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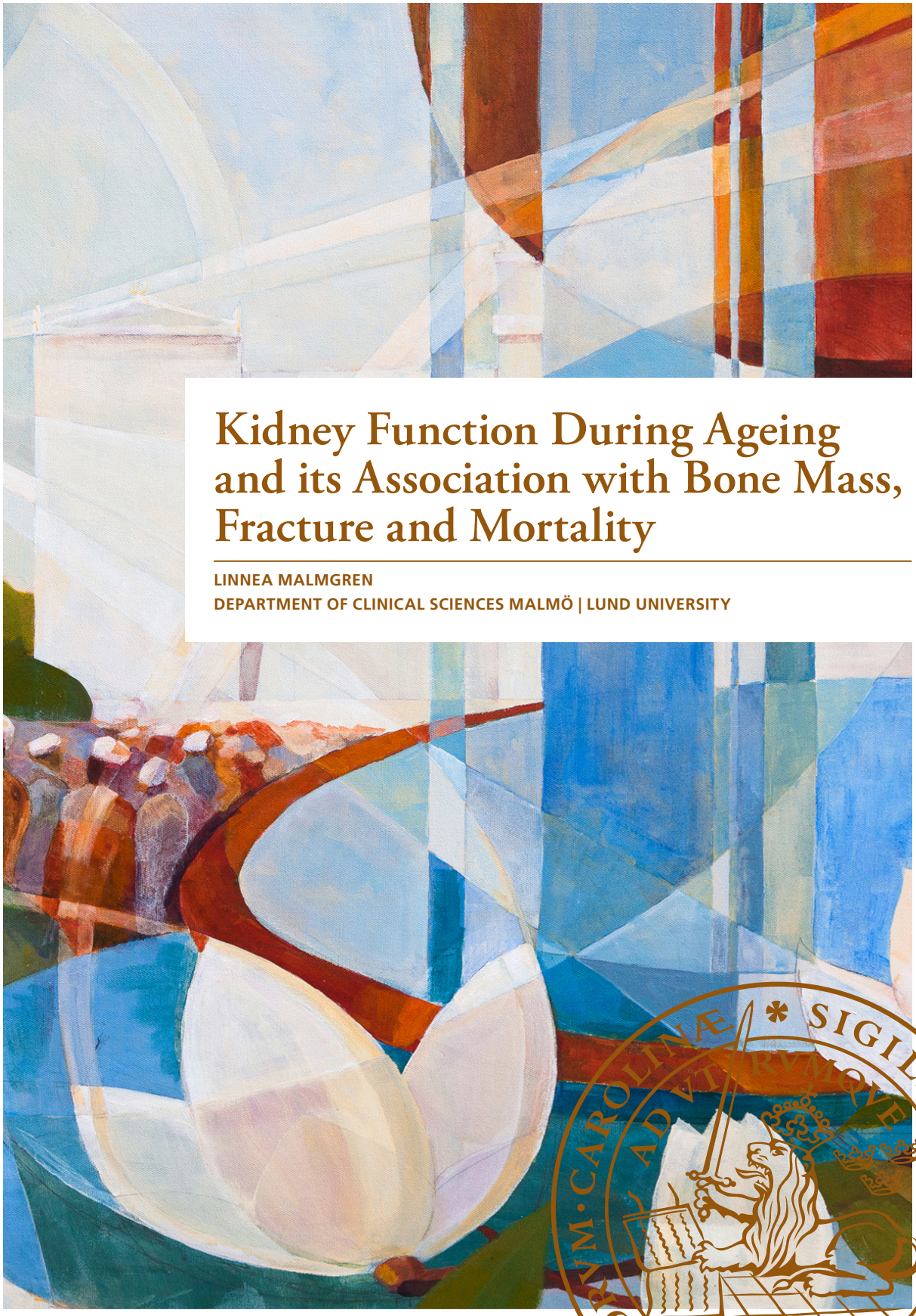
2020

Document Version:
Publisher's PDF, also known as Version of record



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Bone mass, Fracture and Mortality

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Linnea Malmgren

LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Ortopedens föreläsningssal, Inga Marie Nilssons gata 22, Malmö,
February 14th, 2020 at 9 a.m.

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Anna Nilsson, Sahlgrenska Academy, Gothenburg, Sweden

Organization LUND UNIVERSITY	Document name: Doctoral dissertation
	Date of issue: 14 february 2020
Author: Linnea Malmgren	Sponsoring organization

Title and subtitle
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Abstract
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Data was collected through the Malmö Osteoporosis Prospective Risk Assessment (OPRA) cohort, a prospective cohort of 1044 community dwelling women, all aged 75 and followed for ten years with reinvestigations at age 80 and 85. Data on BMD, fracture and blood biochemistry was available at all three time points.

Estimated kidney function greatly depends on which marker and study equation is used. The discrepancies are to such an extent that could affect whether a person is diagnosed with chronic kidney disease (CKD) or not, of particular importance in the elderly. Only women with the worst kidney function, corresponding to CKD stage 3b-5, had continuously increased mortality risk. This indicates that an age-dependent CKD definition would be of value in elderly women.

Kidney function in elderly women was associated with markers of mineral homeostasis, bone loss and BMD, but the effect size was relatively small compared to other risk factors. Also, fracture risk was increased only in women with mild-moderate reduction of kidney function (CKD stage 3a) and not in women with the worst kidney function (CKD stage 3b-5). Low BMD was associated with increased fracture risk independent of kidney function. Having *both* reduced kidney function *and* osteoporosis could present an additional risk increase.

In conclusion, estimated kidney function in elderly women greatly depends on method of estimation and the results advocate for an age-adapted CKD definition. Maintaining adequate kidney function is important for maintaining bone health, although in old age it is probable that the effect size of any single specific risk factor is smaller compared with younger individuals.

Key words: kidney function, bone mieral density, fracture, mortality, elderly women

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language: English
ISSN and key title 1652-8220		ISBN 978-91-7619-878-0
Recipient's notes	Number of pages	Price
	Security classification	

Signature  Date 2020-01-07

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Coverphoto by Frida Malmgren

Lund University, Faculty of medicine Doctoral Dissertation Series 2020:18
Department of Clinical Sciences Malmö

ISBN 978-91-7619-878-0
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2020

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MADE IN SWEDEN

"It is what we think we know already that often prevents us from learning"

Claude Bernard

To my family

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Original papers included in this thesis

1. Declining estimated glomerular filtration rate and its association with mortality and comorbidity over 10 years in elderly women
   Malmgren L, McGuigan FE, Berglundh S, Westman K, Christensson A, Akesson K
   Nephron. 2015;130(4):245-55. PubMed PMID: 26184510.
2. Longitudinal changes in kidney function estimated using cystatin C and its association to mortality in elderly women
   Malmgren L, McGuigan FE, Christensson A, Akesson K
   (In revision)
3. Reduced kidney function is associated with BMD, bone loss and markers of mineral homeostasis in older women: a 10 year longitudinal study
   Malmgren L, McGuigan F, Christensson A, Akesson KE
   Osteoporosis international. 2017 Dec;28(12):3463-73. PubMed PMID: 29038837. http://creativecommons.org/licenses/by-nc/4.0/
4. Kidney function and its association to imminent, short and long term fracture risk – a longitudinal study in older women
   Malmgren L, McGuigan FE, Christensson A, Akesson K
   Osteoporosis International 2019 Nov 21. PubMed PMID: 31754754 (Epub ahead of print). http://creativecommons.org/licenses/by-nc/4.0/

Original papers not included in this thesis

1. Association Between Vitamin D, Frailty and Progression of Frailty in Community-Dwelling Older Women
   Buchebner D, Bartosch P, **Malmgren L**, McGuigan F, Gerdhem P, Akesson K
   The journal of clinical endocrinology and metabolism. 2019 Dec 1; 104(12):6139-6147. PubMed PMID 31287540

2. Genetic variants associated with circulating fibroblast growth factor 23
   Robinson-Cohen C, Bartz TM, Lai D, Ikizler TA, Peacock M, Imel EA, Michos ED, Foroud TM, Akesson K, Taylor KD, **Malmgren L**, Matsushita K, Nethander M, Eriksson J, Ohlsson C, Mellstrom D, Wolf M, Ljunggren O, McGuigan F, Rotter JI, Karlsson M, Econs MJ, Ix JH, Lutsey PL, Psaty BM, de Boer IH, Kestenbaum BR.
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   Berglundh S, **Malmgren L**, Luthman H, McGuigan F, Akesson K
   Osteoporosis international. 2015 Feb;26(2):727-35. PubMed PMID: 25410434

5. Bone turnover markers and prediction of imminent and long-term fractures in the OPRA study of elderly women
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   (Submitted)

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1. Baljväxt orsakar förgiftning med antikolinergt syndrom
   Malmgren L, Dahlman D, Rosén F, von Wowern F
   Lakartidningen. 2016 Jul 28;113. PubMed PMID: 27483400

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1. P Bartosch, **L Malmgren**, D Buchebner, F McGuigan, K Akesson.
   Frailty as a risk factor for predicting falls and fractures in community dwelling older women.
   IOF, 19-22 April 2018, Krakow, Poland.
   https://www.wco-iof-esceo.org/sites/all/files/wco18/WCO18-AbstractBook.pdf

2. **L Malmgren**, FE McGuigan, K Westman, A Christiansen, K Åkesson.
   Reduced kidney function is associated with increased risk of fractures in older women.
   6th FFN Global Congress, 24-26 August 2017, Malmö, Sweden
   https://fragilityfracturenetwork.org/wp-content/uploads/2018/01/ffn2017_final_programme.pdf

3. P Bartosch, **L Malmgren**, D Buchebner, F McGuigan, K Akesson.
   Frailty status predicts falls in older women: a study in the osteoporosis prospective risk assessment (OPRA) cohort.
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5. D Buchebner, **L Malmgren**, A Christensson, FE McGuigan, P Gerdhem, M Ridderstråle, K Åkesson.
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6. D Buchebner, F McGuigan, **L Malmgren**, K Åkesson.
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   ASBMR, 16-19 September 2016, Atlanta, Georgia, USA
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11. **L Malmgren**, K. Åkesson
    Nedsatt njurfunktion hos äldre kvinnor och dess koppling till bentäthet, förlust av bentäthet och frakturrisk.
    SOF, 15-19 August 2014, Helsingborg, Sweden.

Abstract

Osteoporosis and osteoporosis related fractures are a major health care challenge both in Sweden and globally. The cost and suffering from osteoporosis are expected to increase since the population of elderly is increasing. Bone health can be affected by altered mineral homeostasis, which in its turn can be affected by reduced kidney function. However, the course of age-related decline in kidney function and its association to osteoporosis and fracture in the very elderly need further investigation since longitudinal data are scarce. Therefore, this thesis has two main aims; 1) to investigate kidney function during ageing and 2) its association to bone health in a cohort of elderly women.

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Abbreviations

BMD	Bone mineral density
BMI	Body mass index
BIS1	Berlin initiative study equation
CAPA	Caucasian, Asian, Pediatric, and Adult equation
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CKD-MBD	Chronic Kidney Disease Mineral and Bone Disorder
CG/BSA	Cockroft Gault adjusted for Body Surface Area formula
CVD	Cardiovascular disease
cysC	Cystatin C
DXA	Dual-energy X-ray absorptiometry
ESRD	End-stage Renal Disease
FGF23	Firbroblast growth factor 23
KDIGO	Kidney Disease Improving Global Outcome
LM-rev	Lund Malmö formula revised
MDRD	Modification of Diet in Renal Disease study equation
RBF	Renal blood flow
eGFR	Estimated Glomerular Filtration Rate
mGFR	Measured Glomerular Filtration Rate
PTH	Parathyroid hormone

Populärvetenskaplig sammanfattning

Vad händer egentligen när kroppen åldras? Med ökande ålder sker en generell funktionsförlust i alla kroppens organ. Med andra ord kan exempelvis hjärtats eller lungornas funktion minska med åldern utan att det nödvändigtvis handlar om en kronisk sjukdom. Men eftersom sjukdom ofta definieras som funktionsförlust i ett organ kan det ibland vara svårt att skilja sjukdom från normalt åldrande. Ett exempel på en sådan svårighet är nedsatt njurfunktion. Många kliniskt verksamma läkare vet att njurfunktionen inte är den samma hos en yngre individ som hos en äldre. Till exempel kan samma njurfunktion som hos en yngre individ skulle anses gravt nedsatt och föranleda flertalet besök hos en njurspecialist anses helt normal hos en äldre individ. Det finns därför de som menar att gränsen för vad som anses som njursjukdom bör sänkas med åldern.

Njurarna hjälper till att rena blodet genom att bilda urin, men de har också många andra funktioner i kroppen. Bland annat är de tätt sammankopplade med blodtrycksreglering, vätskebalans och bildandet av röda blodkroppar. Ett annat organ vars funktion är tätt kopplad till njurens är skelettet. Detta beror på att njuren reglerar flera benmetabola markörer, vilket i sin tur kan leda till ökad benomsättning och ökad risk för frakturer.

Det kan vara svårt för läkare och annan sjukvårdspersonal att på ett korrekt sätt uppskatta en persons njurfunktion. Detta beror delvis på att njurfunktionen varierar med kost, dygnsrytm och muskelmassa, men också eftersom de markörer (cystatin C och kreatinin) som används för uppskattningen på ett eller annat sätt påverkas av andra faktorer än själva njurfunktionen. Slutligen finns det många olika formler som hjälper till att skatta njurfunktionen, men de flesta är inte utvecklade hos äldre individer trots att det till stor del är äldre som konsumerar sjukvård.

