non-diabetics and type II diabetics with respect to BP and non-fasting serum lipids profiles, except for diastolic BP, mean BP and cholesterol in men. There were no significant differences between total population and non-diabetic groups, as they were largely overlapping, apart from age in both men and women. Those with non-fasting HDL levels below the gender-specific cut-off points, 1.4% and 0.92% reported using lipid-lowering drugs in men and women, respectively. The same percentages for subjects with non-fasting triglycerides levels above cut-off point were 1.81% and 1.77 for men and women, respectively.

Figure 1 shows the adjusted relative risk of non-vertebral fractures by the burden of metabolic syndrome features (BP, HDL, triglycerides and BMI), as defined earlier. Although less linear for men, the trends were significant for both genders ($p=0.004$ men,$p<0.0001$ women). Accordingly, men and women with the metabolic syndrome defined by having three or more of these criteria were protected against fractures (RR 0.71; 95% CI 0.51–0.99\ and RR 0.66; 95% CI 0.53–0.82, respectively).

Figure 2 shows the relative risk of non-vertebral fracture by quartiles of mean BP, HDL, triglycerides and BMI in men and women in multi-variate models adjusted for age and diabetes mellitus. Due to a significant interaction between HDL and BMI in men, fracture risk was estimated in stratified models for these variables. There was a trend of significantly reduced fracture risk by increasing mean BP among men only ($p=0.04$). Increasing levels of HDL

Table 1 Baseline characteristics of men and women in the fourth survey 1994–1995 (The Tromsø Study)

	Men			Women		
	Total population	Non-diabetics	Type II diabetics	Total population	Non-diabetics	Type II diabetics
Number	12,780	12,557	172	14,211	13,985	196
Total number of fractures	438	425	8	789	764	22
Number of fractures by location[a]	72/84/29/43/80	65/82/27/42/79	4/1/1/1/1	175/359/83/30/59	162/349/81/30/58	12/10/1/0/1
Age	46.7±0.13	46.4±0.13	64.1±0.85[b]	47.2±0.13	46.9±0.13	68.1±0.81[b]
Diastolic blood pressure	80.0±0.1	80.0±0.11	84.8±0.95	76.4±0.11	76.3±0.11	88.0±1.2[c]
Systolic blood pressure	137.5±0.15	137.3±0.15	150.5±1.7[c]	132.3±0.19	131.9±0.19	164.9±1.9[c]
Mean blood pressure	99.2±0.11	99.1±0.11	106.7±1.11	95.1±0.13	94.8±0.13	113.6±1.35[c]
High-density lipoprotein (HDL)	1.34±0.003	1.35±0.003	1.23±0.03[c]	1.64±0.003	1.64±0.003	1.39±0.03[c]
Cholesterol	6.05±0.01	6.04±0.01	6.47±0.1	6.05±0.01	6.04±0.01	6.75±0.09[c]
Triglycerides	1.77±0.01	1.76±0.01	2.34±0.1[c]	1.35±0.01	1.3±0.01	2.44±0.11[c]
Body mass index (BMI)	25.6±0.03	25.6±0.03	28.0±0.3[c]	24.8±0.04	24.7±0.04	29.4±0.42[c]

Data are means±standard error
Blood pressure measured in mmHg. High density lipoprotein (HDL), cholesterol and triglycerides level are measured in mmol/l
Body mass index (BMI) measured in kg/m^2
[a]Hip/ wrist/ proximal humerus/ankle/foot fracture
[b]Mean difference between non-diabetics and type II diabetics, p value <0.0001
[c]Age-adjusted mean difference between non-diabetics and type II diabetics, p value <0.0001

