Types of Diabetes Mellitus and Their Treatment

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Definition

THE DISTINCTIVE characteristics of diabetes mellitus are those caused by deficient metabolism of glucose. Disorders of a vascular, infectious, endocrine or chemical nature commonly co-exist.

Subnormal capacity for utilization of glucose is the most obvious feature of the disease. This results in persistent hyperglycemic glycosuria, deficient glycogen synthesis, and symptoms due to loss of glucose in the urine. The disease shows strong hereditary tendencies, is associated frequently with obesity at onset and with vascular degeneration in its course. It becomes more severe, as a rule, the longer it exists. It is usually of idiopathic origin and permanent, although exceptions may occur.

The anomaly of glucose metabolism with ketosis is capable of control by diet and insulin, but the course of the disorder and the arteriosclerotic complications are not affected to any major degree.

Clinical Varieties

ALL DISORDERS encountered in clinical practice which are suspected of being or known to be diabetic may be subdivided into four main groups. This classification is quantitative rather than qualitative. It takes into account only the extent of the defect of sugar metabolism presumed to exist. Causative factors are not differentiated because almost all diabetes is of idiopathic origin in the present state of knowledge. After diagnosis is established and severity measured, appropriate management is determined by the degree of diabetes found to be present. This grouping attempts to be useful from the standpoints of recognition and therapeutic application, practical rather than academic.

The outline shown in Table I describes different types of diabetes according to severity and preferential methods of management. In the discussions which follow, this classification will be observed and each of the varieties and its treatment considered.

TABLE I

CLASSIFICATION OF DIABETES MELLITUS BY TYPE *

TYPE OF DIABETES	CHARACTERISTICS	MANAGEMENT
I. UNPROVED	Accidental discovery of sugar in urine. Symptoms doubtful or absent.	Accurate diagnostic study. No treatment if proved innocent.
II. MILD	Persistent hyperglycemic glycosuria. Symptoms usually absent or slight. Recent onset or older, obese patients.	Desugarization by diet. Increase diet as tolerated. Weight reduction often advisable.
III. SEVERE		
A. Moderate	Typical diabetic symptoms in history. Sugar uncontrollable by diet alone. Older patients needing insulin.	Diet of moderate glucose value. Maintenance of ideal weight. Protamine insulin once daily.
B. Severe	Most young and thin patients. Postcibal sugar not controlled or nocturnal insulin shock with protamine zinc insulin.	Separate doses of protamine and ordinary insulin. Protamine insulin mixtures. Globin insulin.
C. Labile ("Brittle")	Many children, some adults. Diabetes of long duration. Unpredictable waves of sugar or insulin shock.	Multiple injections daily. Insulin mixtures twice daily. Some glycosuria unavoidable to prevent insulin shock.
IV. ACUTE COMPLICATIONS	Acidosis of any degree. Acute infections. Management during surgery. Cardiac decompensation.	Dependence on ordinary insulin in frequent dosage. Large doses often necessary. 6-hour emergency program preferable.

* Reprinted from *Diabetes Mellitus in General Practice*, (Arthur R. Colwell, 1947) by courtesy of The Year Book Publishers, Inc., 304 South Dearborn St., Chicago.

Group I

Unproved Diabetes—Diagnosis

LIKE ALL OTHER diseases, diabetes mellitus must be diagnosed before it is treated. This simple fact seems too obvious for mention, but violation of the principle is altogether too common in diabetic practice. Strict adherence to it can prevent much incompetent and ineffective management, particularly in very mild and borderline situations.

Pre-diabetic and potential diabetic states undoubtedly exist, probably more commonly than modern diagnostic methods can reveal, possibly as often as manifest diabetes can be detected. Yet if ordinary stigmata of diabetes cannot be found with the aid of any of the excellent diagnostic methods which are available, it is probably unwise to impose any form of treatment. Instead, frequent observation seems indicated, because there appears to be no advantage in treating subclinical forms of the disease, and because treatment may do harm if diabetes does not exist. Conversely, if detectable diabetes mellitus is present in fact, such casual and inconsistent treatment as is usually prescribed in doubtful situations is not good enough to prevent progress in severity in a phase when there is much to be gained by careful and consistent control.

Therefore, the primary objective in good diabetic management consists of an unequivocal decision regarding the presence or absence of any demonstrable impairment of sugar-

utilizing capacity. No treatment is indicated if none is found; good control, if any is found.

From the practical standpoints of diagnosis and treatment of human patients who show sugar in the urine, differentiation between non-diabetic and diabetic meliturias is necessary. For almost all situations methods of study are available which, when properly applied and interpreted, are capable of doing this.

NON-DIABETIC MELITURIAS

Excessive sugar in the urine which does not originate in a diabetic type of disorder is ordinarily innocuous and may be ignored when proved to be non-diabetic. The various meliturias of this type may be recognized by a variety of characteristics, all different from those of diabetes mellitus.[1] They all should be considered before treatment for an asymptomatic melituria is imposed.

Identification of sugar in urine

Sugars other than glucose may be identified by their fermentation, rotary and osazone characteristics. Glucose is a fermentable, dextro-rotary reducing substance. Any sugar which fails to ferment with yeast or which is not dextro-rotary, therefore, is not glucose, even though, like glucose, it reduces copper in alkaline solution. If it is proved not to be glucose, diabetes mellitus does not exist. Confirmatory proof can be obtained by identification of its osazone crystals formed by reaction with phenylhydrazine and, for certain reducing substances, by other specific reactions.

Table II summarizes the optical and fermentation characteristics of sugars which are commonly found in urine, including glucose. In addition to the use of these properties

for identification of sugars, the following specific reactions may be useful in doubtful situations.

