Case Report

INCREASED ACTIVITIES OF SERUM ENZYMES PREDOMINATING IN HEART MUSCLE IN PATIENTS WITH HYPOTHYROIDISM
REPORT OF TWO CASES

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INCREASED activities of serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) in patients with hypothyroidism have been reported recently1-3 and clinical usefulness of the CPK determination in this disease is emphasized4. However, little is known of the source of the elevated serum enzymes in hypothyroid state so far.

In this report, the changes in serum levels of CPK, LDH, glutamic oxalacetic transaminase (GOT) and LDH isoenzyme patterns in two patients with hypothyroidism were reported, and a possible source of the elevated serum enzymes or isoenzymes was discussed.

ENZYME ASSAYS

The activities of glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were estimated by the method of Reitman-Frankel5. Estimation of creatine phosphokinase (CPK) was based on the method of Nutall-Weiden5. Lactate dehydrogenase (LDH) activity was assayed by the method of Cabaud-Wróblewski.

LDH isoenzymes were determined by tetrazolium-linked reaction using agar gel electrophoresis. The method is described in detail elsewhere.

REPORT OF CASES

Case 1: A 51-year-old woman was admitted to the hospital because of edema, palpitation and dyspnea. Two months before entry swelling of the face and extremities, palpitation and exertional dyspnea developed. She was found to have hepatomegaly, cardiomegaly, hypertension and anemia at another hospital, and had treatment for two weeks without remarkable effect. No past history of serious illness.

Physical examination revealed anemia, and edema in the eyelids and legs. Pulse was 68 a minute, regular and blood pressure was 154/96 mmHg. The apex beat was located in the fifth left intercostal space in the anterior axillary line. The left cardiac border coincides with the left anterior axillary line, the right with the right midclavicular line and the upper with the third rib. Auscultation revealed a grade 2 systolic murmur at the apex. Lungs were clear. The liver and spleen were not palpable. No ascites was proven.

The chest X-ray film (Fig.1-A) showed a large heart with a cardio-thoracic ratio of 83 per cent. There was a small round shadow overlying the right middle pulmonary area. An electrocardiogram (ECG) (Fig.3) disclosed a decrease in voltage, and inverted or flat T waves.

Blood examination gave Hb 9.6 g/dl, red blood cells 3.1 million, white blood cells 3200/cu.mm. with neutrophils 65 per cent, lymphocytes 28 per cent, eosinophils 6 per cent and basophils 1 per cent. Erythrocyte sedimentation rate (ESR) was 70 mm in the first hour. Routine urine and stool examination revealed no abnormality. Basal metabolic rate (BMR) was -34 per cent. Laboratory data were as summarized in Table I. Remarkable elevations in LDH, LDH-1,
Fig. 1. Chest X-rays of Case 1. (A) on admission; (B) after treatment.

Fig. 2. Chest X-rays of Case 2. (A) on admission; (B) after treatment.
<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOT</strong></td>
<td>10–40 U</td>
<td>64</td>
<td>70</td>
</tr>
<tr>
<td><strong>GPT</strong></td>
<td>5–35 U</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td><strong>CPK</strong></td>
<td>35 U</td>
<td>—</td>
<td>180</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>100–400 U</td>
<td>740</td>
<td>1870</td>
</tr>
<tr>
<td><strong>LDH isoenzyme</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH-1</td>
<td>18–34%</td>
<td>36.7</td>
<td>46.1</td>
</tr>
<tr>
<td>LDH-2</td>
<td>31–44%</td>
<td>40.5</td>
<td>34.9</td>
</tr>
<tr>
<td>LDH-3</td>
<td>19–31%</td>
<td>13.6</td>
<td>11.8</td>
</tr>
<tr>
<td>LDH-4</td>
<td>4–9%</td>
<td>4.6</td>
<td>3.6</td>
</tr>
<tr>
<td>LDH-5</td>
<td>2–8%</td>
<td>4.6</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Serum protein</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>55–68%</td>
<td>55.3</td>
<td>57.0</td>
</tr>
<tr>
<td>α1-globulin</td>
<td>2–3%</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>α2-globulin</td>
<td>5–10%</td>
<td>6.7</td>
<td>7.9</td>
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<tr>
<td>β-globulin</td>
<td>9–13%</td>
<td>11.9</td>
<td>9.7</td>
</tr>
<tr>
<td>γ-globulin</td>
<td>13–20%</td>
<td>23.9</td>
<td>23.2</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>140–240 mg/dl</td>
<td>308</td>
<td>374</td>
</tr>
<tr>
<td><strong>BUN</strong></td>
<td>8–18 mg/dl</td>
<td>11.7</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Na</strong></td>
<td>135–150 mEq/L</td>
<td>142</td>
<td>140</td>
</tr>
<tr>
<td><strong>K</strong></td>
<td>4.0–5.0 mEq/L</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>Cl</strong></td>
<td>95–110 mEq/L</td>
<td>101</td>
<td>104</td>
</tr>
<tr>
<td><strong>Triosorb</strong></td>
<td>26–37%</td>
<td>18</td>
<td>19</td>
</tr>
</tbody>
</table>