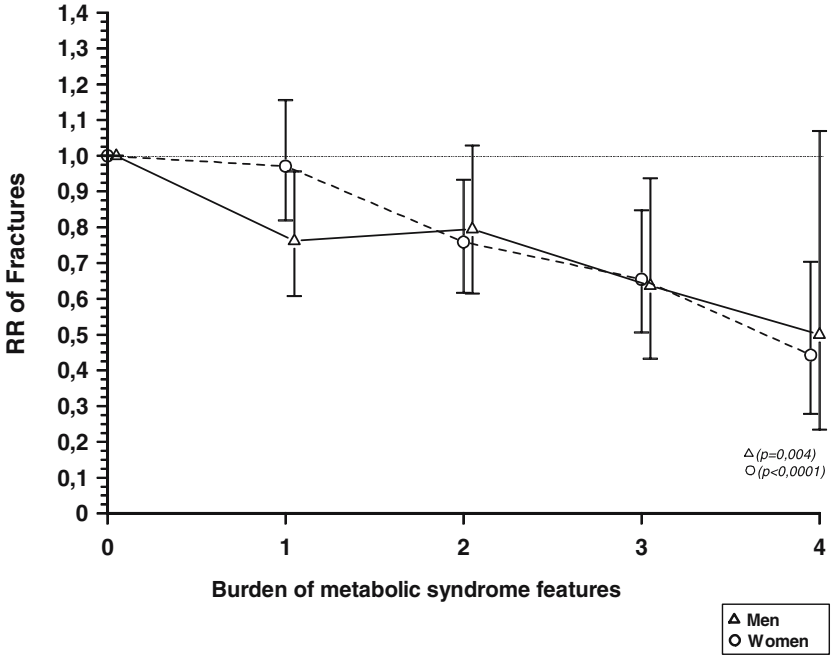

Fig. 1 Relative risk (RR) of non-vertebral fractures and 95% confidence interval (CI) by burden of metabolic syndrome features among men and women in the fourth survey 1994–1995 (The Tromsø Study). Blood pressure (BP), high-density lipoprotein (HDL), triglycerides and body mass index (BMI)

increased fracture risk significantly in men with BMI greater than 28.3 kg/m^2 (p=0.046) whereas among women, increased fracture risk by increasing HDL (p=0.023) and reduced fracture risk by increasing BMI (p= 0.004) were unaffected by each other.

Accordingly, in women, the independent risk of non-vertebral fractures associated with one standard deviation change in each feature of the metabolic syndrome was significantly increased for increasing level of HDL (RR 1.12; 95% CI 1.05–1.21) and decreased for increasing BMI (RR 0.91; 95% CI 0.84–0.98). In men, the non-vertebral fracture risk was independently decreased for increasing mean BP (RR 0.89; 95% CI 0.8–0.99) and increased for increasing level of HDL with high BMI (RR 1.51; 95% CI 1.2–1.9). In men with low levels of HDL, increasing BMI decreased fracture risk without reaching statistical significance (RR 0.77; 95% CI 0.6–1.01).

When applying the NCEP definition of the metabolic syndrome on the features in multi-variate models, only women had independently reduced fracture risk associated with high triglycerides and BMI, as shown in Table 2. Among men, although there was interaction between HDL and BMI, stratifying the model by BMI did not show significant association between dichotomised HDL and

