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Dyslipidaemia

DYSLIPIDAEMIA IN SOUTH AFRICA: HISTORICAL PERSPECTIVE

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The history of dyslipidaemia in South Africa is as much the history of coronary heart disease (CHD), with which dyslipidaemia is so closely related epidemiologically, pathogenetically and therapeutically.

We do not know when the CHD epidemic began in this country, but during the middle of the 20th century clinicians in the Cape[1,2] and Natal[3] and pathologists in Johannesburg[4,5] documented the striking interethnic differences in the prevalence of the disorder.

In 1955 Bronte-Stewart, Keys and Brock[6] published their landmark study showing that the differences between whites, coloureds and blacks were correlated with cholesterol levels and the intake of animal fat. Many other studies followed, attracting outstanding researchers in a variety of disciplines — epidemiology, clinical medicine, genetics, biochemistry and pathology. Collaboration was the order of the day — regionally, nationally and internationally. What follows are some selected highlights with the emphasis on population studies.

In the 1960s surveys showed that CHD was rare, even in elderly[7] and diabetic[8] blacks. However, the disease had emerged in blacks and, as might have been expected, detailed investigation of the early sufferers showed that they were considerably westernised, with an atherogenic biochemical profile.[9] Also at this time biochemists at the South African Institute for Medical Research were the first to report that whites, especially those with CHD, had higher serum triglyceride levels than blacks[10] and that this was probably diet- rather than race-related.[11]

The early 1970s saw the exciting but disturbing discovery of the high prevalence of familial hypercholesterolaemia (FH) in South Africa. Credit for this must go to Evan Stein who, as a young house physician at the Transvaal Memorial Hospital for Children, observed and documented the characteristics of a large series of FH patients.[12] Many studies followed, including a paper entitled 'A host of hypercholesterolaemic homozygotes in South Africa' that attracted international attention.[13] Remarkably heterozygous FH was found to occur in as many as 1 in 70 Afrikaners,[13] Jews[14] and possibly Indians, thereby contributing to the high incidence of CHD in these populations. A major series of collaborative studies between the universities of the Witwatersrand, Cape Town and Stellenbosch identified many of the responsible genetic mutations in these peoples.[15]

In the late 1970s epidemiology came to the fore with Cyril Wyndham's[16-18] careful analysis of death certificate data. He found that CHD mortality rates for South African whites and Indians were among the highest in the world, that Indian rates were even higher than those of whites, that rates for blacks were very low and that those for coloureds were intermediate between whites and blacks.

Wyndham's work was followed in the 1980s by a large number of epidemiological studies systematically documenting the prevalence of dyslipidaemia and other CHD risk factors in Cape white rural Afrikaner communities,[19] coloureds[20] and blacks[21] in the Cape Peninsula,and blacks,[22] whites[23] and Indians[24] in Durban. The studies revealed that CHD risk factors were very common in these populations. However, dyslipidaemia correlated best with the ethnic prevalence of CHD, being pronounced in whites, Indians and coloureds and uncommon in blacks.

Risk factor epidemiology continued into the 1990s when the first comprehensive survey of serum lipids and other metabolic variables was undertaken in male scholars aged 15 - 20 years who were representative of the major population groups, both ethnically and socio-economically.[25] This showed that dyslipidaemia and other metabolic risk factors were much commoner and more severe in white, Indian and coloured groups than in blacks. Also, the CHD risk factor profile was worse in the higher than in the lower socio-economic groups.

I end with the important THUSA study in the late 1990s of a large number of physical and psychological variables in North West Province blacks stratified socio-economically into deep rural, agricultural, informal housing, urban and urban professional groups.[26] In keeping with other findings the survey revealed that the urban groups had the highest fat intake, total cholesterol levels, body mass index and prevalence of

diabetes. Noteworthy, however, were the high prevalences of overweight, diabetes and also hypertension in rural dwellers. These findings highlight the potential for CHD becoming epidemic in blacks.

