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Diabetes UK and South Asian Health Foundation recommendations on diabetes research priorities for British South Asians

Kamlesh Khunti, Sudhesh Kumar and Jo Brodie

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First Edition

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Professor Sudhesh Kumar

Contents

Foreword

Diabetes UK and the South Asian Health Foundation have worked together on this review, whose principal purpose is to highlight the gaps in our understanding of diabetes in the UK-based South Asian population as well as to identify recommendations and priorities for future research areas. It is the intention that this review should be used by funding agencies that support research and also as a point of reference and information for the research community.

Population migration from the Indian subcontinent countries of India, Pakistan and Bangladesh (South Asia) to many parts of the world has resulted in over two million South Asian people living in the UK today, which represents 4 per cent of the total UK population. Alarmingly, South Asian people who live in the UK are up to six times more likely to have diabetes than the white population, and with diabetes prevalence in England predicted to increase by 47 per cent by 2025, the condition will continue to have a considerable impact on South Asian communities across the UK.

Despite this, our knowledge of the link between diabetes and people of South Asian descent is still very limited. After initial prioritisation of the areas to be focused on for this review, researchers were drawn together from a wide range of disciplines into working groups to evaluate the current evidence and the gaps in research, and recommend priorities for future investigation.

With South Asian people living in the UK at such an increased risk of developing Type 2 diabetes and more likely to experience some of the serious complications associated with diabetes, this review is both timely and essential. It is hoped that it will encourage collaborative relationships and dynamic partnerships to flourish between researchers and organisations alike, to work towards achieving leaps forward in our understanding of diabetes and the South Asian population living in the UK.

Professor Sir George Alberti
Chairman, Diabetes UK

Lord Naren Patel
Patron, SAHF

Executive summary

Diabetes affects 246 million people worldwide and is expected to affect 380 million by 2025. It is estimated to be the fifth leading cause of mortality in the world. In the UK there are 2.5 million people who have been diagnosed with diabetes. It is estimated that 10 per cent of these people have Type 1 diabetes and 90 per cent have Type 2. In addition it is estimated that there are half a million more people in the UK who have diabetes but have not yet been diagnosed. The rising prevalence of diabetes represents a serious clinical and financial challenge to the UK's health system, with 10 per cent of the NHS budget currently being spent on diabetes, which works out at around £9 billion a year. In view of the high prevalence and costs of vascular diseases, the Department of Health recently rolled out the NHS health checks (vascular checks) programme to systematically identify and treat vascular disease risk.

Type 2 diabetes is up to six times more common in people of South Asian descent, and in the UK, people of South Asian origin (of Indian, Pakistani and Bangladeshi descent) are the largest ethnic minority who now comprise the majority ethnic group in several urban locations. Diabetes UK and the South Asian Health Foundation undertook this review of gaps in diabetes research for the South Asian population because of the high prevalence of diabetes and the increased morbidity and mortality associated with diabetes in this ethnic group living in the UK. Published research and priority areas for future research have been identified along with a thorough search of research that is currently being funded. The review process identified 16 broad themes for key areas in research involving people of South Asian origin. The research recommendations from each of these themes are listed below:

Participation in research

- reasons for non-participation of South Asians in research
- effectiveness and cost-effectiveness of different recruitment and data collection strategies
- development and validation of outcome measures for use among South Asians.

Epidemiology

Descriptive epidemiology

- establish large cohort studies of South Asians born in the UK and follow-up of existing cohorts that have not yet been followed up
- establish diabetes registries with ethnicity coding included.

Diet/nutrition epidemiology

- development of validated instruments for self-reported dietary intake, such as the food frequency questionnaire for South Asians
- objective measurement, including use of and development of nutritional biomarkers where applicable
- research in understanding the determinants of dietary behaviour, and factors that might influence behaviour modification in South Asians.

Physical activity epidemiology

- development of validated instruments for self-reported physical activity in South Asians
- objective measurement, including use of movement sensors and combined heart rate and movement sensors
- research in understanding the determinants of physical activity behaviour, and factors that might influence behaviour modification in South Asians.

Genetics

- further characterisation of genes involved in susceptibility to Type 1 and Type 2 diabetes and the replication of known susceptibility genes in sub-groups of South Asians
- genome-wide association studies looking at novel genes based on phenotypic characteristics such as genes associated with insulin resistance and dyslipidaemia
- studies involving MODY genes and their role in polygenic Type 2 diabetes in the South Asian population
- mechanisms of gene–environment interactions of known susceptibility genes in relation to the South Asian population.

Cultural aspects

- studies on the cultural acceptability of different types of exercise and dietary regimens in South Asians
- studies to look at effective intervention programmes to reduce smoking in Bangladeshi men
- studies looking at effective intervention programmes in economically deprived areas to improve access to healthcare and tackle health inequalities
- studies to evaluate novel methods of health delivery, such as social enterprise, to improve access and tackle health inequalities
- studies to understand the cultural factors responsible for poor adherence to lifestyle advice and medication
- studies to develop and evaluate culturally sensitive and effective health promotional material, community educational programmes, DVDs and toolkits.

Screening for diabetes and non-diabetic hyperglycaemia

- screening high-risk South Asian populations such as those who have had a myocardial infarction or stroke to determine the prevalence of Type 2 diabetes and impaired glucose regulation
- qualitative studies leading to an enhanced understanding of cultural attitudes and beliefs, in order to inform the design of appropriate screening strategies
- studies investigating methods of increasing engagement with these populations and uptake of screening invitations
- studies exploring methods of evaluating some aspects of the impact of screening (for example, psychological outcomes) in populations where traditional methods may be inappropriate
- studies to look at solutions to overcoming literacy and language issues.

Prevention of Type 2 diabetes

- large cohort studies in multi-ethnic populations, using objective measures of physical activity and nutritional status to investigate the extent to which differences in lifestyle factors between South Asians and white Europeans account for ethnic specific differences in metabolic and vascular health
- establishing the efficacy and cost-effectiveness of pragmatic lifestyle diabetes prevention programmes, systematically tailored to the needs of South Asian ethnic minorities.

Self-management and education for people with Type 2 diabetes

- additional qualitative studies leading to an enhanced understanding of cultural attitudes and beliefs, in order to inform the design of appropriate educational interventions
- studies investigating methods of increasing engagement and uptake of educational initiatives
- studies exploring methods of evaluating some aspects of the impact of educational interventions (for example, psychological outcomes) in populations where traditional methods may be inappropriate
- well-designed trials evaluating the effectiveness of interventions based on a sound understanding of the needs and attitudes of the target population.

Childhood and adolescent Type 2 diabetes

- development of a cohort of affected children to adequately describe the natural history in UK children of South Asian origin
- determining the most effective screening method for Type 2 diabetes in children and how this is affected by ethnicity
- characterisation of the overlap between obesity, Type 1 and Type 2 diabetes in children and different groups of children

- the efficacy and cost-effectiveness of interventions aimed at children that reverse or delay progression of Type 2 diabetes and its complications, and how effective these are in different ethnic groups.

Gestational diabetes

- developing culturally appropriate interventions specifically targeted at South Asian women
- studies in the role of intervention programmes for prevention of gestational diabetes mellitus in this population
- further studies in the epidemiology of hyperglycaemia in pregnancy, including relationship between glucose and maternal and foetal outcomes in South Asians
- studies in the value of intervention programmes for prevention of diabetes in South Asian women in the postnatal period following gestational diabetes.

Psychological consequences of diabetes

- additional qualitative studies aimed at increasing our understanding of cultural differences related to the type and presentation of the psychological consequences of diabetes
- studies designed to identify and evaluate methods of identifying anxiety and depression in South Asian people with diabetes
- studies seeking to quantify cultural differences related to the psychological consequences of diabetes
- intervention studies that acknowledge and address cultural differences related to the psychological consequences of diabetes.

Treatment and care of people with diabetes

- evidence for benefit of treatment of obesity as defined by lower ethnic specific cut-off points for body mass index and waist
- studies in ethnic differences in the efficacy and adverse effects of various classes of oral hypoglycaemic agents
- studies to examine the reasons for reluctance to initiate insulin therapy early and also the effectiveness of insulin therapy, especially in overweight South Asian patients
- more multifactorial intervention trials to look at better delivery of care and improving care
- more multifactorial intervention trials to look at the effect of treating blood pressure at lower thresholds on the prevention of diabetic renal and eye disease
- research to establish the factors that affect the uptake of evidence-based interventions that reduce morbidity and mortality
- more studies needed on festivals such as Ramadan, in order to improve diabetes management.

Cardiovascular disease and peripheral vascular disease

- epidemiological studies to determine the impact of traditional and novel risk factors, including impaired glucose regulation, insulin resistance and markers of inflammation on coronary heart disease and stroke
- studies to assess revascularisation strategies in South Asian people with Type 2 diabetes
- studies to assess the benefits of revascularisation in patients with silent ischaemia and prognostically significant anatomical disease who have diabetes
- prospective trials to determine the effect of pharmacological interventions aimed at achieving lower than current targets for lipids and blood pressure and effect of modifying the novel risk factors on coronary heart disease and stroke outcome in South Asian people with diabetes
- large-scale, longitudinal studies examining the prevalence of impaired glucose regulation on: ventricular structural abnormalities; markers of ventricular dysfunction (plasma brain natriuretic peptide); inflammatory (C-reactive protein); and prothrombotic stage and pattern of dyslipidaemia in people from South Asian population admitted with myocardial infarction, and its predictive value in terms of short- and long-term mortality
- studies to investigate the epidemiology and pathophysiology of peripheral vascular disease in South Asians with diabetes, and longitudinal studies examining their long-term impact on cardiovascular disease outcomes
- investigations to determine the impact of using non-invasive techniques on earlier detection of asymptomatic cardiovascular heart disease in people with Type 2 diabetes.

