CORRELATION BETWEEN NECK AND WAIST CIRCUMFERENCE IN PREDICTION OF TYPE II DIABETES IN EGYPTIAN INDIVIDUALS

Thesis

Fulmitted for partial fulfillment of the M.L.C degree
In
Internal Medicine

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2010

ABSTRACT

Diabetes has been known for centuries, although it has not been fully understood, and the disease takes its name from the Greek for "passing through" because of one of its main symptoms - excessive urine production. During the fifteenth century the word Mellitus was from the Latin for "honey" when it was noted that many patients with diabetes had high levels of sugar in their blood and urine. Diabetes mellitus, which is simply referred to as diabetes these days, is a metabolic disorder which in particular affects the metabolism of carbohydrates. The condition requires medical treatment and, more often than not, a number of lifestyle changes. To function properly the human body requires a source of energy and derives this from the food that we eat. A normal diet comprises of a mixture of carbohydrates, proteins and fats with carbohydrates accounting for up to three-quarters of this mix. There are a wide variety of high carbohydrate (sometimes referred to as high starch) foods and these include bread, bran, cereal, beans, rice and pasta. Food is broken down by the digestive process into a variety of organic compounds and one of these, which forms the body's prime source of energy, is glucose. Glucose is then carried to various parts of the body by the blood and is transferred to the cells of the body to fuel both cell growth and cell repair. An essential element in the transfer process is the presence of insulin in the bloodstream. Insulin is produced by specialized cells (known as beta-cells) which are located in an area of the pancreas called the Islets of Langerhans. Diabetes sufferers fall into two broad categories – those with type I diabetes (formerly known as "juvenile" or "childhood" diabetes) and those with type II (or adult) diabetes. There is also said to be a third form of diabetes known as type III or gestational diabetes but, despite the fact that there are a few differences, this is basically nothing more than type II diabetes which occurs during, and because of, pregnancy. In type I diabetes sufferers develop a problem with the insulin producing beta-cells of the pancreas and are unable to produce sufficient insulin to transfer glucose from the bloodstream to the cells of the body. This means that it is necessary to closely monitor levels in the blood and to administer insulin so that glucose can be transferred and the glucose levels in the blood returned to normal. In type II diabetes the body usually continues to produce insulin normally but the body's cells develop a resistant to it and insulin levels begin to increase in the blood. In the early stages of type II diabetes this can often be counteracted by reducing the intake of glucose producing carbohydrates, exercising and losing weight, particularly when weight loss is aimed at removing fat from the area of the abdomen. If this approach does not do the trick then the condition can usually be controlled through the use of medication. There is currently no cure for either type I or type II diabetes and, while treatment can usually reduce the symptoms of both considerably, most sufferers will require ongoing treatment throughout life.

Acknowledgment

First of all, I would like to express my deepest thanks to Professor Dr Mohamed Sheta professor of Internal medicine Cairo University, for his kind supervision and for his continuous encouragement and guidance. he offered me much of his kind advises and scarified much of his valuable time to complete this work

I would also like to express my sincere thanks to Professor Dr. Salwa Fayez Professor of Biochemistry-Cairo University, as she offered me much of her effort and time in working in my samples

and for her continuous support for me along this work and till now.

would also like to express my thanks and appreciation to Professor Dr. Eman Rusdy , professor of Internal medicine -Cairo University, for her support and guidance for me in every step of this work. Neither did she save her effort nor her time for accomplishment of this work.

My special thanks to my father, my mother, my brother, my sister Their care, love, and generosity can never be sufficiently acknowledged.

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List of abbreviations

(A cell):	**Alpha cells**
(B cell):	**Beta cells**
(Delta cell):	**delta cells**
AA:	**amino acids**
ADP:	**adenosine di phosphate**
ATP:	**adenosine tri phosphate**
BMI:	**body mass index**
FA:	**fatty acid**
GLUT:	**glucose transporter**
GTT:	**glucose tolerance testing**
HDL:	**high density lipoprotein**
HFCS:	**high fructose corn syrup**
HOMA:	**homeostatic model assessment**
IDDM:	**insulin dependent diabetes mellitus**
IL:	**interleukin**
IR :	**insulin resistance**
IRS:	**insulin receptor substrate**
LBO:	**lower body obesity**
LDL:	**low density lipoprotein**
MG:	**magnesium**
MODY:	**mature onset diabetes of the young**
NAFLD:	**non alcoholic fatty liver disease**
NC:	**neck circumference**

