Hyperlipidaemia, Obesity and Drug Misuse in a Diabetic Clinic

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SUMMARY

A study of middle-aged and elderly patients attending a diabetic clinic has revealed a disturbing state of affairs. Hyperlipidaemia and obesity were very common but little attention was paid to implementing appropriate dietary regimens. Management was largely confined to the control of hyperglycaemia by using oral hypoglycaemic agents, especially combinations of sulphonylureas and diguanides.

This situation is deplored. Firstly, it ignores the correction of factors which are as important, if not more so, than hyperglycaemia, in regard to the development of the most lethal complication of maturity-onset diabetes, namely occlusive atherosclerosis. Secondly, it substitutes for dietary therapy, which is physiological, treatment by drugs which are potentially harmful. It is probable that a similar situation obtains in many other diabetic clinics.

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We present the results of a study of insulin-independent patients attending a diabetic clinic, in which we measured serum cholestrol and triglyceride levels, and examined their relationship to the factors of age, sex, body mass, form of therapy, and degree of diabetic control. The findings are not new, but they strikingly illustrate the consequences of neglecting the principles of comprehensive diabetic care.

THE CLINIC, PATIENTS AND METHODS

The Diabetic Clinic at the Johannesburg Hospital is held once a week, and patients are seen by appointment at intervals of one to two months. At each visit the mass and blood pressure are recorded, and the urine is examined for glucose and protein with Clinitest tablets and Albustix strips, respectively. Two days before the visit the blood sugar level is measured (ferricyanide method in the AutoAnalyzer) in a post-breakfast specimen. Tests for urinary ketones are done when glycosuria is heavy. Regular clinic attenders number about 800 and they are served by 10 doctors.

Dietary advice has followed conventional lines. Diets are prescribed which aim at nutritional balance and desirable body mass. Sugar and foods rich in sugar are banned, starch, fat and fruit are allowed in reduced amounts, while protein and most vegetables are unrestricted. Advice is given on proper spacing of meals and on the effects of exercise. A dietitian is available, but because of pressure of work she is unable to offer a regular service. To encourage adherence to the diet we rely mainly on regular weighing, and interrogation and exhortation by the doctors.

Between September 1971 and June 1972 we studied 170 White patients selected at random from regular attenders who were more than 35 years old, whose duration of diabetes was at least one year, and who were not clinically nephrotic, myxoedematous, jaundiced or severely uraemic. One hundred and thirty-five patients were on treatment with diet or oral agents and are the subjects of this study. The remaining 35 patients were receiving insulin; this group was too small for meaningful analysis and is not considered further.

Serum triglyceride[1] and total cholesterol[2] levels were estimated in fasting venous samples.

Body mass was expressed as a percentage of the ideal body weights (IBW) listed in Ciba-Geigy *Scientific Tables* (7th edition). Three groups of patients were defined: non-obese, ±10% IBW; moderately obese, 11 - 25% IBW; and markedly obese, more than 25% IBW.

The degree of diabetic control was assessed by examining all the blood and urine sugar recordings during the period of one year previous to study. Control was regarded as 'good' if the majority (more than two-thirds) of post-prandial blood sugar levels were less than 175 mg/100 ml and the majority of urine specimens contained not more than 1+ sugar; 'moderate' if the majority of blood sugar values were between 175 and 250 mg/100 ml and glycosuria was not more than 3+; and 'poor' if the majority of blood and urine specimens contained more sugar than 250 mg/100 ml and 3+, respectively.

The Student's *t*-test was used for most of the statistical analyses.

RESULTS

Age and Sex

All but 6 of the 135 patients were more than 45 years old. Serum lipid levels were similar in patients aged 45 - 60 years and in those over 60 years (Table I). There

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were twice as many females as males. Serum cholesterol levels were similar in men and women. The females had higher triglyceride values, but the variation in both sexes was very large and the difference was significant only at the 5% level (Table II). The lipid data were therefore pooled for the remaining analyses.