GOT, GPT, cholesterol and γ-globulin values and decrease in $^{131}I$ resin sponge uptake (Triosorb) test were obtained.

Case 2: A 57-year-old woman was admitted to the hospital because of fatigue and edema of the eyelids. Five years earlier she had a thyroidectomy for hyperthyroidism. Two years later she was admitted to the another hospital because general fatigue, hoarseness and edema; a diagnosis of secondary hypothyroidism was made and thyroid hormone was given. The symptoms improved gradually by the treatment and she was discharged on the ninety hospital day. In the interim after discharge thyroid hormone therapy was continued and she had been well. Seven months previously she discontinued thyroid hormone, and general fatigue, weakness and edema of the eyelids developed. There was no past history of serious illness.

On admission, physical examination disclosed a woman of average physique. She was pale and had edema of the eyelids but no peripheral edema. Pulse was 70 a minute, regular, the blood pressure being 130/90 mmHg. The heart and lungs were normal. The liver and spleen were not palpable.

An X-ray film of the chest (Fig.2-A) revealed borderline enlargement of the heart, showing a cardiothoracic ratio of 48 per cent. The ECG (Fig.3) demonstrated a decrease in voltage in limb leads and flat T waves.

Laboratory data revealed: Hb, 11.5 g/dl; red blood cells, 3.4 million; white blood cells, 6000/μl; 65 per cent neutrophils; 32 per cent lymphocytes; one per cent monocyte; and 2 per cent eosinophils. Urinalysis was negative. ESR was 41 mm in the first hour. BMR was −30 per cent.

Other laboratory findings were shown in Table I. Elevated serum levels were observed in CPK, LDH, LDH-1, GOT, cholesterol and γ-globulin. Triosorb test was reduced.

**TREATMENT AND CLINICAL COURSE**

The diagnosis of primary hypothyroidism for Case 1 and secondary hypothyroidism for Case 2.

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was made respectively, and administration of desiccated thyroid hormone was started. In each case remarkable clinical response to the therapy was encountered, however, administration of thyroid hormone was discontinued in Case 1 after 19 days because of development of epigastric fullness and anorexia.

Chest X-ray films and ECGs taken before and after treatment in each case were shown in Fig.1, 2 and 3. Through the treatment the cardiothoracic ratio diminished from 83 per cent to 58 per cent in Case 1, and from 48 per cent to 44 per cent in Case 2 (Fig.1 and 2). The ECGs taken after treatment showed an increase in voltage and height of T waves in all leads (Fig.3).

The changes in levels of serum enzymes and thyroid function tests observed during the treatment were shown in Fig.4 and 5. A fall in levels of LDH, CPK and GOT was accompanied by an improvement of values of BMR and Triosorb test in each patient. Subsequent serum LDH isoenzyme patterns were illustrated in Fig.6. Gradual return of LDH isoenzyme pattern to normal range, namely a decrease in LDH-1 with an increase in LDH-3, was observed in each case within 40 days.

