The Relationship between Insulin like Growth Factor-1 and Bone Mineral Density among Diabetic Elderly

Thesis

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INTRODUCTION

Insulin-like growth factor 1 (IGF-1) is considered an important anabolic hormone; it is secreted mainly by the liver ***(Janssen and Lamberts SW, 2002).*** In the serum, IGF-1 circulates in two states: free and bound to one of six binding proteins. Insulin-like growth factor binding protein 3 (IGFBP-3) binds 95% of circulating IGF-1 and in association with an acid-labile subunit forms a stable tertiary complex that prolongs the half-life of IGF, This complex is restricted to the vascular space and limits bioavailability of IGFs to target tissues***(Tritos and Mantzoros, 1998).***

IGF-I is a polypeptide that is important for cell growth and differentiation ***(Rosen et al., 1994)*** which consists of single-chain polypeptide of 70 amino-acid residues ***(Masanobu, 2009).*** IGF-I stimulates linear growth in all mammals, and its circulating concentration during growth is directly related to the pulsatile release of GH ***(Rosen et al., 1994).***

In the skeleton, IGF-I and its binding proteins (IGFBPs), are synthesized by osteoblasts and regulated by GH as well as several endocrine and autocrine factors ***(Rosen et al., 1994).*** IGF-I is important for bone cell proliferation, differentiation, and collagen synthesis ***(Rosen et al., 1994).***

During active bone resorption, IGF-I is released from the bone matrix to recruit new osteoblasts to the remodeling surface. It is likely that skeletal IGF-I is one of several coupling factors in the bone remodeling process, IGF system has an important role in bone metabolism: a decrease in IGF-1 may decrease osteoblasts function and cause low turnover osteoporosis ***(Eriksen et al.,1996).***

In the study conducted by **Sigridur** ***and his colleagues in 2010*** among 1319 older people aged 65 years and older, they observed lower IGF-I levels in the higher age Categories**.**

Garnero and his colleagues in 2000 demonstrated that serum IGF-I levels in older individuals were related to hip fracture risk.

Bauer et al. examined the relationship of IGF-I and IGFBP3 to hip fractures in 9,704 women from the Study of Osteoporotic Fractures ,In that study women in the lowest quartile for serum IGF-I had a 60% greater risk of hip or spine fracture, while IGFBP3 did not show any correlation.

Hala M. Raslan and her colleagues in 2010 found that patients with osteoporosis of the proximal femur and lumbar spine showed lower IGF-1 than patients without osteoporosis. IGF-I is an important factor regulating bone mass in humans ***(Masanobu et al.,2009).***

Osteoporosis is a common disorder that results in over 1.3 million fractures annually in the U.S. alone ***(Melton et al.,1997).*** Although a juvenile-onset form of osteoporosis exists, osteoporosis primarily affects the elderly, and, in particular, women.

Insulin like Growth Factor-I and insulin had similar effects on the inhibition of hepatic glucose production rate, as well as a similar increase in glucose uptake ***(H.L. Simpson et al., 1998).***

Patients with NIDDM have reduced IGF-I and IGFBP-1 levels compared to normal controls, and show blunted responses to fasting when compared with age-matched controls ***(Bang et al.,1994).***

Aim of the Work

The aim of this work is to study the relationship between insulin like growth factor-1 and Bone Mineral Density in elderly diabetic patients.

REVIEW OF LITERATURE

CHAPTER (1): OSTEOPOROSIS IN ELDERLY

Definition:

Osteoporosis is a global health problem whose importance is going to increase with the aging of the population, it is defined as a systemic disorder of the skeleton characterized by low bone mass and deterioration of the micro- architecture of the bone tissue, with the consequent increase in bone fragility and the greater susceptibility to fractures ***(NIH., 2001),*** It is also defined by low bone mass, increased fragility, decreased bone quality, and an increased fracture risk. It is the most prevalent metabolic bone disease in the world ***(Phillips et al., 2003).***