Dyslipidaemia

- statin efficacy studies in South Asian people to evaluate pharmacokinetic and pharmacodynamic properties
- studies to determine the pattern of lipid-lowering management of South Asians with and without diabetes as compared to white Europeans
- multicentre study to evaluate outcomes of intensive versus conventional statin therapy
- newer high density lipid (HDL) cholesterol-raising treatments are being developed and clinical endpoint trials would usefully include South Asian individuals, given their lower HDL cholesterol levels and greater vascular risk; the same is true for newer formulations of nicotinic acid
- appropriate risk algorithms incorporating ethnicity, and interventional studies using these algorithms, are a key priority for primary prevention of cardiovascular disease.

Diabetic nephropathy

- benefits of early screening – including non-diabetic hyperglycaemic states such as impaired fasting glycaemia and impaired glucose tolerance
- larger cohort studies to establish the epidemiology of diabetic nephropathy in South Asians, especially to evaluate progression rates of varying levels of albuminuria and decline in renal function; such studies to provide an insight into possible pathogenetic differences among differing populations
- interventions to establish ethnic-specific treatment targets for risk factors such as glycaemia and blood pressure in South Asians with varying degrees of renal impairment, in an attempt to reduce the rate of progression and ultimately reduce the prevalence of end-stage renal disease
- cardiovascular risk and survival in patients with end-stage renal disease
- prevalence of non-diabetic kidney disease in South Asians with diabetes.

Diabetic retinopathy

- the epidemiology of retinopathy and the relationship of risk factors for retinopathy in the different South Asian communities in the UK
- the barriers to screening for retinopathy and methods for enhancing uptake in culturally and socio-economically diverse South Asian communities
- the feasibility and benefits of aiming for lower thresholds for blood pressure control in South Asians with retinopathy
- differences in pathogenesis and pattern of retinopathy and the relationship to other non-diabetic eye diseases.

Bariatric surgery

- epidemiology of relationship between body mass index and waist size to diabetes in the South Asian diaspora in longitudinal cohort studies
- studies to investigate the benefits and risks associated with bariatric surgery, particularly laparoscopic gastric banding and other bariatric procedures at lower thresholds of body mass index in South Asian people with diabetes; more data on long-term effects are needed and can be achieved by establishing a cohort
- studies investigating acceptability and effect on perceived quality of life in patients who require this procedure and the effect of surgery on these parameters.

This review identifies a number of major and important gaps in research that we hope will inform funding bodies about research priorities. The review will also be invaluable for those planning and co-ordinating research into diabetes in South Asians.

Chapter 1: Participation in research

Paramjit S Gill and Cathy E Lloyd

Context

South Asians are a heterogeneous group of people of Indian, Pakistani, Bangladeshi and Sri Lankan origin, with differing religion, language, culture and rates of diabetes, particularly Type 2 diabetes[1]. They live in all areas of the UK, with clustering in certain areas reflecting migration patterns. For example, there is a high concentration of Indians residing in Greater London as well as the East and West Midlands, whereas there is a relatively low proportion of Pakistanis in Greater London and a greater concentration of this subgroup in West Yorkshire and the West Midlands. People of Bangladeshi origin are found predominantly in Greater London particularly in Tower Hamlets, although there are growing numbers in the West Midlands. This clustering may affect research studies, for example in terms of sampling, and also the ability to draw general conclusions from research findings, hence the need for large multicentre studies. Currently, most studies focus on single ethnic groups such as Bangladeshi, Pakistani or Gujarati people, and it has been argued that there is a need to be more inclusive, as outlined below.

Summary of current evidence

In order to ensure that healthcare serves a diverse population, it is important that all ethnic groups participate in health research. This not only ensures the generalisability of research results, but also improves the quality of care[2–5]. Time, resources and attention to the research proposal are all important but, equally, researchers need to devote time to addressing the challenges of recruiting and retaining participants, as to date very few quality studies in the UK have included South Asians[6–9]. Hussain-Gambles[10] investigated reasons for non-participation in clinical trials, including motivation (eg helping society, improving one's health); and deterrents (eg busy lifestyles, previous experiences and language problems). Professional views included a lack of time and resources and inadequate support. It has also been highlighted that South Asians are often explicitly excluded due to perceived cultural and communication difficulties[11–16], including studies where there might be language/literacy problems in obtaining informed consent. It has also been shown that many individuals from South Asian backgrounds are unwilling to participate because they accept their illness as an unalterable punishment from God or have a fear of what research actually entails[17].

Recruitment of South Asian participants to some research studies may be further compromised, for example in Sylheti there is no agreed written form of the main spoken language. This presents challenges when it comes to completing standard data-collection forms/questionnaires, specifically by the traditional paper-and-pencil method[18]. Furthermore, prior to entry into any study, individuals must be approached and persuaded to participate in the research[19]. This may be from NHS settings such as primary care or outpatient clinics or from the communities themselves. This involves provision of (usually written) information on the study and ensuring the giving of informed consent from individuals, which is the first challenging aspect of the research process[20–23], and may be one reason why many studies have low response rates[2,24,25]. Indeed, added responsibilities are often placed upon those researching in areas of high illiteracy and where understanding of the issues may be problematic, in terms of having to devise more innovative ways of carrying out studies[21], and also in terms of presenting consistent patient information prior to the obtaining of consent.

However, as Bhutta[20] states, though the notion of illiteracy does not mean that potential participants are unable to comprehend complex information, it does mean that information may need to be presented in alternative ways. In all the international guidelines on informed consent, including those of the World Medical Association and the European Union guidelines, written consent is considered preferable, with verbal consent appropriate only where participants are non-literate. There appears to be a dearth of published studies where alternative methods of delivering patient information and obtaining informed consent are reported, and their effectiveness remains to be assessed.

The successful participation of South Asians in research can depend on the type of data collection planned. For example, in the UK Asian Diabetes Study[26], the collection of questionnaire data pertaining to diabetes self-management was found to be problematic, although recruitment of individuals to the study was straightforward. Clinical data was easily collected, but the collection of psychosocial data was compromised because a high proportion of those approached were unable to complete standard questionnaires without the assistance of support workers[18]. This led to new ways of data collection, an integral part of which was to develop innovative ways of obtaining informed consent from non-literate participants[27,28]. Further, to maximise participation a range of strategies need to be adopted including engaging with local communities and media, ethnic, sex and language matching of the research team, and adequate resources to undertake the research including interpreting and translation costs[29]. The use of audio media or the telephone[30] for data collection is currently not widely used.

Gaps in research

Recruitment of South Asians to research studies poses major challenges for researchers. This is a key area that needs investment if many of the research gaps that have been identified in this report are to be addressed successfully. One major impediment is the lack of appropriate coding for ethnicity and language in most primary care databases, and more work is needed to support routine coding of ethnicity within primary care. It has been suggested that South Asians are less likely to volunteer to take part in clinical trials; the reasons for this should be explored and some investment may be required to ensure that their participation is facilitated.

Research priorities

- reasons for non-participation of South Asians in research
- effectiveness and cost-effectiveness of different recruitment and data collection strategies
- development and validation of outcome measures for use among South Asians.

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Chapter 2: Epidemiology

Sarah Wild and Nita Forouhi

Context

There is plentiful evidence that South Asians experience high rates of: 1) non-diabetic hyperglycaemia with high risk of conversion to diabetes 2) Type 2 diabetes and its complications 3) and premature cardiovascular mortality and morbidity, at least partly as a consequence of diabetes. This section summarises the current evidence and presents suggestions for future research in South Asian diabetes epidemiology in the following categories: 1) definition of diabetes 2) descriptive epidemiology 3) the importance of lifestyle factors 4) and emerging risk factors.

There has been considerable debate over the optimum definition of Type 2 diabetes, particularly the role of fasting and/or two-hour post-glucose-challenge glucose levels and HbA1c levels. The Australian Diabetes, Obesity and Lifestyle study (AusDiab) group have questioned whether a standard 75g glucose challenge is appropriate for all people[1]. Even after adjusting for multiple factors, HbA1c levels among people with impaired glucose tolerance were higher among ethnic minority groups than for white people in the USA[2].

Summary of current evidence

Data on incidence of diabetes are sparse in the general population, and even more so in South Asians. Difficulties in ascertaining incidence arise because this would require a large cohort study with follow-up phases, or establishment and maintenance of complete and accurate population-based registers. The existing data suggest similar incidence of Type 1 diabetes in European and South Asian children but higher incidence of Type 2 diabetes in South Asian than in European children in the UK[3–5]. Estimates derived from a large primary care dataset suggest that, compared with the white reference group, the hazard ratios adjusted for age, body mass index, family history and smoking status for risk of Type 2 diabetes were 4.07 (95 per cent confidence interval 3.24–5.11) for Bangladeshi women, 4.53 (3.67–5.59) for Bangladeshi men, 2.15 (1.84–2.52) for Pakistani women, 2.54 (2.20–2.93) for Pakistani men, 1.71 (1.49–1.97) for Indian women, and 1.93 (1.70–2.19) for Indian men[6].