**DISCUSSION**

An increased serum creatine phosphokinase (CPK) in patients with hypothyroidism was first reported by Graig and Ross, and this was confirmed by Griffiths and Fleisher et al. Elevations of serum lactate dehydrogenase (LDH) and glutamic oxalacetic transaminase (GOT) as well as CPK in this disorder was also pointed out by Fleisher et al. Furthermore, a return of elevated serum CPK level to normal during treatment was reported. In the present paper, observation of gradual return of increased serum CPK, LDH, LDH-1 and GOT to normal during the treatment was demonstrated in two patients with hypothyroidism. Although the evidences of increase of these enzymes in serum have been observed, the source or mechanism by which enzymes release into serum is still obscure.

CPK is found in highest concentration in skeletal muscle followed by brain and heart, and not found in liver or red blood cells. GOT is contained predominantly in heart, liver and skeletal muscle. Regarding the organ specificities of CPK and GOT, concomitant increase of both of them encountered in the present cases suggests
that the source of these enzymes may be heart or skeletal muscle. However, further differentiation between these two organs is impossible so far as CPK and GOT are concerned.

LDH exists in many tissues as isoenzymes and different tissues possess different concentrations of the individual isoenzymes. LDH-1 is found in high concentration in myocardium, erythrocyte and kidney, while LDH-5 in liver and skeletal muscle. An injured tissue is considered to raise the serum concentration of the specific isoenzymes predominating in that tissue, such as LDH-1 in myocardial infarction and LDH-5 in hepatitis, respectively. Therefore, isoenzyme determination permits more precise recognition of tissues of origin than is possible by determination of total enzyme activity alone.

The finding of an increase in LDH-1 but not in LDH-5, observed in the presented two cases, indicates that LDH is originated from heart muscle.

It can not be excluded that serum LDH, CPK, and GOT derive from different organs each other. However, the same source of these serum enzymes, namely heart is strongly supported by the fact that during the treatment by thyroid hormone levels of all these enzyme activities and concentration of LDH-1 fell in parallel to a decrease in heart size and improvement of ECG findings in both cases.

On the basis of available evidences, it seems likely that cardiac muscle contribute to the increased serum enzyme levels in hypothyroid state. However, we can not conclude the origin of elevated serum enzymes since our material is only two cases and there is a patient with hypothyroidism who showed an increase in concentration of LDH-5 including elevated activities of LDH, CPK and GOT!!

Little is known of the factors which regulate

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**Fig.4.** Changes in levels of serum enzymes and in thyroid function tests during therapy in Case 1. (The broken lines indicate upper limit of normal value.)

**Fig.5.** Changes in levels of serum enzymes and in thyroid function tests during therapy in Case 2. (The broken lines indicate upper limit of normal value.)
the release of certain enzyme from tissue into circulation in hypothyroidism. However, some hypothetical possibilities are postulated. The first is the inhibitory effect of thyroid hormone on enzyme activity which is supported by the fact that thyroxine in vitro strongly inhibit the activity of CPK, and triiodothyronine reduce the liver LDH activity. Thus, depletion of thyroxine seen in hypothyroidism may accelerate these enzyme activity in blood stream. The second possible explanation is altered membrane permeability. It is shown that the patients with hypothyroidism show a marked increase in capillary permeability which rapidly returns to normal with thyroid hormone.

In order to elucidate the origin of elevated serum enzymes and real mechanism regulating serum levels of enzymes in hypothyroidism, further investigation should be undertaken.

SUMMARY
An elevation of serum levels of CPK, LDH, GOT and concentration of LDH-I in isoenzymes was observed in two middle aged female patients with hypothyroidism. During treatment with thyroid hormone these enzyme activities fell parallel to the improvement of thyroid function tests, cardiomegaly and findings of electrocardiogram. An increase in CPK, LDH and GOT activity indicates that the source of these serum enzymes may be heart or skeletal muscle. Among two organs heart was considered to be an major source of increased serum enzymes by further analysis of LDH isoenzymes.

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REFERENCES

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