In 1994 the World Health Organization (WHO) established some definitions based on measurements of bone mass in the lumbar spine, hip or forearm of white postmenopausal women Thus, normal bone mass is considered to be having a bone mineral density (BMD) value higher than -1 standard deviation (SD) in relation to the average for young adults (T-score >-1); osteopenia, having BMD values between -1 and -2.5 SD (T-score between -1 and -2.5); osteoporosis, having BMD values lower than or equal to -2.5 SD (T-score lower than -2.5), and osteoporosis is established when, along with the above conditions, are associated one or more fragility fractures ***(WHO.,1994).***

Osteoporosis is a silent epidemic that constitutes a great socio-economic problem, which carried a great negative impact both on morbidity and mortality ***(Hadjidakis etal., 2005).*** It is not symptomatic until there is a pathologic fracture. Thus, the true occurrence of osteoporosis may be significantly underestimated because many women who suffer minimal trauma fractures still are not being evaluated for osteoporosis ***(Guardia et al., 2008).***

The most recent National Institutes of Health consensus statement defines osteoporosis as, "a skeletal disorder characterized by compromised bone strength that results in an increased risk of fracture". The concept of bone strength has evolved to integrate those traditional measures of bone quantity (e.g. BMD) with more recently examined components of bone quality, namely i) macro-architecture (bone size and geometry), ii) micro-architecture (cortical thinning, porosity; trabecular size, number, connectivity), iii) bone turnover, and iv) material properties of bone (e.g. mineralization, microfracture, collagen cross-linking)***(Bouxsein ,2003).***

- **Epidemiology:**

The global burden of osteoporosis is significant, with approximately 9 million new osteoporotic fractures worldwide in the year 2000 ***(Johnell and Kanis ., 2006)***

It is a process which is preventable and treatable, but which lacks warning signs prior to the appearance of fractures, leading to the fact of few patients being diagnosed at early stages and treated effectively. Therefore, in some studies it has been confirmed that 95% of patients who presented with a fracture did not have an earlier diagnosis of osteoporosis ***(Castel et al., 2001).***

In the United States, the prevalence of osteoporosis increases from 15% in 50- to 59-year-old women to 70% in women aged 80 years. Epidemiologic studies in other countries have reported similar findings ***(Kanis, 2000).***

Data from the third National Health and Nutrition Examination Survey (NHANES III) indicate that 13–18%of women in the United States over age 50 have osteoporosis and an additional 37–50% have low bone mass at the hip, The disease results in more than 350,000 hip fractures alone each year in the United States ***(Sue and Julie,2004).***

The most direct consequence of osteoporosis is an increase in fragility fractures. Osteoporotic fractures are those located in zones of low BMD, or those which happen after falling over. The presence of fragility fractures is associated with a higher risk of having new osteoporotic fractures, as well as an increase in mortality and a reduction in the quality of life in men and women ***(Kanis et al.,2003).***

❖ Risk factors for osteoporosis:

National and international guidelines have been implemented to address the question of screening for osteoporosis in an evidence-based and cost-effective manner ***(Brown, 2002)***, Several risk factors such as age, low body mass index, previous fragility fractures, a family history of fractures, the use of glucocorticoids and active cigarette smoking have to be taken into account ***(Kanis, 2002).***Lifestyle is one of the well-known factors that affect BMD and risk of fracture ***(Lunt et al., 2001).***

Diagnosis of osteoporosis:

Early diagnosis of osteoporosis requires a high index of suspicion as elderly patients may concurrently have other co-morbidities such as cardiovascular diseases or cancer that receive more attention. Because bone loss occurs insidiously and is initially an asymptomatic process, osteoporosis is frequently only diagnosed after the first clinical fracture has occurred ***(Unnanuntana et al., 2010).***

The measurement of BMD by dual energy X-ray absorptiometry (DEXA) is a valid method to diagnose osteoporosis and to predict the risk of fracture ***(Cummings et al.,2002).***

Current diagnosis of osteoporosis is largely based on measurement of BMD, using DEXA of the hip or lumbar spine. An individual BMD value compared with the mean of a healthy young population in terms of the number of standard deviations (SD) is termed the T score. The WHO has defined osteoporosis as a T score of less than or equal to -2.5 SD ***(WHO, 1994).***

