THE EFFECT OF SWEETENERS ON BLOOD GLUCOSE IN DIABETES MELLITUS

THESIS SUBMITTED FOR PARTIAL FULFILMENT OF

THE MASTER DEGREE IN MEDICINE

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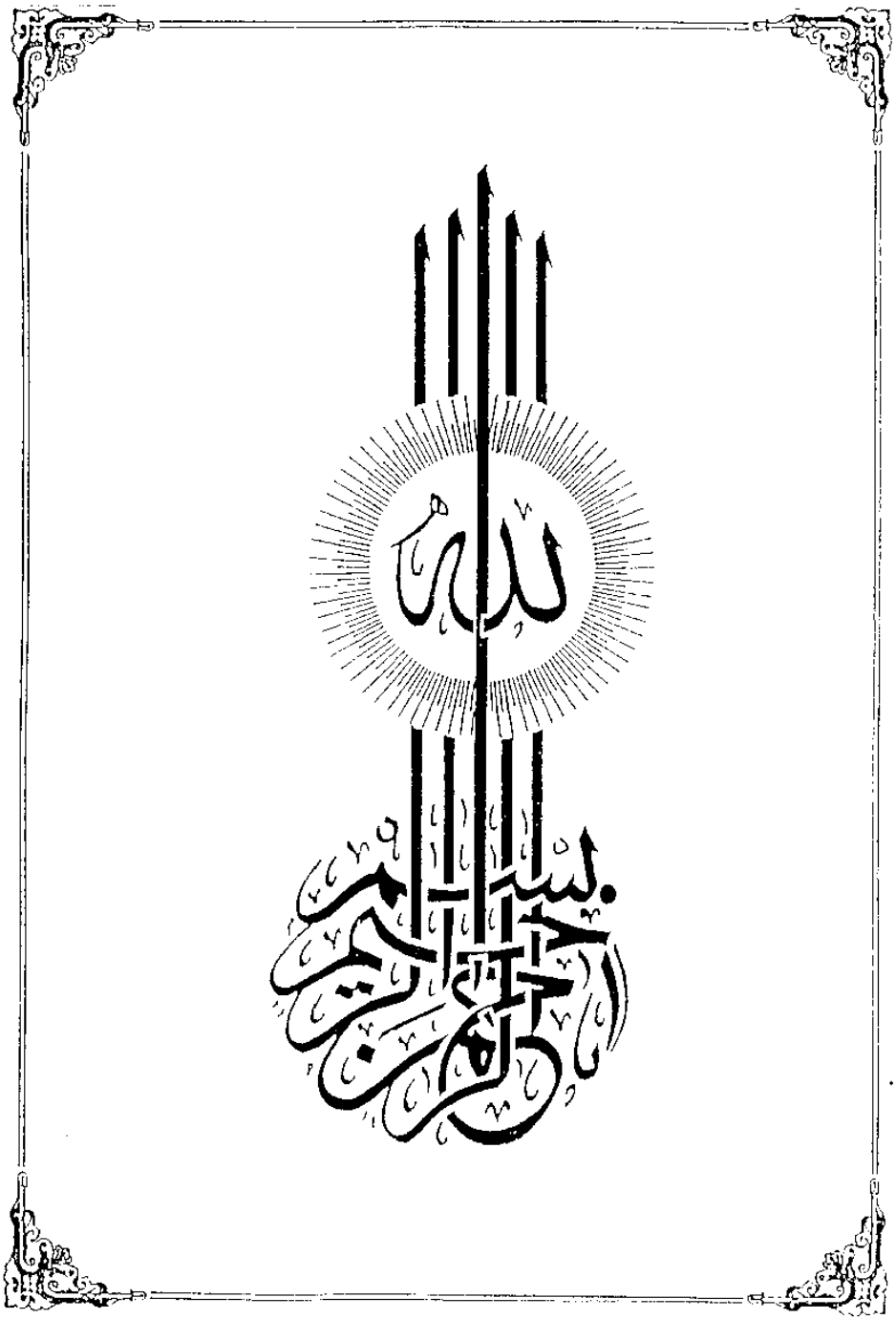
صدق الله العظيم



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Patients with diabetes mellitus not being allowed free glucose or sucrose intake, some are allowed sweets and jams containing artificial sweeteners, as fructose, sorbitol, aspartame, or saccharine, instead.