Denna avhandling består av fyra studier som syftar till att bättre beskriva sambandet mellan njurfunktion och benhälsa i åldrande genom att undersöka detta samband hos en grupp av 75-åriga kvinnor hemmahörande i Malmö. Kvinnorna har följts i tio år.

Resultat från studie ett och två visar att kvinnorna förlorar i snitt mellan en fjärdedel och en femtedel av sin njurfunktion mellan 75 och 85 års ålder, vilket leder till att många hamnar under gränsen för njursjukdom. Den uppskattade njurfunktionen skiljer sig mycket beroende på vilken formel som använts, men också beroende på vilken markör som använts. Bara kvinnor med sämst njurfunktion hade ökad risk för att dö på kort och lång sikt.

Resultat från studie tre visar att nedsatt njurfunktion är kopplad till benmetabola biomarkörer, men också till bentäthet och benförlust. Dock tyckts den sammanvägda effekten vara liten jämfört med andra faktorer och sambandet försvinner när kvinnorna fyllt 85.

Den sista studien undersöker hur njurfunktionen är kopplad till risk för benbrott. Förvånande nog kunde vi inte se att kvinnorna med sämst njurfunktion hade ökad risk för benbrott utan istället var det kvinnorna med medelförsämring av njurfunktion som i ökad utsträckning drabbades av benbrott. Det kan möjligen bero på att kvinnorna med sämst njurfunktion dör i högre utsträckning och därför inte hinner få frakturer i samma omfattning.

Sammanfattningsvis klassificeras en stor del av äldre kvinnor som njursjuka enligt det nuvarande systemet, men bara kvinnorna med allra sämst njurfunktion har ökad risk för död. Vi anser därför att gränsen för njursjukdom bör sänkas hos äldre individer. Fortsättningsvis finns det ett samband mellan nedsatt njurfunktion och benmetabola markörer, bentäthet och fraktur, men detta samband tycks försvagas med tiden i de högsta åldrarna.

Rationale for this thesis

This thesis was originally planned as a study investigating the association of BMD and fracture with kidney function. The rational for this investigation was, that a reduction in kidney function can affect bone metabolic markers, thus affecting the bone remodelling process. And although many studies have shown an association between end-stage renal disease and fracture risk, the association between the normal age-related reduction of kidney function and fracture in community dwelling women has been less studied.

However, the final structure of the thesis differed from that originally planned, since the initial literature search highlighted an area of uncertainty, namely which study equation was best suited to estimate kidney function in a population of elderly women. After discussing this matter with a specialist in nephrology, we realised this was a serious gap in knowledge that warranted further investigation. For example, the most common study equation did not include any elderly individuals and was developed in an all-male population. Also, reference material regarding what constitutes a *normal* kidney function in elderly women was largely missing, mainly because longitudinal studies are unavailable.

Based on this gap, the thesis began with a chiefly descriptive paper investigating age-related change in kidney function in elderly women and how estimations of kidney function differed depending on study equation. After finishing study I, cystatin C was analysed in order to approach the "full picture" on age-related change in kidney function. Cystatin C has been proposed more accurate for use in the elderly and study II was planned as a sister study to study I.

With the third and fourth study, we finally addressed the association between kidney function and bone health. With this thesis we feel confident that an important knowledge gap has been filled.

Introduction

Osteoporosis is one of the biggest health care issues in Sweden today, resulting in over 70 000 osteoporosis related fractures per year. In the European Union, an annual total of 3.5 million fractures per year are reported, with reduced quality of life and survival as a consequence [1, 2]. In 2010, the cost of osteoporosis in Sweden was estimated at almost 1500 million euros, but only two percent of that cost was related to pharmacological fracture prevention. The remainder was accounted for by first year fracture costs and long-standing costs, such as residence in a nursing home. Osteoporosis related costs in Sweden are expected to increase by almost 25% in 2025 [3]. Prevalence of osteoporosis in women over the age of fifty is three to four times greater than that of men and approximately 400 000 Swedish women and just over 100 000 Swedish men were estimated to have osteoporosis in 2010 [2, 3]. The concern of osteoporosis is a growing one due to a growing elderly population worldwide.

Bone – a dynamic organ

Bone serves both as an organ system and a tissue, facilitating motion, protection of other organs and mineral homeostasis. Bone has four cellular components: osteoblasts, osteocytes, osteoclasts and bone lining cells [4, 5].

Bone is not a static tissue, but a dynamic, complicated and continuous process of tissue formation by osteoclasts and resorption by osteoblasts, called bone remodelling (Figure 1). This process is affected by systemic factors such as estrogen and local factors such as growth factors [6]. In healthy bone the formation and resorption are equal, however, in some conditions resorption exceeds formation, resulting in a more fragile bone increasing the risk of fractures.

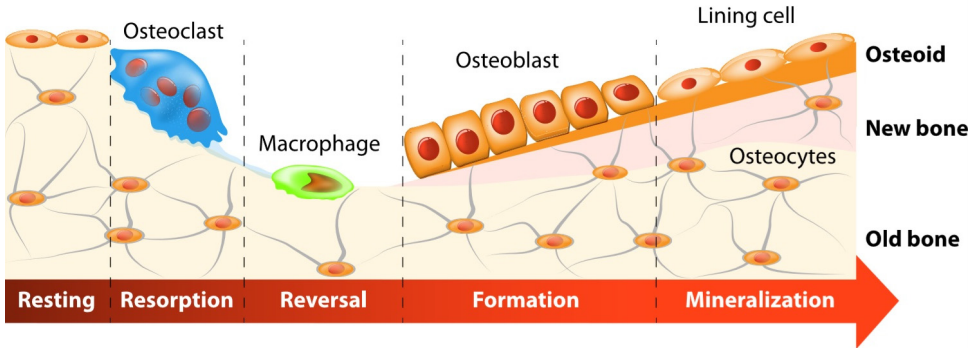

Figure 1. The bone remodelling process is a continous process of tissue formation and resorption
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Within the human skeleton, two different types of bone exist: cortical and trabecular. Cortical bone surrounds the marrow cavity, constituting the diaphysis (shaft) of long bones. It also surrounds trabecular, or cancellous, bone at the end of joints and the vertebrae. Cortical bone makes up approximately eighty percent of the adult skeleton [(7)].

Osteoporosis – definition and diagnosis

One of the most common conditions in which bone resorption exceeds formation, transforming physiology into pathology, is osteoporosis (Figure 2). Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [(8)].

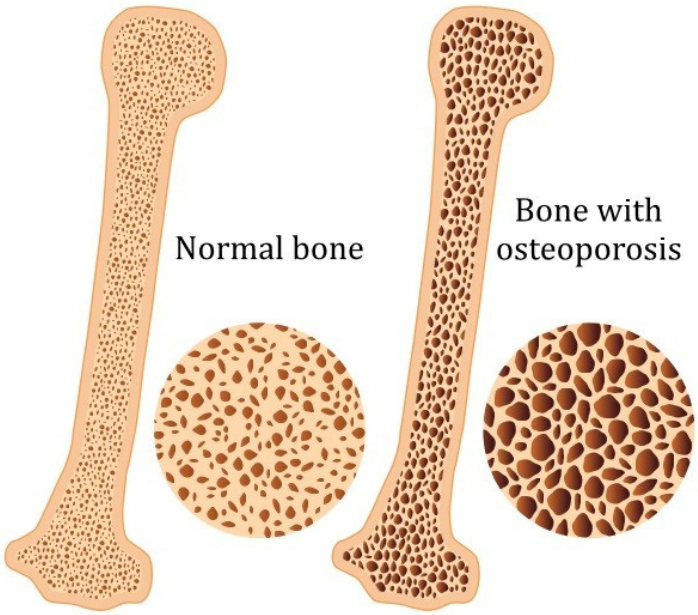


Figure 2. The osteoporotic bone
iStock.com/Neokryuger

Osteoporosis is diagnosed using dual-energy X-ray absorptiometry (DXA), which measures bone mineral density (BMD), expressed as bone mass per unit area (g/cm^2). For diagnosis, BMD is often reported as a T-score which describes how a patients BMD differs from the mean value in young and healthy individuals, using standard deviations. Osteoporosis is defined as a T-score -2.5 SD below normal at the femoral neck, while osteopenia is defined as a T-score between -1 and -2.5 SD below normal [9, 10].

Although considered the gold standard for diagnosing osteoporosis, DXA has some limitations. Firstly, a T-score of -2.5 was set as the threshold because it was associated with a sufficiently high fracture risk in epidemiological studies. Thus, a low BMD increases the risk of fracture. But fracture risk is affected by many other factors not captured in a DXA scan, such as bone quality and bone strength. Hence, not all those with a low BMD go on to fracture, and many who fracture have a normal BMD. Also, BMD cannot differentiate between osteoporosis and osteomalacia, which results from poor nutrition in the elderly [10]. Furthermore, in elderly patients, common degenerative changes in the spine can give a falsely high DXA value, despite presence of osteoporosis [11]. This is one of the reasons femoral neck BMD is most often used for diagnosis of osteoporosis, particularly in the elderly.

Osteoporosis – aetiology

During childhood and adolescence there is a rapid bone growth, but increases in bone mass continue for years culminating in maximum or 'peak bone mass' being reached. Peak bone mass is reached in the third decade of life [12], thereafter bone mass reaches a plateau from which it slowly decreases. For women this continues until menopause, after which oestrogen levels drop, which accelerates bone loss (Figure 3). During the decade following menopause, women have rapid bone loss [4]. Rate of bone loss may differ at different sites due to bone composition [7]. Compared to women, men lose around one third less bone during their life time [4] and this is reflected in the higher proportion of women diagnosed with osteoporosis.

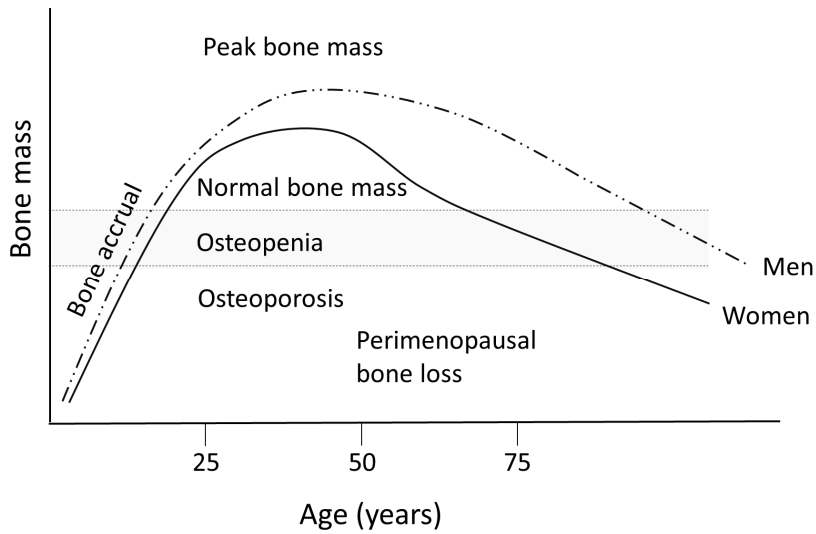


Figure 3. Bone mass during life in women and men
Bone loss in women is accelerated during late perimenopause and early postmenopause, resulting in an increased risk of osteoporosis.

The full picture behind osteoporosis is complicated and multifactorial, and genetics play an extensive part [13]. Osteoporosis can be defined as primary or secondary. Bone loss due to age or oestrogen deficiency is known as primary osteoporosis. Secondary causes of osteoporosis include endocrine system disorders, such as glucocorticoid-induced osteoporosis or hyperparathyroidism, but also factors affecting the gastrointestinal tract (celiac disease, eating disorders), autoimmune disorders such as rheumatoid arthritis and certain cancer therapies for example aromatase inhibitors [14]. Other risk factors for developing osteoporosis include lifestyle and environmental factors such as smoking, physical activity, body size, alcohol use and nutrition (Table 1) [15, 16].

Table 1. Risk factors for osteoporosis
The most common modifiable and nonmodifiable risk factors for osteoporosis

Nonmodifiable	Modifiable
Old age	Smoking
Female sex	Low body weight
Early menopause	High alcohole intake
Hypogonadism	Glucocorticoid therapy
Family history of osteoporosis/fractures (i.e. genetics)	Malnutrition/inadequate intake of calcium and vitamin D
Chronic diseases	Physical inactivity
	Propensity to fall

Osteoporotic fractures

The clinical outcome of osteoporosis is fracture (typically the distal radius, proximal humerus, hip, pelvis and vertebrae) often resulting from low-energy trauma. Close to eighty percent of fractures in the elderly are non-vertebral and occur after the age of 60 [(17)]. Distal radius fractures are usually the first osteoporotic fracture to occur, at the median age of 65 and as a result of a fall. Hip fracture occurs later in life (median above age 80) and has the most serious consequences; up to one fifth of patients die within one year of their hip fracture. Vertebral fractures can occur with only minimal trauma and not all are clinically diagnosed since they can be asymptomatic. When symptomatic, vertebral fractures cause pain, deformity and functional impairment [(2, 18)].

Fracture risk

The overall lifetime risk of fracture increases from the age of fifty to approximately seventy years, thereafter the risk plateaus and then decreases when the risk of death surpasses the risk of fracture [(19)]. Swedish women have a particularly high fracture risk, close to fifty percent for the remaining life time, from the age of fifty [(20)], compared to approximately twenty to thirty-five percent in other European countries [(21)].

