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Relation between Serum Ferritin, Serum Creatinine and Albuminuria in Type2 Diabetes with or Without Nephropathy

Thesis

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List of Abbreviations

ADA	: American Diabetes Association
HDL	: high-density lipoprotein
GFR	: glomerular filtration rate
ACE	: angiotensin-converting enzyme
ATP	: adenosine triphosphate
HbA1c	: glycated hemoglobin
CAPD	: continuous ambulatory peritoneal dialysis
CCPD	: continuous cyclic peritoneal dialysis
IPD	: intermittent peritoneal dialysis
ESRD	: end-stage renal disease
CKD	: chronic kidney disease
HH	: hereditary hemochromatosis
ELISA	: enzyme-linked immunosorbent assay
so	: serum ferritin
LFT	: liver function test
ALT	: alanine transaminase
AST	: aspartate aminotransferase
GGT	: gamma glutamyltransferase
CRP	: C-reactive protein
ANA	: antinuclear antibody
AGEs	: Advanced Glycosylation End Products
CVD	: cardiovascular disease
NHANES	: National Health and Nutrition Examination Survey
IR	: insulin resistance
BMI	: Body mass index
GLP-1	: glucagon-like peptide-1
DPP-4	: dipeptidylpeptidase-4
IRS-1	: Insulin Receptor Stimulator – 1
GLUT	: glucose transporters
GAD	: glutamic acid decarboxylase
LADA	: Latent autoimmune diabetes in adults
TCDD	: Tetra chloro dibenzoparadioxin
VEGF	: vascular endothelial growth factor
EDHF	: endothelium-derived hyperpolarizing factor
ET	: endothelin
no	: nitric oxide
COX	: cyclo oxygenase

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Introduction

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and relative insulin deficiency, resistance, or both .It affects more than 120 million people worldwide, and it is estimated that it will affect 220 million by the year 2020***. (Kumar, Clark, 2002).***

Nephropathy, a complication of type-2 DM, poses a serious problem in terms of financial load, morbidity and mortality in the developed world. To demonstrates nephropathy as an effect of progression of type- 2 diabetes estimated from serum creatinine, as recommended by the American Diabetes Association and the National Institutes of Health, stating that glomerular filtration rate (GFR), calculated from serum creatinine, at least once a year, for detection of renal dysfunction***.(Dabla, et al, 2010).***

Diabetic nephropathy develops in approximately 40 percent of all patients with type 2 diabetes and has become the leading cause of end-stage renal disease. Therefore, the early identification and subsequent renoprotective treatment of all patients at risk are of utmost importance. The screening of urine for albumin has revealed that patients with type 2 diabetes and so-called microalbuminuria have a risk of diabetic nephropathy that is 10 to 20 times that of patients with normo albuminuria. ***(Parving H-H, et al 2000).***

The first step in the screening and diagnosis of diabetic nephropathy is to measure albumin in a spot urine sample, collected either as the first urine in the morning or at random, for example, at the medical visit. This method is accurate, easy to perform, and recommended by American Diabetes Association guidelines ***(American Diabetes Association, 2004).***

Strong relationship between elevated serum ferritin and increased risk for diabetes mellitus have been reported ***(Yan Ren, et al 2004)***

Serum ferritin concentrations were remarkably increased in type 2 diabetes, especially in newly diagnosed patients. Subjects with higher concentrations of ferritin consequently had higher HbA_{1c}, glucose, and

insulin concentrations. These results further proved a positive association between type 2 diabetes and high plasma ferritin concentrations. ***(Yan Ren, et al, 2004).***

So iron may be considered as risk factor for diabetes mellitus, and so chelation of iron by deferoxamine leads to improvement of endothelial dysfunction in patient with type 2 diabetes mellitus and increased serum ferritin level *(**Fernandez, et al, 2002**).*

Raised Serum Ferritin may possibly be related to the occurrence of long term complications of diabetes, both micro vascular and macro vascular ***(Eshed I, et al, 2001).***

Poorly controlled patients of DM have hyper ferritinemia which co relates with diabetic retinopathy, diabetic nephropathy and vascular dysfunction. ***(Mascitelli L, et al (2006).***

Aim of work

This study was carried out to examine the relationship between serum ferritin, serum creatinine and albuminuria in type 2 diabetes mellitus.

