The Relationship between Trace Elements, High sensitivity C - Reactive Protein and Bone Mineral Density in Elderly Diabetic Patients

Thesis

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List of Abbreviations

ADL Activities of daily living

BMD Bone mineral density

BMI Body mass index

Cu Copper

DEXA Dual energy x-ray absorptiometry

DM Diabetes Mellitus

DPP-4 Dipeptidyl Peptidase-4

FPG Fasting plasma glucose

2-hPG 2-hr plasma glucose

GDS Geriatric depression scale

GI Gastrointestinal

GLP-1 Glucagon-like peptide-1

hs- CRP High sensitivity C- reactive protein

IADL Instrumental activities of daily living

IL-6 Interleukin- 6

Mg Magnesium

MMSE Mini-Mental State Examination

MNA Mini Nutritional Assessment

T2DM Type 2 diabetes mellitus

Zn Zinc

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Introduction

Diabetes mellitus is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extra cellular hyperglycemia which results in tissue damage and chronic vascular complications in both types 1 and 2 Diabetes Mellitus ***(Amanullah et al., 2010)***.

Prevalence of diabetes by age 65 years or older is 18.4% of all people in this age group ***(National Diabetes Statistics fact Sheet, 2003).***

Osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures ***(Hwang and Choi, 2009).*** According to the American National Osteoporosis Foundation osteoporosis is prevalent in about 12% in population ***(Patrick, 2002).***

There is an increased risk for low bone mineral density and particularly for bone fractures in patients with type 1 and to a lesser extent type 2 diabetes mellitus ***(Schneider, 2002)***. On the other hand ***Gerdhem et al. (2005)*** found that BMD values in patients with type 2 diabetes were 11% higher compared with healthy controls.

Trace element deficiencies are frequently associated to chronic diseases or to problems with their absorption. Chronic hyperglycemia may cause significant alterations in the status of some micronutrients and on the other hand some of these micronutrients can directly modulate glucose homeostasis and promote the development of diabetic complications ***(Kazi et al., 2008)***.

Osteoporosis is a common condition in the elderly; one factor contributing to bone density loss in the elderly may be magnesium (Mg), zinc (Zn) and/or copper (Cu) deficiencies due to a reduced dietary intake and reduced absorption of these micronutrients. Mg, Zn and Cu are essential cofactors for enzymes involved in synthesis of various bone matrix constituents ***(Abrams and Atkinson, 2003)***.

Several lines of evidence implicate inflammation in the development of insulin resistance and metabolic syndrome ***(Devaraj et al., 2004).*** And also many factors including proinflammatory cytokines and C-reactive protein (CRP) have been implicated in the pathogenesis of osteoporosis. CRP is an acute phase reactant that increases in response to tissue damage, inflammation and infection ***(Ferrari et al., 2003)***. Higher serum levels of high sensitivity C - reactive protein (hs-CRP) are associated with lower BMD ***(Koh et al., 2005)***, higher levels of bone turnover markers ***(Kim et al., 2007)***, and recently greater risk of fracture ***(Pasco et al., 2006).***

Among several markers of inflammation, hs –CRP is found to be significant in people with diabetes ***(Shan et al.,***

2009). Several studies demonstrate that hs-CRP remained a significant predictor of diabetes risk even after adjusting with other factors ***(Pradhan et al., 2005)*** and found to be increased in patients with hyperglycemia especially uncontrolled type 2 diabetic subjects ***(Martha and Fernado, 1999).*** Higher CRP levels in people with diabetes are associated with increased cardiovascular mortality risk ***(Chiriboga et al., 2009).***

Aim of the Work

The aim of the work is to study the relationship between trace elements (Zn, Mg and Cu), high sensitivity C - reactive protein and bone mineral density in elderly diabetic patients compared to control.

Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extra cellular hyperglycemia which results in tissue damage and chronic vascular complications in both types 1 and 2 DM ***(Amanullah et al., 2010)***.

The resulting chronic hyperglycemia damages blood vessels and nerve cells throughout the body producing microvascular diseases such as retinopathy, neuropathy, and nephropathy. Moreover the risk for cardiovascular disease is considerably elevated in patients with type-2 diabetes compared to the general population. As a consequence type-2 diabetes represents a major public health problem that causes high economic costs, increased morbidity and affect quality of life ***(Kazi et al., 2008).***

Prevalence of diabetes by age 65 years or older is 18.4% of all people in this age group ***(National Diabetes Statistics Fact Sheet, 2003).***

Diabetes has the potential for accelerating the aging process, if aging defined as “a loss of reserve capacity.”