The aetiology behind a fracture is multifactorial and many factors besides BMD affect fracture risk, including bone quality and propensity to fall [(15)]. Additional risk factors include female sex, family history, high age, Asian or Caucasian race, smoking, glucocorticoid therapy, visual impairment and excessive alcohol consumption [(19)]. A first fracture is a key risk factor for a subsequent fracture [(22)], and a fracture of the distal radius is considered a 'signal' event.

Based on known risk factors for fracture, patients with a suspected high fracture risk can be identified for further investigation or treatment, for example, by using the fracture risk estimation tool FRAX® which includes independent risk factors such as

smoking and history of previous fracture. FRAX®, which can be used with or without BMD, provides a 10-year probability of hip and osteoporotic fracture [23]. The tool does have some limitations; it does not consider polypharmacy or history of falls, nor does it consider different time frames for fracture risk probability (see below).

Different time frames for fracture risk

As mentioned above, fracture risk is highly age dependent and in the oldest, death may occur before a fracture can take place [19]. A Swedish study showed that among women who sustained a hip fracture, increased short term mortality leads to relatively fewer subsequent hip fractures in the elderly; 10-year fracture risk was 50% percent in women <75y compared to 26% in women >85y (who are unlikely to survive for an additional ten years). Time to re-fracture was also age dependent and in the oldest old, half of all re-fractures occurred within the imminent/short time frame of two years [24]. This is confirmed in a recent retrospective study showing that age was an important risk factor increasing imminent fracture risk [25]. Hence, the *time frame* for fracture risk predictions becomes highly relevant in the elderly and the 10-year fracture risk probability given by FRAX® is probably not meaningful in this age group.

Fracture risk intervention

Fracture prevention can be divided into pharmacological and non-pharmacological. Non-pharmacological fracture prevention addresses modifiable risk factors. For example, to reduce the risk of falling an intervention could be balance training or withdrawal of drugs related to falls [26, 27]. In addition, to improve bone health, all fracture patients should be given lifestyle advice regarding smoking, alcohol, nutrition and exercise [28].

Pharmacological fracture prevention may be through antiresorptive or anabolic agents. Antiresorptive agents, which supress osteoclast activity resulting in reduced bone resorption and increased BMD, are the most common osteoporosis treatment [29]. Anabolic agents increase bone formation [30].

Bisphosphonates in combination with calcium/vitamin D supplementation are the first line antiresorptive treatment. Bisphosphonates reduce vertebral fracture risk by approximately 45-70 percent and non-vertebral fractures by 16-25 percent [29, 31]. Bisphosphonates are not approved for patients with severely reduced kidney function [32]. Another antiresorptive agent is the human monoclonal antibody denosumab. Denosumab binds to the RANK-ligand, inhibiting osteoclast formation and increasing BMD, but the effect on BMD is reversible on drug withdrawal. An advantage of denosumab is that it can be prescribed in patients with severely reduced kidney function and the drug has actually been shown to improve estimated glomerular filtration rate

in patients with normal kidney function [31, 33, 34]. Denosumab reduces the risk of vertebral and non-vertebral fractures in postmenopausal women by approximately 70 and 20 percent, respectively [29].

Teriparatide is a synthetic version of the human PTH and an anabolic treatment that stimulates bone formation. While continuous PTH exposure increases bone resorption, intermittent treatment with teriparatide leads to augmented bone formation and BMD increases. It is yet not know why continuous versus intermittent PTH exposure has different effects. Teriparatide reduces the risk of vertebral fractures by 65% and non-vertebral fractures by 53% [30, 31].

Despite documented effects on secondary fracture prevention, there is a large treatment gap, both internationally and in Sweden. Only 14% of women aged 50 and over receive pharmacological treatment 6-12 month after a fracture, according to a report from the Swedish National Board of Health and Welfare [3, 35].

Kidney disease mineral and bone disorder

Estimation of a patients kidney function is not only important for correct dosage of pharmacological fracture prevention, but reduced kidney function is closely linked to bone health in a syndrome called chronic kidney disease mineral and bone disorder (CKD-MBD). In this syndrome, chronic kidney disease leads to disturbances in mineral homeostasis, lowering levels of vitamin D and calcium and increasing levels of phosphate, parathyroid hormone (PTH) and fibroblast factor 23 (FGF23). Bone abnormalities and vascular calcification are also part of the syndrome, resulting in cardiovascular disease (CVD), mortality and fractures (Figure 4) [36, 37].

Although fractures are a known outcome of CKD-MBD, it was not until 2017 that the KDIGO work group changed their recommendations allowing for the utility of DXA measurements to assess fracture risk in patients with CKD. The new recommendations were based on four longitudinal studies [38].

CVD is a key component of CKD-MBD [36]. Historically, the link between CKD and CVD has been known since the nineteenth century [39] and CKD is closely related to CVD and death from CVD [40], even when risk factors such diabetes are accounted for [41]. Studies indicate that cystatin C and cystatin C based eGFR might be a better predictor than creatinine for cardiovascular events and mortality [42, 43].

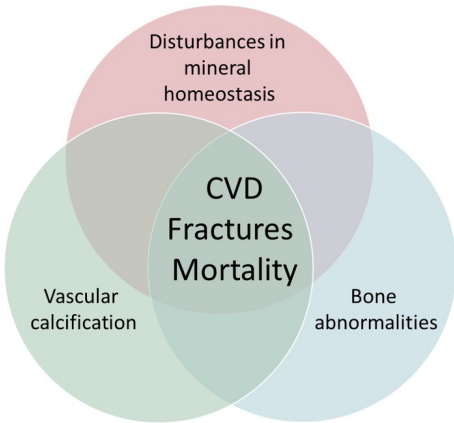


Figure 4. The syndrome of CKD-MBD
Figure modified from EraEDTA Scientific Working Groups (www.era-edtaworkinggroups.org)

Kidney function and mineral homeostasis

The pathophysiology behind CKD-BMD is complex with interactions and feedback systems for the hormones controlling bone health (Figure 5). In the kidney, vitamin D is transformed to its active form calcitriol ($1,25(OH)D_3$), hence reduction of kidney function can lead to lower vitamin D levels. Adequate levels of vitamin D are essential for normal calcium and phosphate homeostasis since it stimulates their uptake from the intestine. Low vitamin D and calcium levels stimulate PTH synthesis, resulting in secondary hyperparathyroidism. While levels of PTH and vitamin D are affected early in CKD, changes in calcium and phosphate are not seen until later in CKD [44-46]. The role of FGF23 in this process is covered later in the thesis (in future perspectives).

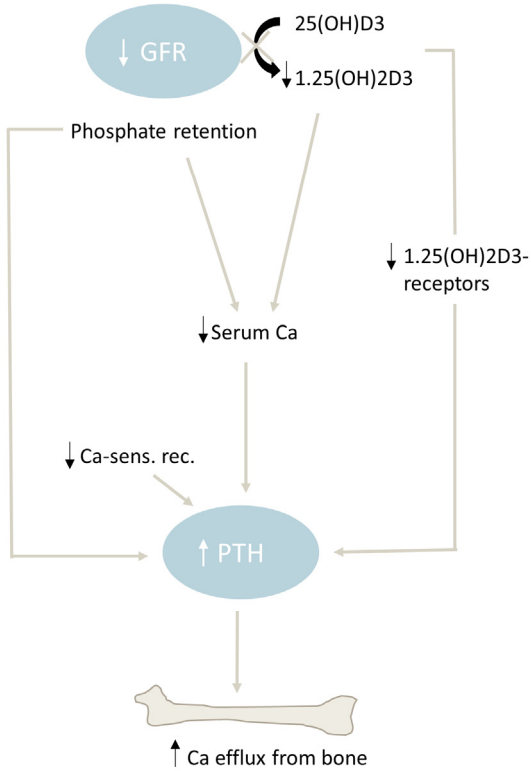


Figure 5.
Reduced kidney function can lead to disurbances in mineral metabolism

Kidney function and fracture

Fracture is a major outcome of CKD-MBD [47-52]. The risk increase is not explained by reduced bone mass alone, bone quality is also affected [53].

Although the link between poor kidney function and bone health is established in individuals with diagnosed CKD, the association between an age-related decline in kidney function and bone health is more complicated. In the first instance, elderly individuals are much less likely to develop end-stage renal disease [54]. Also, prevalence of both CKD and osteoporosis increases with age and the two conditions naturally co-exist to a large degree [55]. Hence, there is a need to separate the CKD-MBD syndrome from these two age-related, co-existing conditions.

Physiology of the kidneys

The kidneys are the most vascularized organ in the body (Figure 6) and play a vital role in many of the body's most important physiological functions [56]. The healthy kidney helps regulate excretory, endocrine and metabolic functions [57, 58], and among other things promotes bone health, erythropoiesis and regulation of blood pressure.

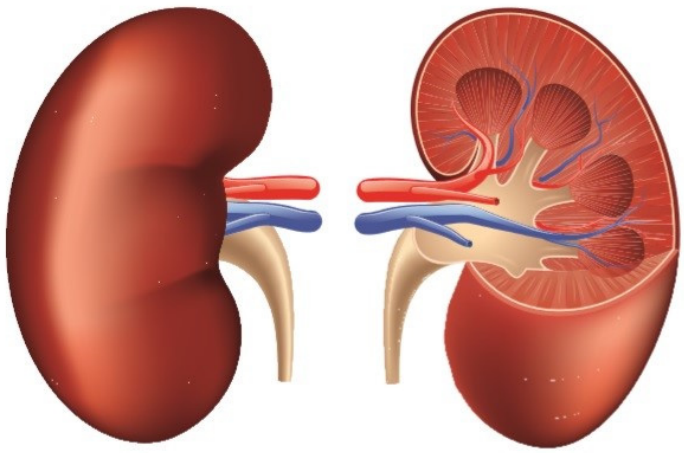


Figure 6. The kidneys are the most vascularized organ in the body
iStock.com/ andegro4ka

The nephron is the functional unit of the kidney (Figure 7), around 1 million of which work in parallel [59]. The nephron consists of a renal corpuscle (glomerulus and Bowman's capsule) connected to a renal tubule. Urine is produced through filtration of blood to Bowman's capsule and thereafter excretion and reabsorption in the tubular system.

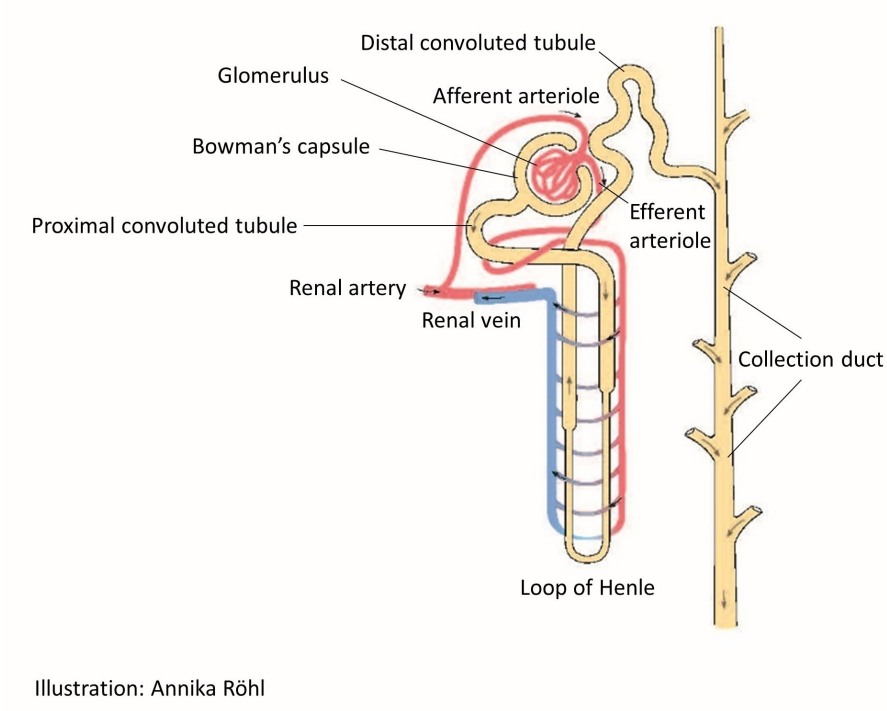


Figure 7. The nephron
The nephron is the kidneys functional unit and around 1 million nephrons work in parallel, every minute of the day.

Renal blood flow (RBF) amounts to 20-25% of the cardiac output, roughly 1000-1200ml of blood per minute, but only the plasma can cross through the glomerulus. Approximately one fifth of the plasma flow is filtered through the glomerulus into Bowman's capsule, constituting the glomerular filtration rate (GFR, mL/min). GFR, which represents the glomerular filtration per a specific time unit, can therefore be considered a measurement of kidney function [56, 60].

Measuring kidney function

GFR can be *directly* measured (mGFR) through the clearance of an exogenous marker in the urine/plasma. Inulin clearance is generally considered the "gold standard" [61], but other methods include iohexol [62], iothalamat [63], EDTA [64] and DTPA [65]. The GFR of a healthy young individual in the third decade of life is circa 120 mL/min [66]. However, GFR varies throughout the day and is also affected by activity level and meal composition [67-69].

Estimating kidney function

Measuring GFR is both time consuming and expensive, hence, GFR is often *estimated* (eGFR) in everyday clinic. Estimated kidney function is an important tool for the clinician, not only as an indication of current kidney function, but also for correct dosage of medication.

