4

Sex hormones and stroke

4.1 Endogenous sex hormone levels and risk of stroke in the elderly

Summary

Background - There is controversy as to whether sex hormones, and in particular estradiol, are related to the risk of stroke. The relation between endogenous sex hormones and risk of stroke in men and postmenopausal women is not yet clear.

Methods - We analyzed cohort of 6,735 participants from the population-based Rotterdam Study, who were free from previous stroke, reported no hormone therapy and had a blood sample taken at baseline (1990-1993). The cohort was followed for stroke until January 1 1998. A total of 217 strokes occurred. Total and bioavailable estradiol and testosterone were measured in stroke cases and a subcohort of 1,372 random participants. The relation between sex hormones and stroke in men and women was assessed using a case cohort approach and Cox regression.

Findings - Endogenous sex hormone levels were not related to the risk of stroke in women. In men, higher estradiol levels were related to a decreased risk of stroke, although not statistically significant. Higher testosterone levels were related to a lower risk of stroke and cerebral infarction (RR 0.44 (95% CI 0.26-0.77) and 0.39 (95% CI 0.22-0.71) per SD increase in bioavailable testosterone, respectively). A statistically significant interaction was found between current smoking and testosterone. Particularly in male non-smokers, higher testosterone levels were related to a lower risk of stroke.

Interpretation - Endogenous sex hormones are not related to the risk of stroke in postmenopausal women. Higher testosterone levels are related to a lower risk of stroke in men, particularly in those who do not smoke.

Introduction

Sex hormones, and in particular estradiol, may play a role in the differences between men and women in the occurrence of cardiovascular disease. Yet, several studies on estrogen replacement therapy in women failed to report a beneficial effect on stroke.[1,2] The role of endogenous sex hormones in elderly men and women is not yet clear. With ageing, hormone levels decline in both sexes, with women experiencing a rapid decline after menopause and men having a more gradual decrease with age.[3,4] To date, it is unclear whether lower endogenous sex hormone levels are related to an increased risk of stroke. Hospital-based studies have reported decreased levels of testosterone in men with coronary artery disease and acute stroke.[5,6] However, this relationship has not yet been investigated in a population. We hypothesized that a low estradiol level in women, and a low testosterone level in men is related to an increased risk of stroke. We investigated this relationship in an elderly population of elderly men and postmenopausal women.

Methods

Study population

The study was conducted in the Rotterdam Study, a population-based, single-center cohort study on chronic diseases in the elderly.[7] All inhabitants of Ommoord, a district of Rotterdam, aged 55 years or older were invited to the study. People living in homes for the elderly were also included. The Medical Ethics Committee of Erasmus University Rotterdam approved the study. Written informed consent to retrieve information from treating physicians was obtained from all participants. Participation rate of those invited to the study was 78% and in total 7,983 subjects participated. Baseline measurements were obtained from 1990 to 1993 and consisted of an interview at home and two visits to the research center for physical examination. For the present analysis, 6,732 persons (2,727 men and 4,005 women) were eligible who had a blood sample taken, had no history of stroke and did not use any hormone therapy at baseline.

Study design

We used a case cohort approach.[8] Among the 6,732 eligible persons, we selected a random subcohort of 1,372 participants, including 647 men and 725 women. All eligible persons were followed-up for stroke until January 1 1998. A total of 217 strokes had occurred. Among these, 51 occurred in the subcohort.

Steroid hormone measurements

We took non-fasting blood samples during the baseline-visit to the research center. Samples were taken between 8.30 AM and 4.00 PM. Platelet-free plasma was obtained by two-stage centrifugation, first for 10 minutes at 1,600 g at 4˚C and then for 30 minutes at 7,000 g. Platelet-free samples were immediately frozen in liquid nitrogen and transferred to the laboratory. At the laboratory the plasma samples were stored at -80°C until hormone assessment. Plasma levels of steroids (testosterone and estradiol) and sex hormone binding globulin (SHBG) were estimated in 12 batches using coated tube or double antibody radioimmunoasays, purchased from Diagnostic Systems Laboratories (Webster, Texas, USA). Because of the relatively small volumes of plasma available, all values reported are single sample estimations. Intra-assay coefficients of variation, determined on basis of duplicate results of internal quality control plasma pools with 3 different levels of each analyte, were below 4% (SHBG), 21% (estradiol) and 13% (testosterone). The results of all batches were normalized by multiplying all concentrations within a batch with a factor, which equalized results for the internal quality control pools. Assays were performed blinded for outcome. Bioavailable estradiol and testosterone (non-SHBG bound) were calculated on the basis of hormone and binding protein levels and respective affinity constants according to the method described by Södergård [9] and Van den Beld et al.[10] Total testosterone and estradiol were measured in 613 and respectively 494 men and in 718 and respectively 587 women. We were able to measure bioavailable testosterone and estradiol in 457 (74.6%) and 331 (67.0%) men, respectively. Corresponding numbers for women were 579 (80.6%) and 438 (74.6%), respectively. Missing hormone values did not differ according to case status.

