CLINICAL VITAMIN DEFICIENCIES *in patients with* DIABETES MELLITUS

By BARKLEY BEIDLEMAN, M.D.

VITAMIN DEFICIENCIES appearing clinically in patients with diabetes mellitus may be divided into two groups. The first group includes those deficiencies which appear in diabetics who are eating a diet low in total calories and fat for reduction of weight and prevention of atherosclerosis. These deficiencies are usually multiple and differ in no way from those occurring in non-diabetic patients under similar conditions of dietary deficiency. The second group includes those deficiencies which appear in diabetic patients who are apparently adequately nourished but whose diabetes has been poorly controlled for variable periods of time. These deficiencies are frequently single and their chief manifestation is peripheral neuropathy.

GROUP I

Recent trends in the dietary therapy of diabetes mellitus have been toward considerable restriction of the fat intake, in an effort to limit the tendency of diabetics toward atherosclerosis and fatty infiltration of the liver. That these ends can be accomplished on the low fat diets currently in vogue is in considerable doubt. Nonetheless, the trend continues, and with it the increased likelihood of mild clinical deficiencies of the fat-soluble vitamins.

The only vitamin in this fat-soluble group which seems to be of real clinical importance is vitamin A, which is absorbed as such from dietary sources or is synthesized in the liver or gastrointestinal mucosa from dietary carotenoid precursors. Full-blown vitamin A deficiency is manifested by nyctalopia, perifollicular hyperkeratosis and dryness of the skin, xerophthalmia, keratomalacia, and metaplasia of the mucous membranes of the upper and lower respiratory tracts and the lower urinary system. In our clinical experience, the most frequently encountered of these manifestations have been perifollicular hyperkeratoses and dry skin—especially over the arms, legs and anterior abdominal wall. It is probably of speculative interest only to question whether or not the above-mentioned metaplastic changes of cornification and desquamation in the upper respiratory tract, trachea, bronchi, renal pelves, and ureters predispose toward the infections in these areas so frequently encountered in diabetics. We have not had occasion to measure night vision in these patients, nor have we encountered the full-blown picture described above.

Theoretically, vitamin D deficiency could result under the same conditions. Actually, we are not aware of any increase in the incidence of rickets in diabetic children or of osteomalacia in diabetic adults. In theory, vitamin D deficiency might conceivably impair carbohydrate metabolism through increased

Formerly of the Benjamin Franklin Clinic, the Pennsylvania Hospital, and Jefferson Medical College, Philadelphia, Pa.; now of the Medical Center Clinic, Pensacola, Florida.

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excretion and impaired absorption of phosphates. This could result in the reduction to less than adequate amounts of organic and inorganic phosphorus in the body fluids to form the glucose-phosphate derivatives and the enzyme-phosphate energy compounds necessary for their metabolism. So far as we are aware, no such clinico-chemical condition has been described.

Poorly controlled diabetes may produce fatty infiltration of the liver (see below) with the possibility of attendant hemorrhagic tendencies. In this instance, however, the bleeding would be due to faulty utilization of vitamin K and not due to an insufficient intake of the vitamin itself. We have seen several patients in whom there was such a tendency, not apparent clinically, but noted during the performance of prothrombin time tests as a part of liver function evaluation.

There is no clinical syndrome definitely ascribable to a deficiency of vitamin E in humans, diabetic or non-diabetic.

Of the water-soluble vitamins, those of the B group are of the most importance in our present concern. Fourteen or fifteen members of this group have been identified, but many are of no clinical significance. Deficiencies of of the more important ones are frequently encountered in diabetic patients under two sets of conditions.

First, diabetic patients are often given weight-reduction diets of 900 to 1500 calories. In patients with or without diabetes, such a diet will usually not contain the average normal daily requirement of these B vitamins. In the absence of supplementary vitamin therapy, clinical deficiency signs or symptoms may develop.

Second, there is a feeling in some circles that the carbohydrate metabolic cycle in diabetic patients may require more vitamin-containing coenzymes per gram of carbohydrate utilized or per calorie produced than are necessary in non-diabetic patients. We have nothing new to contribute to one side or the other of this thesis. If it is valid, then a patient with diabetes mellitus should develop the clinical evidences of avitaminosis B on a dietary intake that would prevent the development of similar signs in a subject without diabetes.

In either instance, the most frequently observed symptoms attributable to an absolute or relative lack of these substances have been neurasthenia, mild peripheral neuritis, anorexia, burning sensations in the mouth, soreness of the tip of the tongue, and, perhaps, mild conjunctivitis. The physical findings most often encountered have been mild conjunctival injection, a reddened tongue with smooth and serrated edges, cheilitis, mild to moderate tenderness along the major peripheral nerve trunks, and absent tendo Achilles reflexes.

We are not at all sure that these signs and symptoms can be dissociated one from another and individually attributed to a deficiency of a single member of the B group. The signs and symptoms referable to peripheral neuritis may clear with the administration of thiamine alone. However, lesions of the skin and mucous membranes have been reported as improved by the individual use of thiamine, riboflavin, niacin, and even pyridoxine (vitamin B_6) or biotin.