New decision-making tools such as the fracture risk assessment tool (FRAX) have integrated clinical risk factors with the DEXA based BMD to predict an individual's 10-year risk of sustaining a hip fracture as well as the 10-year probability of obtaining a major osteoporotic fracture, defined as clinical spine, forearm, hip or shoulder fracture ***(Unnanuntana et al.,2010).***

BMD and age are not the only factors that affect the frequency of fractures; other indicators, usually used in combination with BMD assessments, include biochemical indices of bone resorption and clinical factors such as age, previous fragility fracture, premature menopause, family history, and use of oral corticosteroids ***(Kanis et al., 2004).***

Hazards and clinical implications of osteoporosis:

Osteoporotic fragility fractures impose a considerable financial burden on health services due to reduced mobility, hospitalization, and nursing home requirements ***(Melton et al., 2004).***

In most of the developed countries, it is currently recommended that postmenopausal women, with the highest risk, should be screened for osteoporosis and a 10-year probability of fracture assessed for each individual to determine intervention thresholds ***(Kanis et al., 2002).***

Despite these recommendations, osteoporosis is frequently not diagnosed even after the first vertebral fracture has occurred In this review, we discuss the evidence that supports the need for cost-effective diagnosis and treatment prior to a first fracture ***(Reginster and Burlet, 2006)***

Prevention of osteoporosis:

Healthy lifestyle has an important role in prevention of osteoporosis, Studies indicate that physical activity is associated with

higher bone mass density at hip site and walking is a protective factor against osteoporosis ***(Nihlsson et al., 2012).***

Therefore, to decide when to initiate treatment for osteopenia not only is BMD evaluated, but also the individualized absolute risk of fracture at 5-10 years, incorporating risk factors independent of BMD such as age, sex, weight, previous fractures, family antecedence of fractures, smoking, consumption of glucocorticoids, intake of alcohol, and others***(Muñoz et al.,2010)***.

In both women and men, current and also past physical activity have a positive effect on bone density. Also in women, current walking is a protective factor. In addition, a balanced diet can prevent osteoporosis by increasing bone density and changing bone turnover ***(Lunt et al., 2001).***Thus, in studies on the effects of diseases on bone metabolism considering environment factors especially lifestyle is crucial.

Treatment of osteoporosis:

Osteoporosis therapies fall into two classes, anti-resorptive drugs, which slow down bone resorption or anabolic drugs, which stimulate bone formation. Currently, several approved treatment options exist for the management of osteoporosis that effectively reduce the risk of vertebral, non-vertebral and hip fractures ***(Greenspan et al., 2007)***.

In fact, clear evidence of vertebral fracture risk reduction is a necessary requirement for any novel osteoporotic agent to be registered Amongst the anti-resorptive drugs, bisphosphonates, with their high affinity for bone and long safety record, constitute the largest class, Bisphosphonates can be administered either orally or intravenously and are most widely used because they can be inexpensive and used across a broad spectrum of osteoporosis types, including postmenopausal, male, and steroid-induced osteoporosis as well as Paget’s disease. Other anti-resorptive drugs such as raloxifene, strontium ranelate, and most recently,

denosumab, may represent alternatives for women with postmenopausal osteoporosis ***(Rachner et al., 2011).***

Bone-anabolic agents that build up new bone, rather than preventing its loss, are limited to the full length parathyroid hormone (PTH 1–84) or its N-terminal fragment, teriparatide (PTH 1–34). Both are given subcutaneously, but transdermal application forms of PTH 1–34 are in development ***(Daddona et al.,2010).***

Non-pharmacological management:

Reduction of the potentially modifiable risk factors along with exercise and calcium and vitamin D supplementation form an important adjunct to pharmacologic management of osteoporosis.

Exercise Physical activity may have a twofold contribution to reducing fracture risk:

1) It may enhance bone strength by optimizing BMD and improving bone quality.

2) It has the potential to reduce the risk of falling.