In view of its decreased insulin stimulation and reduced perturbation on plasma glucose response to sugar ingestion, fructose would seem superior to sucrose and glucose as a dietary sweetening agent (Bohannon,et al., 1978).

Sorbitol is a sugar alcohol of slow absorption from the gastrointestinal tract, this allows it to serve as a sweetening agent, without marked elevation in the blood glucose level (Joslin,1973).

Sucrol is an artificial sweetener composed of equal parts of sorbitol and mannitol.

Aspartame is a nutritive sweetener (L-aspartyl-L-phenyl alanine methylester), when given orally, induces no increase in blood glucose concentration. So that ingestion of aspartame sweetened beverages by fasting subjects, with or without diabetes does not affect blood glucose homeostasis (Horwitz et al.,1988).

AIM OF THE WORK

The aim of the work is to evaluate the acute effect of oral fructose, sucrol, and aspartame on blood glucose level, in healthy and diabetic subjects as compared to that of glucose ingestion.

The study will comprise 30 subjects, 20 diabetic patients (10 insulin dependent diabetics and 10 non-insulin dependent diabetics), and 10 healthy control subjects with no family history of diabetes mellitus

Each patient will be subjected to:

- Full medical history.
- Thorough medical examination.
- Estimation of blood glucose level after 14 hours fasting and then 1/2, 1, 1 1/2, and 2 hours following each sweetener, done on different days , one on each day.

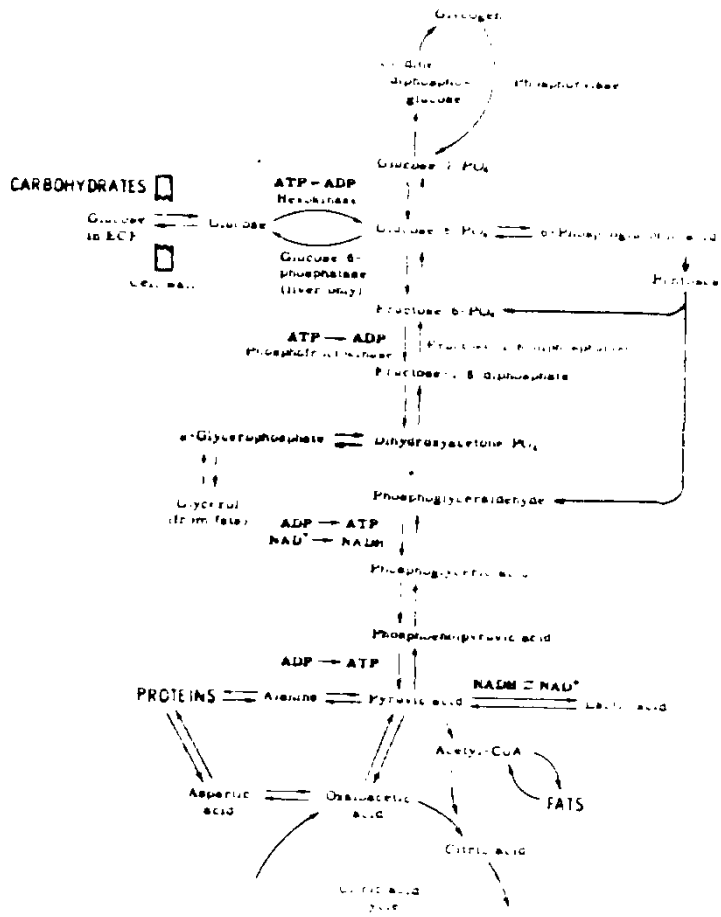
REVIEW OF LITERATURE

ROLE OF INSULIN IN CARBOHYDRATE METABOLISM

The principal product of carbohydrate digestion and the principal circulating sugar is glucose. The normal fasting level of glucose in peripheral venous blood, determined by the highly specific glucose oxidase method, is 60-80 mg/dl. In arterial blood the glucose level is 15-30 mg/dl higher than in venous blood (Ganong,1983).