Body surface area represents the size of the kidneys which in turn represents kidney function. Hence, to compare kidney function between individuals or for the purpose of comparison with reference values, eGFR needs to be adjusted to body surface area. For this purpose, the body surface area used is $1.73m^2$ [70] and when eGFR is adjusted to body surface it is expressed as $mL/min/1.73m^2$.

eGFR can be estimated using endogenous markers of kidney function in blood, such as concentration of creatinine or cystatin C, both of which have their limitations and drawbacks. Creatinine, the most commonly used marker internationally is affected by muscle mass and diet [71, 72], while cystatin C levels are affected by high doses of corticosteroids and possibly inflammation [73]. Also, the two markers are differently associated with adverse outcomes such as mortality. Reflecting the difficulties of correctly addressing the influence of age, sex and body size on kidney function, numerous study equations to estimate GFR have been developed (Table 2).

Table 2. eGFR study equations for females used in this thesis
Over time, many study equations have been developed to adequately estimate GFR, mirroring the difficulty in correctly adressing kidney function

Study equations to estimate kidney function in females (eGFR)			
Name*	Year	Marker (creatinine/cysC)	Formula
CG/BSA	1976	Creatinine	$eGFR_{CG}$ x 1.73/BSA ((140–age) x weight x 1.04) / p-Cr BSA (m^2) = 0.20247 x $height^{0.725}$ (m) x $weight^{0.425}$ (kg)
MDRD	2006	Creatinine	$175 \times (\text{p-Cr} / 88.4)^{-1.154} \times age^{-0.203} \times 0.742$
CKD-EPI	2009	Creatinine	p-Cr ≤62 µmol/L: $144 \times (\text{p-Cr} / (0.7 \times 88.4))^{-0.329} \times 0.993^{age}$ p-Cr >62 µmol/L: $144 \times (\text{p-Cr} / (0.7 \times 88.4))^{-1.209} \times 0.993^{age}$
	2012	Cystatin C	p-CyC ≤0.8 mg/L: 133 x $(\text{ScysC}/0.8)^{-0.499}$ x 0.996^{Age} x 0.932 p-CyC >0.8 mg/L: 133 x $(\text{ScysC}/0.8)^{-1.328}$ x 0.996^{Age} x 0.932
LM-rev (adj. for lean body mass)	2011	Creatinine	$eGFR = e^{X-0.0070 \times age + 0.00694 \times eLBM}$ X (p-Cr <150)= 3.43 + 0.0121 ×(150-pCr) X (p-Cr ≥150)= 3.43 - 0.926 × ln(p-Cr/150) eLBM = (0.438 × ln(age) - 0.0088 × age-0.93)/0.00694
BIS1	2012	Creatinine	$3736 \text{ X } (\text{p-Cr}/88.4)^{-0.87} \text{ X } age^{-0.95} \text{ X } 0.82$
CAPA	2014	Cystatin C	$130 \text{ x p-cysC}^{-1.069} \text{ x } age^{-0.117} - 7$

* CG/BSA – Cochcroft-Gault adjusted for Body Surface Area, MDRD – Modification of Diet in Renal Disease, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, LM-rev – revised Lund-Malmö study equation, BIS1 – Berlin Initiative Study 1, CAPA – Caucasian, Asian, Pediatric and Adult cohort study equation

Today, there is yet no agreement on which is the best study equation. For example, in the elderly the MDRD study equation [74] has been reported to *over*estimate kidney function, while the previously widely used Cockcroft-Gault study equation [75] which was developed only in males, is said to *under*estimate kidney function [76]. As a consequence, neither MDRD nor Cockcroft-Gault study equations are commonly used clinically. The CKD-EPI study equation is currently recommended rather than MDRD, although very few elderly were included in its development [77]. In Europe, the BIS1 has been proposed excellent for an elderly population [78], while LM-rev performs well in a Swedish population [79]. CKD-EPI can be used with creatinine and cystatin C [80], as can CAPA, although CAPA probably performs better in older age groups [81].

Kidney function and ageing

The kidney function of a young healthy adult lies around 100-120 mL/min/1.73m^2 [82, 83]. Kidney function declines during ageing, most likely starting somewhere in middle age and declining around 1 mL/min/1.73m^2 per year [61, 84-86]. However, longitudinal studies in age-related kidney function change are scarce [87, 88] and most estimates of decline in kidney function are based on cross-sectional studies with a large age span in the individuals included [61].

Apart from the lack of longitudinal studies, another problem relating to descriptive data on age-related change in kidney function is that many studies are heterogeneous with regard to study populations and methods to estimate kidney function in terms of which marker and study equation is chosen. Consequently it is difficult to determine what constitutes "normal" kidney function in the elderly [59]. And while we do know that kidney function in an elderly individual differs from the young, the question we really need to ask is whether this change is *physiological* or *pathological*?

Chronic kidney disease

Chronic kidney disease (CKD) is the common name for a heterogeneous disease with various clinical expressions. The *Kidney Disease Improving Global Outcome* (KDIGO) workgroup has defined CKD as "abnormalities of kidney structure or function, present for 3 months, with implications for health" [57]. Depending on eGFR level, CKD is staged from 1-5 (Table 3), where stage 3-5 is considered disease. In order to be diagnosed with CKD at stages 1 or 2, other signs of kidney damage must also be present, usually determined by an increased albumin/creatinine ratio. Clinically, this definition means that any patient with a persistent reduction of eGFR (corresponding to stage 3-5) can be diagnosed with CKD.

Table 3.
CKD stages 1-5 as defined by the KDIGO work group

CKD stage	GFR (mL/min/1.73m2)	Description
1	≥ 90	Normal or high kidney function, other signs of kidney damage needed for diagnosis
2	60-89	Mildly decreased kidney function with other signs of kidney damage
3a	45-59	Mildly to moderately decreased kidney function
3b	30-44	Moderately to severely decreased kidney function
4	15-29	Severely decreased kidney function
5	< 15	Manifest kidney failure

The threshold of 60 mL/min/1.73m^2 for CKD diagnosis was chosen because of the increased mortality risk observed below this eGFR level [89]. But this association might be partly age dependent; among younger individuals mortality risk may be increased at higher eGFR (<75 mL/min/1-73m^2, stage 2), while in the elderly the association appears at a considerably lower eGFR (<45 mL/min/1-73m^2, stage 3b-5) [40, 90, 91]. Hence, the discussion is ongoing as to whether CKD should be age dependent [92, 93], rather than a "one size fits all".

CKD prevalence

The CKD prevalence in Europe varies between countries, from one to six percent, and this variation is not altogether explained by established risk factors such as diabetes, hypertension and obesity [94]. It is probable that the disparity is partly explained by heterogeneity of the studied populations [95]. Data from America suggests a similar prevalence around seven percent [96].

Reflecting that kidney function and therefore CKD prevalence varies with age, among the elderly CKD prevalence from forty to fifty percent has been reported [97, 98]. Apart from age, prevalence varies with geography, sex and ethnicity. For example, CKD prevalence appears to be higher in women compared to men, while African Americans have a higher risk of developing CKD compared to White Americans [92, 94, 96].

The most severe outcome of CKD is kidney failure or End-stage Renal Disease (ESRD), often defined as an eGFR <15 mL/min/1.73m^2. Only approximately one percent of patients with CKD will eventually require dialysis or transplantation [57]. Early CKD is often asymptomatic with a slow disease progression over decades; early diagnosis and interventions might prevent this [57]. The risk of progression towards ESRD is much higher in younger and middle aged individuals compared to older ones; by age 65-85, taking into consideration age-related deterioration, eGFR needs to decline to 15 mL/min/1.73m^2 before the risk of ERSD exceeds the risk of death [54].

Need for an age-adapted CKD definition?

The logical consequence of kidney function naturally declining with age, is that the proportion of men and women with an eGFR corresponding to CKD increases with age. But in contrast to, for example the age-adjusted definition of chronic obstructive pulmonary disease [91], the KDIGO definition of CKD does not take age into consideration. However, the clinical implications of age-related decline in kidney function are debated with the suspicion that the present definition is unnecessarily classifying too many elderly with disease [99-102].

In summary, there are large gaps in knowledge relating to the concept of age-related decline in kidney function and its consequences for bone health in an elderly population, which motivated the investigations leading to this thesis.

Aims

The overall aim with this thesis was to explore kidney function during ageing and its association to bone health, through markers of bone and mineral metabolism, BMD and fracture risk, and mortality. The specific aims were:

1. Evaluate kidney function during ageing using both creatinine and cystatin C and a range of study equations to determine:
   1.1. What constitutes normal kidney function in elderly and very elderly women?
      - What is the pattern of decline over 10-years from age 75-85?
      - Is an eGFR equivalent to chronic kidney disease (CKD stage 3-5) common?
   1.2. Does choice of endogenous marker (creatinine or cystatin C) affect estimated GFR in elderly and very elderly women?
   1.3. Does choice of study equation affect estimated GFR at different ages?
   1.4. What is the association between kidney function and mortality during ageing? Should the CKD definition be age adapted?
2. Determine the association between age-related reduction of kidney function in elderly women and:
   2.1. Markers of mineral homeostasis
   2.2. Bone mass and bone loss
   2.3. Fracture risk across different time-frames
3. Investigate the utility of BMD assessment by DXA for fracture prediction in elderly women with reduced kidney function.

Method

Study population

All papers in this thesis are based on the Osteoporosis Prospective Risk Assessment (OPRA) cohort. With participants randomly chosen from the city archives of Malmö in the south of Sweden, the OPRA cohort is a population based study of community dwelling older women. 1604 women were invited by letter one week after their 75th birthday. No exclusion criteria were applied. The age of 75 was chosen to capture the maximum number of fractures. The 1604 women invited represented one third of the 75 year old women living in Malmö at the time of recruitment (1995-1999). Participants were prospectively followed for fractures and mortality up to October 2012 [103] (Figure 8).

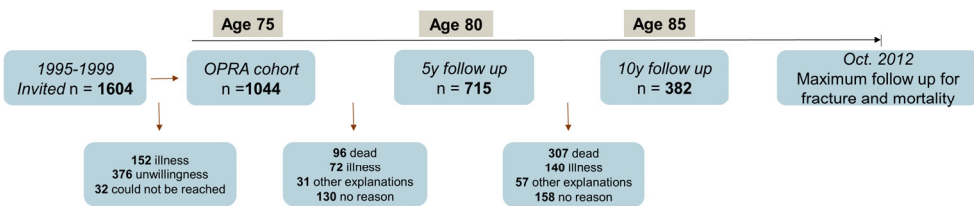


Figure 8.
Participation at each investigation and reasons for non-attendence in the OPRA cohort

While 1604 women were invited, 152 and 376 women respectively stated illness and unwillingness as a cause for non-participation. In addition, and despite several attempts, 32 women could not be reached, leaving 1044 women for baseline participation (65% response rate). Re-investigations were made after five (age 80) and ten (age 85) years, with a limited reinvestigation after three years (age 78). The papers in thesis have a maximum follow up of ten years from baseline. For participation rate at follow up, see Table 4.

Table 4.
Participation rate and avaliable participants in the OPRA cohort

Age (years)	*Participation rate (%)*	*Participated in investigations (n)*	*Available creatinine values (n)*	*Available cystatin C values (n)*
75	65%	1044	1011	981
80	75%	715	689	685
85	76%	382	363	365

At study start and each follow up visit, assessments included BMD measurements using DXA, anthropometrics, blood sampling and a questionnaire collecting detailed information regarding medications, nutrition, lifestyle, smoking habits and diseases.

Blood biochemistry

All blood samples were drawn non-fasting before noon and stored at -80°C degrees. Analyses were performed at the Department of Clinical Chemistry, Skåne University Hospital, Sweden.

Plasma creatinine

Plasma creatinine (p-Cr) was analysed according to routine procedures at the accredited clinical chemistry laboratory. Due to the study duration, methodological updates were implemented. Samples were analysed using the Jaffe reaction with a Beckman synchron LX20–4 (Beckman-Coulter, Ca, USA) or using an enzymatic method (Cobas autoanalyzer, Roche Diagnostics, Mannheim, Germany; [CV 1.4 – 1.7%]), the current standard in use at the clinical chemistry department. The data used in the statistical analyses have been adjusted to the Cobas method to ensure homogeneity of all values and allow comparison between the different time-points. All values are IDMS traceable, which means that the method is calibrated using reference materials.

Plasma cystatin C

Plasma cystatin C (cysC) from all visits was analyzed in batch in 2015 using a Cobas auto-analyzer, adjusted to the international cystatin C reference calibrator ERM-DA 471/IFCC (CV ranging from 2.2-1.1%).

Estimation of kidney function

Kidney function was estimated with both creatinine and cystatin C. When estimating function using creatinine, the following equations were applied:

- Cockroft Gault adjusted for body surface area (CG/BSA) [104, 105]
- Modification of Diet in Renal Disease study equation (MDRD) [106]
- Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [107]
- Lund Malmö formula revised adjusted for body surface area (LM-rev) [79]
- Berlin Initiative Study (BIS1) [78]

For eGFR based on cystatin C, the following study equations were used:

- Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [80]
- Caucasian, Asian, Pediatric, and Adult equation (CAPA) [81] (Table 5)

Table 5. The different study equations used in paper I-IV.
In all studies, CKD-EPI has been used as the main equation and is therefore marked in bold.