Much of the data suggesting a relationship between bone strength (measured as BMD) and physical activity is cross-sectional, however, and cannot prove a cause and effect relationship***(Manish and Chad,2002).***

Resistance training increases bone mass and prevents age-related declines in BMD ***(Bravo et al.,1996).***

A recent meta-analysis of the role of exercise showed that both impact and nonimpact exercise had a positive effect on lumbar spine bone density in postmenopausal women, whereas only impact exercise probably had a positive effect at the femoral neck ***(Wallace et al., 2000).***

The emphasis of physical exercise programs in elderly patients with osteoporosis should be on improving muscle strength and balance. Older patients should be encouraged to participate safely in any activity in a frequent, regular, and sustained manner. The exercise should be weight bearing and easy to complete and should fit into their daily routine ***(Manish and Chad., 2002).***

A program of walking, sitting, and standing exercises, or water aerobics, can be recommended to start with and gradually increased to more rigorous activity. For patients who have already had an osteoporotic fracture, physical exercise program can help reduce pain and increase functional capacity. The program should increase the patient's ability to perform routine daily activities while minimizing the risk of further fractures. For patients with vertebral fractures, back flexion exercises have been found to be harmful and to increase the risk of new vertebral fractures. These patients will benefit from resistance exercises that strengthen back extensor muscles ***(Manish and Chad, 2002).***

Calcium and vitamin D:

Deficiency of calcium and vitamin D contributes to alterations of bone remodeling and bone integrity. Low calcium intake and vitamin D deficiency have been repeatedly observed in the elderly population. In elderly women, low fractional calcium absorption in the setting of low calcium intake increases the risk for hip fracture, although vitamin D and calcium alone have little effect on bone mass in the early menopausal years, they can have substantial effects on bone mass and fragility fractures in the elderly population ***(Ensrud et al., 2000).***

Pharmacological management *(Manish and Chad, 2002):*

The primary goal of an intervention is to reduce the risk of fracture. The evidence-based approach requires proof of efficacy from adequately powered randomized controlled trials in which fracture is the primary

endpoint. Adequately powered randomized controlled trials with fracture as the primary endpoint exist for alendronate, raloxifene, risedronate, and calcitonin. For hormonal replacement therapy (HRT), the evidence for anti-fracture efficacy is based mainly on observational data.

Bisphosphonates:

- Bisphosphonates are compounds that bind avidly to hydroxyapatite crystals on bone surfaces and are potent inhibitors of bone resorption. The two bisphosphonates approved by the United States Food and Drug Administration (FDA) are alendronate and risedronate.

o Alendronate:

Alendronate was the first bisphosphonate approved by the FDA (1995) to treat osteoporosis. In the phase III trial, almost 1000 postmenopausal women (mean age, 64 years) were randomized to alendronate or placebo for 3 years. Alendronate resulted in an increase in BMD of 8.8% in the lumbar spine and of 5.9% in the femoral neck as compared with placebo ***(P***< 0.001) ***(Liberman et al.,1995)*** Similar results were seen from two other trials ***(Tonino et al.,2000).***

o Risedronate

In a randomized, double-blind, placebo-controlled trial ***(Fogelman etal.,2000)***,risedronate (5 mg/d) increased the lumbar spine BMD from baseline by 4% at 24 months contrast to no-change in the placebo group (***p***< 0.001) and BMD at femoral neck and trochanter increased by 1% and 3%, respectively, compared with placebo.

The Vertebral Efficacy with Risedronate Therapy study had two arms: North American and multinational. In the North American arm ***(Harris et al., 1999),*** risedronate decreased the cumulative new vertebral fracture incidence and non-vertebral fractures by 41% (***p*** = 0.003) and

39% (***p*** = 0.02), respectively. In the multinational arm, risedronate reduced the risk of new vertebral fractures by 49% (***p*** < 0.001) and non-vertebral fractures by 33% (***p***= 0.06) compared with placebo ***(Harris et al., 1999).***

The Hip Intervention Program (HIP) study enrolled 5445 women (range, 70 to 79 years old) with osteoporosis and 3886 women older than 80 years old with non-skeletal risk factors for osteoporosis (and not low bone mass). All womenwere randomly assigned to receive treatment with oral risedronate, 2.5 mg or 5 mg, or placebo for 3 years ***(McClung et al.,2001).***

The BMD at the femoral neck and trochanter was higher in the risedronate group as compared with the placebo group at 6 months and at all-time points thereafter. These changes in BMD were similar in both the younger and older group. The incidence of hip fracture in the group of women 70 to 79 years old was 1.9% among those assigned to risedronate and 3.2% among those assigned to placebo (41% reduction, ***p*** = 0.009).In the group of women 80 years of age and older who were recruited on the basis of clinical risk factors, however, risedronate had no significant reduction in fracture rates. It can be concluded that even at age 80 years, measurement of BMD is important in identifying patients who will benefit from a bisphosphonate.

