

BLOOD LACTATE LEVELS IN DIABETICS ON DIFFERENT MODES OF THERAPY

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SUMMARY

Blood lactate levels were measured in different groups of diabetics. Blood lactate levels were highest in untreated diabetics followed by those on insulin treatment. Elevated lactate levels came down after control of diabetes, irrespective of the drugs used. Phenformin-treated diabetics did not have significantly elevated lactate levels. Use of small doses of the drug in carefully selected patients might have been responsible for this finding.

INTRODUCTION

The discovery of the oral hypoglycemic agents was a landmark in the management of diabetes. However, several of these drugs have been incriminated as causing or aggravating various complications. Interest in blood lactate metabolism in diabetics has been kindled recently, following several reports on Phenformin induced lactic acidosis,^{1,6} which led to the subsequent banning of this drug in some countries.

To study the magnitude of the problem in our country, a project has been in progress at this centre, for the past four years. The preliminary observations have been presented already.⁷ This paper presents a detailed evaluation of this study.

MATERIAL AND METHODS

Blood levels of lactate and pyruvate were measured as a routine, at this centre, in untreated diabetics, and in diabetics on different drug therapies. This study group comprised of 391 maturity onset diabetics and 26 normal controls. Of these, 100 patients had received no treatment at the time of the study and others were receiving insulin or oral drugs for periods ranging from 6 months to several years. In every patient a detailed history of drug therapy was recorded. The details of drug therapy are shown in Table 1.

TABLE 1 — Details of Drug Therapy

Drug	No. of patients	Usual dose/day
Insulin	30	40 — 100 un'its
Glybenclamide	41	2.5 — 10 mgs.
Phenformin	25	25 — 100 mgs.
Other		
Sulphonylureas :	25	
Chlorpropamide	11	100 — 500 mgs.
Tolbutamide	14	0.5 — 2 gms.
Phenformin +	170	12.5 — 50 mgs.
Glybenclamide		+ 2.5 — 5.0 mg.

Every patient was subjected to a thorough clinical examination. A special search was made for clinical symptoms or signs of any type of acidosis. Patients were also investigated to note the presence of vascular complications.

Blood levels of lactate and pyruvate were measured in the fasting samples and the lactate/pyruvate ratio calculated. Lactate was measured by the method of Barkar and

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Summerson⁸ and pyruvate by the method of Friedmann and Haugen.⁹

Serum electrolytes were measured in every case and the anion gap was calculated.

RESULTS

Table 2 lists the concentration of lactate, pyruvate, the L/P ratio and the anion gap in different study groups.

TABLE 2 — Lactate, Pyruvate and L/P Ratio in the Different Study Groups.

Study group	No. of patients	Lactate mgs% + SD	Pyruvate mgs% + SD	L/P ratio + SD	Anion gap mEq/l + SD
GROUP A Controls	(26)	12.1 ± 3.1	0.9 ± 0.3	12.4 ± 2.1	12.8 ± 2.9
GROUP B Untreated Diabetics	(100)	19.3 ± 8.1 P < 0.001	1.9 ± 0.6 P < 0.001	10.6 ± 3.9 P < 0.001	14.2 ± 3.0 N.S.
GROUP C Treated Diabetics	(291)				
1. Insulin treated	(30)	17.6 ± 9.2 P < 0.01	1.7 ± 0.4 P < 0.001	9.7 ± 3.3 P < 0.001	14.8 ± 3.0 N.S.
2. Glybenclamide	(41)	14.5 ± 3.9 P < 0.01	1.7 ± 0.3 P < 0.001	8.9 ± 3.2 P < 0.001	13.5 ± 2.8 N.S.
3. Phenformin	(25)	15.1 ± 7.6 N.S.	1.5 ± 0.4 P < 0.001	9.7 ± 3.9 P < 0.01	14.0 ± 2.9 N.S.
4. Other Sulphonylureas	(25)	17.1 ± 6.8 P < 0.01	1.7 ± 0.5 P < 0.001	10.3 ± 5.2 N.S.	13.9 ± 2.8 N.S.
5. Phenformin + Glybenclamide	(170)	14.3 ± 4.1 P < 0.01	1.6 ± 0.5 P < 0.001	10.8 ± 4.3 P < 0.01	13.9 ± 3.0 N.S.

P — values in comparison with the control group. Numbers in brackets indicate the number of subjects.

It may be noted that the mean lactate concentration in untreated diabetics (Group B) was significantly high ($P < 0.001$). The different groups of treated diabetics (Group C) showed moderate elevations in lactate, but they were less significant. In the drug treated group, patients on insulin showed the highest mean concentration of lactate. It is worth noting that in the group which

received phenformin alone, there was no significant elevation of lactate levels.