TABLE I. AGE AND SERUM LIPID LEVELS (MEANS ± SD)

Age (years)	% of cases	Triglyceride (mg/100 ml)	Cholesterol (mg/100 ml)
45 - 60	36	222 ± 203	240 ± 56
>60	60	190 ± 108	257 ± 52

TABLE II. SEX AND SERUM LIPID LEVELS (MEANS ± SD)

Sex	% of cases	Triglyceride (mg/100 ml)	Cholesterol (mg/100 ml)
Male	33	164 ± 69	238 ± 62
Female	67	222 ± 170	256 ± 48

Serum Lipid Distribution

Mean (± SD) cholesterol and triglyceride levels were 251 (± 52) and 203 (± 147) mg/100 ml, respectively. Hypercholesterolaemia, defined as a cholesterol level greater than 250 mg/100 ml, was present in 45% of cases (Fig. 1) and hypertriglyceridaemia, defined as a triglyceride level greater than 150 mg/100 ml, in 58% (Fig. 2). In 71% one or other lipid value was raised and in 33% both were elevated.

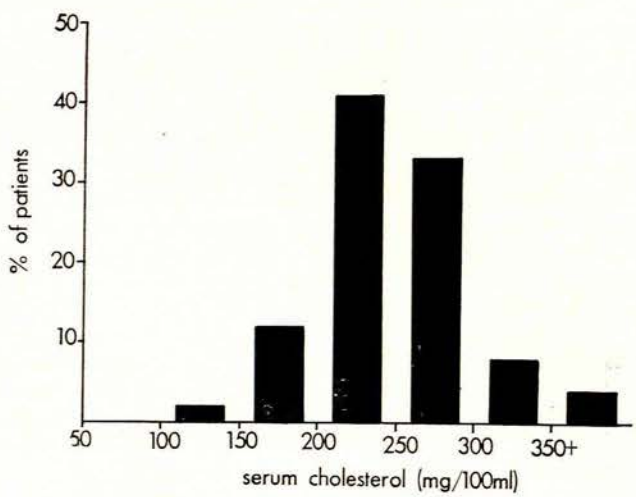

Fig. 1. Distribution of serum cholesterol levels in insulin-independent diabetics.

Serum Lipids and Body Mass (Table III)

Obesity was found in 81% of patients, this being moderate in 31% and severe in 50%. No less than 91% of the women were overweight. This was severe in 62% and moderate in 29%, the corresponding figures for men being 23% and 39% ($P<0,001$ for the difference in frequency of severe obesity between the sexes). Mean triglyceride, but not cholesterol, levels rose with increasing body mass ($r = +0,21$; $P<0,05$).

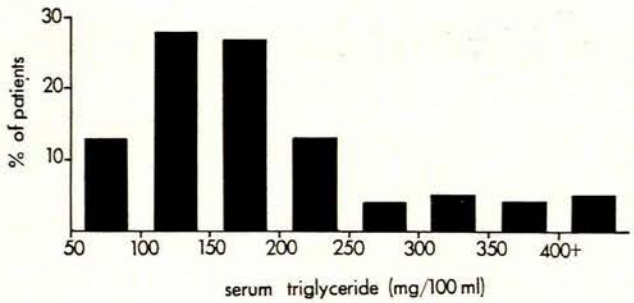

Fig. 2. Distribution of serum triglyceride levels in insulin-independent diabetics.

TABLE III. BODY MASS AND SERUM LIPID LEVELS (MEANS ± SD)

Ideal body mass	% of cases	Triglyceride (mg/100 ml)	Cholesterol (mg/100 ml)
± 10%	19	162 ± 70	234 ± 38
+ 11 - 25%	31	187 ± 99	250 ± 54
More than + 25%	50	214 ± 172	252 ± 57

Serum Lipids and Diabetic Control (Table IV)

Control of the blood sugar level was good in the majority of patients. Mean triglyceride levels were highest in the small minority of poorly controlled diabetics, but did not differ significantly from values in the two better-controlled groups.

