Papers and Originals

Renal Glucose Threshold Variations with Age

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Each year some millions of urine samples are examined routinely for glycosuria in hospitals, clinics, and practices to screen patients for diabetes mellitus; and many more are tested by sufferers from this condition to assist in the management of their individual cases. Such tests rightly assume that there is some relation between the concentration of glucose in the blood and that in the urine. Thus the concept of the "renal threshold for glucose," though not strictly correct from a physiological point of view, retains a practical utility in these clinical situations. Despite this, surprisingly little attention is paid to its variations in populations or to its level in individual patients. In many important texts either there is no quantitative indication of the blood-sugar significance of glycosuria (Best and Taylor, 1961; Danowski, 1964; Dunlop *et al.*, 1964) or there is a choice of values for the renal threshold quoted as 170 mg./100 ml. Loeb (1959), as 180 mg./100 ml. by Lawrence (1955), Lister (1959), and Houston *et al.* (1962), and as 200 mg./100 ml. by Ellenberg and Rifkin (1962). Peters and Van Slyke (1949), who examined this question in some detail, give the normal range as 140 to 200 mg./100 ml. It has been suggested that the renal threshold may be raised in older diabetics (Lawrence, 1955; Loeb, 1959) and that it is higher in women than in men (Steinberg, 1965), while Robertson and Gray (1953) have studied some diabetics with low renal thresholds.

With regard to the management of diabetes, Lawrence (1955) and Joslin *et al.* (1959) are among the few who emphasize the importance of establishing the renal threshold in individual cases.

So far as detecting diabetes is concerned there is a widespread realization that finding glucose in a random postprandial urine sample is far from establishing directly a diagnosis of diabetes. In most cases subsequent glucose-tolerance tests will show that the glycosuric person is not diabetic (College of Gen. Pract., 1962; Butterfield, 1964; Keen, 1964; Sharp, 1964).

In contrast to the non-diabetic glycosurics, the 1962 Bedford Survey indicated clearly that there were also many hyperglycaemic people without glycosuria in the population. The possibility that unrecognized hyperglycaemia might be an important factor in vascular disease (Keen *et al.*, 1965; Ostrander *et al.*, 1965; Kingsbury, 1966), and our clinical experience with established diabetics, in whom we found renal thresholds as low as 45 and 60 mg./100 ml. and as high as 320 mg./100 ml., stimulated us to re-examine the data about glycosuria from the Bedford Survey and consider them in terms of the detection and management of diabetes.

Definitions

Test for Glycosuria.—Clinistix (Ames Co.): the appearance of a blue colour on the test strip one minute after dipping in

the specimen shows the presence of glucose exceeding 0.1 g./100 ml.

Capillary blood sugar results two hours after 50 g. of glucose by mouth (arbitrarily divided into the following groups): normal <120 mg./100 ml.; hyperglycaemic >120 mg.; borderline diabetic 120-199 mg.; diabetic >199 mg.

Methods and Material

The subjects studied were adult citizens of Bedford not known to have any disturbance of carbohydrate metabolism. All persons on the Electoral Roll were asked to provide a specimen of post-breakfast urine and 25,701 people had their urine tested, of whom, excluding known diabetics, 4% were found to have glycosuria. These were termed the glycosurics.

An age/sex stratified random sample of 535 subjects drawn from the entire co-operating population underwent standard 50-g. oral glucose-tolerance tests. Blood sugar levels were estimated by a modification of the microferricyanide reducing method in the autoanalyser (Whicelow *et al.*, 1967) on capillary samples taken fasting and at 30, 60, 90, 120, and 150 minutes after the administration of a drink containing liquid glucose equivalent to 50 g. of dextrose monohydrate. It was possible to test for glycosuria the urine passed between 60 and 120 minutes by 295 randomly selected persons. Since the presence of any small quantity of sugar-free urine in the bladder before the glucose-tolerance test could have diluted the post-glucose glycosuria, the presence of glucose and not its concentration will be considered here. It should be pointed out, under these circumstances, that from the presence of glycosuria we can only deduce that the renal threshold was lower than the peak value found, and that in the absence of glycosuria the renal threshold was higher than the peak value.

The age/sex composition of the random sample and the subsample also tested for glycosuria are shown in Table I.

