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Mini Review Article

Current and former smokers and hip fractures

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Abstract

The purpose of this review is to examine the correlation between tobacco smoking and hip fractures. The literature that was used for this article was based on studies that investigated not only the direct correlation between smoking and hip fractures but also the effect of smoking on bone mineral density. In general, the incidence of hip fracture was found to be higher in current smokers in both genders. Compared with never smokers, former smokers had a slightly higher risk of hip fracture that was inversely proportional to the cessation span. The relative risk (RR) of hip fracture in current male smokers was higher than the RR for nonsmokers (never and former smokers). In postmenopausal women former and current smoking increased the RR. In premenopausal and postmenopausal women, cessation of smoking decreases the risk of hip fracture. Risk rises with greater cigarette consumption. Risk declines among former smokers, but the benefit is not observed until 10 years after cessation.

Keywords: Smoking, Former smoker, Current smoker, Hip fracture, Non-smokers

Introduction

Hip fracture represents the second leading cause of hospitalization for elderly people as it is the most frequent fracture among this age group. It is not rare for a hip fracture to result in permanent disability, institutionalization or death and therefore there is a pronounced morbidity and excess mortality worldwide[1,2]. The number of incidents rises in ageing populations (630.2 per 100.000 for men and 1289.3 per 100.000 for women, between 60-80 years old)[2]. The number of hip fractures worldwide is expected to surpass 6.26 million by the year 2050, while in 1990 the corresponding number was 1.66 million[3]. Cigarette smoking remains a popular habit among adults of all ages. The number of people who smoke in the world today is over a billion, and this could result in 6 million deaths globally every year[4]. The fact that cigarette smoking is associated with great morbidity and mortality, justifies the prediction of one billion deaths of male and female smokers in the 21st century as a result of their detrimental habit[4,5]. However, the good news is that the harmful effects of smoking are dose-related and therefore it may be reversible by cessation. Smoking among its other negative impacts on human health is also associated with low Bone Mineral Density (BMD)[6,11] and increased risk of fracture in both men and women as it has been proved that BMD is a major predictor of fractures[6]. Additionally, delayed fracture union is often due to smoking[4,12]. The correlation between smoking and hip fractures however, is yet not fully understood. Possible pathways for the effect of smoking on bone include: A) Reduced blood supply to the bone B) Influence of smoking on sex hormones in both genders because of an increased oestrogen catabolism[13]. C) Negative impact of smoking on skeletal remodeling. In an experiment conducted on animal model there was a decrease in bone formation after nicotine exposure[4,6,7]. D) Association with increased bone resorption. There is clinical evidence that smokers present with lower levels of parathormone (PTH) and 25-hydroxyvitamin D comparing with nonsmokers. This is well explained by the fact that there are increased levels of calcium from resorbed bone as a result of decreased calcium absorption due to smoking. E) Smoking is associated with increased concentrations of ROIs (Reactive Oxygen Intermediates) that are related with free radicals and is also associated with reduced levels of antioxidant vitamins[3,14]. There are several other factors that affect bone health in a population of smokers except smoking. Body mass index, alcohol intake, physical activity, diet etc. Also,

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Table 1. Basic characteristics of the main studies used in this review.

