Staff Meeting Bulletin
Hospitals of the . . .
University of Minnesota

Glycosuria

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STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
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William A. O'Brien, M.D.

I. LAST WEEK

Date: March 18, 1937

Place: Nurses' Hall
Recreation Room

Time: 12:15 to 1:20

Program: Movie: Pacing the Thoroughbreds

Abstract: Anuria

Case Reports: 2

Present: 114

Discussion: A. K. Doss
E. T. Bell
I. McQuarrie
C. J. Watson

II. MOVIE

Title: Sun Chasers

Released by: Paramount Film Corp.

III. ABSTRACT

GLYCOSURIA

B. A. Watson

Definition

Glycosuria is the excretion of dextrose in the urine. (See discussion of low renal threshold for glucose.)

Incidence

In routine urine examinations, glycosuria will be present in from 1 to 2% of the cases.

Significance

From 16 to 20% of patients showing glycosuria on one examination will have a definitely disturbed carbohydrate metabolism as demonstrated by the glucose tolerance test.

Tests for glycosuria

1. Benedict's - qualitative
2. Haines' - qualitative
3. Benedict's - quantitative

All the above tests depend upon the fact that in strongly alkaline solution glucose reduces cupric hydrate to cuprous hydrate (yellow) or cuprous oxid (red).

1. Benedict's test: (More sensitive than Haines')

Put 5 c.c. of reagent in tube, heat to boiling, add 8 to 10 drops of urine. Keep at vigorous boiling for 1 to 2 minutes, then cool slowly. Glucose, if present, may give red, yellow or green color. Traces, if present, will give color on cooling. In lieu of boiling individual tubes over flame, place tubes in boiling water bath for period of 5 minutes. Will detect .015 to .02% dextrose in urine.

2. Haines' test:

Put 4 c.c. of Haines' solution in test tube, boil, examine carefully for a precipitate, and finding none add 6 to 8 drops of urine while keeping reagent hot but not boiling. Yellow or red precipitate shows the presence of sugar. A flocculent sediment or simple discolorization should not be mistaken for a positive reaction. The test will detect about .1% dextrose.

In recording readings, it is suggested sugar be recorded merely as present or absent as neither test is in any sense

quantitative. However, it may be recorded as follows if some indication of the amount of sugar in the urine is desired.

S.T. - slight trace: No reduction is evident during 2 minutes' boiling, or 5 minutes in water bath with 8 to 10 drops of urine, but it appears upon cooling.

T. - trace: With 8 drops of urine, the reaction occurs after about one minute's boiling.

M.A. - moderate amount: With 8 to 10 drops of urine, the reaction occurs after 10 to 15 seconds boiling.

L.A. - large amount: Reduction occurs almost immediately after adding 2 drops of urine to boiling reagent.

3. Benedict's quantitative test:

For purposes of brevity this method will not be discussed.

Reducing substances other than glucose which may be found in the urine:

a. Less common sugars, e.g. levulose, lactose, galactose, maltose and pentose.

Differential - glucose will ferment.

b. Certain normal substances if in excess in the urine may reduce the solution, especially mucin, uric acid and creatin. (Benedict's solution is not reduced by uric acid, creatinin, chloroform or the aldehydes.- Todd-Sanford)

Differential: Dilute urine if concentrated and use no more than in the regular test, e.g. 6 to 8 drops of urine. If glucose is present, reduction will still occur.

c. Drugs such as chloral, chloroform, acetanilid, morphine, sulfanol, salicylates, balsams excreted with glycuronic acid and formaldehyde after taking urotropin.

Differential: History of drug ingestion and stopping drugs previous to tests.

4. Certain rare metabolic disturbances:

a. Homogentisic acid or alkaptonuria.

b. Dehydroxyphenylalanine or tyrosinosis.

Differential: Homogentisic acid turns dark quickly on exposure to oxygen.

Differential of glucose from other reducing sugars:

(1) Use of fermentation tube.

(2) Simpler fermentation test.

Obtain 100 c.c. of urine, take specific gravity, add 1/4 cake of yeast, allow solution to remain in a warm room over night, and again take specific gravity. If there is a difference in specific gravity readings, fermentation has occurred. By multiplying the differences in the specific gravity by .26, one may approximate the number of grams of glucose per 100 c.c. of urine.

Example:
1.030 - 1.018 = 12 x .26 = 3.12 gms. / 100 c.c.

