Effect of Glucose, Sucrose and Honey on C-peptide Level of Diabetic Children

Thesis

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Introduction

The glycemic effect of any foodstuff is defined as its effect on blood glucose level postprandially. Both the glycemic index (Gl) and the peak incremental index (PII) are used to assess the glycemic effect of different food stuffs ***(Jenkins et al., 1981). Jennie et al. (2003)*** who studied the use of low glycemic index diets in the management of diabetes found that diets with low glycemic indices (GI), compared with conventional or high-GI diets, improved overall glycemic control in individuals with diabetes, as assessed by glycemic index, peak incremental index, reduced HbAlc and fructosamine. They concluded that using low-GI foods in place of conventional or high-GI foods has a clinically useful effect on postprandial hyperglycemia similar to that offered by pharmacological agents that target postprandial hyperglycemia. Similarly, the ***American Diabetes Association (2002)*** stated that the use of low-GI foods may reduce postprandial hyperglycemia.

Honey is the substance made when the nectar and sweet deposits from plants are gathered, modified and stored in the honeycomb by honey bees. It is composed primarily of the sugars glucose and fructose; its third greatest component is

water. Honey also contains numerous other types of sugars, as well as acids, proteins and minerals ***(White, 1980)***. Among honey benefits are its anti-inflammatory ***(Al Waili and Boni, 2003)***, anti-oxidant ***(Frankel, 1998)*** and anti-microbial effects ***(Mclan, 1992)***. Furthermore several studies have shown that honey produced an attenuated postprandial glycemic response when compared with sucrose in both diabetics and normal subjects ***(Ionescu-Tirgoviste et al., 1983, Shambaugh et al., 1990, Samanta et al., 1935 and Al Waili, 2004)***.

C-peptide is considered to be a good marker of insulin secretion and has no biological activity of its own ***(Ido, 1997)***. Measurement of C-peptide, however, provides a fully validated means of quantifying endogenous insulin secretion. C-peptide is co secreted with insulin by the pancreatic cells as a byproduct of the enzymatic cleavage of proinsulin to insulin. Consequently, serum C-peptide level can be used as a true indicator of any change in the insulin level which is the main determinant of plasma glucose level. Several studies were performed in healthy and in type 2 diabetic patients to evaluate the effects of honey on the insulin and C-peptide levels, and the results were controversial ***(Ionescu-Tirgoviste et al., 1983, Bornet et al., 1985 and Watford, 2002)***.

Aim of Work

The aim of this work is to compare the effects of honey, sucrose and glucose on plasma glucose and C-peptide levels in children and adolescents with type 1 diabetes mellitus.

Diabetes Mellitus

Definition:

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, and blood vessels ***(ADA, 2007).***

Classification:

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories.

One category, type 1 diabetes, the cause of which is an absolute deficiency of insulin secretion.

In the other, much more prevalent category, type 2 diabetes, the cause of which is a combination of resistance to insulin action and inadequate compensatory insulin secretory response ***(ADA, 2007***).

The etiological classification recommended by the American diabetes association (ADA) and the World Health Organization (WHO) expert committee on the classification and the diagnosis is shown in table 1 with minor modification.

Type 1 diabetes is one of the most common childhood illnesses.The incidience of type 1 dibetes increasing rapidly worldwide, and it is also presenting an earlier age ***(Devendra et al., 2004)***.

The goal of medical care for people with diabetes is to optimize glyceamic control and minimize complications. Treatment that maintains blood glucose levels near normal in type 1 diabetes delays the onset and reduces the progression of microvascular complications ***(ADA, 2007).***