Significance and consequences of dyslipidaemia and CHD epidemiology in South Africa

The epidemic proportions of dyslipidaemia and CHD in whites, Indians and coloureds were documented, as was their emergence in blacks. Important was the finding that, as elsewhere, the epidemics originated in childhood. A priority of current and future epidemiological research will be the monitoring of the further course of these disorders in response to corrective measures. Evidence suggests that CHD mortality rates have fallen in whites, Indians and coloureds,[27] but this may be due to better treatment rather than prevention and adoption of healthy lifestyles.

The South African experience substantially supports much other evidence that dyslipidaemia is not just a risk factor for CHD, but a fundamental cause. Therefore in FH, dyslipidaemia alone — in the absence of other recognised risk factors — can be responsible for premature and severe CHD. On the other hand, in blacks without dyslipidaemia CHD is rare despite the high prevalence of hypertension, smoking and diabetes.

Most importantly the epidemiological studies stressed the frequency with which dyslipidaemia coexists with other CHD risk factors, which therefore mandates a comprehensive approach to prevention and treatment in populations and individuals. This is exemplified by the national guideline for the 'Diagnosis,management and prevention of the common dyslipidaemias in South Africa', published in 2000.[28]

Much clinical, therapeutic and laboratory research was stimulated throughout South Africa. This deserves a story of its own.

The Lipid and Atherosclerosis Society of Southern Africa was established in 1989 to provide a forum for research in this area both nationally and internationally. In addition lipids and their relation to arterial disease have become a major part of the activities of other scientific organisations such as the Society of Endocrinology, Metabolism and Diabetes of Southern Africa, the Southern African Hypertension Society and the Nutrition Society of South Africa.

All in all South African achievements in lipid and CHD research over the past 50 years have been impressive by any standard. We can look forward to the next 50 years with confidence.

References available on request.

GENETICS OF DYSLIPIDAEMIA

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The leading causes of death worldwide are expected to shift towards cardiovascular disease (CVD) and therefore the development of new molecular tools for accurate diagnosis and targeted treatment is a health care priority.

Modern management of cardiovascular risk is beginning to incorporate genetic alterations underlying dyslipidaemia or modulating the risk of atherosclerosis. Although numerous mutations in major genes may exert a significant effect on risk of CVD, the major disease burden is caused by the aggregate effect of multiple loci that individually have a minor influence on lipoprotein levels. Since atherosclerosis is a multifactorial disease, functional polymorphisms affecting haemostasis and tissue inflammation are also of relevance.

DNA diagnostics

CVD is to a large extent preventable provided that appropriate therapy is implemented at an early stage. This goal can be achieved by applying basic genetic principles in the primary care setting. By obtaining information on family history of CVD and age of onset, it will be possible to assess the appropriateness of genetic testing which could significantly enhance diagnostic reliability. Once the disease-causing mutation(s) has been identified in the index patient, family members can be screened for the same mutation at much reduced cost to confirm or exclude the gene defect with 100% accuracy. Many of the monogenic dyslipidaemias can now be diagnosed at the genetic level using molecular technology (Table I). Informed consent for genetic testing is an important consideration, since identification of a gene defect in the index patient implies that other family members may carry the same mutation. Pre- and post-test counselling is recommended, especially in complex conditions or when no effective treatment is available for the condition in question.

Recent advances linked to the Human Genome Project have led to the development of cost-effective genetic assays that allowed us to take molecular testing from a

Table I. Genetic conditions associated with dyslipidaemia and premature myocardial infarction

Disease	Affected gene	Mode of inheritance	Disease frequency
Familial hypercholesterolaemia	LDLR	Dominant	1 in 500
Familial defective apolipoprotein B-100	Apo B	Dominant	1 in 700
Type III hyperlipoproteinaemia	Apo E	Dominant and recessive	1 in 5 000
Familial apoA1 deficiency	Apo A1	Recessive	Very rare
Tangier disease	ABC1-transporter	Recessive	Very rare
Low HDL syndrome	ABC1-transporter	Dominant	Common
Familial lipoprotein lipase deficiency	LPL	Recessive	Very rare
Familial combined hyperlipidaemia	Unknown, loci on chr 1 and 19	Dominant	Unknown
Niemann-Pick disease (types A,B,C,D,E)	SMPD, NPC	Recessive	Rare
Sitosterolaemia	Unknown, 2p21	Recessive	Rare
Cerebrotendinous xanthomatosis	CYP 27A	Recessive	Rare

