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REPRINTS AND REFLECTIONS

Diabetes Mellitus: Its differentiation into insulin-sensitive and insulin-insensitive types*

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In previous publications[1,2,3,4,5] it has been shown that the efficiency with which insulin acts in the body is governed by an unknown factor or condition which renders the body sensitive both to injected and pancreatic insulin. When this sensitising factor is limited the efficiency with which each unit of insulin depresses the blood-sugar is decreased, and when it is abundant the efficiency of each unit is correspondingly increased. It can easily be seen that if this sensitising factor is limited below a certain degree, then the insulin in the body will be relatively powerless and the symptoms and signs of hypoinsulinism, clinically recognisable as diabetes mellitus, will appear. This consideration led me to suggest[4,5] that a type of diabetes mellitus might exist which was due, not to lack of insulin, but rather to lack of this sensitising factor. An investigation of cases of diabetic patients from this point of view was therefore commenced.

At first sight the simplest method of testing this hypothesis would appear to be by comparing in different diabetic subjects the rate and extent of fall of the blood-sugar after a standard dose of insulin. Such comparison of insulin depression curves from diabetic patients is, however, impossible. Insulin depression curves are only comparable when obtained from one and the same subject and, even then, only if the initial blood sugar values of the different curves are within a few mg. per 100 c.cm of the same level.[3] A new test was therefore sought and found in the application of an observation previously made on animals.[3] If glucose and insulin are given simultaneously to a normal animal, then the extent to which the injected insulin suppresses the hyperglycæmia can be gauged by comparing the blood-sugar curve resulting from glucose alone with the curve resulting from glucose plus insulin.

The test

The patient receives no food or insulin after supper the previous evening and the test is carried out next morning. Blood-sugar estimations are performed on capillary blood. Three resting samples are taken. The patient is given the appropriate dose of insulin intravenously and immediately afterwards the appropriate dose of glucose to drink. A blood sample is taken 5 minutes after the insulin injection, the next 10 minutes, and subsequent samples at intervals of 10 minutes until the hour is reached, and then two more samples at 15 minute intervals. The test is thus completed in 90 minutes.

The doses of insulin and of glucose can conveniently be based on the surface area of the patient. The patient's height and weight being known this is determined from the appropriate nomogram.[6] In our tests 30 grammes of glucose and 5 units of insulin per square meter of body surface were allowed. The glucose was given dissolved in half a pint of cold water and flavoured with citric acid and essence of lemon; the insulin used, for which I am indebted to Dr. J. W. Trevan of the Wellcome Physiological Research Laboratories, was a sterile solution of crystalline insulin assayed at 10 units per c.cm.

Various precautions are necessary to obtain satisfactory results. Firstly, the test must not be carried out if the patient shows signs of nausea or faintness. In these cases absorption from the stomach is delayed and a fallacious result obtained. Secondly, if it is desired to compare a series of curves, the patients must all be receiving diets containing approximately the same amount of carbohydrate, as I have previously shown that the insulin sensitivity of a normal subject is determined by the amount of carbohydrate utilised.[5] In the case of diabetics care should be taken that sugar us not being excreted in the urine in such amounts as to reduce materially the carbohydrate supply of the body. Thirdly, conditions of exercise will very probably affect the test. This factor did not apply in my cases, as all the subjects were hospital in-patients and advantage was taken of this fact to perform the test under ''basal conditions''.

Results

The work had not proceeded far before it became clear that by means of this test diabetics can be differentiated into two types: those in whom the injected

* Part of this work done during the tenure of a Beit memorial research fellowship.
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insulin produces an immediate suppression of the hyperglycæmia which normally follows ingestion of glucose alone; and those in whom the insulin has little or no effect in suppressing this hyperglycæmia. In Fig 1 a typical curve from each type of patient is shown. In patient 1 the insulin has had little effect, which in patient 2 not only has the hyperglycæmia been suppressed but an actual depression of the blood-sugar level has been produced. Patient 1 is insulin-insensitive; patient 2 is insulin-sensitive. Point is lent to these results when it is noted that patient 1 passed only small amounts of sugar when receiving 20 units of insulin a day, whilst patient 2 required 95 units of insulin a day to keep her sugar-free. Reference to the curves marked ''capillary blood'' in Fig 2 show that in patient 3, who is insulin-insensitive, there is very little difference between the curve after glucose alone (3. A) and the curve after giving the same dose of glucose and in addition insulin (3. B) whilst the capillary blood curves for the insulin-sensitive patient 4 differ widely when in one case only glucose is administered (4. A), and in the second glucose and insulin (4. B).