When a patient becomes so deficient as to develop one of the more severe and distinct syndromes, such as beriberi or pellagra, it is still true that, although the major deficiency is of a single vitamin, clinical deficiencies of other members of the B complex coexist and account for an appreciable part of the symptomatology.

It is important to recall at this point the specific roles of several members of this B group of vitamins in the metabolism of carbohydrate.[1,2,3] Thiamine, as its pyrophosphate or "cocarboxylase," is essential to an integral step in carbohydrate metabolism in which the utilization of pyruvic and related keto acids is promoted. Riboflavin is one of the components of the flavoprotein group of enzymes which serve to oxidize the reduced forms of the coenzymes in the oxidation-reduction chain responsible for carbohydrate metabolism. Niacin, similarly, is incorporated into the structure of the coenzymes, I and II, mentioned immediately above. Guest[4] and his group feel strongly that clinical and subclinical deficiencies of these vitamins may seriously interfere with carbohydrate metabolism in the

diabetic and specifically urge their introduction into the regimens for the treatment of diabetic coma. Although we have adopted this suggestion[3] we have not seen any patients with or without clinical signs of avitaminosis B in whom the omission or addition of large doses of this vitamin complex has seemed to influence the rate of recovery from ketotic coma.

Except as mentioned above, pyridoxine deficiency is of no apparent clinical importance, nor are deficiencies of biotin, pantothenic acid, or inositol.

The other water-soluble vitamins other than the B group which are of interest include vitamin C or ascorbic acid, and "vitamin P" or rutin. We have not seen clinical evidences of scurvy, mild or otherwise, among diabetics. The use of these two vitamins has been suggested for the treatment and prevention of diabetic retinopathy. The reasoning seems to be that these two substances have something to do with the integrity of the capillary wall, ascorbic acid through its contribution to the formation of intercellular ground substance, and rutin in an unascertained manner. Diabetic retinopathy consists of hemorrhages and exudates, both presumably extravasations. Therefore, the two vitamins considered may be of some help. We have had no patient in whom this therapy—or any other, for that matter—has reversed the retinopathy. There is a glimmering of an impression that their use slows the progression of the retinopathy, but we can offer no statistical support. We are currently prescribing a single tablet containing 100 mg. of ascorbic acid and 20 mg. of rutin to be taken thrice daily.

Group II

The second group of deficiencies includes two sets of manifestations.

First, many patients with diabetes mellitus of considerable duration have clinical enlargement of the liver. This is especially true of children and diabetics whose control has been intermittently poor. Histologic examination of biopsies from such livers has shown diffuse fatty infiltration of the hepatic parenchymal cells. Laboratory studies may or may not reveal evidences of mild impairment of hepatic function. Those that do have shown no characteristic pattern. The prothrombin time is occasionally abnormal, as mentioned above.

When choline is added to the patient's therapeutic regimen, the liver edge may shortly become impalpable. It is known that choline mobilizes fatty acids, donates methyl groups, and increases the phospholipid fraction in the circulating blood. All of these "lipotropic" mechanisms are apparently active in removing the fatty infiltration and thereby in reducing the size of the liver. Whether or not there is an absolute, relative, or metabolic deficiency of choline in these diabetic patients has not been determined, but the therapeutic results seem highly suggestive.

The second set of manifestations occurring in this group are neuropathic in type. For a review of this subject, the reader is referred to two recent papers[5,6] and their bibliographies.

It is important to remember that the signs and symptoms of peripheral neuritis in a diabetic patient may be due to thiamine deficiency and will respond to treatment with adequate amounts of that vitamin. There is also a somewhat vague entity known as "ischemic neuropathy." The manifestations are those of peripheral neuritis, but nerve-trunk tenderness is usually absent. The symptoms in these cases are supposed to be due to neural damage from deficient blood supply through arteriolar sclerosis of the vasa nervorum. If the local circulation is capable of responding to various therapeutic vasodilatation measures and if the neuritic symptoms are improved concomitantly, then, in retrospect, one diagnoses "ischemic neuropathy."

Finally, one is left with the true diabetic neuropathies. The manifestations include nocturnal muscular cramps, paresthesias, hypesthesia, and hypalgesia, loss of vibration and position sense in the lower extremities, muscular weakness and atrophy, trophic ulcers, optic neuritis, Argyll pupils, Charcot joints, and autonomic imbalances affecting the bladder, superficial circulation, and sweating and pilomotor responses.

No one as yet knows why diabetics develop such neuropathy. Evidence is accumulating that it is a manifestation of a nutritional deficiency. The similarity to the combined system disease of pernicious anemia is obvious. When it is noted that many of these diabetic patients also have a sprue-like steatorrhea without creatorrhea, smooth red tongue, gastric anacidity, and increased spinal fluid protein, the similarity increases. Many of these diabetic patients also have an anemia, but it is more frequently normocytic than macrocytic.