Epidemiological surveys do not distinguish between Type 1 and Type 2 diabetes and rely on recall of a diagnosis. The most recent self-reported data on diagnosed diabetes prevalence for South Asians in the UK is available from the Health Survey for England 2004[7]. After adjusting for age, doctor-diagnosed diabetes was 2.5–5 times more common among the South Asian population than the general population (with variation by sex and ethnicity).

Medical records are limited by poor recording of diabetes in hospital admissions data and of ethnicity on GP and hospital records in many parts of the UK[8]. However, relevant data was available for 3.7 million people for development of the QDScore (an online tool for calculating the risk of developing Type 2 diabetes over the next 10 years)[6], although prevalence was not reported by ethnicity. The National Diabetes Audit gives estimates of Type 2 diabetes prevalence in children by ethnicity[9] but these are based on very small numbers (eg 22 Asian children), so these are not reliable, and improvements are needed in the quality and use of routine data.

Data on population-based estimates of diabetes prevalence using oral glucose tolerance tests among South Asians in the UK are available from studies based in Coventry, Southall, South London, Newcastle and Manchester; all of them showing four- to six-fold higher prevalence in South Asian people compared with Europeans[10–13].

Data from the Pho-Brent-ScHARR (PBS) diabetes population prevalence model[14] used data from some of the previously noted studies to generate estimates of diabetes prevalence for the UK in 2001. The Phase 3 PBS model[15] further estimates prevalence in 2005, and projects diabetes prevalence to 2025. As well as giving prevalence in England, prevalence by ethnic group is included, showing greatest diabetes prevalence among South Asians.

The only source of data on trends in diabetes prevalence in South Asians comes from self-reported doctor-diagnosed diabetes prevalence in the Health Surveys for England of 1999[16] and 2004[7]. The prevalence of doctor-diagnosed diabetes in 2004 was higher than in 1999 in most minority ethnic groups but numbers were small and there may have been confounding by age.

Lifestyle factors: the potential contribution of diet/nutrition and physical activity to diabetes risk in South Asians

Diet/nutrition

There is now compelling evidence that lifestyle intervention including a 'prudent or healthy' diet is of major benefit in the primary prevention of diabetes[17–18]. However, there is uncertainty about the specific components of diet that are most beneficial or harmful in terms of the future risk of diabetes. Previous epidemiological studies in the UK mostly either did not measure diet, or did not measure diet accurately with validated instruments. Literature on dietary factors and insulin resistance and/or metabolic syndrome risk in India show that South Asians have higher intakes of carbohydrate, saturated fatty acids, n-6 polyunsaturated fatty acids (PUFA) and trans-fatty acids, and lower intakes of n-3 PUFA, and fibre, compared with other populations[19,20]. Thus far, dietary studies have mainly focused on describing the distribution of dietary intake[21,22] rather than on its association with diabetes incidence in South Asian populations. Furthermore, diet/nutrients have been largely studied in South Asians in the context of coronary heart disease (CHD)[20,23–24] or cancer[25,26], not diabetes.

Two specific nutritional biomarkers are of particular interest in South Asians: fruit/vegetable intake and plasma vitamin C; and vitamin D.

One of the key public health dietary recommendations for the prevention of chronic disease is to eat at least five portions of fruits and vegetables a day. In contrast to prevailing assumptions, the international INTERHEART Study showed that South Asians had a lower daily intake of fruits and vegetables than people from 47 non-South-Asian countries[27]. Plasma vitamin C is a good biomarker of fruit and vegetable consumption[28]. In the Wandsworth Heart and Stroke Study, it was reported that plasma vitamin C concentration was significantly lower in South Asians than in European whites, for both men and women[29]. In a largely white population, it has recently been demonstrated that there is a striking inverse dose-response association between plasma vitamin C (as a marker of fruit/vegetable intake) and risk of the incidence of diabetes[30].

A dose-dependent pattern of inverse association between serum vitamin D concentration and the risk of prevalent diabetes was reported by ethnicity (white, Hispanic, African-American) in the USA[31]. The association between vitamin D deficiency and the risk of diabetes has not been reported in South Asians. There are, however, several reports of lower concentrations of vitamin D in South Asians compared with Europeans. For instance, one in eight Europeans versus one in three South Asian people was found to be vitamin D deficient in a Birmingham (UK) study[32]. South Asian women in particular have much lower levels of vitamin D[32,33]. Recent evidence also shows that otherwise healthy South Asians in India have low levels of vitamin D[34].

Physical activity

Physical inactivity is a well-established risk factor for diabetes and cardiovascular disease. However, the degree to which physical activity patterns differ between ethnic groups remains uncertain. The studies so far conducted have been based on self-reported physical activity levels and suggest that physical activity levels are lower in South Asian adults compared with other groups[35,37]; limited data suggest a similar pattern in children[38,39]. Time since immigration might also be an important factor in determining levels of physical activity[40]. Most studies have identified particularly low levels of physical activity in South Asian women, and it is thought that, among this group, it may be easiest to intervene in low leisure time physical activity[41]. Research into barriers to physical activity among South Asians is sparse, but includes cultural factors and a lack of awareness of the benefits of physical activity[42,43].

The objective measurement of physical activity with accelerometers has revolutionised physical activity research in European populations[44]. These methods have not been widely used among South Asians yet, and would open up new research frontiers in understanding the role of physical activity in diabetes and CHD risk in South Asians.

The Indian Diabetes Prevention Programme showed that lifestyle intervention, including regular physical activity, yielded a relative risk reduction in diabetes over three years by 28.5 per cent compared with usual care[18]. However, as with other prevention trials, it is not possible to tease out the independent effects of diet and physical activity interventions.

Novel and emerging risk factors

The evidence for novel risk factors for diabetes has recently been reviewed and categorised into factors that are derived from adipose tissue, hepatic fat, the endothelium or inflammatory markers[45]. Some of these factors might well be of importance just as much, or more, among South Asians than in Europeans. For instance, there is already evidence that C-reactive protein levels are higher and adiponectin levels lower in South Asians. The potential role of liver ectopic fat is another area of interest.

Gaps in research

Further work is required to establish whether the relationships between fasting glucose, post-challenge glucose and HbA1c have important differences by ethnicity, and some of this work could be addressed in cross-sectional studies. It is not clear whether the increased risk of macrovascular and microvascular complications associated with diabetes have similar associations with glucose cut-off points in different ethnic groups. This information could only be reliably provided by a large cohort study.

Current studies in Leicester, Glasgow and Edinburgh are using glucose tolerance testing in selected sub-groups of the population who are at high risk of diabetes, but it would be valuable to have more up-to-date population-based estimates of diabetes prevalence that could provide information about the proportion of undiagnosed diabetes (existing evidence suggests that this proportion is lower in South Asian than in white populations).

Better-quality, population-based data are required to describe trends in diabetes prevalence in the UK, and this gap needs to be filled using prospective studies that measure diet accurately and objectively using nutritional biomarkers or using prospective food diaries.

Further investigation of the relationship between South Asian ethnicity, fruit and vegetable intake (or vitamin C levels as a proxy) and diabetes risk requires three specific approaches:

- an ethnic difference in plasma vitamin C levels should be confirmed
- studies specifically examining the association between plasma vitamin C and the risk for incident diabetes (and CHD) in South Asians
- whether to examine if plasma vitamin C, as a marker of fruit and vegetable intake, can help to explain the greater risk of diabetes (or CHD) in South Asians compared with white Europeans.

The association of vitamin D concentration and the risk for Type 2 diabetes in South Asians merits study, as do the questions of whether lower vitamin D concentrations in South Asians can help to explain their higher risk for diabetes (and/or coronary heart disease) and whether there is a role for vitamin D supplementation.

Key areas for research also include: 1) confirmation of the association between physical activity and diabetes risk among South Asians in prospective studies and clinical trials in different settings 2) and the use of objective measurement of physical activity to avoid the problems of biased estimates and imprecision inherent in self-reported physical activity. Such research should be conducted in parallel with good-quality research into descriptive epidemiology and lifestyle factors (diet/nutrition and physical activity).

Research priorities

Descriptive epidemiology

- establish large cohort studies of South Asians born in the UK and follow-up of existing cohorts that have not yet been followed up
- establish diabetes registries with ethnicity coding included.

Diet/nutrition epidemiology

- development of validated instruments for self-reported dietary intake, such as the food frequency questionnaire for South Asians
- objective measurement, including use of and development of nutritional biomarkers where applicable
- research in understanding the determinants of dietary behaviour, and factors that might influence behaviour modification in South Asians.

Physical activity epidemiology

- development of validated instruments for self-reported physical activity in South Asians
- objective measurement, including use of movement sensors and combined heart rate and movement sensors
- research in understanding the determinants of physical activity behaviour, and factors that might influence behaviour modification in South Asians.

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Chapter 3: Genetics

Srikanth Bellary and Anthony H Barnett

Context

The prevalence and severity of diabetes varies significantly among populations[1]. While environmental factors are known to greatly influence disease susceptibility, they alone do not fully explain the differences between ethnic groups[2]. Genetic factors often determine an individual's response to the environment, so recognising the role of these factors is essential to our understanding of the molecular mechanisms involved in the causation of diabetes. Epidemiological studies have shown that the prevalence of Type 2 diabetes among South Asians is significantly greater than in many other ethnic groups[3]. This increased susceptibility to diabetes is thought, in part at least, to be determined by genetic factors. Despite this, our understanding of the genetic aspects of diabetes in this population is poor.