Osazone crystals: Most sugars, when heated with phenylhydrazine and a little acetic acid, combine to form characteristic osazones which crystallize in identifiable forms at given rates. The osazone crystals separate from hot solutions at different rates (from ½ to about 30 minutes) in the following order: mannose, levulose, glucose, galactose, sucrose. The osazone of lactose remains in solution when it is hot. Melting points of the various crystals range from 196° to 206°. They can usually be recognized by microscopic study.

Reduction of alkaline copper solutions: Benedict's solution is reduced in a few hours at room temperature (and in 10 minutes at 50° to 60° C.) by pentoses, levulose

TABLE II

FERMENTATION AND ROTARY CHARACTERISTICS OF VARIOUS SUGARS FOUND IN URINE *

SUGAR	FERMENTATION WITH YEAST	SPECIFIC ROTATORY POWER	
		DEXTRO-	LEVO-
Pentoses	No	None	None
Glucose	Yes	53° (1)	
Levulose	Yes		92°
Galactose	Yes	80.5°	
Lactose	No (2)	55°	
Sucrose (3)	Yes	66.5°	

(1) B-hydroxybutyric acid is levo-rotatory. Urine containing it along with glucose, therefore, shows a different rotatory power.

(2) With certain yeasts containing lactase slow fermentation may occur.

(3) Sucrose does not reduce alkaline copper solutions until after hydrolysis.

* See footnote, page 5.

and mannoheptulose. Heat is required for most of the other sugars unless they are present in strong concentration.

Exton's reagent: At constant temperatures various sugars reduce the disodium-dinitro-salicylate reagent developed by Exton at different rates.[2]

Seliwanoff reaction: Urine is boiled with equal amounts of 25% hydrochloric acid, a few crystals of resorcinol are added and the mixture boiled actively for a few seconds more. If levulose is present, a red color and a dense reddish-brown precipitate which is soluble in alcohol will form.

Bial test: Pentose gives a green solution and precipitate on gentle heating of urine containing it with about equal parts of a reagent containing orcinol 1.5 gm., 10% ferric chloride 2 cc. and fuming hydrochloric acid 500 cc.

Alkaptonuria: Urine containing homogentisic acid turns dark brown or black on standing, on addition of alkali, or after ammoniacal decomposition. This may occur even before voiding.

Conjugated glycuronic acids: These may reduce alkaline copper solutions if present in large quantities after ingestion of certain drugs such as phenol, menthol, chloral hydrate, camphor and turpentine. They are not fermented by yeast.

Mannoheptulose: After ingestion of moderate quantities of avocado Blatherwick has found this sugar in the urine of normal individuals in amounts sufficient to reduce Benedict's solution even without heat.[3] It is not fermentable by yeast.

Barfoed's reagent: This reagent, a solution of cupric acetate in acetic acid [$Cu(OOCCH_3)2$] is reduced to

cupric oxide less readily by hexodioses than by monoses. It is, therefore, useful in distinguishing lactose from glucose and other monosaccharides. The mucic acid test may also be used for the identification of lactose, and the Tollens test (phloroglucinol-hydrochloric acid) for galactose.

Mycological methods: Castellani has described laboratory methods (which are not in common use) for the identification of various sugars by their fermentation characteristics with specific bacteria and fungi.[4]

The positive chemical identification of any reducing substance other than glucose in the urine removes all obligation to perform other diagnostic procedures. All non-glycosuric meliturias are considered to be harmless, inborn errors of metabolism or else normal secretion of non-utilizable reducing agents. These anomalies are all relatively uncommon, however, with the possible exception of the lactosuria of late pregnancy and lactation. Innocent glycosurias are encountered much more frequently than any of them. When the urinary sugar is determined to be glucose, further distinction between renal glycosuria and diabetes mellitus is mandatory for accurate diagnosis.

Renal glycosuria

It has been estimated that about 1% of all spontaneous, persistent, glycosurias are non-diabetic. Renal glycosuria (sometimes inaccurately called "renal diabetes") is an innocuous disorder of renal physiology in which small to moderate amounts of glucose are excreted more or less constantly in the urine of otherwise normal subjects. The amounts are seldom very large (usually 1 to 2% of the total glucose

intake),[5] associated blood sugar concentrations are normal or slightly low, diabetic symptoms almost never are present, a strong hereditary tendency exists, the disorder is non-progressive, and the glycosuria is virtually unaffected by insulin administration in dosage sufficiently great to result in insulin reactions with hypoglycemia. Phlorhizin causes a similar but more intense form of glycosuria.

Renal glycosuria is very common in pregnancy.[6] It may be intermittent or continuous, depending on the diet and the renal defect which permits abnormal glycosuria despite normal blood sugar levels. A majority of pregnant women exhibit some degree of glycosuria following the ingestion of 100 gm. glucose in a single dose. Williams and Wills found repeated glycosuria in 5.4% of 640 unselected pregnant women.[7] Rowe, Gallivan and Mathews found it occasionally in 35% of their series.[8] Richardson and Bitter observed it twice as often as during the immediate post-partum period.[9] Small doses of phlorhizin (2 mg.) injected intramuscularly cause abnormal glycosuria in fully 90% of gravidae,[10] a fact which has led, in the past, to the use of phlorhizin for the diagnosis of pregnancy. Abnormal amounts of glucose in the urine have been detected at lower blood sugar concentrations than normal during pregnancy as compared with the post-partum period in the same patients. In addition a slight lag in the blood sugar curve following 100 gm. glucose orally is observed on the average in pregnancy.[11] Glycosuria of a renal type may, therefore, be considered as physiological during pregnancy, disappearing after delivery.

Diabetes mellitus may also appear during pregnancy and gestation take place among diabetics. Renal glycosuria may also occur in diabetic patients during pregnancy. Its incidence serves to emphasize the importance, particularly