Once it enters the cell, glucose is normally phosphorylated to form glucose-6-phosphate, the enzyme that catalyzes this reaction is hexokinase. In the liver there is in addition an enzyme called glucokinase, which has greater specificity for glucose and which, unlike hexokinase is increased by insulin and decreased in starvation and diabetes. The glucose-6-phosphate is either polymerized into glycogen or catabolized. The steps involved are outlined in fig. (1).

The liver is quantitatively the most important site of insulin action in the disposal of an oral glucose load. Since glucose is absorbed via portal system, the extent to which an oral glucose load is available for uptake by peripheral tissues depends on its escape from the splanchnic bed. During the 3 hour period following ingestion of 100 gm of glucose, approximately 60 gm are retained in the liver (Felig et al.,1975).



Outline of the metabolism of carbohydrate in cells showing some of the principal enzymes involved

Fig (1)

The glucose retained within the liver is used for glycogen and triglyceride formation. In fact the liver is quantitatively a far more important site for conversion of dietary carbohydrate into fat than is the adipose tissue. The total amount of glucose escaping hepatic uptake (40 gm) exceeds the basal rate of hepatic glucose output by only 15 gm. Thus, the total amount of glucose made available for peripheral (non hepatic) insulin dependent utilization is only 15 percent of the ingested food Table 1).

Hepatic uptake	60 gm.
- Glycogen synthesis.	
- Triglyceride synthesis.	
- Glycolysis.	
Hepatic glycogen sparing.	10-15 gm
- Uptake of glucose ingested by non-insulin dependent tissues (brain, blood cells thereby sparing liver glycogen.	
Increased peripheral utilization of glucose	15 gm
Insulin dependent glucose uptake by fat and muscle tissues.	

Table (1) Disposal of 100 gm of oral glucose in a normal individual.

A 100 gm glucose load is, however, not representative of either the magnitude of carbohydrate intake or the magnitude of blood glucose excursions observed in healthy individuals ingesting mixed meal.

The blood glucose level at any given time is determined by the balance between the amount of glucose entering the blood stream and the amount leaving it. The principal determinants are therefore the dietary intake, rate of entry the cells of muscle, adipose tissue and other organs, and glucostatic activity of the liver. (Sanberg, 1983).

In circumstances of mixed meal intake, the blood glucose in normal man generally varies by no more than 30 to 40 mgm per 100 ml over 24 hours not exceeding 140 dl (Service et al.,1970

True "tight control" of blood glucose regulation is determined by the exquisite sensitivity of the liver to small increases in insulin secretion. When the blood glucose rises by only 10 to 15 mg/dl, there is 50 to 100 percent increase in peripheral insulin levels and a virtually complete inhibition of hepatic glucose output (i.e. sparing of hepatic glycogen with no increase of peripheral glucose utilization (Felig,and Wahren,1971).

Thus as compared to the liver, muscle and adipose tissues represent relatively minor sites for disposal of large glucose loads, and are less sensitive than the liver with respect to small increase in plasma insulin. Nevertheless, with significant peripheral hyperinsulinemia, glucose uptake by adipose and muscle tissue helps to minimize the fluctuations in systemic blood glucose level.

The rise in insulin which accompanies carbohydrate feeding acts not only to promote glucose uptake and storage by the liver but also serves to inhibit gluconeogenesis. This action of insulin involves inhibition of hepatic uptake of alanine, the key gluconeogenetic precursor.

Interestingly, the inhibition of gluconeogenesis requires greater concentrations of insulin than does inhibition of glycogenolysis (Chiasson et al.,1976).

In addition to regulating carbohydrate disposal in the fed state, the basal concentration of insulin plays an important role in maintaining glucose homeostasis following an overnight fast. By its restraining effects on hepatic glycogenolysis and gluconeogenesis and its ability to minimize the stimulatory influence of glucagon on these processes, the basal insulin level insures that glucose production is maintained within relatively narrow limits. In this manner glucose is made available to the brain while hyperglycaemia is prevented.