Blood pyruvate was significantly high in all groups of diabetics, the maximum value being in the untreated group.

Because of the concomitant increase in both lactate and pyruvate, in all diabetics, the L/P ratio was lower than normal.

The anion gap was within normal limits

in all cases. The differences in the mean anion gap between various groups were not significant.

Lactate levels above 20 mgs% were taken as hyperlactatemia. Table 3 shows the incidence of hyperlactatemia in each group studied.

The largest incidence of hyperlactatemia

TABLE 3 — Incidence of Hyperlactatemia in various groups of diabetics

Untreated diabetics	Insulin	Glyben-clamide only	Phenformin only	Other Sulphonyl-ureas	Phenformin + Glyben-clamide
42%	36.8%	19.5%	16%	32%	17.6%

was in the untreated group followed by those treated with insulin.

The highest lactate concentration seen in this series was 52.5 mg%. This was seen in two patients, one of them was an untreated diabetic and the other had been on insulin all along. The L/P ratios were 15.7 and 17.2 respectively and the anion gaps were normal. Both the patients had no signs of acidosis. The lactate levels came down to normal within a week with control of hyperglycemia.

The relationship of hyperlactatemia with incidence of vascular complications was studied. The results are shown in Table 4.

Illustrative cases of patients who initially had elevated blood lactate levels and in whom the levels came down are presented in Table 5.

In all these cases, the concentration of lactate came down with control of diabetes. Significant lowering in pyruvate levels also was seen, but the values remained above normal in all cases in the follow up so far.

DISCUSSION

The blood lactate levels in diabetics appear to be related more to the status of the disease than to the mode of therapy. Untreated diabetics showed highest mean lac-

TABLE 4 — Incidence of vascular complications in patients with hyperlactatemia.

	Untreated diabetics	Insulin	Glyben-clamide alone	Phenformin alone	Other Sulphonyl-ureas	Phenformin + Glyben-clamide
No. with complications	5	1	None	None	1	5
No. without complications	37	10	8	4	7	25

Thus in this series the presence of elevated lactate was unrelated to the presence of vascular complications.

FOLLOW-UP:

Long term follow up studies of diabetics with and without elevated lactate levels are in progress. At the present time, only short term follow up data is available. The lactate levels were repeated in 20 diabetics with elevated lactate levels after control of hyperglycemia. It was found that there was a decrease in lactate levels in all patients with control of blood sugar

tate concentration, as well as the largest incidence of hyperlactatemia. Though the duration of follow-up has been short, results so far indicate that blood lactate levels in diabetics come down with the control of diabetes irrespective of which drug is used.

The high mean lactate levels observed in insulin-treated patients is most probably related to the severe degree of diabetes in them.

A few cases with mild degree of vascular complications have been treated with oral

TABLE 5 — *Short term follow up of cases with hyperlactatemia.*

No.	Date	Status of diabetes	Treatment given	Lactate mg %	Pyruvate mg %	L/P ratio	Anion gap mEq/l
Case 1	14.8.78	Severe	Phenformin	35.0	2.0	17.5	15
	19.8.78	Under control	+ Glybenclamide	13.0	1.3	10.0	11
Case 2	31.7.78	Severe	Glybenclamide	52.0	3.3	15.7	14
	5.8.78	Under control		14.0	1.4	10.0	13
Case 3	29.3.78	Severe	Phenformin	27.6	2.0	13.8	14
	5.4.78	Under control	+ Glybenclamide	15.6	1.5	10.0	12
Case 4	22.12.75	Severe	Phenformin	29.0	2.7	10.8	12
	1.2.76	Under control	+ Glybenclamide	13.5	1.7	10.8	12

drugs. No adverse effects on lactate metabolism has been noted in these cases.

It is significant that phenformin treated diabetics did not show very high lactate levels. Many of these patients had been receiving phenformin for over 2 years. The results are in agreement with our previous report on lactate levels in diabetics receiving phenformin⁷ and also with the observations of others.¹⁰⁻¹³

Viswanathan et al¹⁵⁻¹⁸ have pointed out that the average doses of all oral hypoglycemic agents used by them are much smaller than those reported by western authors. Mohan Viswanathan et al¹⁴ have reported that the low incidence of hyperlactatemia noted in patients on phenformin could possibly be related to the smaller doses of the drug used. This view has been expressed by other workers also.¹⁹⁻²⁰

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