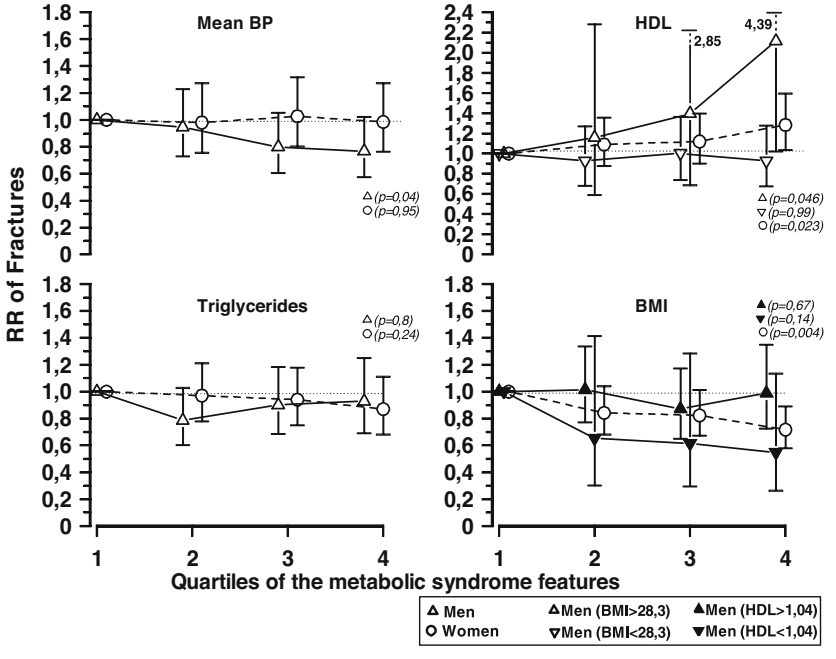

Fig. 2 Relative risk (RR) of non-vertebral fractures and 95% confidence interval (CI) by quartiles of mean blood pressure (BP), high-density lipoprotein (HDL), triglycerides and body mass index (BMI) in multivariate models adjusted for age and diabetes mellitus among men and women in the fourth survey 1994–1995 (The Tromsø Study). Relative risk (RR) for men is stratified by BMI for HDL quartiles and by HDL for BMI quartiles

Table 2 Relative risk (RR) and 95% confidence interval (CI) of non-vertebral fractures for abnormal values of features of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP 2001) in gender-specific multi-variate models adjusted for age, diabetes mellitus, smoking and physical activity (The Tromsø Study)

	Men	Women
BP ≥130/85	0.81	0.95
	0.65–1.01	0.81–1.11
HDL<1.036 mmol/l (men)	0.89	0.83
<1.295 mmol/l (women)	0.68–1.17	0.68–1.01
Hypertriglyceridemia	0.96	0.83
≥1.695 mmol/l	0.78–1.18	0.7–0.99
BMI >28.3 (men)	0.79	0.81
>27 (<women)	0.6–1.03	0.68–0.95

fracture risk in men with high BMI. Adjusting the models for hypertension treatment did not alter the association between BP and fracture risk in either men or women. Including only those treated for hypertension, the analysis showed non-significant 30% and 18% fracture risk reduction in men and women, respectively. Further adjustment for medications such as oral steroids and lipid-lowering drugs (only among those younger than 70 years) did not alter the risk estimates although using lipid-lowering drugs independently protects against fractures only in women (RR 0.11; 95% CI 0.01–0.8).

In separate analyses restricted to those attended the second phase of the survey, elevated non-fasting serum levels of glucose in both continuous and dichotomous forms showed no association with non-vertebral fracture risk in both men and women. Limiting the analysis to type II diabetics, no association was found between features of the metabolic syndrome and non-vertebral fracture risk (Table 3). However, including those who developed type II diabetes after the start of follow–up (n=191) to the diagnosed type II diabetics showed a borderline significant >50% reduction in fracture risk associated with hypertriglyceridemia (p=0.053) in women.

Table 3 Relative risk and 95% CI of non-vertebral fractures for abnormal values of features of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP 2001) among *type II diabetic* in sex specific multivariate models adjusted for age, smoking and physical activity (The Tromsø Study)

	Men	Women
Blood pressure≥130/85	1,84	1,02
	0,35–9,65	0,39–2,66
HDL<1,036 mmol/l (men)	0,95	0,7
<1,295 mmol/l (women)	0,17–5,43	0,28–1,74
Hypertriglyceridemia	0,92	0,68
≥1,695 mmol/l	0,2–4,27	0,28–1,68
BMI>28,3 (men)	0,37	1,29
>27 (women)	0,01–2,0	0,5–3,29

Discussion

There was a significant protective effect against non-vertebral fractures by increasing burden of metabolic syndrome features. We found reduced risks of non-vertebral fractures with increasing BP in men and for increasing BMI in women, and an increased risk of fractures with increasing levels of HDL among women and obese men.

Bias considerations

This study included a large numbers of men and women with a wide age range at base line. The external validity refers mainly to a Caucasian population. The potential for selection bias was limited, with 77% of the eligible population included in the analyses. With the prospective design of this study, risk factors included were measured and/or classified without knowledge of future risk of fractures. The limited power constitutes a major limitation in this study with respect to the analyses among type II diabetics. Interpretation of results were limited to the effect of non-fasting serum levels of HDL and triglycerides on non-vertebral fracture risk. With respect to non-fasting glucose, interpretation of results was limited mainly to men and women older than 55 years.