Assessment of stroke

A previous stroke was assessed during the baseline interview by asking "did you ever suffer from a stroke, diagnosed by a physician?" Medical records of subjects who answered 'yes' were checked in order to verify the diagnosis.[11] Once subjects enter the Rotterdam Study they are continuously monitored for major cardiovascular events through automated linkage with the files from GP's. Information on vital status is obtained at regular intervals from the municipal authorities in Rotterdam. When an event or death has been reported, additional information is obtained by interviewing the GP and by scrutinizing information from hospital discharge records in case of admittance or referral. Information on all possible strokes was reviewed by a neurologist (PJK) who classified the stroke as definite, probable or possible and assessed subtypes, based on neuro-imaging.[12] A stroke was definite if the diagnosis was based on typical clinical symptoms and neuro-imaging excluded other diagnoses. A stroke was considered probable in case typical clinical symptoms were present but neuro-imaging was not performed. For fatal strokes, other causes of death, especially cardiac should have been excluded. A stroke was classified as possible if clinical symptoms were less typical and neuro-imaging was not performed, or if a cardiac cause of death could not be excluded in case of a reported stroke.

Cardiovascular risk factors

A computerized questionnaire was used to obtain information on current health status, medication use and medical history at baseline, including history of myocardial infarction, coronary bypass surgery (CABG) and coronary angioplasty (PTCA). All reported myocardial infarctions and TIAs were verified by using medical records. History of intermittent claudication and angina pectoris was assessed through the Rose questionnaire.[13] A history of cardiovascular disease was considered to be present if the participant had one of the following conditions: a history of myocardial infarction, TIA, CABG, PTCA, intermittent claudication or angina pectoris. Medication use was classified according to ATC-codes.[14] Functional status was assessed using the Disability Index of the Stanford Health Assessment Questionnaire.[15] Smoking status was assessed during the baseline interview and participants were classified as current, former or never smoker. In women, age at menopause was assessed during the interview. At the research center, height and weight was

measured and Quetelet's body mass index (kg/m^2) was calculated. Diabetes mellitus was defined as use of oral glucose lowering drugs or insulin or post-load serum glucose level higher than 11.0 mmol/L. Ultrasonography of both left and right carotid artery was performed using a 7.5 MHz linear array transducer (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, U.S.A.). According to the protocol of the Rotterdam Study the mean common carotid intima-media thickness was measured.[16]

Data analysis

We evaluated the relation between endogenous sex hormones and risk of stroke and cerebral infarction with a Cox proportional hazards model, with modification of standard errors, based on robust variance estimates.[17] We used the method according to Barlow[17] in which the subcohort is weighted by the inverse of the sampling fraction from the source population. Men and women were analyzed separately. We examined total and bioavailable (non-SHBG bound) plasma levels of testosterone and estradiol in quintiles. Participants in the lowest quintile were taken as the reference. Subsequently we analyzed estradiol and testosterone as a continuous variable per standard deviation increase. In order to optimally adjust for age, we used age as timescale. Entry time was defined as age at study entry. Censoring age was defined as age at stroke, death or end of the study, whichever came first. We further adjusted for diabetes, history of cardiovascular disease, smoking, blood pressure, medication use, body mass index, disability index, blood pressure and common carotid intima-media thickness. Since smoking influences hormone levels, we performed separate analyses within the non-smokers. Results are presented as rate ratios with corresponding 95% confidence intervals. All analyses were performed using SAS software.