Author	Study	Country	Year	Number of Participants	Subject
Forsen et al.[18]	Cohort	Norway	1998	35767	M +W
Høidrup et al.[19]	Cohort	Denmark	2000	30772	M + W
Cornuz et al.[23]	Cohort	Switzerland	1999	116229	W
Hemenway et al.[25]	Cohort	USA	1994	50000	M
Cummings et al.[26]	Cohort	USA	1995	9516	W
Mussolino et al.[27]	Cohort	USA	1998	2879	M
Jutberger et al.[39]	Cohort	Sweden	2010	1412	M
Jenkins et al.[40]	Case-control	Texas, USA	2008	190	W
Trimpou et al.[36]	Cohort	Sweden	2010	7495	M
Baron et al.[28]	Case-control	Sweden	2001	5669*	W
Høidrup et al.[41]	Cohort	Denmark	1999	6159	W
Cauley et al.[29]	Cohort	USA	2016	5994	M
Grisso et al.[30]	Case-control	USA	1997	758*	M
Holmberg et al.[35]	Cohort	Sweden	2006	22444	M
Paganini-Hill et al.[20]	Cohort	USA	1991	13649	M + W
Cumming et al.[31]	Case-control	Australia	1994	419*	M + W
Stolee et al.[21]	Cohort	Canada	2009	40276	M + W
Melhus et al.[14]	Cohort	Sweden	1999	66651	W
Olofsson et al.[37]	Cohort	Sweden	2005	2322	M
Robbins et al.[42]	Cohort	USA	2007	93676	W
Koh et al.[38]	Cohort	Singapore	2009	63257	M + W
La Vecchia et al.[32]	Case-control	Italy	1991	1658*	W
Kreiger et al.[43]	Case-control	Canada	1992	533*	W
Michaëlsson et al.[33]	Case-control	Sweden	1995	1140*	W
Meyer et al.[22]	Cohort	Norway	1993	52313	M + W
Fors. et al.[13]	Cohort	Norway	1994	38356	M + W
Thorin et al.[44]	Prospective	Sweden	2015	1044	W
Kiel et al.[34]	Cohort	USA	1992	2872	W
Johnell et al.[24]	Case-control	South Europe (Multicentral)	1995	5618*	W
Jaglal et al.[45]	Case-control	Canada	1993	1919*	W
Oyen et al.[8]	Cohort	Norway	2014	5094	M + W

*M=Men, W=Women, *Shows the sum of the subjects with fracture and the individuals from the control group.*

female smokers tend to have an earlier menopause than nonsmokers. Previous hyperthyroidism, use of long-acting benzodiazepines or anticonvulsants are also significant factors of hip fractures. Therefore is difficult to analyze the effect of smoking on bone. For that reason we had to include studies and reviews that except smoking also examined age, body weight, estrogen intake, exercise, dietary habits and alcohol consumption that affect BMD too.

Methods

An extended search of the existent literature was performed including original investigation studies, meta-analyses, cohort and case-control studies. All studies chosen for this review were written and published in the English language. Search was applied to Pubmed and the Cochrane data base and included the terms: Cigarette, tobacco, nicotine, smoking, hip fracture, fracture, current smokers, former smokers. Inclusion criteria for this review were that the studies had to: 1) be published between 1991 and 2017 in peer-reviewed journals 2) include and compare patients in different smoking status and determine the duration of smoking cessation, 3) report the relative risks (RR) and their 95% Confidence Intervals of hip fracture in different populations according to smoking habits. From 124 articles from our initial search we identified 31 relevant studies and 6 meta-analyses. Those 31 articles contained in their title either the words "smoking" and "hip fracture" or the terms "hip fracture" and "risk factors" as well as the terms "risk factors" and "fractures". Almost all of those articles presented a comparison between current and former smokers and between current and non-smokers. Out of the six meta-analyses, three[3,6,15] examine the direct association between smoking and hip fracture. Out of the other three meta-analyses, two examine the correlation between smoking and fracture risk in general[16,17] and one examines the impact of tobacco smoking on Bone Mineral Density[7]. Cohort Studies[18,22] investigate the association between smoking and risk of hip fractures in both genders and so they are being used in the meta-analyses[3,15] with their data separated according to gender in each meta-analysis for female[15] and male[3] smokers respectively. The majority of the studies that investigate the association between smoking and hip fracture, except the use of tobacco, also include other risk factors like BMI, alcohol intake, general health status, physical activity or inactivity, weight and menopausal status. Cornuz et al.[23] and Johnell et al.[24] also included calcium and caffeine intake as risk factors. Table 1 demonstrates all the studies that were used for this review. It is important to mention that the studies[13,18,20,22,34], are repeated in the meta-analyses[3,6,15,16]. The purpose of the other articles that are included in this review but not in Table 1 was to show the effect of smoking on bone mineral density and not the correlation between smoking and hip fractures.

