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## INSULIN RESISTANCE

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Insulin resistance is defined as a condition in which daily requirement of insulin exceeds 200 units for at least two days in the absence of significant ketoacidosis or coma.<sup>(13,18)</sup> It is usually classified as either primary or secondary.<sup>(21)</sup> Secondary insulin resistance occurs in association with other diseases such as infection,<sup>(9,10)</sup> non-pancreatic endocrinopathies,<sup>(8)</sup> liver disease,<sup>(16)</sup> hemochromatosis<sup>(5,18)</sup> and collagen diseases.<sup>(6)</sup> The resistance usually disappears after the primary diseases are cured. Primary insulin resistance is a relatively rare condition with an incidence of 0.1% of all insulin treated diabetics.<sup>(20)</sup>

This report describes three patients with primary insulin resistance who were treated with prednisone resulting in marked decrease of insulin requirement.

### Case I.

A 72 year old female admitted to Chulalongkorn Hospital for the fifth time on August 24th 1967. She was known to have diabetes mellitus for 10 years and was first admitted to this hospital in 1964 with melena probably secondary to peptic ulcer but upper G.I. series demonstrated no lesion. She was admitted again in the same year for lens extraction. She was readmitted in 1966 with lobar pneumonia and in February 1967 with recurrent melena. On admission upper G.I. series showed a questionable lesion at

the pylorus and she was treated with an ulcer regimen.

During each of her hospital stay she was treated with insulin for short time and subsequently discharged with oral agents. (Diabenes 375 mg. + DBI 25 mg.)

One month prior to her fifth admission in August 1967 she began having fatigue, insomnia and heavy glycosuria. She was then admitted for control of diabetes mellitus.

Physical examination revealed an obese woman in no acute distress, looking worried and apprehensive. Vital signs were normal. Both fundi showed retinitis proliferans. She had greatly diminished visual acuity being capable of only light perception. The heart was not enlarged and there was no murmur. Lungs were clear to auscultation. Liver and spleen were not palpable. There was diminished pain sensation of both lower extremities and no deep tendon reflexes were elicited.

Laboratory tests were as follows : Hb, 12 gm%, WBC, 7,500 cell/cumm<sup>2</sup>., Neutrophil, 58%, Lymphocyte, 42%, Urine sugar, 3 plus and negative for albumin and sediment. BUN, 20 and Creatinine, 1.5 mg.% serum Na, 147 mEq/lit., K, 3.7 mEq/lit., FBS, 195 mg.%.

Chest X-ray was normal

Upper GI series was normal

EKG : Borderline left ventricular hypertrophy.

After admission the patient was given regular insulin on sliding scale according to urine sugar. In the first five months of hospital stay her diabetes was not controlled in spite of high doses of insulin. The blood sugar was ranged from 190 to 270 mg.% without ketoacidosis. Insulin was gradually increased up to 360 units. Phenformin (DBI), Tolbutamide and Chlorpropamide were tried without benefit. She continued having heavy glycosuria and weight loss. Finally steroid was tried since upper G.I. was normal and she had no abdominal pain during this admission. Prednisone 20 mg./day was started on Jan. 18, 1968 for 5 days with no good result. Then it was increased up to 60 mg./day. Two days later the blood sugar and glycosuria were lower. Insulin dosage and prednisone were gradually decreased. The patient was then maintained on 80 units of NPH and 10 mg. of prednisone. During these time she was carefully observed for possible G.I. bleeding, antacid was given and daily examination of her stool for blood was performed. She did well and was discharged on April 1968. Since she had history of melena prednisone was stopped periodically with reappearance of glycosuria and hyperglycemia. Prednisone 15 to 10 mg./day was continued until June 1968 is She was seen at the emergency room with massive G.I. bleeding and acute myocardial infarction and expired on the next day with cardiac arrest.

**Case II** (A.T 030586/12) A 68 year old woman was admitted for the second time to Chulalongkorn hospital on March 4, 1969. complaining of weakness, light headache loss of appetite for 2 or 3 months. One year previously she was hospitalized because of erythema multiforme secondary to Diabenes which she was treated for newly discovered diabetes mellitus. Her

diabetes was controlled with NPH insulin 20 units daily for 2 months until she developed symptom of hypoglycemia. Treatment was changed to DBI and was continuously given for 8 months following which she became uncontrolled and had to be admitted for the second time.