TABLE I.—Structure of the Random Sample

Age	Men		Women	
	Total	No. Tested for Glycosuria	Total	No. Tested for Glycosuria
20-29	46	25	48	26
30-39	43	23	49	25
40-49	46	27	45	25
50-59	43	35	48	23
60-69	38	20	48	37
70-79	39	25	42	27

Results

During the screening survey 4% of the population were found to have glycosuria (after breakfast) whereas 30% of the random sample subjects had glycosuria during the glucose-tolerance

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TABLE II.—Prevalence of Glycosuria at Survey and During Glucose-tolerance Test

Age	Men		Women	
	% at Survey	% at G.T.T.	% at Survey	% at G.T.T.
20-29	4.3	40	2.8	4
30-39	4.9	22	2.3	24
40-49	5.3	33	1.9	24
50-59	7.5	52	2.0	30
60-69	7.9	30	2.8	27
70-79	7.8	52	4.5	26

test. Table II shows the percentage of subjects in each group having glycosuria at the survey and during the glucose-tolerance test. At the survey, but not during the glucose-tolerance test,

FIG. 1.—Peak blood sugar levels during glucose-tolerance tests in random sample men. FIG. 2.—Peak blood sugar levels during glucose-tolerance tests in random sample women. FIG. 3.—Blood sugar levels two hours after 50 g. of glucose in random sample men. FIG. 4.—Blood sugar levels two hours after 50 g. of glucose in random sample women.

the prevalence of glycosuria rose with age in both sexes, and also was about twice as high in the men as in the women.

Figs. 1 to 4 show the peak and two-hour blood sugar levels during glucose-tolerance tests plotted against age for both sexes, indicating those subjects with and without glycosuria. The peak blood sugar (which usually occurred at 60 minutes) rose with age (Figs. 1 and 2) and there tended to be more people, especially women, who had sugar-free urine despite high blood sugar levels (over 180 mg./100 ml.) among the older age groups. There were a large number of young persons, particularly young men, with glycosuria despite low peak levels.

It will be seen from Figs. 1 and 2 that renal threshold values as low as 130 mg. and as high as 305 mg./100 ml. were found. There were 20 men with renal threshold values below 180 mg., and 9 lower than 160 mg., whereas 14 men had peak blood sugars above 180 mg. with no glycosuria (Fig. 1). Among the

women 12 had renal thresholds below 180 mg. and six below 160 mg., while 30 had peak blood sugars above 180 mg. with no glycosuria.

Discussion

Wide Variation of Renal Threshold: High Thresholds in the Elderly

It is clear that in many individuals the renal threshold was lower than 160 mg./100 ml. or higher than 200 mg./100 ml., and that it appeared to rise with age.

The postprandial blood sugars at the survey were probably much lower than after a test glucose load (Kenny and Chute, 1953) as is indicated by the higher prevalence of glycosuria after 50 g. of glucose. The prevalence of glycosuria was much higher among men than women at the survey but less so during the glucose-tolerance test (Table II). The best explanation for these findings would be that more men have on average lower renal thresholds than women, rather than that there is any difference in the sex incidence of diabetes, or that women diabetics had been removed from the survey group through the detection of diabetes at antenatal clinics, as was thought earlier.

Recognizing Diabetics in Clinical Practice

What do the foregoing results mean to the practitioner routinely testing the patients' urine to detect diabetes? Table III shows the probability that any postprandial urine test result indicates that the patient will be hyperglycaemic (see Definitions). It will be seen that young glycosurics are unlikely to have diabetes, but that, though older people are more likely to have diabetes if they have glycosuria, the absence of glycosuria does not preclude diabetes, particularly among women. If the patients are given a 50-g. glucose drink and the urine is tested for the presence of sugar between one and two hours later, not only will the number of false positives (persons with glycosuria and normal blood sugars) be greatly increased, but there is still a 10% chance that diabetics (see Definitions) will not have glycosuria, and that their diabetes will go undetected (Figs. 3 and 4).

TABLE III.—Probability of Diabetes in Glycosuric and Non-glycosuric Subjects

Subjects	Postprandial Glycosuria	Sex	% Likely to be Hyperglycaemic (2-hr. B.S. >120 mg./100 ml.)
Under 50 years	Negative	Men	7%
		Women	9%
	Positive	Men	11%
		Women	17%
50 and over	Negative	Men	15%
		Women	27%
	Positive	Men	35%
		Women	73%

Since diabetes is defined in terms of blood sugar levels (W.H.O. Expert Committee, 1965) the only satisfactory solution to the problem of diabetes detection is to measure the blood sugar level (we have found a single estimation two hours after a 50-g. oral glucose load to be the most satisfactory). This emphasizes the need to provide the general practitioner with a quick, simple, and valid blood sugar method for the diagnosis of diabetes, preferably one which can be carried out in the surgery.