Results

We mainly focused on the three meta-analyses[3,6,15] which examined the direct association between smoking and hip fractures. Law and Hackshaw[6] designed a meta-analysis of several published cohort and case-control studies. The majority of the studies concerned female smokers. The total number of subjects with hip fracture was 3889. The authors represented the risk of hip fracture in postmenopausal women according to smoking habit and age. Only in one study[22] a small number of the subjects were premenopausal. Hip fractures caused by high-energy trauma and hip fractures in metastatic bone were excluded. BMD measurements were recorded in the femoral neck, radius, or calcaneus (femoral neck was preferred). The investigators made all the necessary adjustments for data that concerned differences in bone density since the bone density units varied between studies with different measurement techniques and for data that concerned age when the mean age of the subjects was not the same. Adjustments were also made for the mean age of premenopausal and postmenopausal women. The results of the impact of smoking on BMD in postmenopausal women showed that by the age of 80, bone density was 0.45 SD (6%) lower in smokers than non-smokers. The RR of hip fracture was calculated as RR in smokers relative to non-smokers according to age which was predicted from the differences in bone density (from the relation between femoral neck bone density and risk of hip fracture) and as direct estimates of risk of hip fracture. By the age of 50, 60, 70, 80 and 90 the estimates (with 95% Confidence Intervals) were 0.96 (0.81-1.13), 1.17 (1.05-1.30), 1.41 (1.29-1.55), 1.71 (1.50-1.96) and 2.08 (1.70-2.54) respectively. While smoking has no effect as a risk factor at the age of 50, it increases the risk in older women 17% greater in smokers than nonsmokers at the age of 60, 41% greater at age 70, 71% greater at age 80, and 108% greater at age 90.The average daily consumption for current female smokers was about 15 cigarettes/day. It was shown that the risk of hip fracture was depended on the number of cigarettes smoked. In former smokers the impact of smoking on BMD and its importance on the risk of hip fracture was intermediate between that in current smokers and never smokers. The results relating to age showed that 19% of current smokers and 12% of never smokers would have a hip fracture by the age of 85, 37% and 22% respectively by the age of 90. Overall, above 13% of all hip fractures in women are attributable to smoking regardless of age.

Women continue to be the main subject of investigation in the next meta-analysis by Guang Si Shen et al.[15]. This study was designed exclusively for female patients and the authors presented a detailed analysis of their findings splitting subjects and characteristics with their results in subgroups. The investigators used the data from 10 prospective cohort studies (Table 1). Almost 360.000 women were included in this study and their age ranged from 20 to 93 years old. The follow-up period was extended up to 13 years in some cases. In the statistical analysis, $p<0.10$ was set as level of significance and the authors used the I^2 statistic. Variables such as age, geographic region, length of follow-up and their effect on outcomes were evaluated in subgroup analyses. A positive association between smoking and risk of hip fracture was shown in all of the selective studies. In total, the Relative Risk of hip fracture for current smokers versus never smokers was 1.30 (1.16-1.45, 95% CI). Three of the selected studies[19,22,23], incorporated cigarette consumption as well. There was a raise for the RR from 1.11 (0.89-1.33) in the low-dose smokers (less than 15 cigarettes per day) to 1.26 (1.02-1.51) in the high-dose smokers (more than 15 cigarettes per day).In the subgroup analyses the results showed a strong positive association between smoking and risk of hip fracture except in individuals younger than 49 years old. When former smokers were compared with never smokers, the Relative Risk was similar (RR: 1.02). Three

Table 2. General characteristics of the included prospective cohort studies.