Diabetes Mellitus

Diabetes is a metabolic disease in which the body does not produce or does not properly utilize insulin. Type1 diabetes results from cellular-mediated autoimmune destruction of the beta cells of the pancreas ***(Katz et al., 2007)***

Carbohydrate, protein, and fat metabolism are altered when insulin the mediator of fuel, is not available. Insulin deficiency can result from defects in insulin secretion and/or diminished tissue response to insulin.The result of this defect in insulin secretion and/or insulin resistance is hyperglycemia ***(Westerfield J, et al., 2008).***

Type 2 diabetes usually begins as insulin resistance, disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin. Diagnosis usually occurs in adult patient's age 40 years and above; however, an increased risk and diagnosis of the disease has been identified in children and adolescents. Physical inactivity and unhealthy dietary habits create an environment that promotes obesity and diabetes. About 90% to 95% of people with diabetes have type 2; approximately 80% are overweight ***(Tang T, et al., 2009)***

Epidemiology of Diabetes Mellitus:

According to the American Diabetes Association(ADA), the prevalence of diabetes has increased eight-fold since 1958, but the sharpest acceleration in prevalence has occurred since 2000.As of 2012 ,25.8 million Americans, have a diagnosis of diabetes. In addition، an estimated 7 million people have diabetes but remain undiagnosed ***(American Diabetes Association, 2012).***

The most common types of diabetes are type1and type 2. However, gestational diabetes is also relatively common and is a source of significant morbidity and mortality. Gestational diabetes is first recognized in pregnancy, usually after 27 weeks of gestation, and typically resolves after the birth of the child ***(American Diabetes Association, 2009).***

Type 1 diabetes develops most often in children or young adults and accounts for about 5% to 10% of cases of diabetes diagnosed in the United States ***(Palomba et al., 2007)***

All adults older than 45 years of age should be screened for type 2 diabetes every 3 years or every 2 years if they have any risk factors ***(Childs BP, et al., 2005).***

When glucose levels cannot be adequately controlled with oral medications, the use of inject able medications is necessary. If elevated blood glucose levels are untreated and continue to rise, the result can be hyper osmolar hyperglycemic non ketotic syndrome and ultimately death ***(Edelman SV, et al., 2007).***

Risk Factors

Age older than 45 years Body mass index (BMI) greater than or equal to 25 kg/m2Family history of type 2 diabetes Habitual physical inactivity Race/ethnicity (e.g., African American‹Hispanic American, Native American‹Alaska Native, or Pacific Islander)Impaired glucose tolerance or elevated fasting glucose Previous history of gestational diabetes or giving birth to a child weighing more than 9 pounds Hypertension (i.e., blood pressure greater than 140/90 mm Hg in adults)Abnormal lipid levels (i.e., high-density lipoprotein [HDL] level <35 mg/land/or triglyceride level >250 mg/dL). Polycystic ovary syndrome History of vascular disease Acanthosis nigricans (most common among individuals of African descent) ***(Childs BP, et al., 2005).***

Etiology:

Appropriate treatment of type-2 diabetes is dependent upon the knowledge of the path physiology of the disease, the mechanisms underlying hyperglycemia, and the efficacy of various oral agents and insulin's to improve fasting or postprandialhyperglycemia.Type-2diabetes is clearly a heterogeneous, complex, interrelated disease involving multi genic etiologies. The classical disturbances in this condition are characterized by a combination of insulin resistance and progressive beta cell deterioration resulting in impaired insulin secretion and release, increased hepatic glucose production as the result of enhanced glycogenolysis and gluconeogenesis. The disease demonstrates a wide

variance from the predominantly insulin resistant to the predominantly insulin deficient ***(Tuomi et al., 1999).***

In the vast majority of type-2 diabetics, no single genetic defect has been elucidated to explain etiology of this process, but results from the combined effects of multi genic heterogeneous and complex and related causes. In a very small percentage of those individuals with monogenic causes of type-2 diabetes, inheritance of two mutant genes from both parents or autosomal inheritance are responsible ***(Groop, 2009).***

These monogenic causes can effect:

1. Beta cell function as in maturity onset diabetes of youth (MODY) of which six types of different effected genes exist. All these genes except the glucokinase gene, which affects glycolysis, are transcription factors that affect development or gene expression at the beta cell level.

2. Insulin gene mutations demonstrating excessive proinsulin and defective insulin molecules with reduced function at the target tissues.

3. Insulin receptor mutations of which greater than 50 exist involving both production and function, including Leprechaunism, Rabson Mendenhall syndrome, and Type A severe insulin resistance syndrome.