Role of genetics in diabetes

Genetic factors are known to play a significant role in the pathogenesis of both Type 1 and Type 2 diabetes. This assertion is truer for Type 2 diabetes and is supported by high concordance rates in studies involving monozygotic twins[4]. Type 2 diabetes, however, includes a wide spectrum of clinical disorders, and the extent to which these disorders is influenced by genetic factors varies significantly[5].

Monogenic forms of Type 2 diabetes are predominantly due to single gene defects and account for less than 5 per cent of all cases of Type 2. They manifest early, have high phenotypic penetrance and are less influenced by environmental factors. In contrast, the genetics of more common polygenic forms is complex and involves polymorphisms of several genes and a greater gene–environment interaction. These polymorphisms confer only a modest risk to the individual but the effects are often greater at a population level.

Techniques/approaches for genetic studies in Type 2 diabetes

Two major approaches have commonly been used in the search for Type 2 diabetes genes – candidate gene and genome-wide association studies[5]. Significant progress has been made in the characterisation of monogenic forms of Type 2 diabetes using these techniques but the study of the complex polygenic Type 2 diabetes has, until recently, been much slower. Significant advances in recent years following improved genotyping techniques and the completion of the Human Genome Project have allowed identification of several susceptibility genes, offering new insights into the pathogenesis of this complex condition[6].

Summary of current evidence

Type 1 diabetes

The prevalence of Type 1 diabetes in South Asians is thought to be very low compared to that in white populations. This perception is being challenged by recent studies in migrant South Asians that have shown a steady increase in the incidence of Type 1 diabetes[7]. The role of genetic factors in the causation of Type 1 diabetes is complex. Studies in white populations have shown that certain haplotypes within the major histocompatibility complex are associated with an increased risk of Type 1 diabetes (eg HLA-DRB1, -DQAI, DQBI), while others may be protective (DQ6)[8]. Significant differences between ethnic groups have also been observed. Such studies are, however, lacking in South Asians. Clearly, if the incidence of Type 1 diabetes is increasing in this group, more studies are needed to understand the role of genetic factors.

Type 2 diabetes

Monogenic Type 2 diabetes

To date, at least seven different types of monogenic forms of diabetes (MODY) have been described[5,9]. Much of our understanding of these forms of diabetes comes from studies in white populations. Studies involving South Asians are very rare and there is a considerable overlap of common Type 2 diabetes with MODY, making it difficult to estimate its true prevalence. It is, however, reasonable to assume that the prevalence of these forms of diabetes is not significantly different in South Asians. In a South Indian study, the prevalence of MODY was estimated to be around 4.8 per cent and the same group also reported novel mutations in MODY3[10]. These studies have not been replicated in any other subgroup of South Asians. Considering that many of the genes involved in MODY are also candidate genes for polygenic Type 2 diabetes, there is a need for more studies in South Asians.

Polygenic Type 2 diabetes: susceptibility genes

Until recently, there have been very few genetic studies involving South Asians. Overall, the proportion of studies in South Asians compared to western populations is very small. Most of these have been replications and some have shown interesting differences[10]. The Calpain 10 gene was the first important gene associated with Type 2 diabetes to be identified using the genome-wide scanning technique[11]. A haplotype of three important polymorphisms (UCSNP 43, -19 and -63) of this gene was originally shown to be associated with an increased risk of Type 2 diabetes in a Mexican-American population. Replication of this study in other populations has, however, shown mixed results with much lower frequencies in other populations[12]. Studies in South Asians have shown that while the original haplotype does increase the risk of Type 2 diabetes, the frequency of this polymorphism is very low and its contribution to the risk of Type 2 diabetes is therefore likely to be small[10].

The peroxisome proliferator activator gamma (PPAR gamma) gene is an important regulator of glucose and lipid metabolism. A common Pro12Ala polymorphism of this gene has been shown to be protective in white populations[13]. Studies in a South Asian population have shown that this polymorphism is present at the same frequency in both people with and without diabetes, and its presence was not associated with either improved insulin sensitivity or decreased risk of Type 2 diabetes[14]. A recent addition to the list of Type 2 diabetes susceptibility genes is the Transcription Factor 7 Like 2 (TCF7L2). First described in an Icelandic population, and replicated in several other populations, including South Asians, this gene has been shown to have the strongest association with the risk of Type 2 diabetes[15]. The exact role of this gene in the pathogenesis of Type 2 diabetes, however, remains unknown at present.

Many other genes such as PPAR gamma co-activator 1 alpha (PGC-1), ectoenzyme nucleotide polypeptide (ENPP1), uncoupling protein genes (UCP2 and UCP3), insulin receptor substrate (IRS-2), beta cell potassium channel gene (KCNJ11) and adiponectin gene have also been studied in South Asians and shown to have modest associations with Type 2 diabetes[10]. Small sample sizes, however, make it difficult to interpret these studies or to exclude possible associations.

Genes associated with obesity

Genome-wide association studies have also been useful in the identification of genes associated with obesity, a major risk factor for Type 2 diabetes. Common variants of the fat-mass and obesity-associated gene (FTO) were shown to be associated with obesity in European populations[16]. Individuals with these variants were on average 3kg heavier than those who did not possess them. Individuals were also at an increased risk of Type 2 diabetes but this was secondary to the obesity rather than due to the variants of the gene itself. In South Asians, however, the presence of this polymorphism was associated with an increased risk of Type 2 diabetes independent of body mass index (BMI)[17].

Another important gene identified in a study in South Asians and Europeans living in the UK is the Melanocortin 4 Receptor (MC4R) gene[18]. This study found that the variant of the MC4R gene was associated with increased risk of adiposity and insulin resistance. Individuals with variants of this gene had a waist circumference around 2cm larger and insulin resistance (HOMA-IR) approximately 10 per cent greater than those who do not have the MC4R variation. The increased frequency of the risk allele in South Asians has been proposed as an explanation for the increased levels of Type 2 diabetes in this group.

Genes associated with diabetes complications

The predisposition to diabetic complications also varies significantly between ethnic groups. In general, the prevalence of diabetic nephropathy and retinopathy is higher in South Asians than in white populations[19,20]. Risk of these complications, particularly nephropathy, is thought to be genetically determined. As such, searching for genetic variants that predispose to these complications is an attractive

proposition. Various groups have looked at polymorphisms of the Angiotensin Converting Enzyme (ACE1) gene, aldosterone synthase gene (for nephropathy)[21] and the Vascular Endothelial Growth Factor (VEGF) gene[22] for retinopathy. Findings from these studies, however, have not been conclusive and need to be verified in larger cohorts.

Gaps in research

The paucity of genetic studies in South Asians has been a major limiting factor in our understanding of the pathogenesis of Type 1 and Type 2 diabetes in this group. Although this has improved somewhat in recent years, there is still a dire need for more studies. Much of our current knowledge is from studies in South Asian cohorts and there have been only a few studies in other groups. Despite the socio-cultural overlap, there is much diversity within South Asians, with each subgroup having distinct phenotypic characteristics. While important associations in other populations need to be replicated in these subgroups, search for novel genes based on phenotypic characteristics is also needed. These would involve the establishment of larger cohorts and collaboration with other groups.

Research priorities

- further characterisation of genes involved in susceptibility to Type 1 and Type 2 diabetes and the replication of known susceptibility genes in sub-groups of South Asians
- genome-wide association studies looking at novel genes based on phenotypic characteristics such as genes associated with insulin resistance and dyslipidaemia.
- studies involving MODY genes and their role in polygenic Type 2 diabetes in the South Asian population
- mechanisms of gene–environment interactions of known susceptibility genes in relation to the South Asian population.

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Chapter 4: Cultural aspects

Wasim Hanif and Muhammad Ali Karamat

Context

Culture is a complex interaction of multitudes of factors that give a people an ethnic belonging and also has an impact on their lifestyle and predisposition to chronic disease. A number of factors give South Asians their unique sense of identity and belonging. Chief among these is where they come from and how they came to the UK. To understand the impact of culture on diabetes, we need to look at a number of factors, including migration, diet, physical activity, tobacco use, socio-economic status, language barriers, access to health services and attitudes to medical treatment.

Migration of South Asians to UK

The Indus valley civilisation of Northern India is one of the oldest and largest recorded civilisations. It started somewhere around 7000 to 4000 BC and was flourishing by 2700 BC[1]. The origins of South Asians are not clear: some historians suggest that they migrated from the banks of the River Danube in Europe. They are descendants of the Aryans, while the original inhabitants of the subcontinent, Dravidians, mostly live in Southern India[2].

The first wave of mass migration from India to Britain occurred in the early 1950s from three principal areas: the Punjab province of both India and Pakistan, and the province of Sylhet, which is now in Bangladesh.

The first wave can roughly be divided along religious lines into Muslims from Pakistan and mostly Sikhs from India. The people from Sylhet were Bangladeshi Muslims. These immigrants were blue collar workers who lived and worked in factories in inner city areas of the UK. The main concentrations are still found around the West Midlands, Manchester, Bradford and London. They were not well educated and their knowledge of English was poor. Over the last 50 years there have been at least two generations of South Asians born and educated in the UK. Many still live in poor, socially deprived inner city areas. The education and earnings of this group of immigrants is often low and there are still communication difficulties and the level of understanding of English is commonly poor.