It may here be noted that the curve in healthy subjects approximates to that of the insulin-sensitive diabetics.[2] The curve obtained in this type of patient (2 and 4) thus appears capable of easy explanation as being the result of normal insulin action.

The curve in the insulin-insensitive patients (1 and 3) is more difficult to explain. Three distinct possibilities offer themselves: (i) the liver may be pouring so much sugar into the blood that the effect of the injected insulin is swamped; (ii) the liver may be incapable of storing the ingested sugar; (iii) the characteristic action of insulin in promoting storage of blood-sugar in the peripheral tissues may be unable to manifest itself. The first two possibilities involve the portal system, the third the peripheral tissues. If now it is possible to compare the removal of sugar by the peripheral tissues, firstly, when glucose is given alone, and secondly, when glucose is given along with insulin, the site of the functional derangement can be localised either to the periphery or to the portal system. This can be done by measuring the sugar content of the blood entering a limb and the sugar content of the blood leaving the limb.

I have shown that capillary blood taken from the warm ear has approximately the same sugar content as arterial blood, and also that venous blood specimens taken under identical conditions from the same half inch of vein in all tests on the same subject give a reliable if only relative indication of the sugar content of the blood leaving the limb.[2] By performing simultaneous curves on capillary and venous blood (A.V. curves) after ingestion of glucose and after glucose and insulin, and comparing the size of the capillary venous blood difference (A.V. difference), a rough estimation can be made of the extent to which insulin promotes peripheral storage in a particular case. In

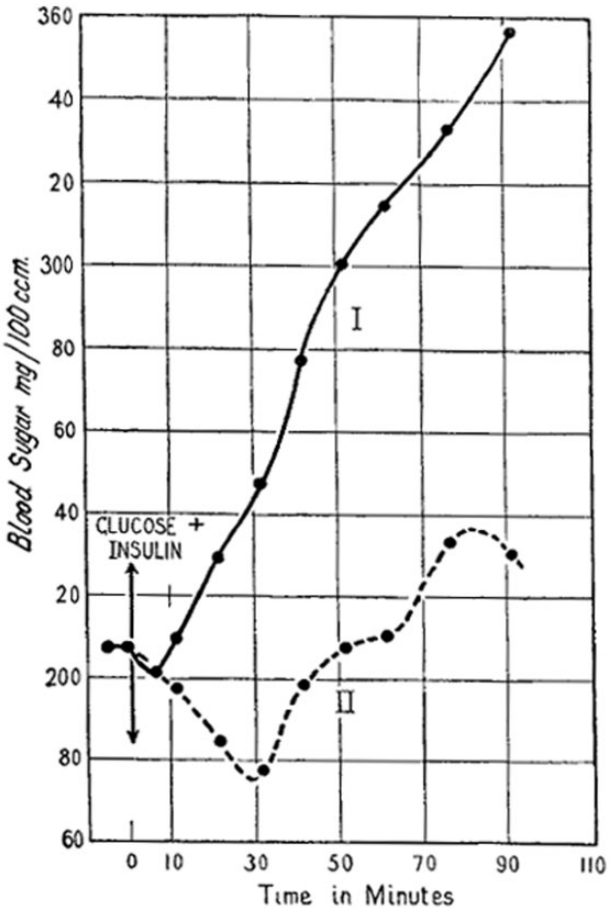

Figure 1 *Simultaneous glucose and insulin test.* Capillary blood-sugar curves.
Patient 1 – Insulin-insensitive. Women, aged 60, on a diet of 1500 calories containing carbohydrate 150 g, protein 80 g, fat 66 g, and 35 units of insulin daily. Passing small amounts of sugar.
Received 7.3 units of insulin intravenously aged 43.8 g of glucose orally.
Fasting blood-sugar 208 mg/100 c.cm.
Patient 2 – Insulin-sensitive. Woman, aged 21, on a diet of 2000 calories containing carbohydrate 208 g, protein 80 g, fat 94 g, and 95 units of insulin daily. Sugar-free. No hypoglycæmic attacks.
Received 7 units of insulin intravenously and 41 g of glucose orally. Fasting blood-sugar 244 mg/100 c.cm.
The curves have been charted so as to start at the same resting blood-sugar level

the normal subject the giving of insulin along with glucose results in a tremendous increase in the A.V. difference as compared with the increase of A. V. difference after glucose alone.[2] This increase is so great as to be quite outside the limits of experimental error. A.V. curves were, therefore, performed on both insulin-sensitive and insulin-insensitive diabetics. The results are shown in Fig. 2.