First Author	Duration (years)	Size	Mean age (range)	Smoking Status (years)	Number of fractured patients	Adjusted Relative Risk (95% CI)	Study Quality	Adjustment for Covariates
Paganini-Hill[20]	7	5049	73	Former	50	1.16(0.73-1.86)	7	Age
				Current	9	2.23(1.04-4.8)		
				Current*	NA	1.94(0.96-3.94)		
Meyer[22]	11	27015	35-49	Former	14	1.25(0.56-2.81)	8	Age
				Current (1-14)	14	0.93(0.41-2.09)		
				Current (≥ 15)	19	1.81(0.84-3.89)		
Forsen[13]	3	18198	≥ 50	Current*	136	1.8(1.2-2.9)	9	Age, leanness, poor health, physical inactivity, self-repoted
Hemenway[25]	6	50000	40-75	Former	29	1.05(0.61-1.81)	7	Alcohol, BMI, Height, smoking status
				Current	6	1.08(0.44-2.67)		
Mussolino[27]	14	2879	≥ 45	Current	71	1.45(0.86-2.42)	7	Alcohol, chronic disease, calcium intake, calories, physical activity, protein intake, smoking status
Forsen[18]	3	14428	50-64	Former	4	2.3(0.3-21)	7	Age, BMI, physical inactive, subjective health
				Current	11	4(0.5-32)		
			65-74	Former	11	4.3(1.0-20)		
				Current	13	5.3(1.2-25)		
			≥ 75	Former	15	1.1(0.5-2.3)		
				Current	18	1.6(0.8-3.3)		
Hoidrup[19]	5-13	17379	20-93	Current	316	1.59(1.04-2.43)	8	Age, alcohol, BMI, menopausal age, physical activity, study of origin, school education
				Former	100	1.16(0.74-1.83)		
Olofsson[37]	30	2322	71	Current	96	3.03(1.02-3.44)	8	Age, alcogol, BMI, chronic diseases, physical activity, marital status, socioeconomic class
				Former	NA	1.87(1.02-3.44)		
Holmberg[35]	16	22444	44	Current*	163	2.20(1.54-3.15)	7	Age, BMI, diabetes, smoking, self-rated health
Koh[38]	7	27913	71.4	Former	80	1.27(0.93-1.72)	6	Age, education, work or sports, year of recruitment
				Current	107	1.23(0.92-1.64)		
Stolee[21]	10	13773	81.5	Current	223	1.58(1.03-2.42)	6	NA
Jutberger[39]	3	1412	69-80	Current	38	2.34(0.97-5.65)	8	Age, BMD, BMI, calcium intake, glucocorticoid treatment, physical activity
Trimpou[36]	30	7495	46-56	Former	86	1.06 (0.81-1.40)	8	Age, alcohol, tall stature, low occupational class, interim stroke or dementia, smoking
				Current	234	1.58 (1.27-1.96)		
Cauley[29]	8.6	5994	>65	Current	97	2.05 (1.05-3.98)	7	Age, BMD, clinic, race

BMD: Bone Mineral Density, BMI: Body Mass Index, NA: Not Available. Current: Current smokers compared with nonsmokers (never and former smokers). The numbers under "Study Quality" refer to the Newcastle-Ottawa quality assessment scale with 9 being the optimum.*

studies[13,20,35] compared current smokers with non-smokers (former and never smokers as well) and the results showed that there was a significant increment of the RR for the current female smokers, RR: 1.54 (1.20-1.87). The authors also compared former smokers with current smokers and they found that quitting smoking leads only to a small decrease in risk when the cessation period is <5 years, RR: 1.01 (0.76-1.26) and between 5 and 9 years, RR: 1.10 (0.60-1.60). But when the cessation period was ≥10 years the RR was measured at 0.70 (0.50-0.90). This indicates that the longer the cessation period is the lower the risk of hip fracture becomes.

The third meta-analysis[3] focuses on men. The authors extracted data from fourteen prospective cohort studies that included 216301 participants who did not receive any medication for osteoporosis and 1922 patients diagnosed with hip fractures. Table 2 shows the general characteristics of the included studies.

Twelve of the included publications in Table 2 (all studies except[13,35]) reported the RRs for current smokers versus never smokers. The pooled RR for those studies was 1.47 (1.28-1.66), (p=0.538, I^2=0%). Eight of the included studies[4,5,7,13,19,24,26,31] reported the RR for former smokers versus never smokers. It was not shown any important positive correlation between former smoker and risk of hip fracture except for Olofsson et al.[24]. The pooled RR was 1.15 (0.97-1.34), (p=0.975, I^2=0%). Three studies[13,20,35], calculated the RRs for current smokers versus nonsmokers (former and never smokers as well). Current smokers presented with a doubled Relative Risk (RR=2.00, 95% CI, 1.46-2.55).