Table (1): Aetiological classification of DM**.**

I. Type 1: (β-cell destruction, usually leading to absolute insulin deficiency) A. Autoimmune B. Idiopathic
II. Type 2: May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance.
III. Other Specific Types: **A) Genetic defects of B-cell function:** 1.Mitochondrial DNA defect. 2. Wolfram's syndrome. 3. Maturity onset diabetes of the young (MODY). a. Chromosome 20q (MODY-1). b. Chromosome 7q (MODY-2). c. Chromosome 12q (MODY-3). **B) Genetic defects in insulin action:** 1-Type A insulin resistance 2-Leprechaunism 3-Rabson-Mcndcnhall Syndrome 4-lipodystrophy. **C) Diseases of the exocrine pancreas:** 1-Pancreatitis, 2-Trauma 3-Pancreatectomy 4-Neoplasia 5-Cystic fibrosi 6-Hemochromatosis **D) Endocrinopathy:** 1-Acromegaly, 2-Cushing syndrome. 3-Glucagonoma 4-Phaeochromocytoma 5-Hyperthyroidism 6-Somatostatinoma 7-Aldostcronoma. **E) Drug or chemical Induced:** 1- Necotinic acid. 2- Glucocorticoids 3- Thyroid hormone. 4-B-adrenergic agonist 5-Thiazides. 6- Phenytoin 7-Pentamidine. 8- Diazoxide. 9- Vacor. 10-Interferon-a. **F) Infections**: 1-Congenital rubella. 2-Mumps 3-Cytomegalovirus. 4- Adenovirus 5- Coxakie B virus. **G) Uncommon forms of immune mediated diabetes:** 1- Anti-insulin receptor antibodies. 2- Stiff-man syndrome. **H) Other genetic syndromes sometimes associated with diabetes mellitus:** 1- Down syndrome 2- Klienfelter's syndrome 3-Turner's syndrome 4-Prader-Wili syndrome. 5-Myotonic dystrophy 6-Laurance-Moon-Biedl syndrome 7-Friadreich's ataxia. 8- Huntington's chorea. 9-Porphyrea. 10-Others
IV. Gestational diabetes.

(ISPAD, 2009)

Diagnostic criteria for diabetes in childhood and adolescence:

Diagnostic criteria for diabetes are based on blood glucose monitoring and the presence or absence of symptoms. Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycemia , must be confirmed, on a subsequent day,by any one of the three methods given in table 2 ***(ISPAD, 2009)***.

Table (2): Criteria for the diagnosis of DM

Symptoms of diabetes plus casual plasma glucose concentration >200mg/dL. (Casual is defined as any time of day without regard to time since the last meal).
Or Fasting plasma glucose >126mg/dL. (Fasting is defined as no caloric intake for at least 8h),
Or 2-h postload glucose >200mg/dL during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water or 1.75g/kg of body weight to a maximum of 75g.

(ISPAD, 2009)

Type 1 Diabetes Mellitus:

This condition is characterized by severe insulinopenia and dependence on exogenous insulin to prevent ketosis and to preserve life its therefore termed insulin dependant diabetes mellitus (IDDM). The onset occurs predominantly in childhood but it may come at any age. Hence, such terms as juvenile

diabetes and brittle diabetes have been abandoned in favor of type 1diabetes mellitus ***(Petrousky et al., 2003).***

Subtypes:

In type 1 there is evidence suggesting an autoimmune origin of β-cell destruction, mostly due to predominately activated autoreactive T-cells that destroy beta cells which results in a progressive loss in insulin secretion and function ***(Ludlow and Sperling, 2005)***. Activated helper Tcells provoke β-cells to produce several autoantibodies which act to destroy insulin producing B cells of the pancreas ***(Haller et al., 2005)***. This autoimmune entity also is associated with certain HLAs. Patients with type 1a are also more likely to have other autoimmune disorders such as autoimmune thyroiditis, Addison's disease, and celiac disease ***(Ludlow and Sperling, 2005).*** Type 1b form of diabetes is characterized by low insulin and C peptide levels similar to those in type 1a, although there is no evidence of an autoimmune etiology of the β-cell destruction. They are prone to ketoacidosis and depend on insulin to prevent metabolic deterioration. This idiopathic diabetes reflects the still limited knowledge of the etiology of many forms of diabetes ***(Ludlow and Sperling, 2005).***

Incidence and prevalence:

Type 1 diabetes is one of the most common chronic diseases in childhood ***(Craig et al., 2001)***. Its incidence varies dramatically between populations and even within the same population, much of this variation is due to genetic defect. The incidence of type 1 diabetes is increasing in all population at a rate of approximately 3% per year and the onset of the condition is occurring at younger age ***(Scharnz, 2002)***.