Burden of metabolic syndrome features To our knowledge, our study is the first to report a reduced risk of non-vertebral fractures by increasing number of the metabolic syndrome features. Features of the metabolic syndrome included were BP, HDL, triglycerides and BMI. For those with one feature, men were more protected than women. The high number of hypertensive men and women in this category explains the difference, as hypertension protects significantly against fractures in men only.

Blood pressure In the study by Cappuccio et al., higher BP in elderly women (66–91 years) was associated with increased bone loss at the femoral neck [2] while Lidfeldt et al. found diastolic and systolic BP to be positively associated with bone density (wrist) among women (50–59 years) [3]. One Canadian study found hypertension to be associated with higher BMD values in men and women 50 years of age and older [17]. As most fractures occur in those aged >65 years and BP increases with age, an increased risk of fractures for increasing BP should be expected. On the contrary, we found no risk associated with increasing BP in women and a protective effect in men. Although higher risk of falls due to episodes of hypotension could be expected among hypertensive-treated patients, adjusting for treatment did not affect the association between hypertension and fracture risk. More-

over, low fracture risk was observed among those using treatment for hypertension although it was not significant.

High-density lipoprotein HDL has been shown to be negatively associated with bone density [3], and as expected, our results showed a high risk of non-vertebral fractures associated with increasing levels of HDL in women and men with high BMI. One possible explanation for this phenomenon in women could be that an unbalanced diet severely limiting calcium intake in order to correct serum levels of cholesterol is a risk factor for postmenopausal osteoporosis and wrist fractures, as found by Varenna et al. [18]. However, the interpretation of our results should be carefully considered, as only non-fasting levels of HDL were used. Why HDL in men is associated with increased fracture risk in the obese only needs further studies.

Triglycerides Triglycerides have been shown to have a positive association with bone density among women [3], which is in accordance with the protective effect on fracture risk of high triglyceride levels for women in our study. Increasing levels of triglycerides was not associated with fracture risk in men. As non-fasting levels of triglycerides were used in this study, further studies including fasting levels are needed to justify out results.

Body mass index The association between BMI and fracture risk was consistently negative among women, which supports earlier findings [19–23]. Among men, there was non-significant association between BMI and fracture risk; but when stratified by HDL levels, risk estimates suggested much lower risk (with borderline significance) in those with low HDL levels only. Although higher impact of a trauma is expected with increased body mass, the lower fracture risk among the obese is thought to be associated with protective layers of fat padding around skeletal structures and better bone mass [19, 21].

Glucose Previous studies have suggested an effect of glucose on bone metabolism; however, conflicting results were reported [24–27]. Our findings showed no significant association between non-fasting glucose levels and fracture risk; however, the interpretation of such findings will be limited to non-fasting levels in older men and women.

Type II diabetes mellitus The new knowledge about features of the metabolic syndrome opens up the possibility for solutions to the conflicting results regarding diabetes mellitus, bone mass and fracture risk. Despite the high risk of fractures among type II diabetic women described previously [6, 7], hyperinsulinemia associated with the metabolic syndrome may be responsible for increased bone density [3, 28]. Our findings show that the risk of fracture associated with type II diabetes is not explained by the metabolic abnormalities preceding the disease. As the other metabolic features, apart from impaired glucose metabolism, are protective or indifferent with respect to fractures, other factors, such as glucose intolerance, effect of medications and other patho–physiological mechanisms should be considered when investigating the fracture risk associated with type II diabetes.

Conclusion

Increasing burden of metabolic syndrome features significantly protect against non-vertebral fractures. Increasing BP in men and BMI in women and decreasing non-fasting serum levels of HDL in women and obese men reduce the risk of non-vertebral fractures.