In the insulin-sensitive patient 4 insulin had the normal effect of greatly augmenting the A.V. difference after glucose. Up to 60 minutes the area enclosed

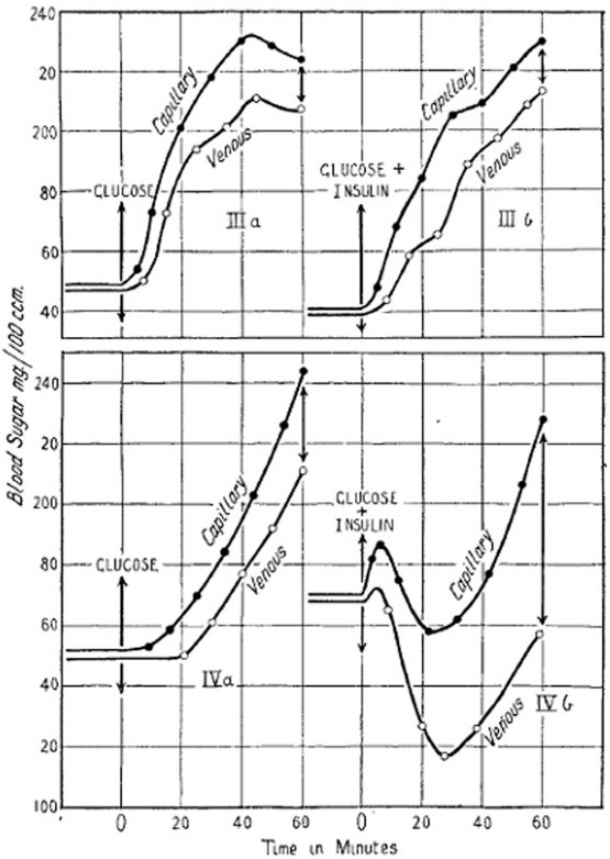

Figure 2 *Simultaneous glucose and insulin test. Simultaneous* capillary and venous blood-sugar curves (A.V.curves).
Patient 3 – Insulin-insensitive. Man, aged 61.

Curve 3a – 53 g of glucose by mouth Resting capillary blood-sugar 149 mg/100 c.cm., venous blood-sugar 147 mg

Curve 3b – 53 g of glucose by mouth immediately preceded by 8.8 units of insulin intravenously. Resting capillary blood-sugar 141 mg, venous blood-sugar 139 mg

Receiving a diet of 1570 calories containing carbohydrate 210 g, protein 70 g, fat 60 g, for the previous ten months. Insulin dosage raised steadily until, on admission to hospital, was receiving 85 units of insulin. This was inadequate. Every specimen of urine passed gave a complete reduction of Benedict's solution, and no hypoglycæmic attacks occurred.

Patient 4 - Insulin-sensitive. Man, aged 48.

Curve 4a – *50 g of glucose by mouth Resting capillary blood-sugar 152 mg, venous blood-sugar 147 mg

Curve 4b – 50 g of glucose by mouth and 5 units of insulin intravenously. Resting capillary blood-sugar 171 mg, venous blood-sugar 169 mg

Receiving a diet of 2493 calories containing carbohydrate 238 g protein 102 g, fat 115 g, and 20 units of insulin a day. Consistently sugar-free.

* These doses of insulin and glucose were chosen before the scheme of dosage based on surface area was adopted. The dose on surface area would have been 58 g of glucose and 9.7units of insulin

between the capillary and venous blood-sugar curves of curve 4.B, as compared with curve 4.A increased by 120 per cent.

In the insulin-insensitive patient the effect is quite different. On comparing curve 3.A (glucose alone) with curve 3.B (glucose + insulin), it will be seen that the insulin has resulted in little or no increase of A.V. difference. By actual measurement of the areas enclosed between the capillary and venous blood-sugar curves the increase is found to be the negligible figure of 9 per cent.