	Study I	***Study II-IV***
Creatinine	**CKD-EPI**, MDRD, LM-rev, BIS1, CG/BSA	
Cystatin C		**CKD-EPI**, CAPA

Based on kidney function, and in accordance with the 2012 KDIGO guidelines [57], women were divided into three categories:

NORMAL

- Normal to mild reduction - eGFR ≥ 60 mL/min/1.73m^2, equivalent to CKD stage 1-2.

INTERMEDIATE

- Mild-moderate reduction - eGFR 45-59 mL/min/1.73m^2, equivalent to CKD stage 3a.

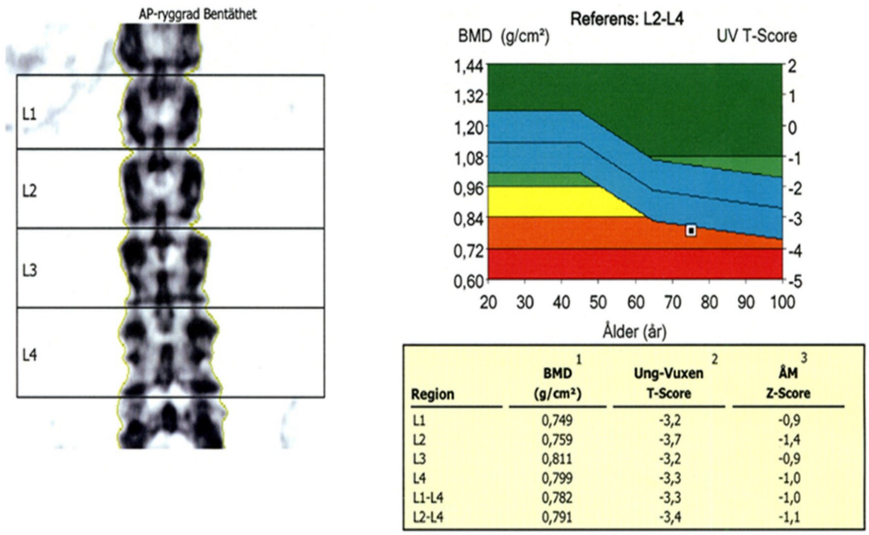
POOR

- Moderate-severe reduction - eGFR <45 mL/min/1.73m^2, equivalent to stage 3b-5.

In additional analyses, intermediate and poor categories were combined into a single group '**REDUCED KIDNEY FUNCTION**', defined as eGFR <60 mL/min/1.73m^2. Change in kidney function was calculated *individually* for every woman as actual eGFR change per five or ten years (mL/min/1.73m^2) or as annual percentage change (%).

Measurement of bone mass using DXA

Bone mineral density (BMD) was determined using dual-energy x-ray absorptiometry (DXA) (Figure 9a and 9b), measured with a Lunar DPX-L (GE Lunar, Madison, WI). Areal BMD (g/cm^2) was measured at femoral neck (FN) and total body (TB) at Skåne University hospital, Malmö. Precision of DXA was assessed by duplicate measurements on healthy individuals. Precision error was 0.009-0.010 g/cm2 at FN and 0.011-0.030 g/cm^2 at TB. No drifts in phantom measured were observed [108].



Region	1 BMD (g/cm²)	2 Ung-Vuxen T-Score	3 ÅM Z-Score
L1	0,749	-3,2	-0,9
L2	0,759	-3,7	-1,4
L3	0,811	-3,2	-0,9
L4	0,799	-3,3	-1,0
L1-L4	0,782	-3,3	-1,0
L2-L4	0,791	-3,4	-1,1

Figure 9a.
A DXA measurement at lumbar spine in an elderly woman (left) with reference values depicted in graph and table (right)

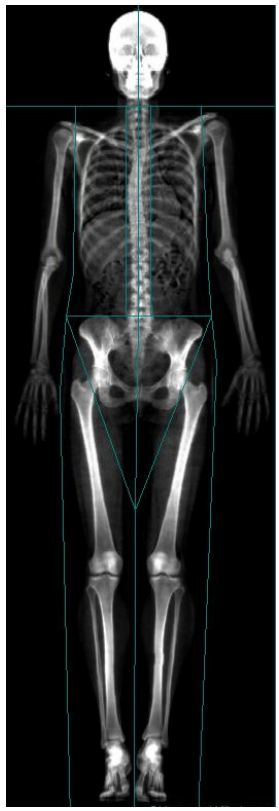


Figure 9b.
The author depicted through a DXA scan

Osteoporosis was defined as a T-score ≤ -2.5 at the FN, and osteopenia as a T-score between -1 and -2.5. Rate of bone loss was calculated individually for every woman as annual percentage change in BMD and as absolute bone loss over five- or ten years.

Fracture assessment

Incident fractures during the ten years of study time (from age 75-85) were registered by a continuous search through the Radiological Department at Skåne University hospital, Malmö (until October 31, 2012; maximum follow up for this study was 10.4 years). This hospital is the only hospital treating fractures in the catchment area, hence, loss to follow up was remarkably low [(109)]. Registration was possible due to participants' personal identification number, unique to every Swedish citizen.

This study investigates hip or major osteoporotic fractures, defined as any of the following: hip, pelvis, vertebral, distal radius or proximal humerus. Pathological fractures and high energy fractures were excluded from analyses.

Estimating fracture risk

Time frames for fracture risk are of particular importance in elderly populations. On this basis fracture risk based on categories of kidney function (normal, intermediate and poor) was investigated in several different time frames: imminent (1 year), short (2 and 3 years) and long (5 and 10 years) (Figure 10).

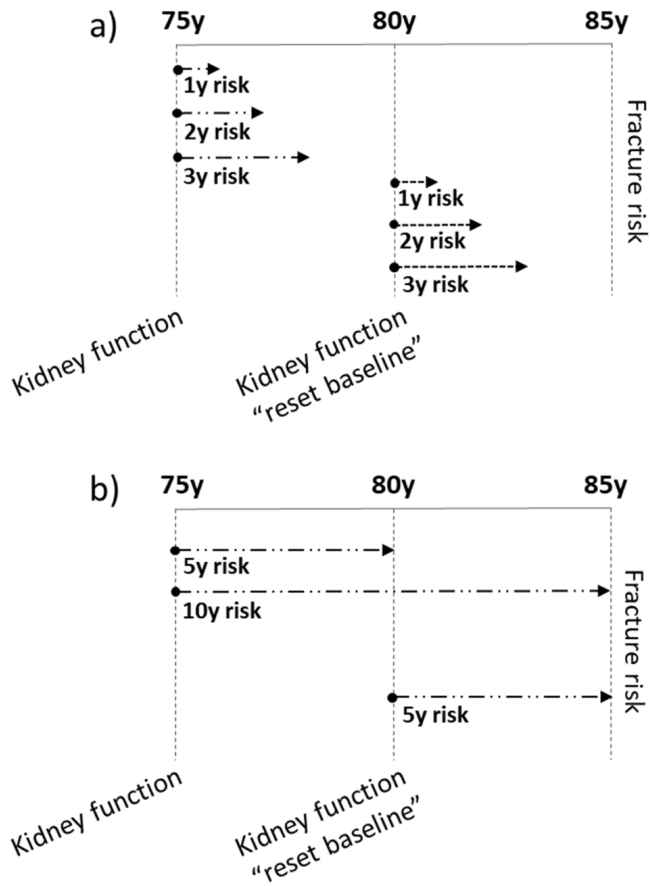


Figure 10. Shematic figure of time frames used for fracture risk calculation.
A) Imminent (1 year) and short (2 and 3 years) and b) long (5 and 10 years).

In addition, to investigate the utility of DXA measurements in those with reduced kidney function, fracture risk was estimated for women based on both kidney function and osteoporosis status:

1. *Normal* kidney function (eGFR ≥60 mL/min/1.73m^2) *without* osteoporosis,
2. *Reduced* kidney function *without* osteoporosis,
3. *Normal* kidney function *with* osteoporosis and
4. *Reduced* kidney function *with* osteoporosis.

Comorbidities

Self-reported medication and co-morbidities were available from questionnaire at baseline and follow up visits. Information on cardiovascular diseases (CVD) and high blood pressure (HBP) was not available at age 75 and therefore derived from their reported medications. HBP was defined as treatment with any anti-hypertensive, while CVD was defined as anti-hypertensive treatment in combination with an anticoagulant or lipid modifying agent, or treatment only with vasodilators (organic nitrates). Therefore, CVD at baseline should be considered an indirect measurement. Information about CVD, HBP and heart failure was available at the 80- and 85 year follow up.

Mortality assessment

Date of death was recorded through the Swedish national population register. Mortality in this study was followed for up to ten years.

Power analyses

The OPRA cohort was designed as a fracture and bone density study, hence, power analyses *a priori* were conducted to determine the sample size needed to detect differences in BMD and bone turnover markers. Based on the supposition of 0.13 g/cm^2 SD in BMD, 850 individuals gives over 80% power to detect a 0.056 g/cm^2 difference between equal groups at a 5% significance level. Assuming that at this age, when fracture prevalence increases, 60 women from the cohort would be expected to sustain a hip fracture during the subsequent five year period; to account for probable drop-outs, an estimated 50 fractures was assumed. Consequently, 50 hip fracture patients and 600 controls were judged neccessary for 80% power (significance level

5%) to detect a 30% difference in bone turnover marker (carboxylated serum osteocalcin). The baseline sample size of 1000 women was therefore deemed adequate.

Statistical analyses

Data is presented in absolute numbers, percentage and mean with standard deviation or median with interquartile range, as appropriate.

Data was analysed with SPSS version 20-25 (IBM SPSS. Armonk, NY: IBM Corp) and in one instance using MATLAB 7.12.0 and Statistics Toolbox 3.1 (MathWorks, inc., Mass., USA).

P-values <0.05 was considered nominally significant.

Study I is based only on women with available plasma creatinine, corresponding to 1011 at age 75. Papers II-IV are based on the 981 women with available plasma cystatin C values at study start (Table 4).

Study I

This study investigates kidney function and its decline over ten years using creatinine and five study equations. Differences in mean eGFR between study equations were compared using the paired samples t-test, while loss of eGFR between quintiles was compared using ANOVA. For women who survived follow up, predicted loss of function over time for each quintile of kidney function loss was plotted.

Risk of co-morbidity for categories of kidney function (normal, intermediate and poor) was analysed using binary logistic regression, while mortality risk was estimated using cox proportional hazard models. Data is presented unadjusted and adjusted for smoking, BMI and co-morbidities.

Study II

Mirroring study I, study II investigates kidney function and its decline over ten years using cystatin C and two study equations, CKD-EPI as most widely used internationally and CAPA, developed mainly in a Swedish cohort. Using paired samples t-test, difference in mean eGFR was compared. Mortality risk for categories of kidney function was evaluated using cox proportional hazard models.

Study III

This study explores the relationship between kidney function, BMD and bone metabolism. For better understanding of the context, the study also includes a non-systematic literature search.

The association between kidney function, estimated using cystatin C and the CKD-EPI study equation, and BMD was investigated using multivariate linear regression analysis. Characteristics and bone loss for categories of kidney function was investigated using ANOVA or Kruskal-Wallis, as appropriate.

Study IV

To examine the association between reduced kidney function and fracture risk, this study estimated kidney function using cystatin C and the CKD-EPI study equation. Fracture incidence per 1000 person-years was calculated as 1000 x *total number of fractures* / total follow-up time (time to death OR end of follow up). Using categories of kidney function, the association to fracture was evaluated using cox proportional hazard models in immediate, short and long time frames. To explore the utility of BMD measurements to estimate fracture risk in women with reduced kidney function, cox proportional hazard models were performed based on osteoporosis status *and* kidney function.

Results

Study I

Introduction

Kidney function declines with age, but longitudinal studies in elderly women are scarce. Creatinine is still more commonly used in a clinical setting compared to cystatin C. Mirroring this, many creatinine-based study equations have been developed. But most of these have not been extensively evaluated in the elderly, in spite of the fact that the elderly are the most common patient group. In this study, kidney function was estimated using five study equations: CG/BSA and MDRD were chosen because they were formerly commonly used, while CKD-EPI is probably the most widely used internationally. LM-rev was developed in a Swedish setting and BIS1 developed for an elderly population.

Methods and subjects

Creatinine was available for 1011 (age 75), 689 (age 80) and 363 (age 85) women from the OPRA cohort and kidney function (eGFR) was estimated using each one of the following study equations: CG/BSA, MDRD, CKD-EPI, LM-rev and BIS1. Kidney function was modelled to investigate whether change was linear or not. Association between kidney function (CKD stage 3a and 3b-5), co-morbidity and mortality were investigated.

Results

Estimations of kidney function differed greatly depending on which study equation was used: MDRD and CKD-EPI predicted higher mean eGFR values compared to the three other equations. This is reflected in the proportions of women with an eGFR corresponding with CKD stage 3-5. As can be seen in Figure 11, the CG/BSA, LM-rev and BIS1 study equations classified proportionally *more* women with CKD stage 3-5 compared to MDRD and CKD-EPI, especially in advanced age. For example, at age

85, 51 percent were classified with CKD according to the CKD-EPI study equation. The corresponding number for LM-rev was 76 percent.