Results

Table 1 shows baseline characteristics of the study population. Mean follow-up time was 4.5 years. A total of 97 strokes occurred in men and 120 in women. Subtyping of stroke in men revealed 55 cerebral infarctions, 12 intracerebral hemorrhages and 30 unspecified strokes. Corresponding figures for women were 58, 10 and 52, respectively. Overall, hormone levels were higher in men than in women (table 1).

Table 1

Baseline characteristics of the subcohort.

	Men (n= 647)	Women (n=725)
Age (years)	69.4 (8.3)	71.5 (9.4)
Body mass index (kg/m^2)	25.7 (3.0)	26.6 (3.8)
Smoking (% current)	28.4	19.5
Systolic blood pressure (mm Hg)	139.2 (21.8)	140.5 (22.3)
Diastolic blood pressure (mm Hg)	75.4 (11.9)	74.0 (11.7)
Diabetes (%)	9.1	7.6
Total estradiol (mean) (pmol/L)	45.0 (23.6)	15.5 (14.4)
Bioavailable estradiol (mean) (pmol/L)	34.5 (18.2)	11.0 (10.7)
Total testosterone (nmol/L)	11.5 (4.0)	1.4 (0.8)
Bioavailable testosterone (nmol/L)	6.8 (2.8)	0.7 (0.4)
History of cardiovascular disease (%)	34.9	19.0
Medication use (number of categories)	1.5 (1.9)	1.9 (2.1)
Mean common carotid IMT (mm)	0.8 (0.1)	0.8 (0.2)
Disability Index	1.2 (0.4)	1.5 (0.6)

Values represent means (SD).

Women

In women, endogenous estradiol and testosterone were not related to the risk of stroke (figures 1 and 2). The results did not change when we used cerebral infarction as outcome. Restriction to non-smokers yielded similar results.

Men

Figure 1 shows that higher estradiol levels were related to a lower risk of stroke in men, although this was not statistically significant (RR per SD increase 0.73 (95% CI 0.42-1.27)). The results for cerebral infarction were similar. Higher levels of testosterone were related to a significantly decreased risk of stroke. Men in the highest two quintiles of bioavailable testosterone had an 11-fold and respectively 5-fold decreased risk of stroke, as compared to the lowest quintile (figure 2). Corresponding relative risks of cerebral infarction were 0.08 (95% CI 0.01-0.45) and 0.15 (95% CI 0.03-0.76), respectively. The risks of stroke and cerebral infarction decreased by respectively 56% and 61% per standard deviation increase in bioavailable testosterone (RR 0.44 (95% CI 0.26-0.77) and 0·39 (95% CI 0.22-0.71), respectively).

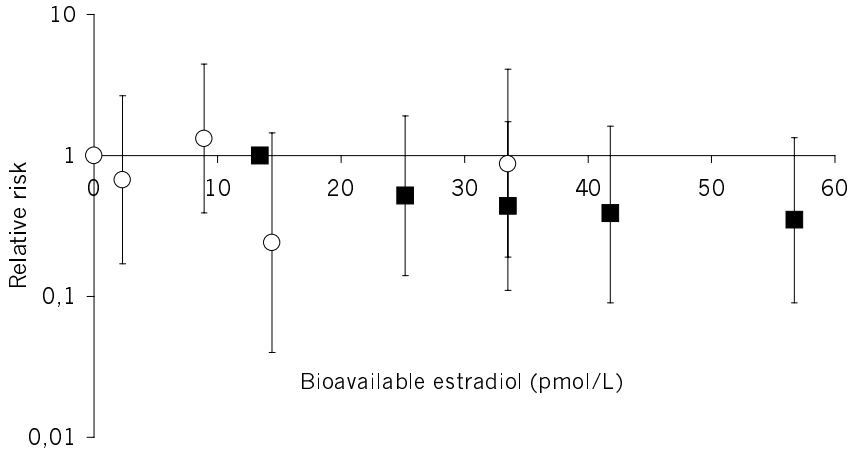

Figure 1

Relative risk of stroke in relation to quintiles of bioavailable estradiol (plotted at its median) in men (black squares) and women (white rounds), adjusted for age, diabetes, systolic and diastolic blood pressure, smoking, body mass index, history of cardiovascular disease, medication use, carotid IMT and disability index.