NIDDM:	**non insulin dependent diabetes mellitus**
PCOS:	**poly cystic ovary syndrome**
PPAR :	**peroxisome proliferation activated receptor**
QUICKI:	**quantitative insulin sensitivity check index**
RBP4:	**retinol binding protein 4**
T2DM:	**type 2 diabetes mellitus**
TCF7L2:	**transcription factor 7 like 2 gene**
TG:	**triglycerides**
TLR4:	**toll like receptor 4**
TNF:	**tumor necrotic factor**
UBO:	**upper body obesity**
UCP2:	**uncoupling protein 2**
VAT:	**visceral adipose tissue**
WC:	**waist circumference**

INTRODUCTION AND AIM OF WORK

All of us know someone suffering from diabetes. This sums up the prevalence of diabetes. It is, apart from being one of the most prevalent diseases in the world, also a disease that opens up a Pandora's Box of many complications. No wonder it is a dreaded disease and people who are diabetic end up getting other medical problems as well. Diabetes is a group of diseases with one thing in common - a problem with insulin. The problem could be that your body doesn't make any insulin, doesn’t make enough insulin or doesn't use insulin properly.

Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water, but the flow is incessant, as if from the opening of acqueducts. The nature of the disease, then, is chronic, and it takes a long period to form; but the patient is short-lived, if the constitution of the disease be completely established; for the melting is rapid, the death speedy.

The aim of this work is to try to help the prediction of diabetes as early as possible using simple anthropometric measures such as BMI and waist circumference as well

Also trying to find correlation between neck and waist circumference in prediction of type II diabetes

PATHOGENESIS OF TYPE II DIABETES

Pathophysiology:

Understanding the pathogenesis of type 2 diabetes is complicated by several factors **(Stumvoll et al., 2005)** Patients present with a combination of varying degrees of insulin resistance and relative insulin deficiency, and it is likely that both contribute to type 2 diabetes **(Beck-Nielsen et al., 1994).**

Furthermore, each of the clinical features can arise through genetic or environmental influences, making it difficult to determine the exact cause in an individual patient. Moreover, hyperglycemia itself can impair pancreatic beta cell function and exacerbate insulin resistance, leading to a vicious cycle of hyperglycemia causing a worsening metabolic state **(li et al., 2004)**

Type 2 diabetes is often accompanied by other conditions, including hypertension, high serum low-density-lipoprotein (LDL) cholesterol concentrations, and low serum high-density-lipoprotein (HDL) cholesterol concentrations that, like type 2 diabetes, increase cardiovascular risk. This constellation of clinical conditions is referred to as the metabolic syndrome **(DeFronzo et al., 1991).**

Hyperinsulinemia occurring in response to insulin resistance may play an important role in the genesis of these abnormalities. Increased free fatty acid levels, inflammatory cytokines from fat, and oxidative factors, have all been implicated in the pathogenesis of

metabolic syndrome, type 2 diabetes, and their cardiovascular complications **(Defronzo et al., 1991)**

Insulin secretion by beta cells requires glucose transport into the cell, which is at least in part mediated by the glucose transporter 2 (GLUT-2). A mouse model with a genetic alteration affecting GLUT-2 expression produced mice with glucose intolerance; similar changes in GLUT-2 could be induced in normal mice fed a high-fat diet and suggests a possible mechanism for the link between high-fat diet and the development of diabetes **(Thorenset al., 2007)**

Impaired insulin secretion has also been demonstrated to occur in mice lacking Abca1, a cellular cholesterol transporter. Mice with inactivation of Abca1 in beta cells have defective insulin secretion, impaired glucose tolerance, but normal insulin sensitivity **(Brunham et al., 2007)**

Insulin resistance

Insulin resistance may be the best predictor of type 2 diabetes. The vast majority of patients appear to have a genetic risk for type 2 diabetes.. It is possible, for example, that insulin resistance becomes more severe with increasing age and weight, thereby unmasking a concurrent defect in insulin secretion in susceptible subjects to cause impaired glucose tolerance and eventually overt hyperglycemia. In normal-weight nondiabetic subjects at high risk for type 2 diabetes, both fasting and post-glucose hyperinsulinemia predict future weight gain, which in turn predisposes to hyperglycemia **(Sigal, Odeleye et al.1997)**

Hyperglycemia itself may contribute to further progression by a toxic effect on beta cells, possibly by decreasing insulin gene expression **(Moran et al., 1997)**

Insulin resistance may, at least in part, be related to substances secreted by adipocytes ("adipokines" including leptin adiponectin, tumor necrosis factor alpha, and resistin) **(Rothman et al., 1995)**