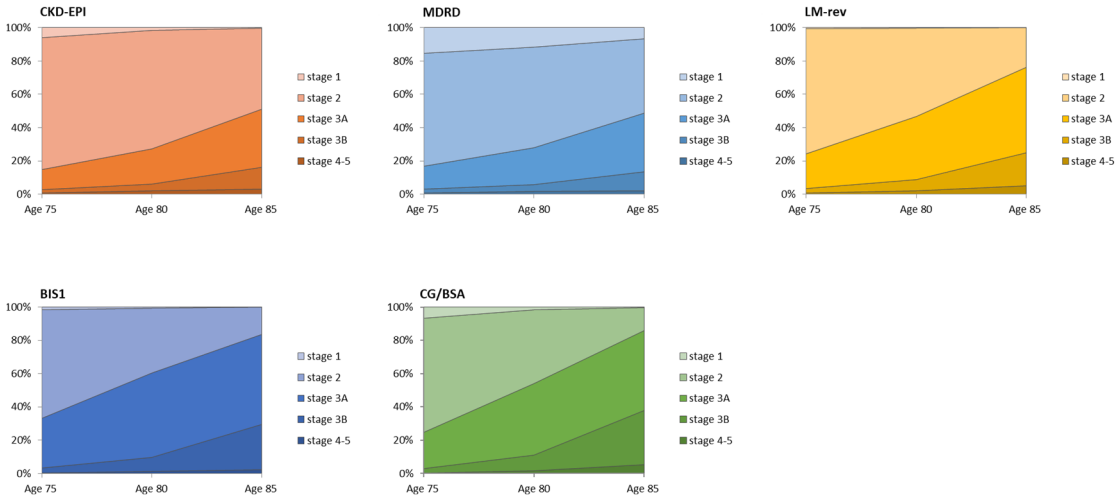


Figure 11. Prevalence of CKD at ages 75, 80 and 85
Prevalence of CKD based on eGFR estimated using the five creatinine-based study equations. LM-rev, BIS1 and CG/BSA class proportionally more women into CKD stage 3a-5 compared to CKD-EPI and MDRD, especially in advanced age.

While the women lost 22% (a mean of 16.6 mL/min/1.73m^2) of their kidney function overall across 10-years of follow up, loss was non-linear and accelerated between ages 80-85.

A moderate-severe (stage 3b-5), but not mild-moderate (stage 3a), reduction of kidney function was associated with a threefold increased risk of mortality. Reduced kidney function was associated with increased risk of co-morbidities.

Conclusion

The five study equations could differ by as much as ten units in their estimations of kidney function and the average loss per year of 1.6 mL/min/1.73m^2 is higher than previous reports of circa 1 mL/min/1.73m^2 in elderly men and women. It is probable that loss of kidney function depends on baseline eGFR and that women in our study might be healthier than non-participants, however, these results highlight that kidney function loss is high even among otherwise healthy older women. While women with the worst kidney function had increased mortality risk, this was not the case for women with intermediate function. We interpret this as reflecting that a slight reduction of kidney function in the elderly is a part of normal ageing and not a disease.

Without direct measurement of kidney function (which was not part of the study protocol) it is difficult say definitively which study equation provides the most precise estimate. However, LM-rev and BIS1 probably gives an accurate estimate of GFR in the OPRA cohort since LM-rev was developed in a Swedish population [79] and the BIS1 study equation specifically developed for an elderly population [78].

Study II

Introduction

This cystatin C based study was planned as a complement to study I which is based on creatinine. By using cystatin C, which has been proposed more accurate in the elderly, this study in combination with our creatinine based study, aims at capturing the 'full picture' of age-related change in kidney function in older women. In addition, since current CKD definitions are age independent, our second aim was to challenge this by evaluating the association between an age-related reduction of kidney function and mortality using two cystatin C based estimations.

Method and subjects

Kidney function (eGFR) was estimated using the cystatin C-based CKD-EPI and CAPA study equations (cystatin C available for 981, 685 and 365 women at age 75, 80 and 85, respectively). Individual kidney function loss was calculated as *actual* or *percentage* loss per year. Association between mortality and kidney function (intermediate and poor, CKD stage 3a and 3b-5) was assessed.

Results

Using CKD-EPI$_{cysC}$, eight out of ten women had an eGFR equivalent to CKD at the end of the study period (age 85), a much larger proportion compared to CKD-EPI$_{crea}$. Both mild-moderate and poor kidney function were associated with mortality from age 75-80, but at older ages (80-85) and in the longer time period (age 75-85) this association was attenuated for women with intermediate function (Figure 12).

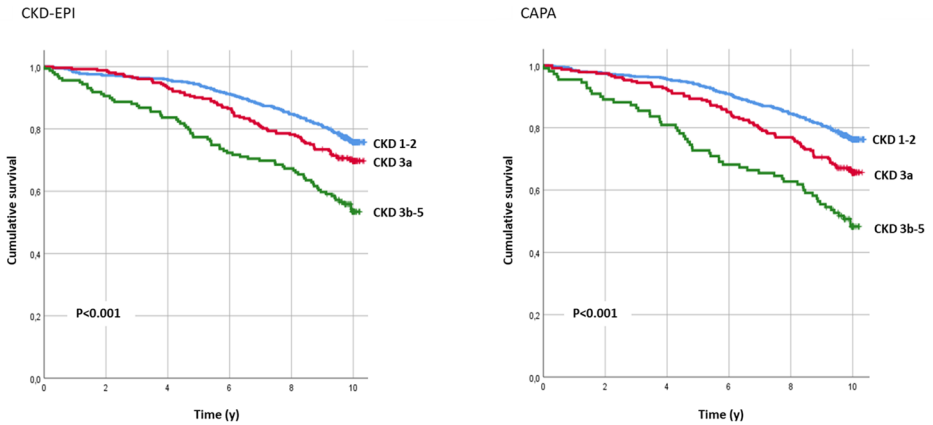


Figure 12. Survival from age 75-85 based on kidney function (CKD-EPI and CAPA) at age 75.
CKD 1-2 equals an eGFR ≥ 60 mL/min/1.73m^2 and is considered a *normal* kidney function. CKD 3a equals an eGFR from 45-59 mL/min/1.73m^2 and is considered a mild-moderate reduction of kidney function. CKD 3b-5 equals an eGFR < 45 mL/min/1.73m^2 and is considered a moderate-severe reduction of kidney function. Survival is considerably lower for women with a moderate-severe reduction of kidney function.

Conclusion

Using cystatin C, the loss of kidney function during follow up equated to one quarter of the original kidney function, and the proportion of women with a kidney function equivalent with CKD stage 3-5 doubled. Only a moderate-severe reduction of kidney function (stage 3b-5) was continuously associated with mortality. The ambiguous association between a mild-moderate reduction (stage 3a) and mortality indicates that an age-adapted CKD definition might be of value.

Study III

Introduction

In chronic kidney disease, markers of mineral metabolism are affected, which in turn affects bone health negatively. This is a part of the syndrome known as CKD-MBD. But although elderly individuals might have an eGFR equivalent with CKD, this decline in kidney function can in actuality be seen as part of normal ageing and not kidney disease. It is therefore of relevance to investigate whether an *age-related decline* in kidney function poses the same threat to bone health.

Methods and subjects

A non-systematic literature review of the association between kidney function and bone mass was first conducted to provide context.

BMD measurements and blood chemistry, including cystatin C, were available for 981 women from the OPRA cohort at study start (age 75), with follow up after five (n=685) and ten (n=365) years. Kidney function (eGFR) was estimated using the CKD-EPI study equation. Association between kidney function, BMD, bone loss and markers of mineral metabolism such as PTH, phosphate, calcium and vitamin D were investigated.

Results

The non-systematic review yielded 20 studies investigating the association between kidney function and bone mass, however, these studies are hampered by heterogeneity in study populations and only three were longitudinal.

In the OPRA cohort, kidney function was associated with BMD at femoral neck at age 75 and 80, although with a small effect size - less than one percent of the variation in BMD could be explained by kidney function. Women with intermediate and poor kidney function had higher bone loss at the femoral neck and total body between ages 75-80. For women with poor kidney function, this amounted to an annual BMD loss of over two percent (Figure 13). Markers of mineral homeostasis also differed between kidney function categories.

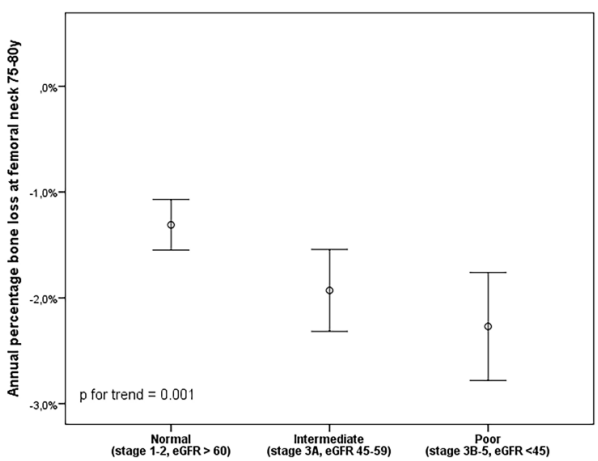


Figure 13. Bone loss at femoral neck between age 75-80 by categories of kidney function
Women with reduced kidney funciton had higher bone loss at femoral neck from age 75-80. Normal kidney function, equals an eGFR ≥ 60 mL/min/1.73m^2. Intermediate kidney function equals an eGFR from 45-59 mL/min/1.73m^2. Poor kidney function equals an eGFR < 45 mL/min/1.73m^2.

Conclusion

The results indicate that there is an association between kidney function and markers of mineral homeostasis in elderly healthy women with an age-related decline in kidney function. There is also an association between kidney function, bone mass and bone loss, although the effect size on these parameters was small and attenuated with advancing age. As a single risk factor, reduced kidney function may be less clinically relevant, more likely it should be considered in addition to established risk factors for osteoporosis. Nevertheless, this study provides important insight in the association between age-related kidney function and bone health on the basis of the longitudinal study design and homogeneous, well defined cohort of community dwelling elderly women.

Study IV

Introduction

Chronic kidney disease and its associated increase in fracture risk is a part of the CKD-MBD syndrome. But the relationship between bone health and CKD is more complicated in the elderly, since both osteoporosis and CKD are age-dependent and co-exist in a large proportion of the elderly population. With this perspective in view, the clinical relevance of the age-related decline in kidney function with regard to fracture remains to be determined. Furthermore, it was only recently that the KDIGO workgroup changed their recommendations, to now indicate the utility of BMD measurements in patients with CKD. But longitudinal prospective studies on the use of DXA in a population with reduced kidney function are still scarce.

Method and subjects

Cystatin C was available in 981 women from the OPRA cohort. Association between categories of kidney function (normal, intermediate, poor) and fracture risk in three time periods; imminent (1yr), short (2 and 3yr) and long (5yr) was investigated. In addition, fracture risk was determined based on combinations of kidney function and BMD.

Results

Women with intermediate kidney function had increased risk of fracture in the short time frames from age 75 (2yr risk hip fracture HR_{adj} 4.15 (95% CI, 1.57-10.96) and

in the first, long time period (age 75-80, 5yr risk hip fracture HR_{adj} 2.00 (95% CI, 1.00-3.98). This association was lost from age 80 and onwards, nor was fracture risk increased in women with the worst kidney function.

As shown in Figure 14, low BMD was associated with increased risk of hip fracture and osteoporotic fracture, independent of kidney function. Having reduced kidney function conferred an increased five year fracture risk, even with normal BMD.

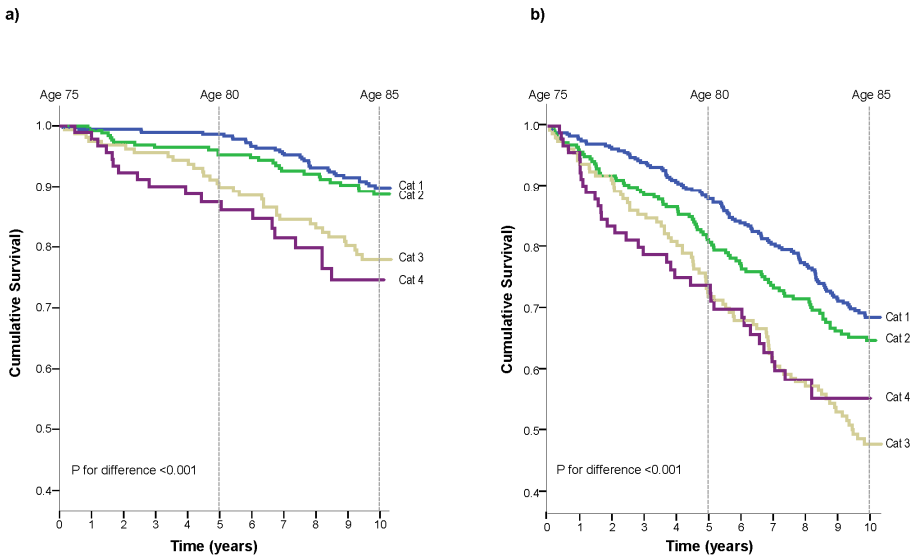


Figure 14. 10 year fracture free survival curves for a) hip and b) osteoporotic fracture based on combinations of kidney function (normal/reduced) and osteoporosis (with/without) at age 75.
Data presented is unadjusted and p-values calculated using the log rank test. *Category 1 (n=379) – normal kidney function (eGFR ≥60 mL/min/1.73m2), without Osteoporosis (FN T-score > -2,5). Category 2 (n=261) – reduced kidney function, without osteoporosis. Category 3 (n=161) – normal kidney function with osteoporosis. Category 4 (n=94) – reduced kidney function with osteoporosis

Conclusion

An increased risk of fracture was observed only in women with intermediate kidney function from the age of 75 and for up to five years. But there was no increased fracture risk in the very oldest or in women with the worst kidney function. The most likely explanation for this somewhat unexpected observation could be the higher mortality in those with the worst kidney function. A low BMD predicts fractures independent of CKD status (i.e. normal or equivalent to CKD stage 3-5) in elderly women, indicating that BMD assessment by DXA is valuable regardless of kidney function.

