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Evaluation of Bone Minerals and its Association with Glycated Hemoglobin in Type2 Diabetes Mellitus Patients in Khartoum State

تقويم مستويات املاح العظام وعلاقتها بالهيموقلوبين المجلكز عندالمرضى المصابين بمرض السكرى من النوع الثانى فى ولاية الخرطوم

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Abstract

Background: Clinical evidence suggests that bone health is affected in some patients with type 2 diabetes mellitus (T2DM) patients. T2DM is associated with an increased incidence of bone fractures, accordingly present study carried out to evaluate the bone mineral and its association with blood glycated hemoglobin (HbA1c%) in T2DM patients in Khartoum State.

Method and Materials: This is a descriptive cross sectional study during the period of March 2013 to April 2014, 300 subjects were enrolled in this study, 150 patients with type2 diabetes mellitus age from 35 to 60 years old considered as case group, and 150 apparently healthy (non - diabetic) volunteers as a control group, age and sex of the control were matched with case group. Venipuncture samples were collected from each participant and plasma was obtained after centrifugation at 3000 r/m, the plasma levels of calcium, phosphate and magnesium were determined enzymatically by using Biosystem BTS-310 spectrophotometric methods, while the glycated hemoglobin was determined using EDTA blood samples after extracted by ion exchange chromatography methods, which used Labona Check^{TM}A1c HbA1c Test Kit. Data was analyzed using SPSS version 19.

Results: The results showed significant decrease in the mean concentration of calcium and magnesium of thpe2 DM patients with (*p*-value 0.000 and 0.000) respectively, and increase in the plasma level of phosphate with (*p*-value 0.000). In diabetic group there was a weak negative correlation between the plasma levels of calcium and HbA1c% and weak positive correlation with duration of diabetes. In diabetic group the plasma levels of phosphate showed a weak positive correlation with HbA1c% and weak negative correlation with the duration of diabetes. In the

diabetic group the plasma levels of magnesium showed a weak positive correlation with HbA1c%, and weak positive correlation with the duration of disease.

Conclusion: The results conclude that, diabetic patients have low plasma calcium and magnesium and high phosphate level, also negative correlation between HbA1c with calcium which indicate decrease calcium level in uncontrolled diabetic patients, which may suggest the bone disease in type 2 DM specially uncontrolled patients.

المستخلص

خلفية:

أشارت الدراسات السريرية بان صحة العظام عند بعض المرضى بداء السكري من النوع الثانى أكثر عرضه لتهشم العظام لوجود عوامل مرتبطة بهذا النوع من المرض .وفقا للدراسة الحالية فقد تم تقويم املاح العظام وارتباطها بالهيموقلوبين المجلكز عندالمرضى بالسكرى من النوع الثانى فى ولاية الخرطوم.

طرق العمل والمواد المستعملة فى هذه الدراسة:

هذة الداسة مقطعية وصفية اجريت فى الفترة من مارس 2013 الى ابريل2014، 300 عنصر قد ادرجوا فى هذة الدراسة، 150 من المرضى المصابين بداء السكري من النوع الثاني اعمارهم تتراوح بين35-60 سنة اختيروا كمجموعة اختباربالاضافة الى 150 من المتطوعين الاصحاء ظاهرياً كمجموعه ضابطه، اعمار وجنس المجموعة الضابطة متطابقة مع مجموعة الاختبار.عينات بزل من الوريد قد جمعت من كل المشاركين للحصول على البلازما بواسطة الطرد المركزى3000 د/ق. لقياس مستويات البلازما كالسيوم والفوسفات والماغنسيوم تم استخدام جهاز سبكتروفوتوميتر بايوسستم310(BTS) وبالنسبة الهيموقلوبيين المجلكز تم استخدام (EDTA blood) والتبادل الايونى اللونى بواسطة جهاز لابونا.وقد تم تحليل العينات إحصائياً باستخدام برنامج التحليل الإحصائي (SPSS).

النتائج :

اظهرت النتائج انخفاض ملحوظ فى متوسط تركيز البلازما كالسيوم والماغنسيوم (p-value 0.000)، وارتفاع في مستوى الفوسفات (p-value 0.000)عند مجموعة الاختبار عند مقارنتها بالمجموعة الضابطة . عند مجموعة المرضى توجد علاقة ضعيفة سالبه بين مستوى الكالسيوم والهيموقلوبيين المجلكز، وعلاقة ضعيفة موجبه مع استمرار المرض. مستوى البلازما فوسفات اظهرت علاقة ضعيفة موجبه مع الهيموقلوبيين المجلكز بالنسبه للمرضى ،واظهرت علاقة ضعيفة سالبه مع استمرار المرض.

مستويات البلازما ماغنسيوم عند المرضى اظهرت علاقة ضعيفة موجبه مع الهيموقلوبيين المجلكز وعلاقه ضعيفة موجبه مع استمرار المرض.

الخلاصة:

أظهرت نتائج هذه الدراسة بانه عند مرضى السكري أن مستويات البلازما كالسيوم والماغنسيوم تنخفض بينما مستويات الفوسفات تزداد، ايضا هنالك علاقة سالبة بين الهيموقلوبين المجلكزوالكالسيوم مما يشيرالى نقصان مستوى الكالسيوم وازدياد امراض العظام عند مرضى السكرى من النوع الثانى الغير مسيطرعليه.