research environment to a diagnostic setting. By using rapid stip-assay technology, it is now possible to simultaneously screen for multiple gene mutations underlying CVD that may individually or in combination with other genes and/or environmental factors increase disease risk. Fig. 1 illustrates the test procedure from blood collection (1 - 5 ml collected in EDTA-containing tubes) to mutation detection (Fig. 1A) applicable to the most common causes of dyslipidaemia in the South African population. Two separate strip-assays include relatively common defects in the low-density lipoprotein receptor (LDLR) gene (Fig. 1B) and its ligands, apolipoprotein B and E (Fig. 1C). The strip-assay shown in Fig. 1C also includes other risk factors for CVD or thrombosis, but the individual tests can also be performed separately. Simultaneous analysis of multiple mutations significantly reduces the cost, especially when many samples are processed at the same time.The test results of such comprehensive analyses need to be reported with a clear interpretation of the implications and appropriate health recommendations should be based on both genetic and clinical data.

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is a common autosomal dominant disease that contributes significantly to the high death rate from coronary heart disease (CHD) in South Africa. A clinical diagnosis cannot always be made confidently, but in families with known disease-causing mutations DNA testing will be conclusive where the phenotype is ambiguous. We have previously shown that 15.6% of at-risk family members may be misdiagnosed when total cholesterol concentration at the 80th percentile for age and gender is used as a biochemical cut-off point for a diagnosis of FH, compared with 12.4% using the 95th percentile.[1] The sensitivity and specificity of FH diagnosis according to total cholesterol values (80th percentile) were shown to be 89.3% and 81.9% respectively. The main advantage of direct mutation detection is its very high specificity compared with clinical critera.[2]

To date, more than 60 different mutations in the LDLR gene have been identified in the South African population.[1] Eight of these mutations found to occur in the majority of affected FH patients in South Africa can be detected simultaneously using a cost-effective strip-assay developed in collaboration with Viennalab, Austria (Fig. 1B).

Other genetic risk factors

The influence of low-penetrance genetic risk factors for CVD may be more pronounced in FH patients compared with the general population, due to additive effects. Potential modifiers of the FH phe-

notype include mutations in the genes encoding apolipoprotein B (apoB) and E (apoE), lipoprotein lipase (LPL), cholesterol ester transfer protein (CETP), paraoxonase, methyleneterahydrofolate reductase (MTHFR) and renin-angiotensin system.[3] These and other genetic risk factors found to be of relevance in the FH population may be tested and assessed within the context of environmental risk factors to eventually design personalised treatment regimens based on individual genetic profiles.

Apolipoprotein B

Mutations in the LDLR binding domain of apoB cause a condition that is clinically indistinguishable from FH, known as familial defective apoplipoprotein B_{100} (FDB). Although FDB appears to be rare in the South African population,[4] the most common mutation R3500Q has been identified in a South African family with FH.[5] Patients with mutations in both the LDLR and apoB genes presented with clinical features that are intermediate in severity between heterozygous and homozygous FH. More recently, Loubser and colleagues[6] reported the presence mutation R3500Q in a South African hypercholesterolaemic patient of mixed ancestry (coloured). Contrary to point mutations in the binding domain of the apoB gene, DNA rearrangements resulting in protein truncations are associated with hypocholesterolaemia.

Apoplipoprotein E

The common thee-allele apoE polymorphism accounts for up to 10% of the phenotypic variance of serum cholesterol concentration in the general population.The apo 4 allele may result in raised serum total and LDL cholesterol levels and the associated risk of coronary heart disease is significantly increased in smokers.[7] Men with this allele appear to be most responsive to dietary interventions and the association between HDL cholesterol concentrations and physical activity may also be apoE-dependent.[8] Dyslipidaemia caused by variation in the apoE gene may be normalised by changes to lifestyle (diet, cessation of smoking, exercise) without the necessity of drug treatment and therefore genetic screening followed by timely intervention would lead to more directed health care. Apo 4 is also a low-penetrance risk factor for the development of late-onset Alzheimer's disease.