Condition giving rise to Glycosuria:

A. Glycosuria occurring in the presence of normal blood sugar values.

B. Glycosuria occurring in the presence of abnormally high blood sugar values.

A. Glycosuria in the presence of normal blood sugar values may be caused by:

I. Low renal threshold for glucose.

II. True renal glycosuria.

III. Pregnancy.

I. Low renal threshold for glucose

When the blood passes through the kidney glomeruli, part of the glucose is filtered through glomerular membranes and reabsorbed in the tubules. The reabsorption mechanism is not perfect normally so that on an average about 140 mg. of glucose are found in the 24 hour specimens of normal men. This amount is so small that ordinary clinical methods will not detect it. If the glucose of the blood rises above 140 to 180 mg. (depending on author), the reabsorbing mechanism of the tubules fails to keep pace with the filtration and some glucose appears in the urine. The point where this phenomena takes place is called renal threshold. Why the ability of the tubules to reabsorb glucose varies so widely in otherwise normal people has not been explained. Certain facts have come from our own personal experience with a large number of glucose tolerance tests done on cases of glycosuria (531 cases, 1931-36).

a. This condition is in no way associated with diabetes mellitus.

b. Renal threshold may be as low as 110 and occasionally lower.

c. The renal threshold may vary in the same individual from time to time.

d. Certain toxic substances and drugs may temporarily alter the renal threshold.

To obtain the true renal threshold for glucose, the only accurate method is to insert catheters into the ureters before ingestion of glucose; then, testing the blood and urine every few minutes until glycosuria occurs.

Because of the normal variations in renal threshold, a distinction is made between a lowered renal threshold, which is not uncommon (11% in our normal series), and true renal glycosuria.

II. Renal glycosuria is extremely uncommon but the term is frequently misused for the condition of lowered renal threshold discussed in the preceding paragraph. In the Diabetic Clinic of the Montreal General Hospital, 4,000 cases of glycosuria were investigated and only 7 cases conformed to the criteria listed below to enable a diagnosis of renal glycosuria.

a. Glycosuria must be constant.

b. Type of sugar in urine must be glucose.

c. Little or no relation between intake or excretion of sugar.

d. No clinical signs or symptoms of diabetes.

e. Ideally no family history of diabetes.

f. Fasting blood sugar and glucose tolerance test must be within normal limits.

g. Utilization of sugar as determined by the respiratory metabolism must be normal.

h. The individual must not subsequently develop diabetes.

III. Pregnancy particularly during the first three months and the 7th to 9th months though it may occur at any time. (Fermentation means glucose and glucose is indication for glucose tolerance test.)

B. Glycosuria in the presence of an elevated blood sugar may be caused by:

I. Diabetes mellitus (most common).

II. Endocrine dysfunctions: pituitary, thyroid, adrenal.

III. Alimentary hyperglycemia, e.g. the blood sugar rises above the upper limits of normal when an excess of carbohydrates are ingested. (This term should entirely replace the term - alimentary glycosuria - which is a misnomer.)

IV. "Cerebral hyperglycemia," due to increased intracranial pressure, inflammatory diseases of the central nervous system or brain tumor.

V. Acute infections. (The glycosuria produced here may last weeks or months.)

VI. Hemochromatosis or bronze diabetes.

VII. Coronary heart disease.

VIII. Gallbladder or liver disease.

IX. Tumors of the pancreas that may destroy islets of Langerhan's.

X. Acute pancreatitis.

XI. Intravenous glucose administration.

XII. Drugs, such as adrenalin, morphine, carbon monoxide and anesthetics may cause a rise in blood sugar with resultant glycosuria.

When glycosuria occurs, one should attempt to classify it as to time of its occurrence.

I. Transient glycosuria, e.g. appearing possibly once every other day, once a week, etc. This type if undiagnosed may progress into the second type.

II. Postprandial glycosuria, e.g. occurring after one or all meals but usually clearing before the next meal. This may progress into the third stage.

III. Persistent glycosuria, e.g. occurring in the urine at all times. This type may be further classified as follows:

a. Persistent glycosuria without clinical signs and symptoms.

b. Persistent glycosuria with clinical signs and symptoms.

c. Persistent glycosuria with clinical signs and symptoms and acidosis.

"a" needs further study before treatment, but "b" and "c" are definite evidence of diabetes mellitus.

History

Once the diagnosis and type of glycosuria are established, the history may be an important aid in differentiating "innocent glycosuria" from diabetes mellitus. Certain important points are:

1. Family history of diabetes or "renal glycosuria." (The latter as well as the former is sometimes seen in members of the same family.)