4. Lipodystrophy with mutations in the LMNA gene and the seipin protein ***(Groop. 2009).***

Despite this genetic heterogenicity a consistent phenotype becomes manifested when the disease condition develops, characterized by:

1. Impaired insulin secretion.

2. Insulin resistance.

3. Increased hepatic glucose production due to both increased glycogenolysis and gluconeogenesis.

4. Impaired incretin release.

Recently, significant attention has been devoted to this incretin effect mediated by several gastrointestinal peptides. In humans, the major incretins are glucagon-like peptide-1 (GLP-1) and glucose dependent insulin tropic polypeptide (GIP). Both the GLP-1 and GIP increase

glucose dependent and first phase insulin secretion and are rapidly deactivated by dipeptidylpeptidase-4 (DPP-4), but only GLP-1 suppresses glucagon secretion. The incretins also have a variety of other systemic effects including appetite suppression by a direct effect on the satiety center, delayed gastric emptying, and an increase in beta cell neogenesis with apoptosis inhibition (animal and in vitro). Both GLP-1 and GIP are released from the intestinal cells in response to nutrient intake with GLP-1 being synthesized from proglucagon in the L cells of the small intestine and GIP in the K cells of the proximal intestinal mucosa***(Gillies ., 2008).***

Natural History of Type -2 Diabetes:

The earliest manifestation of the type-2 diabetes is elevation of postprandial glucose in association with progressive insulin resistance. This results in compensatory islet cell hypertrophy, but eventually insulin production is insufficient to maintain euglycemia. In many instances a loss or delay of early phase insulin release in response to a mealtime glucose load will aggravate beta cell deficiency and contribute to the progressive nature of the disorder. Regulation of postprandial glucose depends upon stimulation of insulin secretion with subsequent suppression of hepatic gluconeogenesis and glycogenolysis. Insulin release subsequently promotes glucose uptake in the muscle and the peripheral tissues. The effect of insulin in suppressing hepatic glucose production and muscle glucose uptake is more potent than the effect of hyperglycemia alone ***(LeRoith. 2002).***

Fasting glucose levels are dependent upon hepatic glucose production (hepatic glycogenolysis and gluconeogenesis), basal insulin levels, insulin sensitivity, and the level and duration of the previous pyramidal glucose. Elevated fasting glucose levels due to excessive hepatic glucose production during the sleeping hours (12 Midnight to 8 a.m.) may be responsible for the majority of the increments in day long hyperglycemia***(Goldstein ., 2002).***

Following a meal or glucose load, elevated glucose levels stimulate insulin release from the beta cell. This secreted insulin binds to the cell surface receptors. Within the receptor site, two extracellular alpha subunits bind to the insulin transmitting a signal to two identical beta subunits via the cell membrane. Type-2 diabetics have either normal or

slightly diminished insulin receptor binding affinity. Following the binding process, the beta subunit is phosphorylated, increasing tyrosine kinase activity, and enhancing the phosphorylation of various endogenous protein substrates. This results in a cascading sequence of reactions responsible for the synthesis of RNA, DNA, protein, and intracellular enzymes. Hepatic glucose output is suppressed and glucose uptake by the peripheral tissues, notably skeletal muscle and adipose cells, is subsequently enhanced ***(Haffner. 2000).***

Type-2 diabetics demonstrate excessive hepatic glucose production despite significantly elevated insulin levels. The combination of increased hepatic glucose production and fasting hyperinsulinemia illustrates the insulin resistance in these individuals. This is because hepatic glucose production is profoundly reduced with small increases in plasma insulin. In fact, we find across all plasma insulin concentrations, including both pharmacologic and physiologic levels, that the ability of insulin to suppress hepatic glucose production is diminished in type-2 diabetics ***(Grundy. 2002).***

One of the most critical effects of insulin is its effects on glucose disposal. As the result of impaired muscle glucose uptake, glucose disposal is significantly reduced resulting in impaired glycogen synthesis, glucose oxidation, and tissue glucose uptake. Glucose transports rate limiting for overall disposal under most normal physiologic conditions. Of the five types of glucose transporters identified, the GLUT-4 protein is referred to as the insulin sensitive glucose transporter. This transporter is found in high concentrations in adipose cells, skeletal and cardiac muscles and is primarily responsible for glucose uptake and its effects. The GLUT-4 proteins are housed in intracellular vesicles and translocation to the cell surface inserting into the plasma membrane upon insulin stimulation. This causes glucose to enter the cell. Type-2 diabetics usually have normal GLUT-4 levels, but impaired glucose transport. This may indicate that a flaw exists in the insulin influenced translocation of GLUT-4 to the cell surface. This defective signaling pathway between the receptor and the transport stimulation results in insulin resistance in these patients ***(Goldstein. 2002).***