In the Hordaland Health Study[8], a study published in 2014 with a big number of participants, the authors investigated in what way cigarette smoking and body fat mass are related to BMD and hip fracture. They split their subjects into categories according to their smoking habits measuring cotinine levels in blood tests. In never and former smokers plasma cotinine levels were 85 nmol/L. In moderate smokers cotinine levels extended between 85 and 1199 nmol/L and in heavy smokers ≥1200 nmol/L. Their results showed that elderly heavy smokers of both genders were at high risk of hip fracture compared to never smokers. The results also showed that individuals who were heavy smokers and had an increased body fat mass were at a lower risk for hip fracture.

Kanis et al.[17] designed a meta-analysis in which they explored the association between smoking and fracture risk and how this risk is also related to age, sex and BMD. The subjects were 59232 (74% female) from ten international prospective cohort studies. The risk ratios were adjusted for age, BMD and BMI. Current smokers, men and women combined had an increased risk of hip fracture (RR: 1.84, 95% CI: 1.52-2.22). When BMD was taken into account the risk ratio was adjusted downward and the RR was 1.60 (95% CI: 1.27-2.02) Ever smokers (current and former) showed an increased risk for hip fracture too but lower than for current smokers. Ever male smokers, RR: 1.11, 95% CI: 0.67-1.83, Ever female smokers, RR: 1.42, 95% CI:1.18-1.72.These results were not adjusted for BMD.

Finally, Vestergaard et al.[16] designed a systematic review and reported the RR's for all types of fractures. This meta-analysis included 51 studies with 512399 subjects in total. The risk estimate for hip fracture was higher in current smokers than in former smokers in both genders. The pooled risk estimate across all studies and both genders combined was for current smokers 1.39 (1.23-1.58) and for former smokers a lower 1.23 (1.08-1.40), (p=0.09). The authors also calculated the attributable risk of hip fracture as a proportion in population. 7% of all hip fractures could be attributable to smoking if the proportion of current smokers in the population was 20%. If, in the same population, 50% of the subjects were current smokers, 16% of all types of fractures could be attributable to smoking. Cessation of smoking was associated with a lower risk but not in a significant level.

Conclusion

Bone Mineral Density (BMD) is a major predictor for hip fractures and has a direct correlation with smoking. When BMD is decreased, risk of osteoporosis and hip fracture is increasing[6-8,24]. BMD decreases as cigarette consumption increases in both men and women[6,7]. By the time menopause is established, smoking in postmenopausal women has an adverse effect in BMD and increases the risk of hip fracture especially in older women >80 years old by about half[6]. In women before menopause, smoking has a minor impact on bone density because of the protective role of oestrogens[6]. The lower risk in former smokers shows that quitting smoking prevents excessive bone loss. All five meta-analyses[3,6,15,17] demonstrated a positive correlation between smoking and hip fracture in both genders. Especially in the two recent meta-analyses[3,15], the results were remarkably similar as the pooled Relative Risks for current and former smokers of both genders were close in numbers. Current female smokers with a reported use of more than 15 cigarettes/day present with a high risk of hip fracture. The RR when comparing female current smokers with never smokers is 1.30 (1.16-1.45, 95% CI) and when comparing current female smokers with non-smokers the RR is 1.54 (1.20-1.87)[15]. The RR turned out to be similar between female former smokers and never smokers (RR:1.02)[2,6,15]. A common finding in the meta-analysis[15] results was the inversely proportional correlation between the RR of former smokers and the cessation of smoking. On contrary, there was not any difference of the RR between current smokers and former smokers with less than 5 years cessation of smoking. Cessation ≥5 years had as a result a small decrease in risk of hip fracture and cessation for >10 years had an inverse effect. The results showed that tobacco smoking is strongly associated with the risk of hip fracture in men too. The RR of hip fracture between current male smokers and never smokers was 1.47 (1.28-1.66)[3]. When compared with non-smokers (former and never smokers), the RR for current smokers was twice as great. On contrary, when comparing former male smokers with never smokers there was no significant relation between smoking and hip fracture in the majority of the studies[3]. The results also showed that there is not any significant positive association between former smokers and risk of hip fracture which suits the case of former female smokers respectively. In summary, the present review implies that cigarette smoking increases risk of hip fracture, especially in current male and female smokers. However, further studies and more meta-analyses worldwide are required to support this case.

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