Following the identification of vitamin B_{12} as the active liver principle lacking in pernicious anemia, and the introduction of suggestive evidence that it is the extrinsic factor of Castle as well, its effect on the neurologic abnormalities was followed with interest. Folic acid, an earlier entrant, had failed to affect these satellite symptoms. Vitamin B_{12} proceeded to produce prompt and lasting neurological remissions in pernicious anemia.

On an empirical basis, founded insecurely on the noted similarity between the two syndromes, diabetic neuropathy was then treated with Vitamin B_{12}. Contrary to the experience of others,[6] many of our patients with mild to moderate neuropathic symptoms experienced prompt and lasting relief from symptoms on 30 μg. of vitamin B_{12} daily for 3 to 5 days. Several patients experienced recurrent exacerbations of their symptoms and are apparently in the position of requiring a maintenance dose. One patient with ataxia, nocturnal diarrhea, peripheral neuritic symptoms, and a left sixth cranial nerve palsy had complete clearing of all these manifestations within a month of therapy with Vitamin B_{12}. On the other hand, several other patients with severe neuropathies have apparently reached an irreversible stage and have been helped only slightly or not at all by much larger doses over longer periods of time.

Sancetta, Ayers, and Scott[7] successfully treated twelve diabetics with neurologic disturbances by giving 15 to 30 μg. of vitamin B_{12} daily for a week or two, and then maintaining a similar dose once or twice a week.

The exact mechanism of the production of this peculiar and unique type of vitamin deficiency in diabetic patients remains undiscovered. The biochemical and patho-physiological processes involved have not been elucidated. The relationship between vitamin B_{12} and pregnant mammalian liver extract[8,9] is undetermined. Most important, the factors determining the success or failure of therapy with these two substances are a mystery.

Conclusions

Clinical vitamin deficiencies in patients with diabetes mellitus occur (a) when patients are given low calorie and/or low fat diets without supplementary vitamin therapy, (b) in otherwise well-nourished patients whose diabetes has been poorly controlled for variable periods of time.

In the first group, the perifollicular hyperkeratosis and dry skin of avitaminosis A and the peripheral neuritis and mucous membrane changes of avitaminosis B are most frequently encountered.

In the second group, hepatic enlargement responding to choline therapy and diabetic neuropathy responding to treatment with vitamin B_{12} are discussed.

Theoretical considerations regarding other deficiencies are recounted.

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Resumen

Hipovitaminosis clínicas en pacientes con diabetes mellitus

Aparecen las hipovitaminosis clínicas en pacientes con diabetes *mellitus:* (a) cuando se suministra a los pacientes una dieta pobre en calorías o en grasas o bien en las dos, sin vitaminoterapía suplementaria; (b) en pacientes de otro modo bien nutridos cuya diabetes ha sido mal controlada durante períodos de tiempo variables.

En el primer grupo, se encuentran con mayor frecuencia la hiperqueratosis perifolicular y el xeroderma característicos de la avitaminosis A, y la neuritis periférica y las alteraciones de la membrana mucosa asociadas a la avitaminosis B.

Del segundo grupo se discuten la hepatomegalia—que responde a la terapéutica con colina, y la neuropatia diabética—obedeciendo a la vitaminoterapía B_{12}.

Se presentan consideraciones teóricas sobre otras deficiencias.

CALORIC VALUES FOR COMMON "SNACK" FOODS

CANDIES	Amount or Average Serving	Calorie Count
Chocolate Bars, 5¢ size		
Plain	1 bar (1¼ oz.)	190
With nuts	1 bar	275
Chocolate Covered Bar	1 bar	250
Chocolate Cream, Bon Bon, Fudge	1 piece 1" square	90
Caramels		
Plain	1 piece ¾" cube	35
Chocolate nut caramels	1 piece	60
DESSERTS		
Pie		
Fruit—Apple, etc.	1/6 pie 1 Average Serving	560
Custard	1/6 pie 1 Average Serving	360
Lemon Meringue	1/6 pie 1 Average Serving	470
Pumpkin pie with whipped cream	1/6 pie 1 Average Serving	460
Cake		
Iced layer—2 layers white cake	1 Average Serving	345
Fruit—thin slice ¼"	1 Average Serving	125
SWEETS		
Ice Cream		
Plain vanilla	1/6 qt. serving	200
Chocolate and other flavors	1/6 qt., ⅔ cup	230
Milk sherbet	1/6 qt., ⅔ cup	250
Sundaes, small chocolate nut with whipped cream	Average	400
Ice cream sodas, chocolate	10 oz. glass	270
MIDNIGHT SNACKS for ICE-BOX RAIDERS		
Cold potato	½ medium	65
Chicken leg	1 average	88
Glass milk	7 oz. glass	140
Mouthful of roast	½" × 2" × 3"	130
Piece of cheese	¼" × 2" × 3"	120
Left-over beans	½ cup	105
Brownie	¾" × 1¾" × 2¼"	300
Cream-puff	4" diameter	450

(Courtesy of Smith, Kline & French Laboratories, Philadelphia)