There was no familial history of diabetes mellitus. Physical examination showed a well developed but thin poorly nourished woman weighing 39 kilos in no acute distress. Blood pressure was 170/90 mm.Hg., the pulse rate 90 per minute and the temperature was 98.9° F. There were opacity of lens in both eyes. Fundi showed no evidence of diabetic retinopathy. Lungs were clear. Heart was not enlarged and there was no murmur. Liver and spleen were not palpated. Neurological examination showed severe peripheral neuropathy of both lower extremities. She had no deep tendon reflexes.

Laboratory tests were as followings: Hb, 11 gm.%, WBC, 11,000 with 73% of neutrophil, eosinophil. 7%, lymphocyte 19% and monocyte 1%.

Urine gave 3 plus sugar with 2 or 3 white blood cell, BUN, 30 mg.%, Creatinine 1.3 gm.%, serum albumin, 3 gm. %, Globulin, 2.7 gm.%, Total cholesterol, 204 mg.%, Na, 130 mEq/lit., K, 4.6 mEq/lit, FBS, 178 mg%. Total bilirubin, 0.4 mg., Direct bilirubin, 0.1 mg.%, CCF, 4 plus Thymol turbidity, 6.6, Alkaline phosphatase, 1.5 Bodansky units, SGOT, 25 units, Serum iron, 80  $\mu$ g%, Iron binding capacity, 200  $\mu$ g%.

Chest X-ray, and EKG were normal. The patient was treated initially with regular insulin, according to urine sugar on sliding scale. In first week the requirement of insulin average 40 units/day and FBS ran between 130 to 160 mg.%. During the

second and third weeks, diabetes became out of control, she developed mild ketoacidosis three times while on insulin and was treated as such. On fourth week she had no more ketoacidosis but the requirement of insulin gradually increased to 420 units. Two weeks later after excluded the conditions which might cause a increase in insulin requirement such as hemochromatosis, infections and liver disease, prednisone 60 mg./day was started. The next day, insulin was dropped to 240 units, and on the 3rd and 4th day blood sugar were normal inspite of no insulin.

She was later controlled with 80 to 100 units of NPH insulin while steroid was tapered gradually to 40 mg/day. 2 weeks later she developed hypoglycemia while on the above regimen and was treated successfully with I.V. dextrose. Unfortunately the same dose of insulin was given inadvertently the next day and the patient expired from profound hypoglycemia despite the usual treatment.

### Cases III.

A 49 year old married Chinese woman was admitted to Chulalongkorn Hospital on November 3, 1970 for control of diabetes mellitus. She had symptoms of polyuria, polydipsia and weight loss for sometime and diabetes mellitus was discovered 1 1/2 year ago. She was treated with oral agents and injection of insulin 40 units intermittently for one year. Her diabetes mellitus has never been well controlled, blood sugar ran between 90 mg to 220 mg.%, In the past 4 or 5 months she began having numbness of extremities, heavy glycosuria and had lost about 10 kilos. of weight A vigorous regimen of diet and insulin was started outside but when her diabetes was still uncontrolled with 140 units of NPH insulin a day she was admitted for control.

She had no history of allergy or diabetes mellitus in the family.

Physical examination at time of admission revealed a thin patient in no distress. Fundi showed no evidence of diabetic retinopathy. Heart was not enlarged and there was no murmur. Lungs were normal. Liver and spleen were not palpable. Neurological examination was all normal except for absent deep tendon reflexes.

Laboratory findings were as following: Hb, 12 gm%, WBC, 6340, N, 74%, E, 3%, L, 22%, BUN, 18 mg%, Creatinine, 0.9 mg% FBS, 230 mg%, Na, 136 mEq/lit, K, 4.6 mEq/lit, Cl, 101 mEq/lit., CO<sub>2</sub>, 20 mEq/lit, Cholesterol, 350 mg.%, Serum iron, 100 µg%, Iron binding capacity, 230 µg%, Total bilirubin, 0.4 mg.%, Direct bilirubin 0.1 µg, Thymol turbidity, 10 units, SGOT, 90 Bodanski Units.