The presence of two copies of the apo 4 allele (Arg158Cys) confers lower cholesterol concentration in most subjects, but predisposes to the development of dysbetalipoproteinaemia when there is additional metabolic stress. In a study of 42 South African patients, including blacks with proven type III hyperlipoproteinaemia, 25% of cases

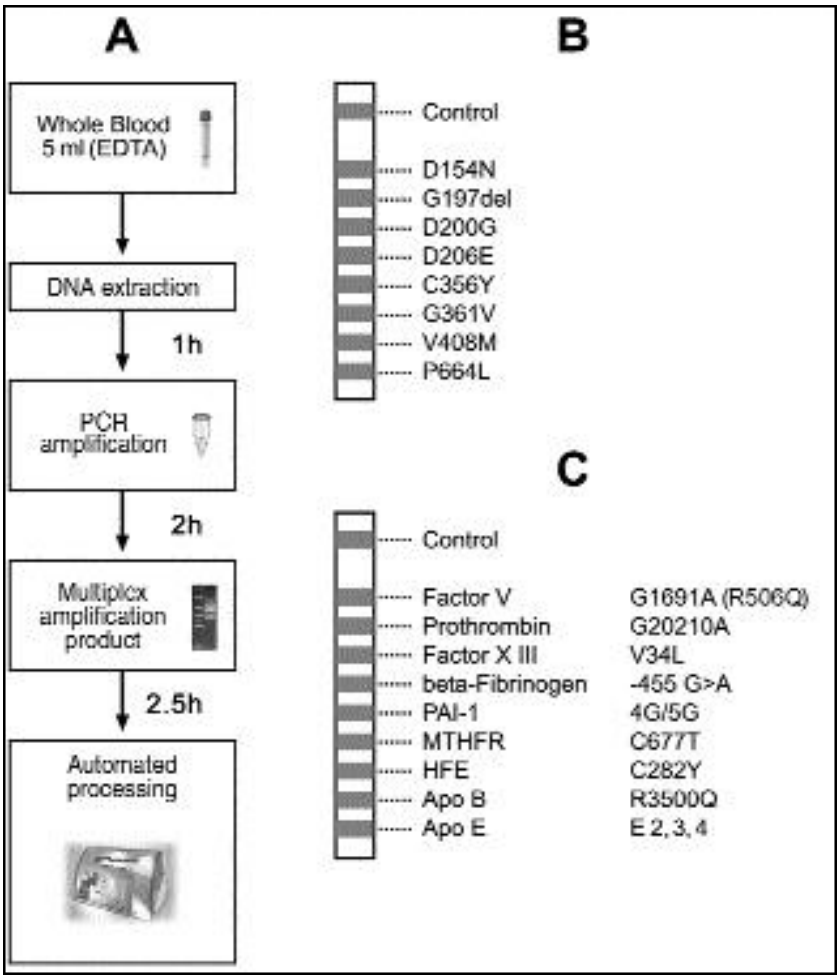

Fig. 1. Screening procedure using the cost-effective strip-assay technology. (A) Test procedure. (B) FH strip-assay to be applied in adults with total cholesterol levels exceeding 7.5 mmol/l and a family history of early-onset CVD. (C) Multigene risk assessment assay for personalised risk reduction based on both the genetic profile and lifestyle factors (e.g. diet, smoking) known to interact with these genetic alterations.

were found to be either heterozygous or homozygous for the rare apo 2 (Arg145Cys) mutation.[9]

Conclusions

Many genes impact significantly on the frequency and severity of coronary disease associated with dyslipidaemia, as well as response to therapy. The demonstration of these genes is becoming part of clinical risk assessment and therapeutic decision making. While patient management is currently based mainly on classic risk factors, the time has come increasingly to use genetic information in a clinical setting of family-orientated preventive medicine.