Pathophysiology of type 1 DM:

When 90% of functioning B-cell have been destroyed, loss of insulin secretion becomes clinically significant. With loss of the insulin which is the major anabolic hormone, a catabolic state develops, which is characterized by decreased glucose utilization and increased glucose production via gluconeogensis and glycogenosis, leading to hyperglycemia. In the state of insulin deficiency, levels of counter regulatory hormones (i.e., glucagons, epinephrine, growth hormone and cortisol) are elevated fatty acids release and keto acids production follow ***(ISPAD, 2009).***

Etiological factors for type 1 diabetes mellitus (TIDM):

The most often cited model of the natural history of TIDM suggests that genetically susceptible individuals with a fixed number of beta cells are exposed to a putative

environmental trigger that induces beta cell autoimmunity. The degree of beta cell destruction required for symptomatic onset is also questioned with recent studies suggesting that 40% to 50% of beta cells are viable at the onset of hyperglycemia ***(Haller et al., 2005).***

1-Auto immunity:

Autoimmunity in TIDM typically has been identified by the presence of circulating antibodies to islet cell antigens, which in addition to their presence at the time of diagnosis often can be detected long before the disease becomes clinically evident. The development of islet reactive autoantibodies is a marker of ongoing autoimmune disease, but it is predominantly activated T cells that destroy beta cells, which results in a progressive and predicable loss in insulin secretory function. Islet cell autoantibodies (ICAs), autoantibodies to glutamic acid decarboxylase (GAD65A), insulin autoantibodies (IAAs), and autoantibodies direct eat a transmembrane tyrosine phosphate (ICA512A) are the most prevalent and best characterized, but the potential for other autoantibody/ autoantigen combinations remains, insulin autoantibodies (IAAs)has an extracellular, transmembrane, and cytoplasmic domain, and autoantibodies to several forms of IAAs has been observed in persons who have type 1 diabetes mellitus ***(Haller et al., 2005)***. IAAs is the first antibodies to appear but it should be measured in the first week

of the start of exogenous insulin therapy, because antibodies to exogenously injected insulin also are detected and are indistinguishable fromIAAs. GAD65A, like ICAs, are observed in 60% to 70% of new cases, unlike ICA, GAD65A often diagnosis ***(Haller et al., 2005)***. It is critical to note that autoantibodies have no known etiologic role in diabetes and-simply put-are believed to represent the "smoke of the fire" in the pancreas and not the itself. Recent studies in animal models of TIDM purposing a crucial role for B lymphocytes in disease development ***(Haller et al., 2005)***. ***Salem et al. (1998)*** proved that anti GAD antibodies could be an important predictor of TIDM and estimation of its level could be part of screening for new cases.

2- Genetic issues:

There is no clear pattern of inheritance of childhood diabetes although there is familial aggregation due to the association of type 1 diabetes with certain genetic markers. In the higher incidence countries the risks to relatives of developing the disease when a member of the family has type 1 diabetes, are as follows ***(ISPAD, 2007).*** The risk of diabetes to an identical twin of a patient with TIDM is about (36%); -For a sibling, the risk is approximately 4% by the age of 20yr and 9.6% by the age of 60yr compared with 0.5% for the general population ***(ISPAD, 2007)***.

The risk is higher in sibling of probands diagnosed at a younger age. TIDM is two to three times more common in the offspring of diabetic men (3.6-8.5%) compared with diabetic women (1.3-3.6%) ***(ISPAD, 2007)***.

3- Environmental factors:

Environmental factors are important because even identical twins have only a 30-60% concordance for type 1 diabetes, and because incidence rates vary in genetically similar population under different living conditions. No single factor has been identified, but infections and diet are considered the two most likely environmental candidates ***(Lamp, 2006).***

A- Infection:

Viral infections may be the most important environmental factors in the development of type 1 diabetes, probably by initiating or modifying an autoimmune process. Instances have been reported of a direct toxic effect of infection in congenital rubella although most of these patients who develop diabetes have HLA and immune markers characteristic of type 1 diabetes ***(ADA, 2007)***. A recent survey suggests that enterovial infection during pregnancy carries an increased risk of type 1 diabetes in the offspring. Paradoxically, type 1 diabetes incidence is higher in areas where the overall burden of infectious disease is lower ***(Lamb, 2006)***. In addition,

coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease ***(ADA, 2007)***.