The second mass migration occurred in the mid 1970s when, due to political disturbances in East Africa, South Asians living there migrated to the UK. These people were mostly Gujaratis; they were well educated and most had been established businesspeople in East Africa. They settled around Leicester and London and most are Hindus.

Other than the above, many others from the subcontinent have come to settle in the UK. These are usually highly skilled, white-collar workers and, according to the latest figures, about 30 per cent of doctors working in the NHS are from the Indian subcontinent. Thus, the South Asian population living in the UK is heterogeneous with different social and economic backgrounds.

Summary of current research

Diet

The question of exactly which aspects of the British South Asian lifestyle predispose to glucose intolerance and dyslipidaemia remains largely unanswered. One uncontrolled experimental trial showed somewhat surprisingly, that a 'traditional' Indian vegetarian diet induced higher and more prolonged rises in plasma glucose and free insulin levels than a 'traditional' European diet in a group of volunteers of mixed ethnic origin[3]. South Asian diets are said to contain more carbohydrate, less fat, less protein and more fibre than indigenous British diets. An epidemiological survey in which dietary intakes of 173 British South Asians and white Europeans were weighed and analysed did not demonstrate any greater coronary risk (in terms of total calories, total fat, proportion of saturated fat, or fibre content) in the South Asian diet, but showed that two-hour, plasma-free insulin levels in the South Asian subjects were directly related to the carbohydrate content of the diet[4].

It must be remembered, however, that the dietary preferences of South Asian ethnic groups are very diverse[5], and generalisations should not be made. Ghee (clarified butter), for example, is in common use in groups originating from northern India and Bangladesh and has been shown to contain atherogenic constituents[6], but ghee is rarely used by people of South Indian origin, whose risk of atherosclerotic disease is equally high[7]. A nutritional analysis of common Punjabi and Gujarati composite dishes from different households, as calculated from the records of weighed ingredients and portion sizes, showed considerable variation in the fat and energy content of different recipes[8], suggesting the use of 'traditional' recipes for nutritional analysis will be inaccurate.

A survey looked at the diversity of eating practices among South Asians with diabetes[9]. According to the survey, most participants continued to consume South Asian foods despite concerns that they may be detrimental to their glycaemic control. Males, reportedly, had little or no input into food preparation. It was noted that many patients believed these foods to be a source of strength and also ate them, as they did not want to alienate themselves from the community.

As part of the diabetes study in Coventry, 612 subjects undergoing glucose tolerance tests from different ethnic backgrounds completed a questionnaire. This study noted that South Asians ate significantly fewer and later evening meals compared to Europeans. South Asians also ate fewer vegetables and less brown rice but more fruit compared to Europeans. South Asians ate more traditional sweets and Western snacks, and Muslims were least likely to be vegetarians or consume alcohol[10].

Physical activity

Physical inactivity is an independent risk factor for diabetes in South Asians[11]. Research has shown that on diagnosis of diabetes, British South Asians are less likely to be physically active than any other ethnic groups[12]. A survey by Williams and colleagues using interview reports of exercise levels showed a lower rate of vigorous exercise in British South Asian men compared to indigenous white males but no difference in women[13]. Dhawan and colleagues, in a case control study of British South Asians and Indian Asians, showed that twice as many of the former took no physical exercise[14]. Researchers looking at levels of physical activity among South Asians noted some awareness of its importance but a lack of putting it into practice[15]. The reasons included cultural norms, social expectations, time constraints and health problems.

A study in which researchers interviewed South Asian women about their understanding of the importance of physical activity noted that the respondents emphasised the cultural importance of being active day to day, rather than the 'western' concept of organised exercise[16]. However, women's principal motivations and attitudes towards physical activity, ie losing weight, socialising and maintaining independence, were culturally similar to 'majority' populations.

The exercise options are also different. One study showed that overweight Bangladeshi women from East London favoured swimming while the least popular activity was running[17]. The great majority of the subjects (96 per cent) reported that they were only willing to take up exercise if they were referred to the gym by their GP as an alternative, or additional, treatment for their complaints. They would not exercise voluntarily.

Smoking, chewing tobacco and betel nut

Smoking is an independent risk factor for both coronary heart disease and Type 2 diabetes[18]. Smoking is overall no more common among migrants to the UK from the Indian subcontinent than in the indigenous UK population, and is much less common in females and non-Muslim groups, particularly Sikhs, than in the indigenous population[19]. However, high rates of smoking in male Bangladeshis (82 per cent) have been reported from east London and under-reporting of smoking status by Asian women may be common[20].

Consumption of betel nut (*Areca catechu*, one of the constituents of the popular paan masala snack) is common among north Indians and Bangladeshis, with a prevalence in British Bangladeshis of 66 per cent overall. Betel nut contains nitrosamines with some chemical similarities to streptozotocin. Though its contribution to the onset of impaired glucose tolerance (IGT) and diabetes has been demonstrated in animals, its role in the aetiology of diabetes in humans is disputed[21].

Socio-economic status

There are differences in socio-economic circumstances, lifestyle and disease among all South Asians and Europeans[22]. For most risk factors it was shown in one study that Bangladeshi men fared the worst. Another study by the same group[23] tried to test the hypothesis that worse socio-economic status was associated with a higher prevalence of ischaemic heart disease and Type 2 diabetes.

There were differences in social and economic circumstances, lifestyles, anthropometric measures and disease both between Indians, Pakistanis and Bangladeshis, and between all South Asians and Europeans. Bangladeshis and Pakistanis were the poorest groups. For most risk factors, the Bangladeshis (particularly men) fared the worst: smoking was most common (57 per cent) in that group; and Bangladeshis had the highest concentrations of triglycerides (2.04mmol/l) and fasting blood glucose (6.6mmol/l), and the lowest concentration of high-density lipoprotein cholesterol (0.97mmol/l). Blood pressure, however, was lowest in Bangladeshis. Bangladeshis were also the shortest: men 164cm tall compared to 170cm for Indians and 174cm for Europeans. A higher proportion of Pakistani and Bangladeshi men had diabetes (22.4 per cent and 26.6 per cent respectively) than Indians (15.2 per cent). By making broad comparisons between all South Asians and Europeans, some important differences are not clearly revealed, but South Asians were still disadvantaged across a wide range of risk factors[22].

Language barrier and education

South Asians living in the UK speak different languages and comprehension of English is predominantly low in the first-generation migrants. Many patients do not speak or read in English, interpreters are still not widely available in healthcare except by prior arrangement, and cultural and religious beliefs make it difficult for patients to attend clinics at certain times or on certain days, to speak openly to members of the opposite sex, or for women to travel alone to clinic appointments[24]. Adherence by South Asians to medical and lifestyle advice has often been questioned. It has been suggested that interactions with patients should not be viewed simply as opportunities to reinforce ideas but to combine the experiences of patients and healthcare professionals to ensure good healthcare delivery[25]. Analysis of in-depth questionnaires completed by Pakistan-born persons in Denmark suggested that health workers would themselves benefit by learning more about positive aspects of culture and religion and the way they impact on the day-to-day care of patients[26].

In a survey on 201 South Asian people living in Manchester it was found that while knowledge about diabetic diets was good (72 per cent), there was a clear lack of understanding about how to manage hyperglycaemia[27]. Of the subjects, 54 were completely illiterate, 45 of whom were women and, on analysis, these were shown to have the poorest glycaemic control. In another study by the same group it was noted that Pakistani women with diabetes, despite knowing less about the condition initially, improved their knowledge levels through health education to catch up with the men within six months[24].

Access to diabetes care

It has been argued that a difference in the prevalence and outcome of diabetes in British South Asians is at least partially attributable to differences in access to NHS services. Difficulties in accessing and using health services by some British South Asians have been well documented in a systematic review by Hawthorne[28], who described instances of racial discrimination in provisions of services.

In a retrospective hospital activity analysis, South Asian patients in Leicester with symptoms of coronary heart disease were significantly less likely to have been referred for exercise stress testing than white British patients[29]. In another retrospective survey by the same authors, fewer South Asian patients with myocardial infarction had been given thrombolysis[30].

A survey of patients seen at a coronary angiography unit showed that those of Indian origin were referred for investigations, on average, 17.4 months after onset of the symptoms of angina, whereas white British patients were referred, on average, after 6.9 months[31]. Another survey based in Leicester showed that while 92 per cent of elderly people of South Asian origin had consulted their GP in the last six months, 88 per cent of them had not heard of the chiropody service and only 3 per cent were receiving treatment from it. This compared with the indigenous elderly population, 37 per cent of whom were currently using chiropody service[32].

It is likely that differences in disease symptomatology, language barriers, poor knowledge of services, difficulties with transport and differences in willingness to seek medical help may all influence the apparent accessibility of services. For example, in Lear and colleagues study[30], differences in the rate of thrombolysis after acute myocardial infarction were almost entirely accounted for by the later presentation of the South Asian patients.

Attitudes to medical treatment

Reviews of the literature on adherence to drugs have shown that non-concordance is a problem across all patient groups and is especially common among people who have no symptoms or have unpleasant side effects. Patients' self-management and adherence to drugs are key to good glycaemic control. However, adherence to prescribed oral hypoglycaemic agents (OHAs) is poor, and some South Asian patients may be less anxious than white patients about adhering to their treatments and may attach less importance to controlling their diabetes. It is increasingly recognised that if adherence is to be improved, patients' perspectives must be better understood.

