

HEMORRHAGIC DIABETIC RETINITIS; A METHOD OF TREATMENT BASED ON THE ELEVATION OF PLASMA ALBUMIN BY DIET

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Serious vascular damage used to be considered a complication of diabetes mellitus; it is becoming more generally recognized that this damage is an integral part of the disease. Previously it was hoped that eradication of hyperglycemia with the aid of insulin would prevent what was considered the "complications" of the disease. The careful observation of patients receiving adequate control of glycosuria and hyperglycemia has led to an ever increasing suspicion that this is not sufficient to prevent progressive vascular degeneration. Such progressive vascular disease leads to the tremendous morbidity and high mortality associated with retinal damage, renal failure, coronary artery sclerosis, and gangrene of long standing diabetes mellitus.

With these facts in mind it has become apparent that a clearer understanding of the fundamental processes involved in the accompanying vascular disease is necessary before we can hope for the development of methods for their prevention. No clinical approach to the diabetic patient is complete, therefore, without a careful appraisal of his vascular status from time to time. In our patients a minimum requirement includes careful examination of the retina by an ophthalmologist, an evaluation of renal function, an estimate of any change in the peripheral vessels, determination of cardiac status, and frequently the taking of an electrocardiogram.

Up to the present time our chief interest in this regard has centered upon the vascular disease of the retina. Particular attention has been given to the study of alteration in plasma proteins which might be a contributing factor in the production of retinal hemorrhage.

Abnormally low levels of plasma albumin might be expected to accentuate a tendency to perivascular exudation and hemorrhage. Induced

hypoproteinemia in rabbits prior to the induction of alloxan diabetes has been observed¹ to result in a striking tendency toward retinal hemorrhage.

It had been previously pointed out^{1,2,3} that in patients with diabetic retinitis plasma proteins are characterized by low albumin and high beta globulin in the presence of total protein values which are normal or only slightly reduced. Similar changes are present in some patients with uncontrolled diabetes mellitus without retinitis. The plasma albumin levels in these two groups respond quite differently to treatment. In the second group with little or no evidence of vascular disease of the retina, "adequate treatment"³ on diets containing 60 to 70 Gm. protein per day promptly restores the plasma albumin level to normal. In the former group with apparently more vascular disease, plasma albumin levels were not readily corrected. Much higher protein intake, ranging from 100 to 200 Gm. per day, must be added to the routine for many months before normal albumin levels are obtainable.

A representative group of 30 cases of diabetic retinitis has been analyzed for the present paper. In each instance the characteristic plasma protein pattern previously described was present. These patients have been selected not because of age, sex, duration or severity of their existing diabetes but because they have had abnormalities in plasma protein pattern. This condition has been present in the majority of a larger group of patients with diabetic retinitis previously studied by us.

By the methods used, normal values for total plasma proteins and their fractions can be defined within a range which can be determined accurately. Our own experience with 21 normal subjects⁴ has shown the following range:

| | Total Protein | Albumin | Beta Globulin |
|---------|----------------|----------------|----------------|
| Range | { 7.82 5.94 | { 5.11 3.72 | { 1.07 0.65 |
| Average | 6.51 | 4.09 | 0.81 |

These values correspond closely with those reported by Longsworth *et al.*⁵ and Luetscher.⁶

The plasma protein values in the group of patients with diabetic retinitis under consideration were as follows:

| | Total Protein | Albumin | Beta Globulin |
|---------|----------------|----------------|----------------|
| Range | { 7.95 5.34 | { 4.19 2.28 | { 1.58 0.94 |
| Average | 6.38 | 3.01 | 1.15 |

Accompanying abnormalities observed in the alpha and gamma globulin fractions and fibrinogen are left for future consideration.

An attempt has been made to raise the low plasma albumin levels to normal by increasing the protein intake while maintaining good control of hyperglycemia. When diabetic retinitis is present it frequently proves very difficult and, in our experience, sometimes impossible to completely correct this abnormality. Diets containing 100 to 200 Gm. of protein per day must be used for many months before strictly normal albumin levels are obtained.

A diet of this type containing 140 Gm. protein per day follows: skimmed or whole milk 1000 cc., 1 egg, lean meat 210 Gm., and casec 50 Gm. The remaining protein is present in bread, crackers, and vegetables.

