

Type II Diabetes: Medication vs Education and Prevention

Harosh I^{1*}, Ciufolini MA²

¹Department of Biotechnology, Obetherapy, Evry, France

²Department of Chemistry, University of British Columbia, Vancouver, British Columbia

*Corresponding author: Itzik Harosh, Department of Biotechnology, Obetherapy, Evry, France, Tel: +33 9 52 62 10 19; E-mail: iharosh@obetherapy.com

Received date: 28 Aug 2017; Accepted date: 25 Nov 2017; Published date: 29 Nov 2017.

Citation: Harosh I, Ciufolini MA (2017) Type II Diabetes: Medication vs. Education and Prevention. *J Dia Res Ther* 3(2): doi <http://dx.doi.org/10.16966/2380-5544.131>

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Abstract

The global prevalence of type II diabetes is rapidly evolving toward a worldwide pandemic. But the condition is a life style disorder, and it can be treated at an early stage of its appearance with no medication, simply by adopting a healthy life style. This includes restricted caloric intake, weight management and exercise. Screening for pre-diabetes and insulin resistance in the overweight and obese population could help prevent type II diabetes and translate into significant economies for health care systems worldwide.

Introduction

Diabetes or more accurately diabetes mellitus [DM] is a condition that results in an abnormally high concentration of blood glucose (hyperglycemia) over a prolonged time span. This ultimately damages blood vessels, increasing the risk of cardiovascular accidents, chronic eye, kidney, and nerve disease, and even cognitive impairment.

Medicine distinguishes several types of diabetes; for instance type I, type II and Maturity Onset Diabetes in Young [MODY]. Type I diabetes, formerly known as juvenile diabetes or insulin dependent diabetes mellitus [IDDM] is an autoimmune disease that results in the destruction of insulin-producing pancreatic beta cells. There is no insulin production; therefore treatment of this disease requires regular insulin injection [1].

MODY is associated with more than 11 mutated genes that affect glycemic levels in the blood [2]. It seems likely that an even larger number of yet-unidentified genes are associated with the condition, since there are many more genes that are involved in maintaining glycemic homeostasis.

Type II diabetes [T2D] previously known as Elderly Diabetes and subsequently as Non Insulin Dependent Diabetes Mellitus [NIDDM], is an insidious condition characterized by hyperinsulinemia and glucosuria, and it is the form of metabolic disorder of greatest current concern. It is linked to excessive weight and obesity more precisely, to the finite amount of space available within adipose tissues to store excess energy in the form of fat [3]. If left untreated, it will evolve into an insulin-dependent condition analogous to type I diabetes.

The number of people suffering from T2D is increasing at an alarming rate worldwide, with the number of patients estimated to soar to more than 366 million by 2030 [4]. It is projected that in the US alone such costs will reach \$ 174 billion by 2034 [5], while global health expenditures for diabetes are expected to increase from 376 billion dollars in 2010 to 490 billion in 2030 [6].

The development of type II diabetes is a long process, which in most cases, starts with weight gain followed by hyperglycemia and hyperinsulinemia. An excessive increase in body weight overloads adipose tissue with fat. But there is only a finite amount of fat-storing space in

adipose tissue: once that space is filled to capacity, excess energy [glucose and fat] will accumulate in the blood as glucose [hyperglycemia] and lipids [hyperlipidemia], or as ectopic fat deposits in the viscera, heart, and vascular system [7,8]. Hyperglycemia initially triggers excessive insulin production, resulting in hyperinsulinemia. Over the long term, this will induce exhaustion and impairment of insulin-producing pancreatic beta cells. If the condition is left untreated, the patient will ultimately develop insulin dependent diabetes.

The Complex Genetic Basis of Type II Diabetes

It is widely accepted that many complex disorders, such as type II diabetes and obesity are the result of the combined effects of multiple genetic and non-genetic factors. Chemotherapeutic intervention often aims to reduce blood sugar concentrations. However, glycemic levels are controlled by many genes which act in harmony in order to maintain glycemic homeostasis. Any gene involved in glucose balance, glycogen synthesis, lipid synthesis, insulin secretion, glucagon secretion, energy [ATP] production, etc., potentially can be implicated in type II diabetes, which therefore is likely to involve hundreds such genes [9]. These are expressed in muscle, liver, pancreas, intestine, adipose tissues, brain, etc. Any mutation of these genes resulting in gain or loss of activity will affect the glycemic level.

For instance mutations within the glucokinase [GCK] gene can cause either hyperglycemia or hypoglycemia. Inactivation of the gene will cause hyperglycemia, while several mutations that activate it result in hypoglycemia [10].

The same is true for the KCN11 gene, which codes for a voltage-gated potassium channel found in pancreatic beta cells. This channel regulates the flow of potassium ions and it opens and closes in response to the amount of glucose in the bloodstream. Mutations of this gene that cause loss of activity will result in hyperinsulinemia and as a consequence in episodes of hypoglycemia. In contrast, mutations resulting in gain of activity will produce hypoinsulinemia and as a consequence, hyperglycemia [2,11].