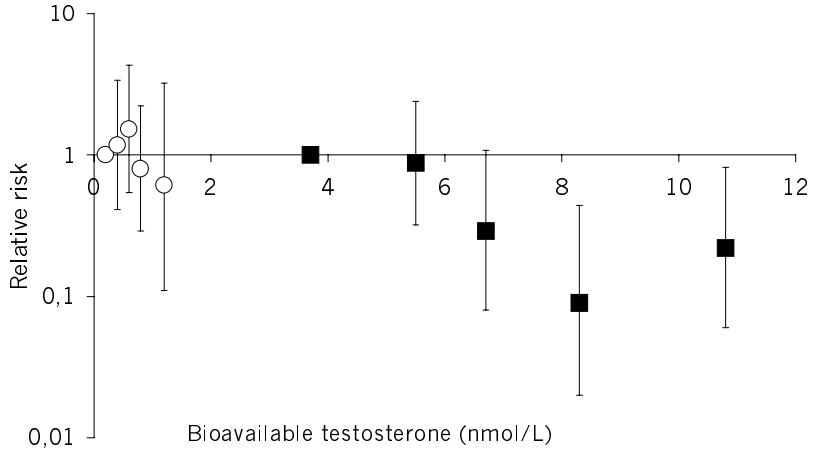

Figure 2

Relative risk of stroke in relation to quintiles of bioavailable testosterone (plotted at its median) in men (black squares) and women (white rounds), adjusted for age, diabetes, systolic and diastolic blood pressure, smoking, body mass index, history of cardiovascular disease, medication use, carotid IMT and disability index.

In men, a statistically significant interaction was found between current smoking and testosterone ($p<0.01$). With restriction to non-smokers, the relationship between testosterone and stroke in men became even stronger, in particular in the highest quintile. Using the same overall cut-off points, men in the fourth and fifth quintile of bioavailable testosterone had respectively 8 fold and 20-fold decreased risk of stroke, as compared to the first quintile (table 2).

Table 2

Risk ratio of stroke in relation to quintiles of testosterone (nmol/L) and estradiol (pmol/L) in non-smokers.

Quintile	Men (n=491)			
	Range	No. of cases	RR*	RR¶
Total testosterone				
Quintile				
1st (reference)	<8.3	19	1.00	1.00
2nd	8.3-10.7	13	0.66 (0.26-1.66)	0.62 (0.20-1.90)
3rd	10.7-12.2	4	0.23 (0.07-0.73)	0.19 (0.04-0.87)
4th	12.2-14.2	3	0·21 (0.05-0.77)	0.12 (0.02-0.71)
5th	>14.2	5	0.39 (0.12-1.27)	0.31 (0.07-1.34)
Per SD increase			0.56 (0.38-0.81)	0.43 (0.25-0.76)
Bioavailable testosterone				
Quintile				
1st (reference)	0-4.71	16	1.00	1.00
2nd	4.71-6.12	10	0.91 (0.36-2.28)	0.91 (0.25-3.26)
3rd	6.13-7.16	8	0.54 (0.20-1.47)	0.31 (0.05-1.90)
4th	7.17-8.66	2	0.17 (0.03-0.82)	0.12 (0.02-0.72)
5th	>8.66	1	0.09 (0.01-0.83)	0·05 (0·00-0·60)
Per SD increase			0.49 (0.32-0.75)	0.32 (0.16-0.64)
Total estradiol				
Quintile				
1st (reference)	<26.8	7	1.00	1.00
2nd	26.8-37.2	7	1.57 (0.44-5.53)	1.52 (0.33-7.01)
3rd	37.2-48.1	7	1.52 (0.44-5.23)	0.99 (0.23-4.32)
4th	48.1-60.3	7	1.32 (0.39-4.48)	0.83 (0.17-4.14)
5th	>60.3	8	1.67 (0.44-6.42)	0.53 (0.11-2.67)
Per SD increase			1.08 (0.73-1.59)	0.72 (0.44-1.18)
Bioavailable estradiol				
1st (reference)	0-18.97	8	1.00	1.00
2nd	18.98-28.91	4	0.67 (0.19-2.37)	0.75 (0.14-3.93)
3rd	28.92-37.55	6	0.80 (0.22-2.89)	0.51 (0.12-2.29)
4th	37.56-47.13	6	0.67 (0.19-2.39)	0.44 (0.07-3.03)
5th	>47.14	6	0.77 (0.19-3.13)	0.30 (0.05-1.79)
Per SD increase			0.85 (0.53-1.34)	0.61 (0.35-1.08)

* Adjusted for age and gender.