Summary of results

In summary, the results from the four studies show that an estimated kidney function equivalent to CKD is very common in otherwise healthy and elderly Swedish women, especially in advanced age, where eight out of ten women has an eGFR equivalent to CKD (depending on marker and study equation). Furthermore, estimations greatly depend on which endogenous marker (creatinine or cystatin C) and which study equation is used, possibly reflecting that most study equations included few elderly in their development. While poor kidney function (CKD stage 3b-5) is associated with mortality even in advanced age, the association between a mild-moderate reduction and mortality is less certain and depends on marker and study equation.

Although kidney function in old women is associated with bone mass and bone loss, the effect size is small and probably attenuates with advancing age. Regarding the association between kidney function and fracture, this appears also to attenuate with age; an intermediate reduction of function is associated with increased risk of hip and osteoporotic fractures from age 75-80, but not in advanced age or in the longer time period of ten years. Lastly, our results confirm the utility of DXA to predict low BMD and fracture risk in women with an eGFR equivalent to CKD.

Discussion

Study I

This primarily descriptive study estimates age-related decline in kidney function using creatinine and five study equations. To further explore how the different study equations perform in elderly women, the association between kidney function and mortality was investigated. Kidney function declined by one fifth from age 75 to 85. In absolute numbers this loss is slightly higher than other studies suggest. But the single age of all the participants in OPRA leads us to believe that we are actually capturing the accurate picture of how kidney function changes in elderly women.

The estimated GFR differed greatly depending on study equation, sometimes by as much as ten units. This finding was not unexpected since only BIS1 was specifically developed in an elderly population. However, an awareness of the discrepancies between the different study equations is necessary when interpreting the literature or where there is no consensus in clinic. This discrepancy is reflected also in the prevalence of CKD in the OPRA cohort (51 - 76 % using CKD-EPI and LM-rev respectively at age 85).

Although there was a strong association between poor kidney function (CKD stage 3b-5) and mortality, CKD stage 3a did not appear to be as clearly linked to survival. Therefore the present risk-based disease definition might be less relevant and incorrectly classifying too many elderly with kidney disease. Not many women progressed to severe kidney dysfunction during follow up, probably because of the strong association between CKD stage 3b and mortality, a finding that has been confirmed in elderly men [(54)]. We also interpret this to mean that in the elderly, reduced kidney function is a part of normal ageing which does not necessarily result in a continuous or rapid decline into severe disease.

Study II

Using cystatin C, study II was designed as a complement to the creatinine based study I with the purpose of moving a step closer towards obtaining a comprehensive picture of age-related change in kidney function in elderly women. Compared to creatinine based equations, cystatin C based study equations yielded considerably lower GFR estimates (at age 85, the mean estimate of CKD-EPI$_{crea}$ was 60 versus 47 mL/min/1.73m^2 using CKD-EPI$_{cysC}$). The differences in estimates could have a serious impact on CKD staging, again with the risk of incorrectly diagnosing a patient with kidney disease. Unnecessarily classifying a person with CKD can lead to needless clinical investigations and in addition, also raises questions and worries for the patient. Also, the large discrepancy between creatinine and cystatin C in GFR estimations in the elderly is of particular interest for most clinicians since creatinine based estimates are still the most commonly used.

As with the creatinine based observations, cystatin C based CKD prevalence in this age group and sex (ranging from forty percent at age 75 to eighty percent at age 85) is high compared to the overall one to six percent reported in Europe. However, looking only at the 75-84 year old age group, the same study shows a creatinine-based CKD prevalence of 40-45 percent in Germany [94] which is very close to the 51 percent estimated using CKD-EPI$_{crea}$ in study I.

Although a large proportion in the OPRA cohort have an eGFR equivalent with CKD, the vast majority are in CKD stage 3a, and as shown in study I, unlikely to progress to severe kidney disease. In accordance with creatinine based results in the same women, those with the worst kidney function (CKD stage 3b-5) had increased mortality risk. Taken together with the data from study I, the cystatin C based results suggest that an age-adapted CKD definition could be valuable, at least in the oldest old.

Study III

Study III focuses on the association between kidney function, bone mass and markers of mineral homeostasis. The non-systematic review conducted before study start identified twenty relevant publications [50, 110-128] with the body of evidence indicating association between kidney function and BMD. It was not clear however, whether this association was mediated through differences in sex, weight or age. Also, there was a clear lack of longitudinal studies and most were performed in non-European populations. Though not performed according to the principles of a systematic review it provided a much needed background in this complicated field in which age and disease definition are so closely linked.

In the OPRA cohort reduced kidney function was associated with markers of mineral homeostasis. Overall, kidney function was associated with BMD, but only a small proportion of the variation in BMD could be explained by kidney function. The small effect size can possibly explained by the fact that at age 75 and onwards, BMD is already low hence any further reductions will naturally be small. Alternatively, perhaps at earlier ages the effect of poor kidney function is more detrimental for bone health.

Cross-sectionally, bone mass was not substantially different between stages of kidney function, however the *rate* at which bone was lost differed and was higher for women whose kidney function was reduced. Clinically, based on the findings of this study, for women at this age it may be more clinically relevant to focus on other risk factors to maintain bone health rather than a pure age-related decline in kidney function; contrary to, for example, an individual who has had sustained, low kidney function for decades. Judging from study III it seems that although kidney function is associated with BMD and bone loss other risk factors might play a bigger part in advanced age.

Study IV

This study investigates the association between normal age-related kidney function and fracture in immediate, short and long time frames.

We hypothesised that fracture risk would increase progressively as kidney function decreased. Contrary to our initial assumptions, instead we found that it was women with a mild-moderate reduction of function who had the highest fracture risk while there was no apparent increase in fracture risk for those with the worst kidney function. This can probably be explained by the fact that these women have considerably lower survival and thereby a shorter time at risk for fracture.

The highest fracture risk was observed in the short time frame of two years from age 75, which is in accordance with the literature and can probably also be attributed to the influence of survival on risk estimates. It also highlights the importance of quickly identifying at risk patients for pharmacological fracture prevention. This also calls into question whether the ten year risk prediction in tools such as FRAX® is the most relevant in the very elderly.

Our results also confirm that measuring BMD by DXA is clinically useful for estimating fracture risk in those with reduced kidney function equivalent to the clinical definition of CKD. Although not unexpected, this supports the (2017) KDIGO guidelines changes stating that DXA is useful also in patients with CKD. Longitudinal studies are scarce and the current guidelines are based only on four such studies. Therefore our data will be an important resource for future meta-analyses.

Clinical implications

This thesis makes an important contribution to the field and to describing the age-related change in kidney function in elderly women and its outcomes. The work has direct clinical applicability since estimated kidney function is a vital part of everyday clinic, and critical for everything from drug dosage to daily assessment of signs of actual kidney damage. Also, due to its association with mortality and a variety of diseases, kidney function in the elderly can also be seen as a proxy for general health.

The glomerular filtration rate is influenced by factors such as meal composition and activity level, among others. It furthermore varies throughout the day. Therefore the GFR represents a specific moment in time; the assumption when you estimate GFR is that this 'snap-shot' accurately reflects the true global health status of the kidneys. Since *estimated* GFR varies further depending on which endogenous marker and study equation is used, the one-time estimation of kidney function becomes an uncertain measurement. In a clinical perspective this uncertainty can have serious implications since medications are often dosed on the basis of one single estimation of GFR only.

Based on a comprehensive assessment of markers and study equations in a large homogenous cohort of elderly women it seems likely that CAPA/LM-rev and BIS1 are best suited to a Swedish geriatric setting, although lacking corroboration by measured GFR for comparison. CAPA/LM-rev was developed in a Swedish population while BIS1 was developed in an elderly population. Age, ethnicity and geography are all important factors influencing kidney function, therefore using a study equation appropriate with regard to these factors is a critical choice for both the clinician and hospital laboratories.

In the oldest old, the majority of women have an eGFR which corresponds to CKD according to present definition. In my opinion, the high prevalence of CKD alone, challenges the currently defined threshold of disease. In combination with the fact that a clear association between CKD stage 3a and mortality is lacking, this thesis supports the concept of an age-dependent CKD definition, which is gaining momentum in the literature. Therefore, this work will be important for future decision making on whether changes in the CKD definition should be implemented.

As for risk of osteoporosis and fracture, a raft of clinical and lifestyle risk factors, each with potentially small effects, but taken together cumulative, needs to be considered since the aetiology of fracture is multi-factorial. This thesis suggests that kidney function is one such factor which should be considered. This is especially true since kidney function can be regarded a marker for general health as well as frailty, subsequently associated with falls and fractures.

Leading on from this, time frames for fracture risk are extremely important in the elderly. Women with reduced kidney function have the highest fracture risk within the

near term. Therefore, timely initiation of pharmacological and non-pharmacological fracture risk prevention is vital.

Overall, a healthy kidney function is undoubtedly important for maintaining bone health, although the consequences of the typical age-related decline in kidney function are probably not as serious as dysfunction in young or middle aged individuals; especially given the considerably longer time at risk for fracture compared to the elderly.

As a resident in Geriatrics, these results are a reminder that all organ systems loose reserve capacity with age and a holistic approach to health is warranted in the typical elderly patient.

Conclusions

This thesis investigates the age-related change in kidney function in elderly women and its association to bone health.

From the age of 75, an otherwise healthy woman can expect to lose between one fifth and one quarter of her kidney function as a normal part of aging. And the very large proportion who have or develop an eGFR equivalent to chronic kidney disease means that the threshold for disease is probably set too high in the elderly.

Further advocating an age-adjusted CKD definition, a woman with only a mild-moderate reduction of kidney function does not have a clear increase in mortality risk in contrast to a woman with the worst kidney function. Hence, adapting an age-adjusted CKD definition and lowering the disease threshold for CKD to stage 3b and lower should be considered, at least in the oldest old.

Even a normal age-related reduction in kidney function is associated with markers of mineral homeostasis and bone loss, but this association is not seen in the oldest old, which could indicate that in advanced age, risk factors other than kidney function might have a greater impact on bone mass.

Kidney function is associated with fracture risk in elderly women, although not in those with the worst kidney function. This finding can probably be explained by the fact that these women have shorter survival and thereby a shorter time at risk for fracture.

Women with low BMD assessed by DXA have increased fracture risk regardless of kidney function, indicating that DXA measurement is similarly useful in elderly women with kidney function corresponding with CKD as in those with normal kidney function.

Validation and generalisation of a research finding

External and internal validity

External validity indicates how generalizable the results of your study are to other populations. Thus, with perfect external validity, the results from this thesis would be absolutely applicable to elderly women living in the south of Sweden today. Internal validity indicates how well the association between exposure and outcome can be explained by the study, i.e. how well the study can remove alternative explanations for a finding. Without internal validity, there can be no external validity. Another description for lack of internal validity is *bias*. Bias, frequently categorised into three groups (see below) [129] is an inevitable part of any study and as a scientist one must be aware of the potential factors that can influence results. Below, factors potentially influencing the external and internal validity of the results from this thesis and how they were addressed are discussed.

Selection bias and external validity

This study was designed to minimise selection bias so far as possible; participants in the OPRA cohort were randomly chosen from the city files of Malmö and the invited women represent one third of all women aged 75 year old and living in Malmö at that time (1995-1999). Hence, the ORPA cohort should sufficiently represent the average elderly woman living in Malmö, and probably Sweden, at that time. Since all OPRA participants are Caucasian, results might not be applicable to other ethnicities. Demographics also change and today one third of Malmö's citizens are born abroad [130] hence the results may no longer be applicable to the average elderly woman of present day Malmö. Also, regardless of ethnicity, lifestyle and environmental factors today most likely differs from the mid-nineties.

In addition, participants who continued participation throughout the study might be healthier than those who declined; we know that baseline kidney function was higher in women who attended follow up compared to those who discontinued or died. In confirmation of this, mortality rates in OPRA participants might be lower compared

to those who declined [131]. At the same time a fracture study might attract participants with a history of previous fractures [132]. Better health in participants compared to non-participants is not a new phenomenon, especially in the elderly [133]. To counterbalance these potential limitations, the OPRA cohort has other advantages, among them the high participation rate, large sample size, prospective study design and long follow up.

Misclassification/information bias

Misclassification can occur when the process to identify exposure (in this thesis chronic kidney disease) is flawed. The KDIGO guidelines state that if eGFR falls below 60 mL/min/1.73m^2, CKD can be diagnosed based on eGFR *alone* if two consecutive eGFR measurements with at least three month apart are available. Calculations in this thesis are based on CKD classified with only *one* eGFR measurement, which might over estimate the number of women classified with CKD i.e. a false positive. This potential over-classification is shared with most other epidemiological publications in this research area [87]. Also, kidney function in this thesis is *estimated* rather than *measured* and thereby affected by choice of endogenous marker as well as by methodological updates. However, this reflects the clinical reality most doctors face today. The longitudinal study design mitigates many of these issues by allowing comparisons over time and also the possibility to determine how many women change CKD status between follow ups, thereby validating our results with regard to CKD prevalence.

Confounding

A confounding factor is associated with both the exposure and the outcome and might obscure the association between these. These factors are identified though subjects and physiology and other studies. In designing a study, many of these confounding factors can be counteracted, for instance by randomisation. Another example is age and sex. Since these two factors are similar for all participants in the OPRA cohort, two very common confounding factors are removed.