The use of genetic algorithms (**www.genecare.co.za**) based on clinical and biochemical parameters represents an important step in the application of personalised cardiovascular medicine aimed at disease prevention. Genome-wide expression profiling could in the future be used routinely to identify patterns of gene expression involving common regulatory mechanisms and pathways that can be targeted for individualised treatment.[9] Knowledge of a significantly increased CVD risk due to genetic predisposition will provide a powerful message that will motivate people to follow preventive regimens. Accurate risk assessment, patient motivation and disease prevention would have a significant impact on future coronary events, not only in high-risk families, but also in the population as a whole.

Acknowledgements

Dr Frans Maritz is thanked for critical reading. Merck & Co., Inc., the South African Medical Research Council, Technology for Human Resources and Industry Programme and the University of Stellenbosch, are acknowledged for their support which contributed to the development and manufacturing of the FH strip-assay at ViennaLab, Austria.

References available on request.

DIETARY STRATEGIES IN DYSLIPIDAEMIA: A PRACTICAL APPROACH

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In the dietary management of dyslipidaemia, it is important to distinguish clearly between the different dietary strategies recommended for the treatment of hypercholesterolaemia and hypertriglyceridaemia (Table I).

Although it has been argued that it is easier to prescribe drugs than to change the dietary habits of patients, one cannot ignore the benefits of aggressive diet therapy. It not only reduces the need for medication, but also enhances the efficacy of drugs and reduces their cost. Diet also favourably alters arterial function and is therefore extremely cost-effective. All patients with dyslipidaemia should be referred to a registered dietitian with experience or a special interest in lipid disorders. The cost of one dietetic consultation is less than the monthly cost of a statin. Even if the dietetic consultation does not result in the patient achieving the target plasma lipid value, it may save a doubling of the statin dose.

Hypercholesterolaemia

Patients with moderate to severe hypercholesterolaemia should ideally be counselled to follow the minimum of a step 2 diet (Table I). A stepwise approach in high-risk patients by initiating the step 1

Table I. Key differences in the dietary management of hypercholesterolaemia and hypertriglyceridaemia

	Hypercholesterolaemia		Hypertriglyceridaemia	
Diet	**Step 2 ↔ 3**	**Step 3**	**Low-fat diet**	**Very low-fat diet**
Total fat (%E)	25	20	20 - 30	10 - 20 (25 - 35 g/day)
SFA (%E)	< 7	< 6		
MUFA (%E)	evenly	evenly		
PUFA (%E)	distributed	distributed		
Dietary cholesterol (mg)	200 - 250	100 - 150	< 300	< 300
Alcohol (g)	10 - 20 g allowed	10 - 20 g allowed	Avoid	Avoid

E = energy; SFA = saturated fatty acid; MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.

Table II. Fat and cholesterol content: foods of plant and animal origin

	Plant foods (100 g)			Animal foods (100 g)				
	Cereal, fruit vegetables	Nuts	Tropical	Fish	Poultry	Red meat	Organs/ eggs	Dairy (milk)
Cholesterol (mg)	0	0	75	75	75	>100	2 - 16	
Total fat (g)	0	55	15	1	5	←15→	Variable	0 - 3.3
SFA	0	+	+++	±	+	++	Variable	+++
MUFA	0	+++	+	+	++	+	Variable	++
PUFA	0	++	0	++	+	±	Variable	+

Table III. Sample menu: very low-fat diet (< 10 g fat)/'rescue diet'

Breakfast:	Orange juice
	Rice Krispies served with fat-free milk and sliced banana
	White toast (no margarine) and honey
Snacks:	Fresh or dried fruit
	Fat-free yoghurt
Lunch:	Baked potatoes or white bread sandwich with fat-free cottage cheese
	Large salad
	Fruit
Dinner:	White rice or pasta and lentil bolognaise sauce (tomato based) (no oil!)
	Selection of vegetables
	Fresh fruit

NB. This diet is nutritionally inadequate for energy and protein and should not be followed for more than 1 week at a time under medical supervision.
Additional calories can be added by including carbohydrate-rich snacks and drinks.

diet (prudent) is neither appropriate nor adequately effective to modify risk and achieve the desired response from diet alone.