Other genes that are involved in hypoglycemia are: GYS2 familial hyperinsulinemia, hepatic deficiency of fructose-1,6 phosphatase PEPCK,

UCP2 and others [12]. However, mutations that cause hypoglycemia are rare since they tend to be fatal before the age of puberty and thus are not passed on to progeny (strong negative selection). Conversely, genetic mutations leading to hyperglycemia cause damage to blood vessels and other organs very slowly, normally at late stage of life thereby allowing individuals suffering from the condition to transmit the mutated or variant genes to their offspring. For this reason, hyperglycemia is much more common than hypoglycemia.

The foregoing suggests that it is very difficult to pinpoint a particular gene as being responsible for T2D and more difficult still to estimate how much a particular gene might contribute to the disorder. It is thus an illusion to think that Genome-Wide Association Study [GWAS], sequence variations or single nucleotide polymorphism [SNPs] may be sufficient to predict the risk of developing type II diabetes. Furthermore, if an SNP or mutation within a particular gene was to be identified then by definition such a mutation would be associated with MODY, and not with type II diabetes. In a like vein, the haplotype map (HapMap) consortium, which started in 2002 with the aim to identify and catalog genetic similarities and differences in humans, has so far failed to identify genes that are directly involved in type II diabetes [13]. A genome wide association study of several major diseases has identified 3 genes with a strong association with type II diabetes: PPAR- γ , KCNJ11 and TCF7L2 [14]. Nevertheless, these 3 genes are not enough to explain the genetics of type II diabetes. More than 79 genes that contribute partially to T2D were already described in the scientific literature [15] prior to the above study and probably several hundred more genes still waiting to be discovered contribute to glycemic homeostasis. One may thus conclude that only small variations or SNPs within the tens of genes that are involved in regulating blood glucose levels contribute to the evolution of type II diabetes: the main factors must be non genetic.

Considerable evidence suggests that losing weight through diet and exercise will resolve the hyperglycemic and hyperlipidemic state of T2D so long as pancreatic beta cells are still viable; i.e., provided that the disorder is still at the NIDDM stage. A noteworthy observation in that sense was recorded a century and half ago by the French physician, Apollinaire Bouchardat [16]. Bouchardat noticed that during the Franco-German war (1870), when Paris was besieged and the population was starving, elderly diabetes disappeared, while juvenile diabetes was not affected. He thus suggested a treatment for elderly diabetes based on diet and exercise in order to lose weight. Even today the first-line of treatment for type II diabetes remains diet, weight control and physical activity. This works perfectly well, as long as the affected person still produces insulin (a trait known as pre-diabetes or NIDDM). We now understand that weight loss frees storage space in the adipose tissue, which can then accommodate excess blood glucose and lipids and resolve the condition. Particularly instructive in that respect is the mechanism of action of thiazolidinedione [TZD] drugs. These medications activate PPAR- γ nuclear receptors. PPAR- γ regulates the transcription of various genes that control adipocytes proliferation (adipogenesis) and lipid uptake [17-19]. Activation of PPAR- γ promotes adipogenesis, generating more fat storage space. This results in an improvement of glycemic and lipidemic level but at the price of weight gain, one of the major side effects of these drugs [20-22].

One may conclude that early-stage type II diabetes can be treated without medication, simply by leading a healthier lifestyle. Moreover, because T2D can be prevented and reverted at early stage of its onset, it should really be considered a lifestyle disorder, rather than a genetic disease like type I diabetes or MODY. That being the case, educating patients and people at risk on how to adopt a healthier lifestyle can

avert the looming pandemic of type-2 diabetes and the associated costs. Furthermore, education should commence at an early age; i.e., in schools. It may also be desirable to introduce suitable screening programs analogous to those already in place for the early detection of many cancerous diseases (prostate, colorectal, breast cancer etc.) and targeting the high-risk population; namely overweight, obese, and pre-diabetic [NIDDM] individuals of any age. As of yet, there seems to be no consensus regarding the appropriate exercise regime to treat T2D. However, 150 minutes of moderate to vigorous aerobic exercise per week-similar to established guidelines for cardiovascular health in general-may be regarded as a reasonable prescription [23].

In summary, type II diabetes is a direct consequence of the lack of room to store excess energy in adipose tissue. It is a lifestyle disorder and it can be prevented and reverted at early stage with no medication: simply by lifestyle changes, diet and exercise [24,25]. Appropriate measures in that sense must be taken at early stage of the disorder, when beta cells are still producing insulin. Once insulin secretion ceases the condition becomes irreversible, and type II diabetes degenerates into a life-threatening disease if not treated with insulin or other anti-diabetic medication.

Acknowledgments

Harosh I researched and wrote the paper. Ciufolini MA edited the manuscript. Financial support for this work was provided by Obetherapy, SA. Harosh I is the guarantor of this article.

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