1. Introduction and Literature review

The association between diabetes mellitus and osteoporosis remains controversial [(1)]. Although the metabolic abnormalities of diabetes potentially affect bone metabolism, structure, and mineral density, the extent of their contribution to the increase in fracture risk noted in individuals with type 1 and type 2 diabetic is still debated. In addition to changes in bone metabolism, there are several other factors that may be important:

- The onset of diabetes in adolescence may result in a decreased peak bone mass.
- The degree of bone loss differs between type 1 and type 2 diabetic. In some studies, type 2 diabetes has been associated with an increase in bone mineral density [(2)].
- Bone fragility, particularly in type 2 diabetic, may contribute to fracture risk independent of bone mineral density, and BMD may not reflect fracture risk in some individuals.
- Bone metabolism may be affected by the late complications of diabetes (eg, renal failure) [(2)].

1.1 Definition of Diabetes mellitus

Diabetes mellitus (**DM**), also known as simply **diabetes**, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.[(3)] This high blood sugar produces the symptoms of frequent urination, increased thirst, and increased hunger. Untreated, diabetes can cause many complications.[(4)] Acute complications include diabetic ketoacidosis and non-ketotic hyperosmolar coma.[(5)] Serious long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes.[(4)]

Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced.[6] There are three main types of diabetes mellitus:

- Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.[4]
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. [4] As the disease progresses a lack of insulin may also develop.[7] This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.[4]
- Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level.[4]

Prevention and treatment involves a healthy diet, physical exercise, not using tobacco and being a normal body weight. Blood pressure control and proper foot care are also important for people with the disease. Type 1 diabetes must be managed with insulin injections.[4] Type 2 diabetes may be treated with medications with or without insulin.[8]Insulin and some oral medications can cause low blood sugar.[9] Weight loss surgery in those with obesity is an effective measure in those with type 2 DM.[10]Gestational diabetes usually resolves after the birth of the baby.[11]

Globally, as of 2013, an estimated 382 million people have diabetes worldwide, with type 2 diabetes making up about 90% of the cases.[12, 13] This is equal to 8.3% of the adults population,[13] with equal rates in both women and men.[14] Worldwide in 2012 and 2013 diabetes resulted in 1.5 to 5.1 million deaths per year, making it

the 8th leading cause of death.[8][15] Diabetes overall at least doubles the risk of death.[4] The number of people with diabetes is expected to rise to 592 million by 2035.[16] The economic costs of diabetes globally was estimated in 2013 at $548 billion[15] and in the United States in 2012 $245 billion.[17]

1.2 Signs and symptoms of diabetes

The classic symptoms of untreated diabetes are weight loss, polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger).[18] Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes. Several other signs and symptoms can mark the onset of diabetes, although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.

1.3 The types of diabetes

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types".[6] The "other specific types" are a collection of a few dozen individual causes.[6] The term "diabetes", without qualification, usually refers to diabetes mellitus.

1.3.1 Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T-cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin.[19] It causes approximately 10% of diabetes mellitus cases in North America and Europe. Most

affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children. "Brittle" diabetes, also known as unstable diabetes or labile diabetic, is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used.[20] Still, type 1 diabetes can be accompanied by irregular and unpredictable hyperglycemia, frequently with ketosis, and sometimes with serious hypoglycemia. Other complications include an impaired counterregulatory response to hypoglycemia, infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's disease).[20] These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.[21]

Type 1diabetes is partly inherited, with multiple genes, including certain HLA genotypes, known to influence the risk of diabetes. In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors, such as a viral infection or diet. There is some evidence that suggests an association between type 1 diabetes and Coxsackie B4 virus. Unlike type 2 diabetes, the onset of type 1 diabetes is unrelated to lifestyle.

1.3.2 Type-2

Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.[6] The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type. In the early stage

of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. Type 2 diabetes is due primarily to lifestyle factors and genetics.[22] A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity (defined by a body mass index of greater than thirty), lack of physical activity, poor diet, stress, and urbanization.[12] Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.[5] Those who are not obese often have a high waist–hip ratio.[5]
Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.[23, 24] The type of fats in the diet is also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk.[25] Eating lots of white rice appears to also play a role in increasing risk.[26] A lack of exercise is believed to cause 7% of cases.[27]

1.3.3 Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery.[27] However, after pregnancy approximately 5–10% of women with gestational diabetes are found to have diabetes mellitus, most commonly type 2.[27] Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy. Management may include dietary changes, blood glucose monitoring, and in some cases insulin may be required. Though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight),

congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A Caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

1.3.4 Other types of diabetes

Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes. Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology [28].

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. [28]

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes

induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

The following is a comprehensive list of other causes of diabetes [29]

- Genetic defects of β-cell function
  - Maturity onset diabetes of the young
  - Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
  - Defects in proinsulin conversion
  - Insulin gene mutations
  - Insulin receptor mutations
- Exocrine pancreatic defects
  - Chronic pancreatitis
  - Pancreatectomy
  - Pancreatic neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
- Endocrinopathies
  - Growth hormone excess (acromegaly)
  - Cushing syndrome
  - Hyperthyroidism
  - Pheochromocytoma
  - Glucagonoma
- Infections
  - Cytomegalovirus infection
  - Coxsackievirus B
- Drugs
  - Glucocorticoids
  - Thyroid hormone
  - β-adrenergic agonists
  - Statins[30]