Importance of Renal Threshold in Management of the Individual Diabetic

Another question of interest to every clinician, brought to light by this study, is the proper interpretation of the results of testing for glycosuria when controlling diabetics.

It is apparent from the foregoing results that the renal glucose threshold should always be established for each diabetic at diagnosis and the results of the subsequent urine tests interpreted in the light of this threshold. From Figs. 1 and 2 it can be seen that many young diabetics may have very low renal thresholds, so that to advise them to adjust their control to keep their urine sugar-free may be to keep them in perpetual danger of hypoglycaemia, as in the two supposedly uncontrollable brittle diabetics (mentioned earlier) found to have renal threshold levels of 45 and 60 mg./100 ml. Failure to realize how low it was had resulted in one of these patients being in hospital for many weeks to the "stabilized." An even greater risk lies in the possibility that the considerable urinary glucose loss may provoke carbohydrate lack and "starvation ketosis" in the diabetic. Heavy glycosuria and ketonuria may then be misinterpreted and lead to increased insulin dosage when what is required is increased carbohydrate intake.

On the other hand, elderly diabetics with sugar-free urine may, in fact, be suffering from persistently high blood sugar levels. If the threshold is elevated in such cases, it may be more sensible to use the sensitive enzyme-impregnated test papers (Clinistix or Tes-Tape) on postprandial urine samples as an index of diabetic control, rather than copper sulphate reduction system tablets (Clinitest) on samples passed before meals, as is so often the case.

Detection of Diabetes: Epidemiological Surveys

With regard to the recognition of diabetes, either in detection drives or in epidemiological surveys, it must be stressed that the presence of glycosuria is by no means diagnostic of diabetes. Only one-third of the subjects with glycosuria at the Bedford Survey were hyperglycaemic. Also, the absence of glycosuria does not preclude diabetes, as 11% of the population we studied were hyperglycaemic, of whom about 90% were non-glycosuric. Some of these non-glycosuric subjects even had two-hour blood sugars over 200 mg./100 ml. at the subsequent glucose-tolerance test. Indeed, it can be calculated from our data that in a British population the preliminary screening by use of postprandial glycosuria will fail to detect over half the diabetics at large with blood sugars over 200 mg./100 ml. at two hours during a glucose-tolerance test. We therefore have to admit that our survey, and indeed many others based simply on glycosuria, failed to detect most of the unrecognized, mainly elderly, diabetics in the community.

Of course, attempts to detect diabetes by glycosuria have been widely used in the past because the techniques are so simple compared with blood sugar estimations. Can urine testing be made a more reliable reflection of hyperglycaemia? Testing the Bedford random sample for glycosuria after the standard oral glucose load showed that the proportion of glycosurics rose from the 4% seen among the population after a random breakfast to 30%. But unfortunately this procedure too will have its limitations; Figs. 3 and 4 show that an occasional diabetic will still be missed as well as a much larger number of borderline cases (see Definitions). Attempts to

screen all members of a community with even a modified form of the glucose-tolerance test involve a heavy burden on the laboratory.

Since the renal threshold can vary so much and reach such high values in old age, earlier ideas, that of diabetes as a disease where a high blood sugar is always associated with glycosuria and dehydration, have to be abandoned. Diabetes mellitus, the "siphoning off of sweetness into the urine," is not necessarily a concomitant of hyperglycaemia. We have to recognize that hyperglycaemia often exists without glycosuria, especially in communities where the proportion of old people is high, and that since we now define diabetes in terms of hyperglycaemia it is only by tests for hyperglycaemia that we shall be able to recognize diabetes and establish its prevalence in the community.

These points will have to be carefully considered by epidemiologists before they undertake further survey work. They will need to decide how many people are to be screened and whether or not they are to be screened for glycosuria, or for hyperglycaemia. Finally, in view of the high prevalence rates of hyperglycaemia in Western communities, the organizers of detection drives will be wise to ask themselves not only about the facilities and manpower available for the survey but also for the subsequent treatment of the cases found.

Summary

The results of testing an age-sex stratified random sample of the Bedford population for glycosuria during glucose-tolerance tests showed that the renal threshold level is very variable, and increases with age, especially among women. Renal threshold values as low as 130 mg./100 ml. were found in young subjects and as high as 300 mg. in elderly subjects. Thirty per cent. of this random sample had glycosuria during the glucose-tolerance test compared with only 4% when tested after breakfast. These findings are discussed in relation to the management of diabetic patients and the planning and execution of diabetes detection surveys.

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