It may thus be seen that, in the insulin-insensitive diabetic, insulin is unable to exert its characteristic action of effecting the transference of sugar from the blood to the peripheral tissues; that even if the insulin-insensitive patient possessed a normal supply of pancreatic insulin such insulin would be unable to act efficiently and the patient would be diabetic. On the other hand, it is seen that in the insulin-sensitive diabetic insulin is able to act, that the giving of this substance produces a normal reaction, and that, therefore, if these diabetics had a greater supply of pancreatic insulin, they would show no signs of diabetes mellitus.

It therefore appears that in insulin-sensitive diabetics the disease is due to deficiency of insulin, whilst in insulin-insensitive patients diabetes mellitus results, not from lack of insulin but from lack of an unknown factor which renders the body sensitive to insulin.

Clinical observations

Sufficient data have not yet been accumulated to permit a precise correlation between the clinical findings and the type of diabetes mellitus as revealed by the glucose-insulin test. But enough observations have been made to allow certain tentative opinions to be expressed.

A general relationship appears to exist between the type of onset of the disease and the type of diabetes. The onset insulin-sensitive patients is as a rule acute; the onset in insulin-insensitive patients is insidious. For example, in the insulin-sensitive patient 2. (a girl aged 21), the diabetes mellitus appeared with intense symptoms, and within 48 hours the patient was in coma; in the insulin-sensitive patient 4., a man aged 48, the disease came on suddenly in December, 1930; in the insulin-insensitive patient 1., a woman aged 60, the patient developed vulvitis without symptoms of thirst or polyuria, the urine was tested and sugar was found; and in the insulin-insensitive patient 3., a man aged 60, sugar was discovered fortuitously at a life insurance examination seven years ago, but none of the classical symptoms of diabetes mellitus have ever been noted and no therapeutic measures were taken until he developed first an external rectus and later a facial nerve palsy. The insulin-insensitive type is more common in but not confined to the elderly,

whilst the insulin-sensitive type is commoner in the young. As diabetes mellitus becomes more frequent with increasing age it would appear probable – and my experience so far supports this deduction—that the commonest type of diabetes mellitus will eventually prove to be that which is not essentially due to insulin deficiency.

A further observation concerns the different reaction of the two types to change in the carbohydrate content of the diet. When high carbohydrate diets were first introduced the claim was made that the carbohydrate content of the diabetic's diet could be raised from the 50 g, then orthodox, to 200 g, without necessitating any increase in insulin dosage.[7,8,9] It has been my experience that in many cases this claim is true, but it has denied by other observers. The differentiation of diabetes into insulin-sensitive and insulin-insensitive types seems to provide the key to the discrepancy. In the cases examined so far key to the discrepancy. In the cases examined so far it appears that insulin-sensitive diabetics will tolerate large increases of carbohydrate in the diet with little or no increase in the amount of insulin required to keep the urine sugar-free; insulin-insensitive patients, on the other hand, pass sugar after only small increases in dietetic carbohydrate. For example, patient 1 was always sugar-free when taking a diet containing 67 g of carbohydrate and 20 units of insulin a day. Increase of the carbohydrate to 148 g, whilst keeping the calorie value of the diet the same, resulted in profuse glycosuria which was not controlled by 35 units of insulin a day. On admission, patient 2, who was insulin-sensitive, was receiving a diet containing 65 g of carbohydrate and was taking 45 units of insulin a day. Her physician had been quite unable to balance her, she was extremely wasted, and her urine contained sugar and ketones in large quantities. She was given a diet containing 200 g of carbohydrate a day and rendered sugar-free with 95 units of insulin daily. After ten days of complete control, in which no hypoglycæmic attacks occurred, she was given an equicaloric diet containing 320 g of carbohydrate. Glycosuria did not appear and some days later the insulin dose had to be reduced because of hypoglycæmic attacks.

It thus appears that the differentiation of diabetics into insulin-sensitive and insulin-insensitive types by means of the insulin-glucose test may prove to be of considerable practical importance as offering a means by which the appropriate diet can be chosen for the particular case. It is hoped that other observers will attempt to arrive at an opinion on this point. One thing, however, I would make clear. The observation that on a low carbohydrate diet a particular diabetic requires least insulin is no proof that the diet is the optimum from the point of view of the preservation of his health.

