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Review

Clinical fractures cluster in time after initial fracture

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ABSTRACT

A history of fractures is a well recognised risk factor for a new clinical fracture. However, this subsequent fracture risk is not constant, but fluctuates over time, with the greatest increase in the years immediately after the initial fracture, followed by a gradual waning of risk toward the population risk. The clustering of fractures occurred regardless of age, gender and initial fracture location. It is therefore likely that fracture risk models, which take into account this fluctuation of fracture risk over time, will be more relevant in predicting an individual's subsequent fracture risk. Regardless of the cause of this clustering, these studies all strongly support the need for early action after an initial fracture to reduce the preventable risk of subsequent fractures with medical interventions that have been shown to immediately decrease the risk of fractures.

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Contents

1. Introduction

The clinical significance of osteoporosis is related to the occurrence of fractures. Fractures are a problem of growing importance in both developing and developed countries. It is estimated that 1 in 2 women and 1 in 3 men aged 50 years will sustain a fracture during their remaining lifetime [1,2].

Hip fractures increase morbidity and mortality and entail high socio-economic costs [2–5]. The mortality rate from hip fractures varies between 10 and 30%. Of those who survive their fracture, half have persistent disability [3,4,6,7]. Mortality is increased after all fractures, not only hip [2,8–10]. In Europe alone, the direct medical costs for hip fractures are estimated at € 24.4 billion in the first year (67.2% of total medical costs for fractures) [4]. Radiographic vertebral fractures are the most common fractures at a population

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level among postmenopausal women. Although only 1 in 3 come to clinical attention, all are associated with increased morbidity, mortality and fracture risk and thus indicate bone fragility, independent of bone mineral density (BMD) [1,2,11]. The most frequent fractures in postmenopausal women presenting with a fracture are non-vertebral, non-hip fractures [12], and these entail the second highest cost of fractures [4].

Numbers of fractures are increasing, due to the ageing of the population and increased lifespan. Since the proportion of elderly people in Europe will increase by 33% over the next 25 years, fractures will place even greater demands on health care planning. Therefore, guidelines on osteoporosis all advocate clinical case-finding to identify those groups of patients at high risk in whom interventions to prevent fractures have been shown to be most effective [13].

2. Clustering of clinical subsequent fractures

2.1. History of fractures

A history of fractures is a well recognised risk factor for a new clinical fracture [5,10,12–35]. In a large meta-analysis the pooled analyses of peri- and postmenopausal women indicated that their subsequent fracture risk was 2.0 compared with women without a fracture history. The pooled analyses including both men and women of all ages, was approximately the same (2.2) [18]. Individualized 5- and 10-year fracture risk prediction models have been constructed, including the FRAX of the World Health Organization <www.shef.ac.uk/FRAX/> [32] and the fracture risk calculator of the Dubbo Osteoporosis Epidemiology Study <www.fracturerisk calculator.com> [33]. These are welcome additions to the existing strategies for identifying patients at high risk for fractures. The similarities and differences of these two models are discussed in a other article, and therefore, this review will not focus on this topic [36].

The two models above are based on the assumption of a stable risk of subsequent fractures over time [32,33]. This may not be optimal as several studies have shown that the risk increment varies over time. Postmenopausal women with a recent prior fracture were at significantly higher risk for sustaining a subsequent fracture than women with an older prior fracture, regardless of age and BMD [34]. Thus, the 10-year fracture risk prediction model developed at Maastricht University discriminates between a recent prior fracture (during the past 5-years) and a prior fracture that occurred longer ago, but after menopause.

A literature search was conducted using Medline to select English articles focusing on the time relation between initial and subsequent fractures. The reference lists of the selected articles were searched for relevant studies. The main aim of this article is to raise awareness that a subsequent fractures occurs soon after the initial fracture, regardless of the fracture location. Therefore, for subsequent fracture prevention it is necessary to act immediately after the initial fracture. Below is a review of studies supporting this variation in fracture risk following a vertebral, hip or any fracture.

2.2. Clustering of fractures after a vertebral fracture

Two studies focused on the time aspect of an initial vertebral fracture and the subsequent fracture. One study in postmenopausal women, with a follow-up period of 3 years, investigated the incidence of subsequent vertebral fractures in the year following a vertebral fracture [22]. In these data, one out of five postmenopausal women who sustained an incident vertebral fracture sustained a subsequent incident vertebral fracture within 1 year after the initial one. Their risk was even higher if they had sustained a vertebral fracture prior to study entry [22].

Another study [35] showed that, in all patients who were hospitalized for a thoracic or lumbar vertebral fracture within a 7-year time period, more women than men and more patients with low- than high-energy trauma initial fractures sustained a subsequent fracture over a mean follow-up of 2 years. Within the first year after the initial fracture the incidence of subsequent hip or all fractures was highest in both men and women, with a 4- to 6-fold increase within the first 6 months compared with the general population. Four years after the initial vertebral fracture the risk of all subsequent fractures had decreased fourfold and for women twofold compared with the risk at 6 months. However, this was still higher than the risk of the general population. The authors concluded that the risk for a subsequent fracture after being hospitalized for a vertebral fracture was not uniform with age, gender or time [35].

2.3. Clustering of fractures after a hip fracture

Three studies have focused on the time relation of an initial hip fracture and a subsequent fracture. One study examined the risk of subsequent fractures in all women with an initial hip fracture [9]; 8% sustained a subsequent fracture over a mean follow-up of 7 years. Of these women, more than one in four sustained their subsequent fracture within the first year [9].

A 9-year follow-up study in long-term care residents with an initial hip fracture [15], also found the highest risk of subsequent fractures within the first year; 12% sustained a subsequent fracture within the first year. Hence, more than half of the patients who sustained a subsequent fracture, sustained the fracture within the first year [15].