The four major objectives of a cholesterol-lowering eating plan are the following:

- Reduce total fat intake to 20 - 25% E, especially saturated fatty acids (SFAs) and trans-fatty acids.
- Change the type of fat. Replace SFAs and trans-fatty acids with mono-unsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), particularly the n-3 PUFAs (of which alpha-linolenic acid is the parent fatty acid).

A Mediterranean-type diet rich in n-3 fatty acids (fish or oil) seems to be more effective in the secondary prevention of coronary events and death compared with a prudent Western diet. Alpha-linolenic acid is known for its beneficial effect on platelet reactivity and arrhythmia. The emphasis on fruit and vegetables also makes for a high intake of antioxidants.[2]

- Reduce dietary cholesterol intake to 100 - 200 mg/day.
- Include foods/margarine enriched with dietary plant sterols that inhibit the absorption of cholesterol, lowering low-density lipoprotein cholesterol (LDLC) by 10 - 15%.

In addition, the diet also needs to be modified to treat any other co-existing risk factors such as hypertension, diabetes mellitus and being overweight.[1]

Knowledge about the amount of cholesterol, total fat and type of fatty acids present in different foods helps in understanding the

dietary recommendations and practical tips outlined below.

As can be seen in Table II, plants contain mainly unsaturated fatty acids (except tropical plants) and no cholesterol.

In contrast, animal foods including meat, chicken and fish contain approximately the same amount of cholesterol per 100 g and the total fat and type of fat vary considerably.

SUMMARY: PRACTICAL TIPS

Decrease amount of f at

- Use fat-free dairy products
- Limit intake of hidden fats in snacks and processed meats
- Use low-fat cooking methods

Change type of f at

- Replace red meat with skinless poultry or fish
- Eat more fish, at least 2 - 3 times per week
- Use olive and canola oils for salads and food preparation
- Replace butter with soft margarine

Decrease dietary choles - terol

- Eat more foods of plant origin (bread, cereals, fruit and vegetables, and legumes as they contain no cholesterol and no fat (Table II), and are also a valuable source of water-soluble fibre)
- Reduce portion size of animal foods (meat, chicken, and fish) to once a day, keeping it to a maximum of 100 - 200 g/day
- Limit egg yolks to 2 every 2 weeks
- Avoid organ meats

Hypertriglyceridaemia

The key difference in the dietary management of hypertriglyceridaemia compared with hypercholesterolaemia is the emphasis on (drastic) total fat restriction to prevent pancreatitis. The level of fat restriction varies, depending on the severity of the triglyceride levels, as this intervention alone may be sufficient to lower triglycerides to a desirable level without the need for medication.

Unlike the diet recommended for hypercholesterolaemia, the intake of dietary cholesterol is not specifically/always limited, but low intakes are recommended particularly in the case of a combined hyperlipidaemia. In addition, patients with hypertriglyceridaemia should avoid alcohol.

A very low-fat diet (< 10 g fat/day) (Table III) — referred to as the 'rescue diet' at the Groote Schuur Hospital Lipid Clinic — is often recommended to reduce triglyceride levels urgently, after which a maintenance plan restricts fat intake to a maximum of 30 g fat per day.

For the dietary management of dyslipidaemia to be effective, a quantified approach, especially in high-risk individuals, needs to be encouraged. Ongoing dietary support and education will also ensure long-term compliance with these dietary guidelines provided they are practical, economical and adapted according to the individual's lifestyle.[1]

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SINGLE SUTURE

Cheerful kids have a shorter life expectancy than gloomier counterparts

An article in *Personality and Social Psychology Bulletin* (2002; **28:** 1155-1156) says that 'children who were rated by parents and teachers as more cheerful/optimistic, died earlier than those who were less cheerful'. This conclusion is based on research among 1 216 men and women who were first assessed in 1922, and who were monitored during their adult lives. The psychologists merged the data on cheerfulness with information on the time and cause of death in the people who had died. They also examined other variables such as adult personality, risky hobbies, smoking, drinking and obesity. The children who were especially cheerful grew up to drink more alcohol, smoke more cigarettes, and engage in riskier hobbies and activities. The data hinted 'that cheerful children grow up to be more careless about their health'.

(Dobson R, *BMJ* 2002; **325:** 733.)