Discussion

I have said that I think it probable that in those cases of diabetes mellitus which are insulin-sensitive the cause of the disease is deficiency of insulin, whilst in those cases which are insulin-insensitive the cause of the disease is not lack of insulin, but the restriction, to a greater or less degree, of an unknown sensitising factor. In previous publications I have communicated the results of work on healthy men and animals which demonstrated the existence of a factor rendering the body sensitive to insulin.[4,5] It is of interest to inquire whether it is the restriction of this same factor demonstrable in healthy subjects which is responsible for the insulin insensitivity of a type of diabetes.

A characteristic of the insulin-sensitising factor of normal people is that the quantity of it present in the tissues at any time is determined by the amount of carbohydrate in the diet.[5] When more carbohydrate is given to a healthy subject the body reacts by rendering itself more sensitive to insulin. Now it has been shown in the previous section that when more carbohydrate is given to an insulin-sensitive diabetic the insulin requirement does not increase and glycosuria does not appear. I have shown elsewhere[4] that this apparent increase in efficiency of the injected insulin can satisfactorily be explained on the basis that these patients react to the increased amount of dietary carbohydrate by becoming more sensitive to the injected insulin. But in the case of the insulin-insensitive diabetic increased intake of carbohydrate results in glycosuria and consequent increased insulin requirement. Thus, these patients are abnormal in being unable to react to increase in dietary carbohydrate by increase in their sensitivity to insulin. It appears, therefore, justifiable to regard the insulin-insensitivity type of diabetes as being due to lack of that same unknown factor which in the normal subject produces sensitivity to insulin.

On the balance of the evidence available I have suggested that this insulin-sensitising factor is an activator of insulin,[1,2] but as yet there is no incontrovertible evidence whether the unknown is a factor, in the sense of being a definite substance, or a condition of the tissues in general which facilitates the action of insulin. It will be seen, however, that the nature of the unknown ''insulin-sensitising factor'' must be such that it is intimately concerned with the action of insulin and that its restriction will result in rendering a proportionate amount of the available insulin powerless.

The term insulin insensitivity has been used in preference to the term insulin resistance for two reasons. Firstly, because in my investigations into the variations of insulin sensitivity in normal subjects I have seen no evidence of any factor which antagonises or resists the action of insulin itself, but only evidence indicating the presence of a factor which is complementary to insulin. Secondly, because the term insulin resistance has already been used with two different meanings.[10] In one sense it appears to mean simply that the patient requires more insulin to

produce hypoglycæmic symptoms than the physician expected. In the other sense it refers to those rare cases in which enormous doses of insulin, such as 1600 units a day, are insufficient to prevent the patient developing and dying in diabetic coma.[11,12] These latter cases cannot be explained on the basis of lack of insulin, but I would suggest that they can be explained on the basis of extreme deficiency of the insulin-sensitising factor.

Summary

It is shown that two different types of disease can be distinguished as causing the symptom-complex of diabetes mellitus. One, the insulin-sensitive type, appears to be caused by deficiency of insulin; the other, the insulin-insensitive type, is apparently due not to lack of insulin, but to lack of an unknown factor which sensitises the body to insulin. A test for distinguishing these two types of diabetes mellitus is described. The appropriate dietetic treatment of the two diseases may differ.

Addendum

Since this paper was written I have read a publication by Boller and Uiberrack in the Falta-festschrift (Wien. Arch. f. inn. Med., 1935, xxvii, 75) which bears on these results. These workers chose diabetics of two types: those who required less insulin than was estimated to produce hypoglycæmic attacks, the ''insulin-sensitive'' group, and those who required more insulin than was expected, the ''insulin-resistant'' group. Amongst the different experiments performed one series is relevant to this paper. Insulin was injected and some hours later when hypoglycæmic symptoms appeared glucose was given by mouth. In the ''insulin-sensitive'' group the oral glucose resulted in a smaller hypoglycæmia than in the ''insulin-resistant'' group. The authors explain their results by the varying sensitivity, in the two types of case, of the mechanism which causes liberation of sugar into the blood stream. As my results show, this cannot be the explanation; for the difference is due not to swamping of insulin action by pouring of sugar into the blood, but to deficient removal of blood-sugar due to inefficient insulin action. Their results, however, are of importance as showing that the type 1 have called insulin-sensitive easily develops hypoglycæmic symptoms, whilst the type named insulin-insensitive develops these symptoms with difficulty.

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