A third study followed 170,000 female and male patients with an initial hip fracture for up to 25 years. Of these, 16% sustained a subsequent hip fracture with a median follow-up of 4 years [16]. Within one year, 9% (i.e. more than half) sustained a subsequent fracture. This is more than a fourfold increase compared with the general population. Within 5 years the cumulative risk was 20%; almost twice that of the general population. The increased risk immediately after the initial hip fracture was observed in women and men in all age groups, but the immediate risk was highest in women and older patients. After 15 years of follow-up the subsequent fracture risk was no longer increased compared with the general population [16].

2.4. Clustering of fractures after any fracture

Four studies investigated the time relation between any initial and subsequent fracture. One analysis, which included all patients aged 50 year and over with a clinical fracture who were treated at an emergency trauma center, found that 6.5% had a subsequent clinical fracture within the first year after the initial fracture[12]. Over just two year of follow-up, significantly more subsequent fractures occurred in the first than in the second year [12].

Another study on osteoporotic fractures focused on the risk for a subsequent fracture in patients with a hip, clinical vertebral or shoulder fracture who were followed up to 5 years [23]. About one third of all subsequent fractures occurred within one year. In addition, the subsequent fracture risk per fracture site (hip, vertebral and forearm) immediately following the initial fracture was higher than in the general population for most of the initial fracture locations, matched for gender and age and remained higher after 5-year follow-up [23].

A third study followed community-dwelling men and women aged 60 years and over up for 16 years, and found that the absolute subsequent fracture risk was similar in men and women, regardless of age (±22%). Of all women and men who sustained a subsequent

fracture, 2 in 5 women and more than half of the men sustained their subsequent fracture within two years after the initial fracture, with a median follow-up of 3 years in women and 2-years in men. For both women and men, the subsequent fracture risk remained increased until 10 years of follow-up compared with the population at risk for an initial fracture. Thereafter the subsequent fracture risk was no longer significantly increased. In addition, the absolute risk of subsequent fracture was increased for both women and men for almost all fracture types and all age groups, but the immediate risk was highest in women and older patients. Of considerable importance, there was no significant difference in the subsequent fracture types according to initial fracture type. Even after an initial minor fracture the risk for a subsequent major or hip fracture was increased [10].

A fourth, and also population-based, study was able to substantiate earlier observations of clustering of fractures and extend them to all postmenopausal women, with any low- or high-energy trauma clinical fracture, and from menopause onwards [37]. Of the postmenopausal women with an initial fracture, 26% sustained a subsequent fracture over a mean follow-up of 9 years. As a result, almost 1 in 4 subsequent fractures occurred within one year after the first fracture, and more than half within 5 years of the first fracture. Compared with having an initial fracture, the relative risk of subsequent fracture was double that of the initial fracture. However, this increased long-term risk proved to be largely driven by a short-term increase in risk, as the risk of subsequent fracture was increased 5-fold in the first year after the initial fracture. After 15 years of follow-up the subsequent fracture risk was no longer significantly elevated compared with the population at risk for an initial fracture. Subsequent fracture risk was increased within the first years after the initial fracture in patients for all fracture types and age groups, but was highest in older women [37].

3. Significance

The clinical significance of clustering of fractures is that patients presenting at the time of fracture warrant immediate attention and consideration of medical interventions, which have been shown to quickly reduce the risk of fractures. All available treatments (except calcitonin) significantly reduced the risk of vertebral fractures, roughly at 40–50% within one year in patients with osteoporosis defined as a prevalent vertebral fracture and/or a low T-score [38]. Early effects on non-vertebral fractures have been reported within 6 months for risedronate [39], and within 12 months for alendronate [40] and of strontium ranelate (in women eighty years of age and older) [41] and within 18 months for teriparatide [42].

4. Summary

Morphometric and clinical vertebral fractures and non-vertebral fractures in elderly women and men cluster in time. It is well recognised that a history of non-vertebral fracture is associated with a doubling of the risk of a subsequent fracture [18]. However, the studies mentioned above have shown that this subsequent fracture risk is not constant, but fluctuates over time, with the greatest increase in the years immediately after the initial fracture, followed by a gradual waning of risk toward the population risk. The clustering of fractures occurred regardless of age, gender and initial fracture location. It is therefore likely that fracture risk models, which take into account this fluctuation of fracture risk over time, will be more relevant in predicting an individual's subsequent fracture risk. Importantly, we need more insight in why fractures cluster in time (e.g. bone-related factors, fall-related factors, vitamin D status, co-morbidities, poor mobility, surgical procedures, plastering) for effective prevention. However, regardless of the cause of this clustering, these studies all strongly support the need for early action after an initial fracture to reduce the preventable risk of subsequent fractures with medical interventions that have been shown to immediately decrease the risk of fractures.

Contributors

Tineke van Geel is the main author of this paper. Geert-Jan Dinant, Piet Geusens are her supervisors in The Netherlands. Jacqueline Center and John Eisman are her supervisors during her stay as visiting research fellow in Australia. All authors are responsible for the content and actively contributed to this review.

Competing interests

John A. Eisman (consulting fees or other remuneration): Amgen, decode, Eli Lilly, Ge-Lunar, Merck Sharp & Dohme, Novartis, Roche-GSK, Sanofi-Aventis, Servier, and Wyeth Australia. Piet Geusens (consulting fees or other remuneration): Amgen, Eli Lilly, Ge-Lunar, Merck Sharp & Dohme, Novartis, Roche-GSK, Sanofi-Aventis, Servier, Wyeth, Shering Plough, Abbott, Pfizer. Other authors: none

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