2. Presence or absence of the three P's of diabetes--polyuria, polydipsia and polyphagia.

3. Recent gain or loss in weight. (Either may occur, the former more usual in older individuals with mild diabetes.)

4. History of unexplained fatigue, neuritis, mild visual disturbances, recent boils, carbuncles or acute infections.

5. Drug ingestion that may give reducing substances in the urine.

6. When specimen was collected? How long after eating and what food was eaten at the meal preceding the test?

7. Cleanliness of urinary receptacle? (Cough syrups, lotions, etc. may give reduction.)

The history should be followed by a thorough physical examination to eliminate the majority of causes of glycosuria listed under "Glycosuria occurring with an elevated blood sugar."

Let us now consider a patient in our office, seen for the first time because an insurance examiner has shown the presence of a reducing substance in the urine.

Don'ts

1. Don't tell the patient to pass and save a urine specimen on arising the next morning and return it to you for examination. (While this is a common practice, it should be noted that the time one is least likely to find sugar is when a patient has not eaten for a matter of 12 to 14 hours.)

2. Don't test the urine and finding no glycosuria dismiss the patient with "Maybe you ate too many sweets or pastries before the other test and as long as I find no evidence of sugar don't worry."

3. Don't forget the possibility of raised renal threshold for glucose. (The commonly accepted threshold at which the kidney tubule is unable to keep glucose from the urine is 140 to 180 mg. This figure varies in the normal individual from time to time. In order people and certain kidney diseases, such as acute nephritis, arteriosclerotic kidney disease, etc., the renal threshold is appreciably raised so that even with a blood sugar of 200 to 300, there may exist true clinical diabetes mellitus without any glycosuria.)

Do

1. Repeated urine tests on specimens collected 2 hours after a high carbohydrate meal to be certain a reducing substance is or is not present in the urine. Also check several 24 hour specimens.

2. If a reducing substance is found and there is any doubt that it is not glucose, a fermentation test may be done.

3. When the presence of glucose is demonstrated, have patient void about 2 hours after each meal saving about 5 c.c. of the sample in a Wassermann tube and return it to you for examination. This will determine whether transient, postprandial or persistent glycosuria exists. (Patient should be warned not to attempt to void before the 2 hour period as urine containing glucose may be lost.)

4. Careful history and physical examination to attempt to rule out the presence of other conditions causing glycosuria other than diabetes mellitus.

5. If persistent glycosuria is found, determine immediately if acidosis exists.

6. A glucose tolerance test at the slightest indication that even a mild disturbance in carbohydrate metabolism is present.

Glucose Tolerance Tests

Precautions before test:

1. Ascertain whether or not patient is on a normal diet. The diet preceding a tolerance test may influence the outcome. As for example, a patient on a markedly restricted carbohydrate, high fat diet might give evidence of a diminished tolerance when in reality a normal carbohydrate metabolism existed.

2. Be certain patient is not suffering from carbuncles, boils, acute upper respiratory infections, etc. when the test is done. (In our experimental observations it has been demonstrated that any of the preceding conditions might give evidence of a diminished glucose tolerance as long as 2 weeks after recovery from such infection.)

3. No exercise or smoking during test as this may raise the blood sugar.

4. Water intake during the test should be limited. (In our series, a maximum of 3 oz. of water was allowed after the ½, 1 and 2 hour blood samples.)

Technique:

The patient is instructed to fast from 6 P.M. of the evening before the test until 8 A.M. the morning of the test when he presents himself at the laboratory. A fasting blood and urine sample are obtained, then 100 gm. of glucose dissolved in 250 c.c. of water is ingested, and blood and urine samples are obtained at intervals of ½, 1, 2 and 2½ hours after the drink.

The blood in this hospital is analyzed for glucose by the Gibson micromethod, the urine is qualitatively tested for glucose with Benedict's solution.

The Gibson micromethod, while it is designated primarily for capillary blood sugar determinations, lends itself to venous blood sugar determinations as well. The gathering of such a small amount of blood by an inexperienced person on the wards may introduce a factor that may lead to considerable error.

Interpretations of Results:

Table I gives the higher normal values from the literature as compared to 83 normal subjects having glucose tolerance tests at the Student Health Service.

Table I

	Fasting	½ hr.	1 Hr.	2 hrs.	2½ hrs.
Published normals	120	180	160	130	120
83 normal subjects	92	135	114	91	83

(Analyses are on venous blood)

Table II compares difference between venous and cutaneous blood sugars as determined by Cavette and Seljeskog.

	Fasting	½ hr.	1 Hr.	2 hrs.	2½ hrs.
Cutaneous blood sugars	95	165	137	97.7	79.9
Venous blood sugars	92.2	151	122	85.4	78.4
Difference	2.8	14	15	12.3	1.5

In a large series of glucose tolerance tests, one sees many different types of curves. Table III gives examples of the most common disturbances encountered.