When a study is conducted and data is collected, the confounding factors can be handled differently. One way can be to adjust for them in a multivariate model, as we have done in study I-IV. Another example could be to exclude certain participants from the analyses. We did this in study III, where analyses regarding the association between kidney function and bone mineral density were conducted *with* and *without* women on bisphosphonates/steroids.

Even when confounding factors have been adjusted for, there might be residual confounding. One reason for this is that a known confounder has not been measured or there are *unknown* confounding factors. Alternatively there are too few events so that

the statistical model does not hold for multiple adjustments, such as was the case for immediate fracture risk in study IV. In this study we chose to proceed with the analyses (including multiple adjustments), but to acknowledge this fact as a limitation of the paper.

Power calculations

Power represent the likelihood of rejecting the null hypothesis (H_0) when another hypothesis (H_1) is true. Power calculations should be made *a priori*, before study start. Without a power calculation, how can you be certain that a negative result really confirms the H_0 and is not just a result of low statistical power?

The power calculations for OPRA were made before study start with the aim of detecting differences in BMD and fracture. Therefore, in the oldest old, calculations with other outcomes such as mortality might be lacking in power at follow up.

We chose not to perform *post-hoc* power analyses since many statisticians claim that post-hoc power analyses are essentially flawed [134, 135] - once the analyses are made, the null hypothesis can be either rejected or confirmed on the basis of confidence intervals and p-values.

A "true" research finding

As a researcher, how can one be certain that your research finding represents the true picture? Were we right in rejecting the null hypothesis or is our finding a false positive one (type one error)? Or have we presented a false negative result (type two error)?

Firstly, a study should be sufficiently powered, with high external and internal validity, as mentioned above. Secondly, the finding should be confirmed or replicated in other studies. Thirdly, hypotheses should be predefined and few if possible.

The risk of a false research finding increases at small effect sizes and in the presence of economic interest [136]. Of note, over half (9/16) of the KDIGO 2012 working group members responsible for the guidelines used in this thesis report connection to drug or device companies [57]. Furthermore, both researchers and journals might be subject to publication bias, or "the bias to publish only results that are statistically or clinically significant", which might affect literature reviews and meta-analyses [137, 138].

Ethics in research

In the autumn of 2014 I attended my first conference at the American Society for Bone and Mineral Research (ASBMR). At the time I had just begun my project by investigating the association between kidney function, BMD and bone loss. My results differed from those presented in a poster that later appeared as reference 142 (in the reference section of this thesis). In the OPRA cohort, there was an association between kidney function and BMD, but the effect size was small and probably of limited clinical significance, since cross sectional BMD did not differ depending on CKD stages of kidney function.

However, roughly a year later, Retraction Watch published a story about a Canadian researcher having manipulated data with the retraction of a paper and a lifelong funding ban as the consequence [139, 140]. In 2016, this story was soon followed by another one, describing a second retraction of a study investigating the association between kidney function and bone loss - the very one presented at the above mentioned conference [141, 142]. Apart from concluding that the leading author of this paper had manipulated data and deleted records, the Canadian Institute of Health and Research (CIHR) stated that this author falsely accused an assistant of the manipulation. Not many months after the second retraction, a third followed [143, 144].

This story about scientific misconduct has lead me to pose the following three questions:

1. *A search for the leading author of reference 142 on PubMed leads to over 100 publications, but even though only three have been retracted, can the other work be trusted?*

In 2017, Kidney Disease: Improving Global Outcome (KDIGO) issued new guidelines regarding CKD-MBD. In their earlier recommendations BMD screening in patients with CKD-MBD was not recommended, primarily due to lack of prospective data [36]. In 2017, however, these recommendations changed to allow the utility of BMD in patients with CKD-MBD [38]. The new recommendations were made on the basis of four new prospective studies [128, 145-147], of which the above mentioned author was the last author on two [146, 147].

Although results from study IV [148] support the utility of BMD in CKD, it is problematic that the KDIGO working group based the change in recommendation on studies from an author of known research misconduct.

After discussing this matter with my supervisors, we decided against any paper in which this author was the first or the last author in my thesis. The rational for this was uncertainty.

2. What are the wider implications for research in the bone field?

The impact of a researcher can be measured through the RG-score and h-index, but to quantify the larger effects in a research field is still a difficult task. Articles can be included in, and potentially sway, meta-analyses, or form the basis of new guidelines. Hence, data generated by scientific misconduct might have a large ripple effect throughout the research and medical community [149].

3. What is the implication of scientific misconduct outside the research world?

As proven by the well-known and infamous story of Dr. Wakefield, the "real world" aftermath of research misconduct can be dire. In Febuary 1998 Wakefield published an article linking the measles, mumps and rubella-vaccine (MMR vaccine) to the onset of bowel disorders and autism in children [150].

This article gained attention and not only in the research community. After a press conference, the media immediately jumped on the band wagon and in 2003 MMR vaccination had dropped to 79% in the United Kingdom, far below the levels of heard immunity, with a similar trend elsewhere [151-154].

A couple of years after the Lancet publication it was discovered that Wakefield's research did not hold up to closer examination. Since 1996, two years before the publication, Wakefield had been secretly receiving money from a lawyer involved in a prospective lawsuit against the vaccine manufacturers. Furthermore, the study participants all had parents who were anti-MMR activists. Additionally, three of the children with "autism" had never been diagnosed with the disease, while five of the children had developmental problems before the vaccine. In 2010, the Lancet retracted Wakefield's article and he was struck off the medical register [155, 156] but the damage had already been done with recurrent measles outbreak in Europe and the States [152].

Although there is no evidence that the example of scientific misconduct in the kidney/bone field mentioned has had as wide consequences as that of the vaccine report, there have been some implications. Fortunately, no patients are thought to have been harmed by the experiment, but a Nature Review Rheumatology paper from 2011 stated that nitric oxide might be an efficient treatment of osteoporosis, citing the subsequently retracted article [157]. Taking a wider perspective, scientific misconduct may lessen the public's trust in research.

Future perspective

The shrunken pore syndrome

Although this thesis explores the normal age-related decline in kidney function, many research questions still remain. One example is the 'Shrunken pore syndrome', described by Professor Anders Grubb for the first time in 2015 [158]. As previously described in the introduction part of this thesis, cystatin C and $eGFR_{cysC}$ is a better predictor for mortality and cardiovascular events than is creatinine or $eGFR_{crea}$ [42, 43, 159]. Introducing the 'shrunken pore syndrome', Grubb et al have provided an explanation for this, namely "a reduction in pore diameter of the glomerular membrane" [158]. This means that smaller molecules such as water and creatinine are freely filtered, while larger molecules (40-85 kDa) such as cystatin C or 2-microglobulin remain in the bloodstream. Clinically, this can be explored using the ratio of $eGFR_{cysC}/eGFR_{crea}$, with the "shrunken pore syndrome" defined as a ratio of 0.6 and lower. This has been associated with increased mortality in patients undergoing coronary artery bypass grafting, even when eGFR was normal (i.e. ≥ 60 mL/min/1.73m^2) [160].

Data from the OPRA cohort do not include access to 2-microglobulin, but the ratio of $eGFR_{cysC}/eGFR_{crea}$ can easily be determined. By investigating its association to mortality and cardiovascular diseases in the OPRA cohort, we can possibly give additional confirmation of this new syndrome and provide further knowledge of the clinical outcome of age-related kidney function change in elderly women.

FGF23

This thesis does not explore the hormone fibroblast growth factor 23 (FGF23) or how it is related to kidney function, bone health and mortality. But this quickly growing area is certainly worth investigating.

FGF23 is primarily produced by osteocytes and osteoblasts [46, 161] and removal occurs through the kidneys [162]. FGF23 signals through FGF receptors (FGFRs) in combination with the transmembrane protein Klotho [163]. Most tissues express FGFRs and it is therefore the expression of Klotho that determines where FGF-23 will aim

effectively (primarily the kidney, but Klotho is also present in the parathyroid glands, pituitary gland, sinoatrial node of the heart etc.) [162-164]. FGF23 is stimulated by increased levels of phosphate and calcitriol and plays an important part in phosphate homeostasis through two major pathways (Figure 15):

1. In the kidneys, FGF23 inhibits 1α-hydoxylase and stimulates 24-hydroxylase which decreases calcitriol. Lower levels of calcitriol results in lower phosphate uptake from the bowels [165].
2. In the kidneys, FGF23 decreases the expression of type IIa sodium-phosphate cotransporter (NaPi2a) in the proximal tubules, thereby decreasing phosphate reabsorption in the kidneys [165].

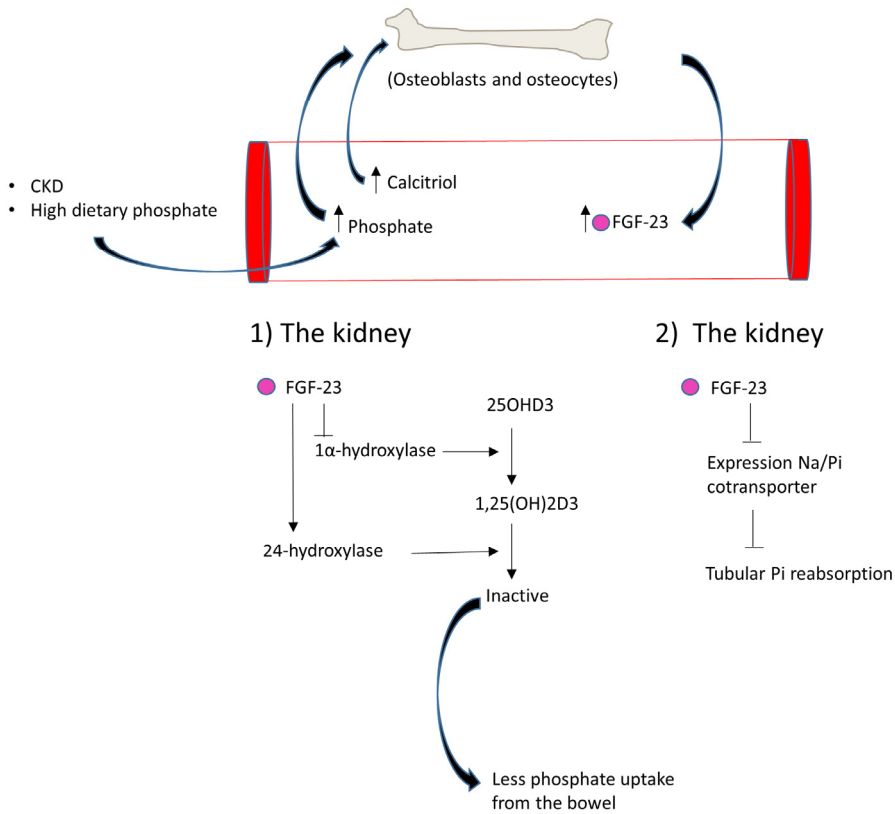


Figure 15.
FGF 23 regulate phosphate levels

In rats, FGF23 directly lowers PTH synthesis through FGFR/Klotho in the parathyroid glands. But the effect of FGF23 on PTH in humans is complex and not completely understood [46, 164, 166].

Levels of FGF23 increase in CKD [163], with a decrease in co-receptor Klotho [162]. Interestingly, in CKD, increases in FGF23 might occur earlier than increases in PTH [167] and have therefore been suggested as an early marker of CKD. However, this might not be the case in elderly individuals with reduced kidney function [168].

FGF23 has been associated with left ventricular hypertrophy and vascular dysfunction/calcification in CKD [161, 169, 170], as well as mortality [171]. Whether FGF23 is associated with BMD [120, 169, 172, 173] and fractures [173-176] is less certain, since studies are inconclusive.

We have analysed FGF23 in the OPRA cohort and our preliminary results indicate that increases in FGF23, PTH and phosphate, is seen at lower levels of eGFR in the very elderly (age 85) compared to the elderly women (age 75).

Acknowledgements

First of all to all the women who participated in the OPRA study, a sincere thanks for the valuable information you have shared, thus contributing greatly to research.

To Kristina Åkesson, for first introducing me to science and by example teaching me the excellence of good science, leadership and mentorship.

To Fiona McGuigan, for countless hours of generous support and guidance. And for teaching me that there is always one last paragraph left to tweak.

To Anders Christensson, for sharing your expert support and exceptional skills in the kidney field.

To Victor, my love and support in life, thank you! This thesis would certainly not be possible without you. And to Valter, for your everyday reminder that life is far more than work.

To my kind and loving mum, for bringing me up and inspiring and supporting me through life. And to Frida, who always know what to say and who make the world a more beautiful place though her art.

To my other family and friends, thank you for your support and love.

To all my colleagues at the geriatric department, thank you for your kind support, both personally and clinically.

To my other research colleagues and co-workers, thank you for filling our work days with laughter and for your inspiration.

And to my wonderful dad, who I know would have been very proud this day.

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Printed by Media-Tryck, Lund 2020 NORDIC SWAN ECOLABEL 3041 0903

Kidney Function During Ageing and its Association to Bone Mass, Fracture and Mortality

Linnea Malmgren is a medical doctor currently undertaking her residency in geriatrics at Skåne University Hospital in Malmö. This PhD thesis investigates the age-related change in kidney function in elderly women and its implications for bone health.

In elderly women, kidney dysfunction corresponding to the current threshold for disease is common in otherwise healthy women. This normal age-related reduction is associated with bone health and the likelihood of fracture in the near future.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2020:18
ISBN 978-91-7619-878-0
ISSN 1652-8220