TABLE IV. DIABETIC CONTROL AND SERUM LIPID LEVELS (MEANS ± SD)

Diabetic control	% of cases	Triglyceride (mg/100 ml)	Cholesterol (mg/100 ml)
Poor	7	434 ± 399	265 ± 75
Moderate	17	205 ± 107	238 ± 41
Good	76	183 ± 101	252 ± 54

Serum Lipids and Form of Therapy (Table V)

Only 8% of patients were on treatment with diet alone. The remainder received a sulphonylurea (mainly tolbutamide or chlorpropamide) or a biguanide (metformin or phenformin), and nearly half were treated with a combination of a sulphonylurea and a biguanide. The mean triglyceride level was lowest in the patients on diet alone but did not differ significantly from the values in the other treatment groups. The cholesterol level in the

patients treated with biguanides was significantly lower than in cases receiving sulphonylureas ($P<0,01$) or sulphonylurea-biguanide combinations ($P<0,05$).

TABLE V. FORM OF THERAPY AND SERUM LIPID LEVELS (MEANS ± SD)

Treatment	% of cases	Triglyceride (mg/100 ml)	Cholesterol (mg/100 ml)
Diet	**8**	**153 ± 50**	**274 ± 89**
Biguanide	**11**	**205 ± 94**	**222 ± 37**
Sulphonylurea	**32**	**193 ± 86**	**258 ± 42**
Sulphonylurea + biguanide	**49**	**219 ± 194**	**248 ± 54**

DISCUSSION

Viewed academically, our observations on serum lipids in maturity-onset diabetics were unremarkable. In essence, hypertriglyceridaemia and hypercholesterolaemia were common; triglyceride levels rose moderately with increasing body mass, which probably explains why the women, who were more obese than the men, had somewhat higher values; triglyceride levels tended to be higher in poorly controlled patients but this was not statistically significant: and lipid levels did not correlate with the type of therapy used except that patients treated with biguanides had lower cholesterol values than those receiving sulphonylureas. Similar findings have been reported by others in respect of hyperlipidaemia prevalence[3-5] and its relationship to mass,[5] control[6,7] and form of treatment.[6]

Practically, however, this study has revealed a state of affairs which is a serious indictment of the management of diabetics in the clinic. Specifically, there are three matters for concern. Firstly, the prevalence of hyperlipidaemia was high. The frequency of raised lipid levels may not be much higher in maturity-onset diabetics than in normoglycaemic controls,[8,9] but this does not make the situation acceptable in view of the serious prognostic significance of hypertriglyceridaemia and hypercholesterolaemia.[10] Secondly, and perhaps even more important, most of the patients were obese and fully one half were severely so. Thirdly, very few were on treatment with diet alone; most were receiving oral hypoglycaemic agents and nearly half were being treated with a combination of a sulphonylurea and a biguanide. Few patients appeared to have been given a proper trial of treatment by diet alone before being placed on these agents. Since in most cases the control of hyperglycaemia was satisfactory, the meaning of all this is clear: management of diabetic patients was largely concentrated on lowering the blood sugar with oral drugs and treatment of other aspects was neglected or overlooked.

This situation is to be deplored because it ignores the correction of factors which on present evidence appear to be as, if not more, important than hyperglycaemia in regard to the development of the complication responsible for most of the morbidity and mortality in diabetics, namely occlusive atherosclerosis. It is generally agreed that this disorder, especially coronary artery involvement, occurs earlier, is more severe and progresses more rapidly in diabetics than in non-diabetics. The reasons for this are complex and not well understood but it is doubtful whether hyperglycaemia *per se* is the whole explanation. For example, critical analyses and careful investigations have failed to demonstrate a convincing relationship between the incidence of cardiovascular disease and the control of hyperglycaemia.[11,12]