A questionnaire-based study asking South Asian patients about their views on OHAs found that participants had complex views, with some who considered them only for symptomatic benefit trying to reduce the dose at every possible opportunity[33]. Similarly, there were misconceptions about OHAs being harmful in combination with certain foods or drugs of if used long term. These views reflected their attitudes towards western drugs in general.

A study looking at the use of traditional medicines among Pakistani migrants in Bradford noted that certain plant-based therapies were still very popular, with two-thirds of the people interviewed preferring them[34].

Gaps in research

Clearly, a lot still needs to be done to improve the level of understanding among some South Asian patients. While lower levels of literacy can make this a challenge, it is something that can only be tackled through combined initiatives from both patients and healthcare workers. There is a paucity of studies on the effects of migration on overall health, and diabetes in particular, in the South Asian population. There is a need for studies on the effects of migration and following a western lifestyle. Future studies of inequalities should be large, separating Indian, Pakistani and Bangladeshi populations, studying men and women separately, and tracking changes over period of time. Attitudes to diet and different types of exercise vary greatly among South Asians.

Research priorities

- studies on the cultural acceptability of different types of exercise and dietary regimen in South Asians
- studies to look at effective intervention programmes to reduce smoking in Bangladeshi men
- studies looking at effective intervention programmes in economically deprived areas to improve access to healthcare and tackle health inequalities
- studies to evaluate novel methods of health delivery, such as social enterprise, to improve access and tackle health inequalities
- studies to understand the cultural factors responsible for poor compliance to lifestyle advice and medication
- studies to develop and evaluate culturally sensitive and effective health promotional material, community educational programmes, DVDs and toolkits.

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Chapter 5: Screening for diabetes and non-diabetic hyperglycaemia

Kamlesh Khunti, Stephen Hiles and Melanie J Davies

Context

In the South Asian population diabetes and non-diabetic hyperglycaemia develops about five to ten years earlier than in Europeans[1,2], and associated complications are encountered more commonly[3].

Type 2 diabetes is often preceded by a lengthy state of impaired glucose regulation (IGR) that can last up to 12 years. During this phase it has been shown that microvascular damage has already started and can be well advanced before a diagnosis of Type 2 diabetes is made[4–6]. Globally, approximately 15 per cent of adults have IGR based on World Health Organisation (WHO) criteria[7,8], defined as either impaired glucose tolerance (IGT) (two-hour glucose concentration of 7.8–11mmol/l after a 75g glucose load) or impaired fasting glucose concentration of 6.1–6.9mmol/l. A proportion of these (5–12 per cent), develop Type 2 diabetes each year[7,8]. Progression to diabetes in this high-risk population may also be as much as three times greater in South Asians compared to white Europeans in the UK[9].

Given the increased risk of this particular group and the rising health service burden of diabetes and its complications, it seems appropriate to advocate early detection in preparation for some type of educational or therapeutic intervention. Modelling studies have suggested that screening for Type 2 diabetes and IGR followed by interventions is cost effective, even in South Asian populations[10]. In view of the high prevalence and costs of vascular diseases, the Department of Health recently rolled out the NHS Health checks (vascular checks) programme systematically to identify and treat vascular disease risk. This includes a diabetes assessment in all individuals aged 40–75, using a combination of risk scores and biochemical testing[11].

Summary of current evidence

The gold standard method of detecting undiagnosed Type 2 diabetes and IGR is an oral glucose tolerance test (OGTT). OGTT is resource intensive and appears to have limited use in a routine healthcare setting, particularly as clinical diagnosis requires a confirmatory OGTT with diabetes range blood values. The shift towards a single test such as a fasting glucose or HbA1c may provide some of the answers as the diagnostic test of choice. However, a fasting glucose test would only detect a small proportion of hyperglycaemic South Asian people, as they display a greater

incidence of IGT[12]. The WHO, American Diabetes Association and International Diabetes Federation (IDF) are considering HbA1c as a diagnostic test for Type 2 diabetes. The current diagnostic criteria have poor sensitivity for glucose intolerance in South Asians. This means that ethnic specific cut-offs may be required or a combination of single tests to identify high-risk individuals ahead of an OGTT[13].

OGTT, however, remains imperative in people who have had a recent cardiovascular event such as myocardial infarction. Several studies have reviewed the post-event assessments of this extremely high-risk group and concluded that anything other than an OGTT does not capture relevant glucose disturbances[14–16].

Given the time and resource cost of an OGTT in the apparently healthy population, diabetes risk scores using data routinely collected in primary care are a popular pre-screening tool for identifying those in most need of further assessment. Self-assessment variables include age, body mass index (BMI), family history of diabetes, waist circumference and history of hypertension. Following completion of the risk score by the healthcare professional or the individual, people can receive an instant estimation of their current and/or future risk. Several such risk-assessment tools have been developed, the most widely validated and used being FINDRISC[17].

FINDRISC was developed in Finland and uses weighted scores from eight risk characteristics to calculate an overall risk score[17]. FINDRISC has been shown to have good sensitivity and specificity for predicting the 10-year absolute risk of Type 2 diabetes in a white European population[17]. Other risk scores have been developed and validated in cross-sectional studies in diverse populations in the UK, India, Germany and the Netherlands[18–22]. The majority of diabetes risk scores have been designed for, and evaluated in, ethnically homogenous groups. These risk-assessment tools provide the first step in multi-step screening strategies. Combining them with a blood test increases the potential utility of a particular risk assessment and reduces the costs of inappropriate testing. One study investigated such an approach for the local South Asian population with positive results, increasing yields with reduced testing[23].

In the UK, general practice computer systems hold a huge amount of data that can be used to produce computer-based risk scores. This huge dataset has been utilised by the QRISK team in Nottingham[24] and allows estimation of diabetes risk over a set time period. Due to its web-based nature, it also allows adjustment for ethnicity and socio-economic status.

For South Asians, the risk of diabetes and cardiovascular disease occurs at lower levels of BMI compared to a European population[25]. Because of variations in body proportions, BMI may not correspond to the same body fat in different populations[25]. As South Asians have higher central adiposity for a lower BMI[26], waist circumference is a more appropriate measure. The IDF's definition of Metabolic Syndrome and the UK's National Obesity Forum give ethnic-specific limits from a large survey of South Asian Indians, and these limits are deemed appropriate for migrant populations[27,28].

Measuring waist circumference would be an easy and cheap method for primary care to identify people at risk for diabetes and cardiovascular disease but would lack specificity to be used alone[29].

The evidence suggests that we have a range of tools that can be used to aid identification through systematic screening of appropriate specific ethnic groups. However, the issue of access for minority groups, particularly in deprived areas, is an overriding concern. These inequalities deny access for people seeking health services and also prevent the local healthcare system from identifying and engaging with these communities to provide comprehensive chronic disease management strategies.

Differences in cultural beliefs towards diabetes and perception of individuals within ethnic groups of their own risk highlight the need to engage and educate. In the Newcastle Heart Project, there was a mismatch between South Asian women's perceptions of their own weight and guidelines on being overweight and obese[30]. A substantial proportion of South Asian women who were overweight perceived themselves as being of normal weight, but European women had the opposite problem – perceiving themselves as overweight when they were not. This mismatch was seen in both those with and those without diabetes and non-diabetic hyperglycaemia. South Asians' knowledge regarding the causes of diabetes and heart disease in the nearby area was extremely poor[31]. This is also true of the perception of a sedentary lifestyle on diabetes susceptibility, particularly among women, and this remains a huge challenge[32]. This perception of risk affects participation in screening and is compounded by perceived cultural and communication difficulties, where there might be language/literacy problems in providing written educational materials and invitations[33].

Overall the evidence is consistent and robust: South Asians are at an increased risk of diabetes and cardiovascular disease but at a younger age, with a lower BMI and smaller waist circumference compared to an indigenous white population. This is highlighted by studies of Indian patients in India that have shown lower thresholds for waist circumference and increased risk of glucose intolerance in South Asians compared with Europeans. For a migrant South Asian population, this difference is increased. The IDF and other leading bodies are recognising this issue through revised recommendations. It is realistic and beneficial to tailor screening programmes to identify the South Asian population at high risk for IGR and diabetes at a younger age. In terms of access, it is vital to engage and promote leadership to raise awareness and provide intra-community focus to study the problem of diabetes in various South Asian groups.

Gaps in research

Research to date has failed to identify clearly effective methods of providing screening for Type 2 diabetes and IGR among South Asian communities in the UK.

The design, implementation and evaluation of appropriate programmes to meet this need present enormous challenges that require further efforts in a number of areas to overcome: their existing health beliefs; knowledge of and attitudes to diabetes; the influence of socio-economic deprivation and other chronic life stresses at the onset and during the course of diabetes; the usefulness of changes to the traditional diet; and the optimum strategy for reducing modifiable cardiovascular risk factors such as smoking, obesity and inactivity.

Research priorities

- screening high-risk South Asian populations such as those who have had a myocardial infarction or stroke to determine the prevalence of Type 2 diabetes and IGR
- qualitative studies leading to an enhanced understanding of cultural attitudes and beliefs, in order to inform the design of appropriate screening strategies
- studies investigating methods of increasing engagement with these populations and uptake of screening invitations
- studies exploring methods of evaluating some aspects of the impact of screening (for example, psychological outcomes) in populations where traditional methods may be inappropriate
- studies to look at solutions to overcoming literacy and language issues.