Adverse events:

Bisphosphonates are generally well tolerated. Gastro-Intestinal side effects may occur, and a small number of patients with erosive esophagitis have been reported with alendronate ***(Lowe et al., 2000).*** Because of this potential problem, patients must take the medication in the morning with a full glass of water (6 to 8 ounces), 30 minutes before first food or drink of the day and remain upright (sitting or standing) for at least 30 minutes after the dose. Esophageal stricture or motility

dysfunction is a contraindication to use of bisphosphonates. Numerous endoscopic studies have compared alendronate and risedronate for adverse effects on the esophagus, stomach, and duodenum with conflicting results ***(Lanza et al., 2000).***

These are short studies (2 weeks), and it is unknown whether these endoscopic lesions will result in clinically significant outcomes.

Novel agents for osteoporosis therapy:

a) Anti-resorptive therapies

- **Denosumab:**

Based on that osteoclasts originate from haematopoietic stem cells and are closely related to monocytes and macrophages, Differentiation from osteoclast precursor cells to fully activated multinucleated osteoclasts depends critically on the presence of receptor activator of NF-kB ligand (RANKL), a member of the TNF family, and the permissive role of macrophage colony-stimulating factor (M-CSF)***(Rachner et al.,2011).***

The development of denosumab, a fully human monoclonal antibody against RANKL, Denosumab displays a higher specificity and affinity for RANKL with superior pharmacokinetic properties, translating into a longer dosing interval of 6 month ***(Bekker et al., 2004).***

A large study program on a wide spectrum of bone diseases, including several types of osteoporosis ***(Brown et al., 2009)*** and bone metastases is currently ongoing with completed phase 3 studies, denosumab is the most advanced of all investigational substances and has recently been approved in Europe and the US for the treatment of osteoporosis.

In summary, denosumab represents a novel and effective anti-resorptive therapy for various metabolic bone diseases. While direct comparative studies with fracture endpoints are not available, evidence from completed trials with established surrogates suggests that it may be as effective as the most potent of the amino-bisphosphonates, zoledronic acid ***(Rachner et al.,2011).***

- **Odanacatib:**

Based on the concept that the protease cathepsin K plays an important rolein enzymatic bone degradation, the use of cathepsin K inhibitors has emerged as a novel therapeutic approach. A high specificity and affinity for cathepsin K over other cathepsins (B, L and S) that are widely expressed, particularly in the skin, was crucial for this class of compound ***(Gauthier et al., 2008).***

Odanacatib is currently the only cathepsin K inhibitor under clinicalinvestigation. Other programs of less specific cathepsin K inhibitors were stopped due to cutaneous adverse side effects, including a scleroderma-like skin thickening and rashes. In phase 1 studies, odanacatib at an oral dose of 50 and 100 mg once a week reduced serum levels of the bone resorption marker C-terminal telopeptide of type I collagen (CTX) by 62%. Daily administration of odanacatib (10 mg) reduced serum CTX by 81%.64 In a phase 2 study, the effects of weekly oral doses of odanacatib were assessed in 399 women with postmenopausal osteoporosis. After 24 months, odanacatib (50 mg) increased the BMD of the lumbar spine and total hip by 5.7% and 4.1% compared to placebo, respectively. Bone resorption markers were dose-dependently suppressed. Of note, odanacatib treatment resulted in a modest and transient reduction of bone formation markers while not suppressing bone formation rate as evident from a subset of 32 women undergoing bone biopsies followed by histomorphometry. Adverse reactions were comparable to placebo and scleroderma-like cutaneous