	Curve of Slow Absorption	Grade I	Grade II
Fasting	90	110	110
½ Hour	100	220	220
1 Hour	160	140	190
2 Hour	140	120	160
2½ Hours	88	100	130

	Grade III	Grade IV	Grade V
Fasting	120	180	200
½ Hour	240	310	350
1 Hour	200	300	360
2 Hour	200	300	400
2½ Hours	160	300	450

Curve of slow absorption:

Probably due to failure of glucose to be absorbed into blood stream as rapidly as normal, hence a delayed peak.

Grade I - curve of diminished tolerance showing only initial rise above normal usually with glycosuria in at least one specimen.

Grade II - curve of mildly diminished tolerance and assimilation usually with glycosuria in one or more urine specimens.

Grade III - curve of moderately severe diminished tolerance and assimilation, usually with 3 or 4 urine specimens showing glycosuria with or without clinical symptoms.

Grade IV - curve of severely disturbed tolerance and assimilations usually with glycosuria in all specimens and more often than not clinical symptoms.

Grade V - curve showing diminished tolerance and little evidence of assimilation as the blood sugar is rising at the 2½ hour period.

It is well to remember that Grade I may be caused by a boil or carbuncle or some other low grade infection.

Grades II and III may be caused by pituitary, thyroid, adrenal dysfunctions, and also by central nervous system lesions, such as tumor, etc.

Grades II, III, IV and V may be associated diabetes; IV and V more commonly.

In closing, it is well to remember if the fasting and 2½ hour blood sugar approximate each other, regardless of the height of the curve, that one is dealing with some disturbance in carbohydrate metabolism other than diabetes mellitus.

CONCLUSIONS

1. Incidence of glycosuria on routine examination, 1 to 2%.

2. Fifteen to 20% of patients showing glycosuria are found to have disturbed glucose metabolism as judged by the glucose tolerance test.

3. Glycosuria may occur under only 2 conditions regardless of underlying disease:

   a. In the presence of a lowered renal threshold for glucose.

   b. With an elevated blood sugar, e.g. above renal threshold for glucose.

4. The fact that there may be an elevated renal threshold for glucose in certain diseases should not be overlooked and that a patient with diabetes may not have glycosuria.

5. A simple fermentation test to differentiate glucose from other reducing substances is given.

6. Glycosuria should be considered evidence of diabetes mellitus until proved otherwise.

7. Determining whether glycosuria is transient, postprandial or persistent will aid in determining severity of underlying disease.

8. Glucose tolerance tests done under carefully controlled conditions are an invaluable adjunct to the early diagnosis of a disturbed carbohydrate metabolism.

9. If fasting and 2½ hour blood sugars are the same, regardless how high the others may go, it is unlikely that diabetes exists.

10. Figures for normal glucose tolerance tests are given.

11. Cutaneous blood has a higher dextrose content than venous blood.

12. Early diagnosis of diabetes means early treatment with good prognosis.

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IV. GOSSIP

The Women's Field Army of the American Society for the Control of Cancer in Michigan actively solicited funds on street corners and in business houses to raise their war chest....The Detroit Receiving Hospital likes Minnesota Interns and their staff gives great credit to Chairman Dr. J. C. Litzenberg, of our Intern Committee, for cooperation in the selection of the right men....Ray Allen, Minnesota graduate, graduate student in anatomy and urology, and one-time associate of the Northwest Clinic at Minot, N.D., is the new dean of Wayne University College of Medicine. He is well liked and making unusual progress.. ..Detroit still remembers our chief pediatrician, Irvine McQuarrie, through his former connection at the Henry Ford hospital. The pediatricians in Detroit invariably inquire for him....Minnesota's most prosperous graduate in Detroit is Mont Wickham. His new home on the river-lake point is worth traveling miles to see....There were many Minnesota representatives, past and present, at the annual meeting of the American Association of Pathologists and Bacteriologists in Chicago. Among others former intern Charles Craft spoke of the joys of being at Minnesota. He is returning after a stay with Dr. Ivy at Northwestern, much reduced in girth....But all is not so well. In some places they are getting fed up on Minnesota's self-estimate of greatness in all fields. Perhaps one feels this more in Michigan when athletics are discussed.....One pathologist, Sabin, of New York, in presenting his work on virus effects in the nervous system, scored first for best presentation of a paper. He spoke after the manner of Milton Cross. Much discussion on experimental malignancy was heard with chief interest in malignant degeneration of virus papillomas in rabbits. This subject will be discussed by Dr. Robert Green at the next meeting of the local association of the Cancer Research.