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Chapter 6: Prevention of Type 2 diabetes

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Context

Approximately 5 per cent of the total NHS resources and up to 10 per cent of hospital inpatient resources are devoted to the care and treatment of individuals with Type 2 diabetes[1]; these figures are set to rise in the future and will represent a serious clinical and financial challenge to the UK's health system[2].

Glucose tolerance may start to decline up to 12 years before clinical recognition of Type 2 diabetes and markedly increases the risk of cardiovascular mortality compared to people with normal glucose tolerance[3–5]. This provides a potential window of opportunity to identify elevated blood glucose levels early, when patients will have been exposed to less hyperglycaemia and fewer co-existing abnormalities. Given these factors, individuals with non-diabetic hyperglycaemia are an important population in the prevention of Type 2 diabetes.

Summary of current evidence

Prevention

There is now clear evidence that lifestyle modification and medicines can substantially reduce the risk of Type 2 diabetes in those with non-diabetic hyperglycaemia regardless of their ethnicity[6]. For example, data from large diabetes prevention studies in the USA and Finland have shown that lifestyle modification programmes, aimed at achieving weight loss through the promotion of physical activity and healthy diet, reduce the risk of Type 2 diabetes by 58 per cent[7,8]. Indeed, per protocol analyses of these studies revealed that the risk of developing Type 2 diabetes was reduced by 80 per cent or more when individuals achieved their prescribed lifestyle change goals[8,9]. Successful lifestyle diabetes prevention programmes have also been carried out in diverse populations and settings, including India[10], China[11] and Japan[12].

Lifestyle modification programmes in South Asians

Given the elevated risk of chronic disease in South Asian communities, and considering the discrepancy between white Europeans and South Asians in many lifestyle factors, such as physical activity, it is vital that lifestyle modification programmes are developed that are suitable for implementation in multi-ethnic settings and can respond to the specific needs of ethnic minorities.

Several qualitative studies have investigated the perceived barriers and challenges to promoting health behaviours among South Asians[13–16]. A study involving South Asians and white Europeans with Type 2 diabetes in Leicester found that South Asian individuals tended to view their diagnosis as inevitable and accepted it with resignation, due in part to a strong family history of Type 2 diabetes[16]. This sense of fatalism is often compounded by religious beliefs among lay individuals[13,16]; however, religious leaders tend to view this fatalism as misplaced[13], which suggests a potential role for religious leaders in behaviour change programmes. It has also been reported that healthcare professionals perceive South Asians as holding fatalistic beliefs surrounding their health status and are reluctant to provide lifestyle advice because of poor cultural and religious understanding[13], thus exacerbating the problem. It has also been commonly reported that traditional social norms and expectations are a major barrier to eating a healthy diet and undertaking physical activity, particularly among South Asian women[13–16]. However, South Asians tend to have a high regard for knowledge and education and were keen to learn more about their condition from healthcare professionals[13,16].

Despite the informative findings from qualitative studies, there has been little attempt to further this knowledge by designing and evaluating diabetes prevention programmes that have been tailored to the specific needs of ethnic minorities in the UK or elsewhere. This is mirrored in diabetes treatment programmes: for example, a recent systematic review identified only five randomised controlled trials investigating diabetes treatment programmes for South Asians living in industrialised countries[17]. These studies were generally characterised by methodological limitations and a lack of detail regarding the development of the tested interventions. This is an important limitation, because interventions designed and evaluated in monolingual and/or monocultural settings are not necessarily generalisable to other settings.

Gaps in research

A reliable estimate of the extent to which ethnic-specific differences in physical activity and other health behaviours account for the difference in the risk of developing diabetes has not been established, due to lack of evidence from studies using robust measures of health behaviour. Given that the global prevalence of Type 2 diabetes is attributable to lifestyle factors and that lifestyle modification is at least as, if not more, effective than pharmaceutical agents at preventing Type 2 diabetes[17], lifestyle change should be the primary focus of diabetes prevention initiatives. Others have pointed out that while this ethnic-specific research offers valuable insights and that a ‘one size fits all’ approach to patient education and health promotion is unrealistic, it is often unhelpful to exaggerate the difference between ethnicities when barriers to, and preferences for, health behaviour are commonly shared across all ethnic groups[15]. Systematic and reproducible methods of developing lifestyle interventions for ethnic minorities aimed at the prevention of Type 2 diabetes are needed. Such interventions also need to be evaluated using well-designed randomised controlled trials with appropriate primary outcomes.

Research priorities

- large cohort studies in multi-ethnic populations, using objective measures of physical activity and nutritional status to investigate the extent to which differences in lifestyle factors between South Asians and white Europeans account for ethnic specific differences in metabolic and vascular health
- establishing the efficacy and cost-effectiveness of pragmatic lifestyle diabetes prevention programmes, systematically tailored to the needs of South Asian ethnic minorities.

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Chapter 7: Self-management and education for people with Type 2 diabetes

Margaret A Stone, Melanie J Davies and Kamlesh Khunti

Context

Health education has been recognised as having a significant role to play in the management of Type 2 diabetes by empowering patients to be involved in their own care. Self-management can contribute to good outcomes in terms of quality of life, current health status and risk reduction relating to complications associated with diabetes. Both the National Institute for Health and Clinical Excellence[1] and the National Service Framework for diabetes in England[2], therefore, recommend patient education as part of diabetes management.

However, in order for interventions aimed at promoting self-management to be effective, it is necessary to understand factors such as knowledge levels, attitudes, health beliefs and practices that may affect people's willingness and ability to play an active role in managing their diabetes. These include being aware of, and understanding, factors that may be either specific or more emphasised in people from a particular ethnic background. A limited number of studies, including some identified by our searches[3–11], have provided information in this area with regard to migrant South Asians with Type 2 diabetes. Topics considered have included: beliefs and practices relating to diet, including perceived links between diet and cultural identity; attitudes to physical activity; health beliefs and their links to religious beliefs, for example fatalistic perceptions; levels of underlying knowledge about diabetes; perceptions about and use of traditional medicines; and attitudes to the concept of self-management itself. In common with other areas of interest relating to people of South Asian origin with diabetes, it is important to bear in mind the heterogeneity of this broad ethnic group and to be aware that the attitudes and health beliefs of specific subgroups may not be common to all migrant South Asians.

Summary of current evidence

Two systematic reviews published in 2008 have identified and considered studies reporting educational interventions for people of South Asian origin with Type 2 diabetes[12,13]. These reviews can be used as a link to the published literature in this area. One of these systematic reviews[12] focused exclusively on educational interventions for migrant South Asians and identified only nine studies that met the inclusion criteria. These studies often involved small samples and included only five randomised controlled trials[14–18]. As the authors of the review anticipated identifying

only a small number of relevant studies, selection was not limited to randomised controlled trials. Four non-randomised studies providing evidence about educational initiatives for South Asians with Type 2 diabetes were also identified[19–22]. 10 of the 11 selected studies were conducted in the UK and involved a range of migrant South Asians originating from Pakistan and India; the other study was conducted in the Netherlands and involved people of Surinamese origin. None of the selected studies involved people of Bangladeshi origin, who have a particularly high risk of having Type 2 diabetes. However, two potentially useful studies involving people from this South Asian subgroup had been excluded from the final sample of selected papers because there was no separate reporting for people with diabetes as opposed to other chronic diseases[23] or by type of diabetes[24].

The interventions evaluated in the selected studies varied widely, ranging from multifaceted tailored care packages to initiatives focused on a specific topic such as dietary advice. Overall, limited clinical effectiveness was reported: although it appeared that it is easier to enhance knowledge levels than to improve biomedical outcomes, the authors of the review noted that it could be argued that increased knowledge is of questionable value if it does not lead to improvements in health outcomes. However, it can also be argued that without knowledge, motivation and tools, it is not possible for people with diabetes to work to improve their own clinical outcomes. Of the three randomised controlled trials that included HbA1c as an outcome measure, only one was able to demonstrate a positive impact[18] and this effect was reduced with longer-term follow-up[25].

The scope of the recent Cochrane review[13] was wider, including people from ethnic minority groups as a broad category rather than people specifically of South Asian origin. A lack of homogeneity was identified in the 11 selected studies, of which only four were conducted in people of South Asian origin. These four studies were also included in the review described above; the other randomised controlled trial selected by Khunti and colleagues was identified by the Cochrane reviewers but excluded from their final sample because the study's authors could not provide some of the data required by their selection criteria. In reviewing their overall selection of studies, the authors of this Cochrane review noted limitations in terms of trial design, including duration of follow-up and the outcome measures used. The effectiveness of the interventions reported in these studies was variable, but provided some limited evidence that culturally appropriate health education may have short-term benefits relating to blood sugar control and diabetes knowledge, when compared to 'usual care'. The authors of both these reviews emphasised the need for further well-designed research.

Since the above two systematic reviews were conducted, an important paper has been published, reporting the findings from a large cluster randomised controlled trial, the United Kingdom Asian Diabetes Study[26]. This trial was conducted in 21 inner city general practices in the UK and the primary outcome measures were changes in blood pressure, total cholesterol and HbA1c levels after two years of

follow-up. The authors identified only minimal benefits and a lack of cost-effectiveness; they concluded that stricter targets are needed in primary care, together with additional measures to motivate patients. However, the intervention in this trial included enhanced practice nurse contact and support from a link worker rather than a structured education programme with a basis in psychological theory.