Physiological changes may occur at a faster rate than in nondiabetic individuals and when coupled with other changes that have been associated with increasing age, this increases the potential for an earlier decline in functional capacity. This may lead to a reduced ability to remain independent in both basic and instrumental activities of daily living ***(Gambert and Pinkstaff, 2006).***

The decline in glucose tolerance as a part of human aging has been well established ***(Meneilly et al., 2001)***. Fasting plasma glucose levels increase by 1–2 mg/dl per decade after age 30, and postprandial glucose levels increase by ∼15 mg/dl per decade ***(Samos and Roos, 1998).***

Despite these age-related changes in glucose concentrations, there is no age adjustment for the diagnosis of DM because the risk for diabetes related complications results from hyperglycemia over time and not age ***(American Diabetes Association, 2006).***

The two most important age associated disturbances in carbohydrate metabolism are reduced insulin sensitivity in muscle, liver and fat and impairment in insulin secretion from pancreatic B-cells ***(Meneilly et al., 2001)***.
Lifestyle factors that contribute to the age-associated decrease in insulin sensitivity include dietary changes, with higher intakes of saturated fats and simple sugars and reduced physical activity with less skeletal muscle mass and reduced strength ***(Meneilly et al., 2001).***

Type 2 DM ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance. This form of diabetes, which accounts for ~90–95% of those with diabetes, previously referred to as non-insulin dependent diabetes. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region ***(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).***

Symptoms and signs of T2DM in elderly

People with type 2 diabetes (T2DM) often have no symptoms at all. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss sometimes with polyphagia and blurred vision. Susceptibility to certain infections may also accompany chronic hyperglycemia. Acute life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome ***(American diabetes association, 2006).***

Many age- related changes affect the clinical presentation of diabetes. These changes can make the recognition and treatment of diabetes problematic. Elderly diabetic patients rarely present with typical symptoms of hyperglycemia ***(Meneilly and Tessier, 2001).***

Classic symptoms of diabetes such as polyuria or polydipsia are rarely present in elderly because the renal thresholds for glucose increases with age, older people do not develop glucosuria until the plasma glucose level is extremely elevated. In addition, older people have impaired thirst mechanisms so that even when they develop hyperglycemia, they often do not develop polydipsia. For this reason, the classic symptoms of diabetes are usually not present in this age group, and the diagnosis is made when the patient goes for routine health screening or is admitted to hospital for an intercurrent illness ***(Meneilly, 2006)***. When symptoms are present they are generally atypical and nonspecific (falls, urinary incontinence or delirium) ***(Meneilly, 2000).***

Diabetes may present for the first time in elderly individuals as a result of screening of a fasting glucose level or be concurrent with the presentation at the time of illness with a complication, such as a myocardial infarction or stroke. nonketotic hyperosmolar coma may be the first presentation of diabetes in older individuals particularly in older nursing home patients this results from decreased access to water associated with osmotic diuresis, impaired thirst, and cognitive dysfunction ***(Diabetes Health Center, 2007).***

Screening of type 2 diabetes

Screening for diabetes should be performed by a health care provider annually, beginning at age of 30 for all patients at risk for developing type 2diabetes. As post-challenge glucose

levels in particular rise with increasing age, the best screening test for DM in older adults is determination of fasting plasma glucose level ***(Unger, 2007).***

Because a substantial number of elderly patients have undiagnosed diabetes, and these patients appear to have an increased incidence of macrovascular events, the current criteria recommend that a fasting glucose value be performed every 3 years in elderly patients at low risk for diabetes and yearly in patients at high risk ***(Shashikiran et al., 2012).***

Routine urine sugar testing for screening diabetes mellitus is inaccurate and is not recommended as benign prostatic hyperplasia and diabetic autonomic bladder dysfunction are commonly found in elderly and it alters the glucose content of urine due to the residual urine present in the bladder ***(Shashikiran et al., 2012).***

Risk factors for prediabetes and DM *(AACE Diabetes Mellitus Clinical Practice Guidelines Task Force, 2007)*

1. Family history of diabetes
2. History of cardiovascular disease
3. Overweight or obese (BMI >25 kg per m^2)
4. Sedentary lifestyle
5. Previously identified impaired glucose tolerance or impaired fasting glucose
6. History of hypertension