The importance of genetic factors in the pathogenesis of type 2 diabetes is suggested by the observation that lean, normoglycemic offspring of parents with type 2 diabetes have reduced nonoxidative glucose metabolism associated with reduced muscle glycogen synthesis **(Rothman et al., 1995)**

Thus, insulin resistance is present years before the onset of hyperglycemia. An increase in intracellular lipid content in muscle has been identified in these insulin-resistant offspring, suggesting that dysregulation of fatty acid metabolism may mediate the insulin resistance in these individuals **(Petersen KF et al., 2004)**

The importance of the combination of genetic and environmental factors is suggested by another study of nondiabetic offspring of two parents with type 2 diabetes. Their insulin sensitivity was similar to that of normal subjects with no first-degree relatives with type 2 diabetes at near ideal body weight; with increasing degrees of obesity, however, the progressive decrease in insulin sensitivity was much more pronounced in those with a family history of type 2 diabetes **(Khan Cr et al., 1994)**

Impaired insulin processing

Insulin production in normal subjects involves cleavage of insulin from proinsulin; 10 to 15 percent of secreted insulin is proinsulin and its conversion intermediates. In contrast, the proportion of immunoreactive insulin that is proinsulin in type 2 diabetes is increased considerably in the basal state (>40 percent) **(Kahn, SE, Halban, PA et al., 1997)**

The difference between normal and diabetic subjects becomes even more pronounced after stimulation with arginine or glucagon. The increase in proinsulin secretion persists after matching for degree of obesity, suggesting that it represents beta cell dysfunction, and not merely the response to the increased secretory demand imposed by the insulin resistance of obesity **(Roder, ME et al., 1999)**.

These finding s suggest that the processing of proinsulin to insulin in the beta cells is impaired in type 2 diabetes, or that there is insufficient time for granules to mature properly so that they release more proinsulin **(Roder, et al., 1999)**

Role of islet amyloid polypeptide

Islet amyloid polypeptide (amylin) is stored in insulin secretory granules in the pancreatic beta cells. It is cosecreted with insulin, resulting in serum concentrations about one tenth those of insulin, and is present in increased amounts in the pancreas of many patients with type 2 diabetes **(Westermark, p, Johnson et al., 1992).**

First-phase serum insulin and amylin concentrations are lower in patients with impaired glucose tolerance compared with patients with normal glucose tolerance, and the concentrations are very low in patients with type 2 diabetes **(Makimattila, S, Fineman et al., 2000)**

High concentrations of amylin decrease glucose uptake and inhibit endogenous insulin secretion, suggesting that amylin may be directly involved in the pathogenesis of type 2 diabetes **(Hull, RL,et al., 2004)**

However, administration of physiologic amounts of amylin has no acute effect on insulin secretion or insulin action in humans. On the other hand, the administration of an amylin antagonist to rats results in a fall in blood glucose and an increase in insulin secretion, suggesting that amylin may tonically inhibit insulin secretion **(Benet WM et al., 1994)**

Thus, it remains unclear whether amylin has a causative role in type 2 diabetes or is merely present in increased amounts as a consequence of the defect in insulin secretion. There is no apparent association between the amylin gene and type 2 diabetes **(Bell GI et al., 1993)**

Pramlintide is a synthetic analog of human amylin that slows gastric emptying, reduces postprandial rises in blood glucose concentrations, and improves A1C concentrations in patients with type 1 and type 2 diabetes when given subcutaneously. **(Bell GI et al., 1993)**

Genetic susceptibility:

Type 2 diabetes most likely represents a complex interaction among many genes and environmental factors. Monogenic causes of type 2 diabetes represent only a small fraction of cases and commonly inherited polymorphisms individually contribute only small degrees of risk for, or protection from diabetes. Most of the genetic risk for type 2 diabetes results from complex polygenic risk factors **(Carrter et al., 1996)**

Observations which demonstrate a genetic influence on the development of type 2 diabetes include

The prevalence of type 2 diabetes varies remarkably between ethnic groups living in the same environment. Type 2 diabetes is two to six times more prevalent in African Americans, Native Americans, Pima Indians, and Hispanic Americans in the United States than in whites **(Carrter et al., 1996)**

Thirty-nine percent of patients with type 2 diabetes have at least one parent with the disease **(Klien et al., 1996)**

Among monozygotic twin pairs with one affected twin, approximately 90 percent of unaffected twins eventually develop the disease **(Barrnet, et al., 2000)**

First-degree relatives of patients with type 2 diabetes frequently have impaired nonoxidative glucose metabolism (indicative of insulin resistance) long before they develop type 2 diabetes **(Eriksson et al., 1989)**.