The protein intake can be increased to 200 Gm. per day by a diet prescription as follows: 7 eggs, bacon 20 Gm., milk 1000 cc., lean meat 300 Gm., and casec 40 Gm., with added bread and vegetables.

In 16 of the 30 patients in this group we have had an opportunity to observe the degree of success attained in correcting the low plasma albumin level by such diets. The values before as compared to those found several months after this additional treatment are as follows:

| | | Total Protein | Albumin | Beta Globulin |
|--------|---------|---------------|---------|---------------|
| Before | Range | { 7.95 | { 4.19 | { 1.58 |
| | | { 5.34 | { 2.28 | { 0.94 |
| | Average | 6.38 | 3.01 | 1.15 |
| After | Range | { 8.22 | { 4.95 | { 1.55 |
| | | { 6.04 | { 3.28 | { 0.82 |
| | Average | 7.1 | 3.84 | 1.19 |

Complete correction of the lowered albumin level was obtained in 10 of the 16 patients. Uniformly successful results occurred only when diets supplied over 100 Gm. protein per day and were taken for six to eighteen months. In 1 instance a fall in albumin occurred while 130 Gm. protein was consumed over a nine-month period. The level subsequently rose on 200 Gm. protein consumed daily for seven months. In general, a rise to normal plasma albumin level accompanied daily intakes of 100 to 120 Gm. Slower rises occurred in a few patients on 80 Gm. per day. In others the same amount of protein was insufficient to maintain the albumin fraction at a stationary level.

The albumin level in the remaining patients failed to show complete recovery during the period of observation on increased protein intakes. One of these had severe hypertension and renal insufficiency; 1 had poor control of hyperglycemia during the last four months of study; 1 received only 80 Gm. protein per day, and 2 were followed for five months or less. These factors, we believe, completely or partially explain failures in the correction of albumin levels.

The elevated beta globulin fraction was not significantly altered by the increased protein prescribed. The significance of this abnormality in plasma proteins is not yet understood.

The retinal findings are of considerable interest in the 10 patients in whom a normal albumin fraction was obtained by this method of management. During the period of observation 7 of these 10 patients showed improvement in that there were fewer or no hemorrhages; the other 3 showed no improvement. These 3 all had proliferating retinitis. The degree of improvement demonstrated by the 7 cases can be judged by the following notes.

One patient originally demonstrated frequent hemorrhage, exudate, edema, optic atrophy, and marked contraction of both form and color fields. After three and a half years of treatment she had only an occasional petechial hemorrhage, no exudate or edema, slight haziness of the optic disks, normal form and color fields, and was able to thread a needle.

A second patient had no hemorrhages eight months after the albumin level had become normal. Visual acuity improved, and the retinae showed only highly refractile bodies. A third patient originally showing numerous hemorrhages had none at the end of two years when the albumin level was normal. The fourth and fifth patients were observed for sixteen months, during which time fewer hemorrhages occurred, and 1 of these had none during the last six months of observation. The sixth and seventh patients were observed for three years before albumin levels became normal. One of these had no hemorrhages at the end of this time. The other still presented occasional petechial hemorrhages.

It appears obvious that factors other than plasma albumin levels are very important, since retinal hemorrhage continues to occur in some patients in spite of normal albumin levels. Further, in view of the high casein diets we have used it is interesting to reflect that rats on choline deficient diets develop not only renal but retinal hemorrhage^{7,8} and that such food factors as may be supplied in diets containing large quantities of casein, methionine, and labile methyl groups are intimately associated with such changes.

Conclusions

1. Abnormally low levels of plasma albumin have been found to be an almost constant accompaniment of diabetic hemorrhagic retinitis in patients studied at this Clinic.

2. Low plasma albumin levels by causing a lowered osmotic tension increase the tendency to exudation and hemorrhage.

3. A method has been described by which such low levels of plasma albumin may be raised by the use of high protein diets.

4. Such factors as poor diabetic control, too short a period of treatment, or renal failure may interfere with the efficiency of such management.

5. In 16 patients treated for two to three and one-half years, the plasma protein pattern was corrected in 10, recurrent retinal hemorrhages were eliminated in 6, lessened in 1.

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