References

1. Meyer HE, Tverdal A, Falch JA (1993) Risk factors for hip fracture in middle–aged Norwegian women and men. Am J Epidemiol 137:1203–1211
2. Cappuccio, FP et al. (1999) High blood pressure and bone-mineral loss in elderly white women: a prospective study. Study of Osteoporotic Fractures Research Group. Lancet 354 (9183):971–975
3. Lidfeldt J, et al. (2002) The influence of hormonal status and features of the metabolic syndrome on bone density: a population-based study of Swedish women aged 50 to 59 years. The women's health in the Lund area study. Metabolism: Clinical & Experimental 51(2):267–270
4. Varosy PD, et al. (2003) Fracture and the risk of coronary events in women with heart disease. American Journal of Medicine 115(3):196–202
5. Isomaa B, (2003) A major health hazard: the metabolic syndrome. Life Sciences 73(19):2395–2411
6. Schwartz AV, et al. (2001) Older women with diabetes have an increased risk of fracture: a prospective study. [see comment]. Journal of Clinical Endocrinology & Metabolism 86(1):32–38
7. Forsen L, et al. (1999) Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. Diabetologia 42(8):920–925
8. Heath H 3rd, Melton LJ 3rd, Chu CP (1980) Diabetes mellitus and risk of skeletal fracture. New England Journal of Medicine 303(10):567–570
9. Seeley DG, et al. (1996) Predictors of ankle and foot fractures in older women. J Bone Miner Res 11(9):1347–1355
10. Schirmer H, Lunde P, Rasmussen K (1999) Prevalence of left ventricular hypertrophy in a general population; The Tromso Study. [see comment]. European Heart Journal 20(6):429–438
11. The-Tromsø-Study, http://www.ism.uit.no/tromso5/forsteskjema-t4-eng.pdf. 1994
12. Expert Panel on Detection, E. and A. Treatment of high blood cholesterol (2001) In: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) [see comment]. JAMA 285(19):2486–9247
13. Han TS (2002) Analysis of Obesity and Hyperinsulinemia in the Development of Metabolic Syndrome: San Antonio Heart Study. Obes Res Sep 10(9):923–931
14. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation [see comment]. Diabetic Medicine 15(7):539–553
15. Joakimsen RM, et al (2001) The Tromso study: registration of fractures, how good are self-reports, a computerized radiographic register and a discharge register? Osteoporos Int 12 (12):1001–1005

16. INSTITUTE, S., SAS/STAT Guide for Personal Computers. Version 6 edition. 1992, Cary, NC (USA): SAS Institute
17. Hanley DA, et al (2003) Associations among disease conditions, bone mineral density, and prevalent vertebral deformities in men and women 50 years of age and older: cross-sectional results from the Canadian Multicentre Osteoporosis Study. Journal of Bone & Mineral Research 18(4):784–790
18. Varenna M, et al (2001) Unbalanced diet to lower serum cholesterol level is a risk factor for postmenopausal osteoporosis and distal forearm fracture. Osteoporosis International 12 (4):296–301
19. Joakimsen RM, et al. (1998) The Tromso Study: body height, body mass index and fractures. Osteoporos Int 8(5):436–442
20. Cummings SR, et al. (1985) Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 7:178–208
21. Grisso JA, et al. (1991) Risk factors for falls as a cause of hip fracture in women. The Northeast Hip Fracture Study Group. N Engl J Med 324:1326–1331
22. Jaglal SB, Kreiger N, Darlington G (1993) Past and recent physical activity and risk of hip fracture. Am J Epidemiol 138:107–118
23. Michaelsson K et al. (1995) Diet, bone mass, and osteocalcin: A cross-sectional study. Calcif Tissue Int 57:86–93
24. McNair P, et al. (1979) Bone mineral loss in insulin-treated diabetes mellitus: studies on pathogenesis. Acta Endocrinologica 90(3):463–472
25. Okazaki R et al. (1997) Metabolic improvement of poorly controlled noninsulin-dependent diabetes mellitus decreases bone turnover. Journal of Clinical Endocrinology & Metabolism 82(9):2915–2920
26. Rosato MT, Schneider SH, Shapses SA (1998) Bone turnover and insulin-like growth factor I levels increase after improved glycemic control in noninsulin-dependent diabetes mellitus. Calcified Tissue International 63(2):107–111
27. Balint E et al. (2001) Glucose-induced inhibition of in vitro bone mineralization. Bone 28(1):21–28
28. Barrett–Connor E, Kritz–Silverstein D(1996) Does hyperinsulinemia preserve bone? [see comment]. Diabetes Care 19(12): 1388–1392