¶ Adjusted for age, diabetes, systolic and diastolic blood pressure, smoking, body mass index, history of cardiovascular disease, medication use, carotid IMT and disability index.

In male non-smokers, the risk of stroke significantly decreased by 68% per standard deviation increase of bioavailable testosterone (table 2). The corresponding risk for cerebral infarction decreased by 71% (RR 0.29 (95% CI 0.11-0.75)). Higher estradiol levels decreased the risk of stroke in male non-smokers. The risk of stroke and cerebral infarction decreased by 39% and 50%, respectively. The risk reduction for cerebral infarction was statistically significant (RR 0.50 (95% CI 0.25-0.98)). Within the male smokers, the relative risks of stroke per SD increase in total and free testosterone were 1.23 (0.38-3.95) and 0.82 (0.18-3.75), respectively. Corresponding relative risks for total and free estradiol 1.14 (0.49-2.64) and 0.86 (0.16-4.37), respectively.

DISCUSSION

We found that endogenous estradiol and testosterone levels were not related to the risk of stroke in postmenopausal women. In men, higher testosterone and estradiol levels were related to stroke, particularly in the non-smokers. The strengths of the present study are its prospective and population-based design. Further, the study was large and based on a relatively long follow-up period. A possible limitation is the impaired long-term stability of hormone levels in blood stored at low temperatures. Deviation of hormone levels due to long storage is independent of cases status. Therefore, misclassification of hormone levels would have led to an underestimation of the associations that we found. Another possible limitation is that we had missing values of hormone levels. However, because missingness of hormone levels was independent of case status, incompleteness of hormone assessment probably has not led to a selection bias. The classification of strokes was done blinded for hormone status. Therefore, misclassification of strokes, if present, would have led to an underestimation of the associations.[18]

Sex hormones and stroke in women

We failed to observe an effect from endogenous estradiol and testosterone on the risk of stroke in women. All women in our study were postmenopausal and hormone levels were very low. It is conceivable that only premenopausal levels are effective. To date, there is controversy about the effect of hormone replacement therapy in women on stroke. Despite positive reports,[19-25] a recent case-control study and the Heart and Estrogen-progestin Replacement Study failed to find a protective effect on stroke.[1,2] It has even been reported that

hormone replacement therapy has no beneficial effect on the secondary prevention of stroke.[26] Although endogenous hormone levels are much lower than the levels achieved by hormone substitution, our findings are in agreement with these negative studies.

Sex hormones and stroke in men

Our finding that a higher testosterone level protects against stroke in men, particularly in non-smokers, remained even when we corrected for atherosclerosis, comorbidity and markers of good health. Estrogen showed a similar, though less strong relationship. Hospital-based studies have reported decreased testosterone levels in men with coronary artery disease and acute stroke. Due to the cross-sectional design of these studies, it could not be established whether low testosterone levels preceded or followed the stroke. The underlying mechanisms of this relationship are not yet clear. One possible explanation is that testosterone is involved in vasodilatation and increased blood flow, as was shown by infusion of physiological concentrations of testosterone in coronary heart disease patients.[27] Experimental studies have hypothesized that the dilating effect of testosterone on the vessel wall might be through binding to testosterone receptors, local conversion into estradiol, antioxidant effects or influence on the endothelium.[27-29] Another explanation is that the effect of low testosterone levels is through increase of arterial stiffness. Studies in prostate cancer patients have shown that a low testosterone level due to orchidectomy is related to an increase in arterial stiffness.[30] Alternatively, a low testosterone level could also simply reflect a worse general health. Although we corrected for medication use, history of cardiovascular disease and functional disability, it is possible that we could not optimally adjust for general health. Our finding that higher estradiol levels are also related to lower risks of stroke in men is most likely explained by the fact that 80% of the estradiol originates from peripheral conversion of testosterone into estradiol. Therefore, the relationship with estradiol is most likely a reflection of the testosterone-effect. In recent years, testosterone replacement therapy in men is increasingly being discussed and suggested to have beneficial effects on mood, muscle strength, libido and well being.[31] Our findings suggest that a low testosterone level is a novel risk factor for stroke in men. This finding merits further research on the effect of testosterone on cardiovascular disease. Confirmation is needed before studies on

the protective effect of testosterone replacement therapy on stroke in men are advocated.

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