B- Dietary factors:

Dietary factors are also relevant. Breastfed infants have a lower risk for type 1 diabetes, and a direct relationship exists between per capita cow milk consumption and incidence of diabetes. Some cow's milk proteins have antigenic similarities to an islet cell antigen such as **bovine serum albumin** and **casein** (which is a major protein faction of cow's milk) ***(Haller et al., 2005).*** Nitrosamines, chemicals found in smoked foods and some water supplies, are known to cause type 1 diabetes in animal models, however, no definite link has been made with humans ***(Lamb, 2006)***.

Presentation and phases of type 1 diabetes *(ISPAD, 2007):*

A. Preclinical diabetes.
B. Presentation of diabetes.
C. Partial remission phase.
D. Chronic phase of life long dependency on administered insulin.

A. Preclinical diabetes:

Preclinical diabetes refers to the months or years preceding the clinical Presentation of type IDM when antibodies can be detected as markers of beta-cell autoimmunity such as ***(ISPAD, 2007):***

1. Islet cell auto antibodies**.**
2. Glutamic acid decaroboxylase auto antibodies.
3. IA2 (also known as ICA 512 or tyrosine phosphatse) auto antibodies.
4. Insulin auto antibodies.

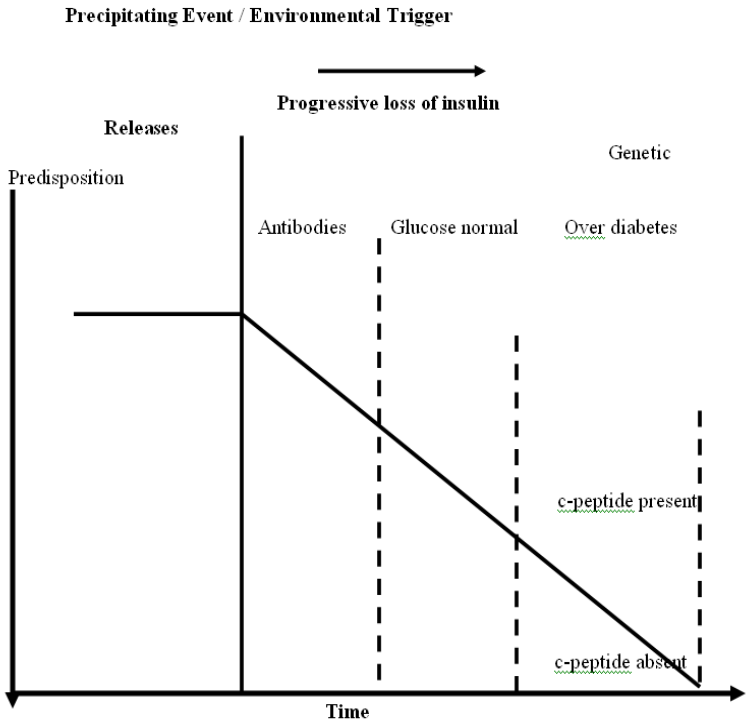

Fig. (1): Progressive loss of B cell mass
(Atkinson and Eisenbarth, 2002).

The development of type I DM has been divided into a series of stages.

Stage 1: Genetic predisposition.

Stage 2: Triggering of autoimmunity.

Stage 3: Development of a series of auto- antibodies.

Stage 4: Loss of B-cell function, as determined by intravenous glucose tolerance testing (metabolic defects).

Stage 5: Overt DM.

Stage 6: Total or near total B-cell destruction with insulim dependence

(Petrovsky and Schatz, 2003)

B- Presentation of diabetes:

1. Symptoms related to increase osmotic pressure:

- Polyuria and nocturia
- polydepsia.
- Blurred vision.
- Drowsiness and dehydration ***(Slama, 2005)*.**

2. Symptoms and signs linked to lack of insulin:

- Hyperglyecemia with massive glucosuria.
- Extreme fatigue.
- Muscle wasting.
- Weight loss.