Urine was 4 plus and positive for sugar, otherwise it was uormal

Chest X-ray, and EKG were normal.

The patient was treated with regular insulin according to urine sugar on a sliding scale. After one week the dosage was up to 320 units of regular insulin per day but urine test were still 4 plus with FBS running around 300 mg%. DBI 25 mg, 3 times a day was added with no improvement in 5 days. The patient was started on prednisone 60 mg./day. Increase five days later to 100 mg./day. Diabetes was still not under control with 320 to 360 units of regular insulin per day. Ten days after starting prednisone the patient finally came under control. Both insulin and prednisone were tapered down rapidly until patient was taking 10 mg of prednisone and 70 units of NPH daily. 4 weeks after starting steroids the patient gained 4 kilos of weight and was under good control, she was discharged on prednisone 5 mg NPH daily. Two months after

discharge prednisone was stopped and patient has been doing very well on 70 units of NPH since.

**Discussion**

Therapeutic preparations of insulin generally contain mixtures of beef and pork insulin. Pure beef and pure pork insulin are also available but not in our country.

Insulin is a polypeptide containing 51 amino acids arranged in two chains. Chain A has 21 amino acids and chain B has 30 amino acids. The two chains are united by two disulfide bridges.

Pork insulin differs from human insulin by one amino acid while beef insulin differs in three. (See Table I) The differences in the number of amino acids cause the insulin to be antigenic in man. Pure pork insulin induces a lesser antigenic response in man than beef insulin. Circulating antibodies to insulin are present within a few months after initiation of insulin therapy.<sup>(2,3)</sup> Insulin resistant diabetes is usually associated with a high level of insulin binding antibody.<sup>(17,23)</sup>

The major cause of insulin resistance is probably the abnormal formation of circulating antibodies.

Other causes such as tissue hyporesponsiveness,<sup>(22)</sup> presence of insulin antagonist<sup>(4,10)</sup> may play some part.

Insulin resistance may occur with or without insulin allergy. Duration of insulin treatment prior to the onset of resistance range from one month to 12 years. Sixty-six percent of patients were receiving insulin treatment lesser than one year.<sup>(20)</sup>

The aim of treatment is to control hyperglycemia, glycosuria and prevent acidosis with a reasonable amount of insulin. The use of tolbutamide<sup>(1)</sup>, phenformin,<sup>(19)</sup> nitrogen mustard<sup>(11)</sup>, insulin from different animal species particularly of pork origin<sup>(7)</sup> and adrenal steroid were tried. Karam et al.<sup>(12)</sup> also reported a case of insulin resistant diabetes treated successfully with insulin withdrawal and weight reduction alone.

Adrenal steroids and ACTH have most consistently altered the resistance<sup>(20)</sup> to insulin. The success of steroid treatment

**Table I.** Differences in amino acid structure between beef, pork and human extracted pancreatic insulin,

Species	A Chain		B Chain
	Position 8	Position 10	Position 30
Beef	Alanine	Valine	Alanine
Pork	Threonine	Isoleucine	Alanine
Human	Threonine	Isoleucine	Threonine

From : Medical clinic. North America, 48 : 941 : 1965.

in most cases confirms the immune basis of insulin resistance. Reduction of insulin requirement occurs in the first two weeks of treatment and commonly occurs within two to five days. The possible effect of steroid in insulin resistance includes the dissociation of antigen-antibody complexes, reduction of insulin antibody formation<sup>(15)</sup> and increase glucose entry into the cells by increasing capillary permeability. If steroid is used, it should be started with 60 to 80 mg% prednisone daily in divided doses. Once the response has occurred the dosage can then be reduced gradually to the maintenance dose of 5 to 10 mg. of prednisone daily which can be given for some time before stopping all together.

Severe hypoglycemia can occur immediately upon the breakage of the resistance and should be carefully watched for as the patient may have much of insulin bound in antigen-antibody complexes which are then resolved by steroids.

### Summary.

Three cases of primary insulin resistant diabetics whom were treated successfully with prednisone were reported. The mechanism of action, dosage and complications were discussed. Steroid is relatively contraindication in diabetes mellitus but it can be used in certain condition.

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