Whatever the reasons, the proper management of diabetes must involve not only the correction of hyperglycaemia but also the elimination or reduction of *all* factors known to increase the risk, or adversely affect the prognosis, of occlusive atherosclerosis, including physical inactivity, gluttony, obesity, hypercholesterolaemia, hypertriglyceridaemia, hypertension and smoking. Of central importance is correct dieting. In general, maturity-onset diabetics require a diet which, firstly, is low in calories and aimed at achieving normal body mass, normoglycaemia and normal serum triglyceride levels. Carbohydrates may have to be particularly restricted in patients whose triglyceride response to ingestion of this nutrient is markedly excessive.[13,14] Secondly, the ratio of polyunsaturated to saturated fat should be high and aimed at attaining and maintaining normal serum cholesterol levels. That such diets are practicable and capable of achieving the aims outlined over prolonged periods has been demonstrated in recent studies.[15] There is also evidence that such diets may in fact reduce the incidence of cardiovascular disease, even when started for the first time in middle-aged subjects.[16] Although this has still to be shown in the diabetic population, the findings are sufficiently encouraging to stimulate a much more vigorous approach to the implementation of dietary measures than is commonly the case at present.

We must re-emphasise the principle that oral hypoglycaemic agents must never be used as a substitute for treatment by diet. They should only be considered when diet has failed or is unlikely to control hyperglycaemia adequately. If tablets are introduced, diet must be continued. There are several good reasons for this advice. Apart from the fact that oral agents have adverse effects, including severe hypoglycaemia, and once started are usually continued indefinitely, there is no good evidence that they do anything to reduce the incidence of vascular disease. In fact, as is now well known, a major finding of the University Group Diabetes Program (UGDP) study was that patients treated with diet plus the sulphonylurea, tolbutamide, or diet plus the biguanide, phenformin, had significantly higher cardiovascular mortality rates than patients treated with diet plus a placebo. These findings have been much criticised,[17] but the UGDP study has been the best of its kind and its findings have been equally vigorously defended.[12]

The reasons why oral hypoglycaemic agents might be associated with an increased cardiovascular mortality are not clear. In regard to the sulphonylureas, pertinent points include the fact that their administration tends to be associated with mass gain,[6] that, as shown here and in a long-term double-blind study,[7] they may not lower serum triglyceride or cholesterol levels despite correction of hyperglycaemia, and that apart from their hypoglycaemic action, they have a variety of pharmacological effects, some of which may be noxious.[18] For example, Lasseter

et al.[19] found that sulphonylureas in concentrations that are attained clinically exerted positive inotropic and chronotropic effects on animal myocardial preparations; in patients with coronary artery disease such stimulation might be deleterious. It is true that the biguanides have been reported to reduce serum lipid levels[20] and body mass[6] but their mode of action is incompletely understood, some of their effects are unphysiological,[21] their triglyceride-lowering effect is variable,[6,22] and it is not clear how much better they are than diet alone in correcting hyperlipidaemia or obesity. Indeed, in the UGDP study the cardiovascular mortality of patients in the phenformin-treated group was higher than that observed in any of the other treatment groups.[12] In this regard it is noteworthy that the phenformin-treated patients exhibited a rise in arterial blood pressure, albeit mild, which continued throughout the observation period of 4¼ years; by contrast, in patients receiving insulin or placebo, a small fall in pressure occurred.[23] Finally, if both sulphonylureas and biguanides are potentially noxious, the possibility exists that given in combination their toxicity may be additive if not synergistic. All in all, while we are fully aware that the last word on the oral agents has still to be said, we believe that for the present they should be used with great circumspection, and never instead of dietary measures which are physiological and harmless. In fact, one diabetic clinic in the USA, as a direct result of the UGDP findings, has gone so far as to abandon the use of phenformin and sulphonylureas almost completely, and was able to achieve satisfactory control with diet alone in 60% of 200 middle-aged patients.[24]

Our clinic, then, despite its name and aims, is not a diabetic clinic, if by that we mean an organisation which provides a system of comprehensive care for the diabetic sufferer. We have found that its activities are largely concerned with prescribing pills, especially in combination, with the principal objective of controlling the raised blood sugar level. It is therefore more accurately described as a 'hyperglycaemic clinic'. Important aspects, such as obesity and hyperlipidaemia and their serious sequelae and concomitants, have been largely ignored.

However, we do not believe that our experience is unique. In fact, we wonder whether the majority of so-called diabetic clinics are not in a similar position. It is the principal objective of this exercise in self-flagellation to stimulate other clinics to examine critically their own practice and record. We do not underestimate the difficulties of providing a proper service for diabetics but we should be able to do better.

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