Two recent papers have addressed the question of meeting the needs of South Asian patients by using modified versions of educational programmes originally developed with the indigenous population primarily in mind. Choudhury and colleagues evaluated a version of the X-PERT Programme modified for people of Bangladeshi origin[27]. Education sessions were conducted in Sylheti by a peer educator and included the use of interactive posters to explain diabetes. Stone and colleagues have described the process of adapting and initially piloting the DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed) module for use in South Asian populations[28]. This modified version is delivered through interpreters and involves a range of visual resources. Adapting existing programmes could provide a cost-effective method of building on previous work, provided that the modifications made, both in terms of content and delivery, are informed by an understanding of specific cultural needs and attitudes. The two small studies described provide some encouragement in terms of the feasibility and acceptability of using modified programmes, but further evidence for the effectiveness of this approach to meeting the needs of South Asian people with Type 2 diabetes is needed.

In a methodology paper reflecting on the evaluation of the modified version of the X-PERT programme described above, Choudhury and colleagues have drawn attention to two additional considerations relevant to research in the field of educational initiatives for South Asian people with Type 2 diabetes[29]. Firstly, difficulties with engaging the interest of these populations in educational initiatives in some South Asian groups can lead to poor uptake. It is important that educational initiatives are acceptable, accessible and seen as a priority, since low uptake would have an important limiting effect on any potential for improving outcomes in the overall target population. Methods of facilitating engagement are therefore an important topic for further investigation. Secondly, Choudhury has also drawn attention to problems related to factors such as language, literacy and attitudes to questionnaire completion, which can present difficulties with evaluating the effectiveness of educational interventions. The limitations of using traditional approaches involving self-completion questionnaires have also been highlighted by a study in which link workers were used to assist with questionnaire completion to assess knowledge and perceived self-efficacy levels in a South Asian population with high levels of illiteracy[30].

Gaps in research

Research to date has failed to clearly identify effective methods of providing education to promote self-management in South Asian people with Type 2 diabetes. The design, implementation and evaluation of appropriate interventions to meet this need all present enormous challenges requiring further efforts in a number of areas.

Research priorities

- additional qualitative studies leading to an enhanced understanding of cultural attitudes and beliefs, in order to inform the design of appropriate educational interventions
- studies investigating methods of increasing engagement and uptake of educational initiatives
- studies exploring methods of evaluating some aspects of the impact of educational interventions (for example, psychological outcomes) in populations where traditional methods may be inappropriate
- well-designed trials evaluating the effectiveness of interventions based on a sound understanding of the needs and attitudes of the target population.

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Chapter 8: Childhood and adolescent Type 2 diabetes

Timothy G Barrett

Context

Paralleling the rise in childhood obesity worldwide there has been a rise in Type 2 diabetes in childhood. The rise in Type 2 diabetes has been documented in the UK from the first cases of childhood Type 2 diabetes in 2000, observed in children of South Asian origin[1] to the successive British Society for Paediatric Endocrinology and Diabetes[2] and British Paediatric Surveillance Unit (BPSU) surveys of non-Type 1 diabetes[3]. While Type 2 diabetes has been reported in all ethnic groups in the UK, it is clear that children of South Asian and African-Caribbean origin are at particular risk. In a national prospective monthly surveillance study in 2005, 76 cases of newly diagnosed Type 2 diabetes, of which 40 per cent were from an ethnic minority, predominantly South Asian, were identified alongside a minimum incidence of Type 2 diabetes of 0.53/100,000/year, but 3.9/100,000/year in Black and South Asian children[3]. 95 per cent of children with Type 2 diabetes were overweight, 83 per cent obese and 84 per cent had a family history of Type 2 diabetes. A follow-up study found no significant overall improvement in weight during the first year after diagnosis. In addition, 42 per cent failed to achieve the American Diabetes Association/European Association for the Study of Diabetes recommended treatment target of HbA1c less than 7.0 per cent. The rise of obesity and reduced activity endemic in British society threatens to produce a continuing rise in the incidence of Type 2 diabetes in UK children. Type 2 diabetes is clearly having an impact on ethnic minority groups who are already disadvantaged in UK society. The recent report from the Royal College of Paediatric and Child Health provided a snapshot and identified 328 children and young people with Type 2 diabetes in England, with a heavy preponderance towards children from ethnic minorities, predominantly South Asian[4].

Summary of current evidence

The increase in childhood obesity has caused concern that it may be difficult to distinguish between obese children with Type 1 or Type 2 diabetes; however, this concern has not been shared by all[5]. It has been particularly difficult to classify children with diabetes related autoantibodies and also obesity and insulin resistance.

The reasons for the ethnic differences in Type 2 diabetes risk are not fully understood; there are differences in body composition even in childhood, with South Asian children having significantly higher percentages in body fat compared to white

children[6]. This relates to tissue insulin sensitivity, and it has been shown that generally South Asian children are more insulin resistant for any given body mass index than their age- and sex-matched white peers[7,8]. As with South Asian adults, declines in cardiovascular fitness and exercise have been documented in South Asian children[9]. Finally, poor dietary habits have been reported among many South Asian children in secondary schools[10].

Besides the acute risks of hyperglycaemia, such as ketoacidosis and non-ketotic hyperglycaemic coma[11], children with Type 2 diabetes are at high risk of developing hypertension, nephropathy, dyslipidaemia and the associated conditions non-alcoholic fatty liver disease and polycystic ovarian syndrome[12]. These complications may be present at diagnosis of Type 2 diabetes, suggesting that Type 2 diabetes may have been undetected for some months before diagnosis. Furthermore, despite being perceived by children and parents as 'mild' diabetes, Type 2 diabetes may appear to have a more adverse complication profile than Type 1 diabetes, with a clear link between Type 2 diabetes and accelerated micro- and macrovascular complications of diabetes[13].

The long-term outcome for children with Type 2 diabetes is poorly understood; the studies from Australia suggest that youth onset Type 2 diabetes is associated with higher risks for complications than Type 1 diabetes[13]. While adults with Type 2 diabetes may develop complications late in their working lives, children are likely to develop complications in early adulthood at a prime time for establishing employment, reproducing and bringing up children[14]. A child with Type 2 diabetes therefore represents not just a potential cost to the NHS through developing complications, but also a loss to the UK workforce and an impact on the next generation through parental illness or death. This knowledge on outcome and management is vital not just for counselling individual patients, but also for planning many adult services, including renal dialysis and ophthalmic and vascular surgery services.

While lifestyle change has been shown in adults to be the best way of preventing Type 2 diabetes[15], studies in childhood have proved to have short-term benefit only, and few patients are compliant with lifestyle changes[16]. Compliance with treatment is often hindered by the lack of severe symptoms at diagnosis in comparison to Type 1 diabetes. Work from Leicester has shown that a low prioritisation of health among young South Asian people is a barrier to achieving a healthy lifestyle[17]. In addition, many patients are in their teenage years and rebelling against authority; and most pharmacotherapy for Type 2 diabetes is not manufactured in paediatric formulations. The only drug with randomised control trial data from a small trial to support use in children with Type 2 diabetes is metformin[18]. Newer treatments such as incretin mimetics and dipeptidyl peptidase 4 inhibitors, which seem to show promise in adult studies, have not as yet been robustly investigated in childhood populations and require phase 2 studies to demonstrate effect size. Extrapolating from adult data is unwise in the growing and/or pubertal child, as growth, the attainment of peak bone mass and progression through puberty are naturally insulin-resistant states.

Gaps in research

The reasons for the ethnic differences in Type 2 diabetes risk are not fully understood and there is a paucity of studies involving children, possibly because the scale of the epidemic in adults dwarfs the small overall number of affected children. There are also no longitudinal data from the more obese and ethnically cosmopolitan UK child population. There is almost no evidence base for effective treatments for Type 2 diabetes in childhood, and little information about which drugs should be used for treatment, and in which groups of children. The numbers of children currently with Type 2 diabetes in the UK are such that only multicentre trials of novel treatments will be sufficiently effective. Having access to a central register from which to select well-characterised patients with clearly delineated comorbidities would facilitate such trials.

Research priorities

- the development of a cohort of affected children to adequately describe the natural history in UK children of South Asian origin
- determining the most effective screening method for Type 2 diabetes in children and how this is affected by ethnicity
- characterisation of the overlap between obesity, Type 1 and Type 2 diabetes in children and different groups of children
- the efficacy and cost-effectiveness of interventions aimed at children that reverse or delay progression of Type 2 diabetes and its complications, and how effective these are in different ethnic groups.

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Chapter 9: Gestational diabetes

Paromita King

Context

Diabetes as a result of pregnancy occurs when pancreatic beta cell function is insufficient to overcome the physiological insulin resistance of pregnancy. Clinically, gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying severity with onset or first recognition during pregnancy irrespective of the glycaemic state after pregnancy[1]. The definition includes a wide range of glucose intolerance from minimal elevations of blood glucose to pre-gestational diabetes, which presents in pregnancy[2].

The diagnosis is based on either a 100g or 75g glucose tolerance test. The former use criteria, defined by O'Sullivan and Mahan[3], designed to identify women at risk of developing diabetes, whereas the latter is based on the World Health Organisation diagnostic criteria for diabetes and non-diabetic hyperglycaemia outside pregnancy[1]. Despite several recent quality publications[4,5], there is still a lack of agreement as to who to test for GDM and how to test, as well as the glucose thresholds and targets for treatment.

Obesity, advanced maternal age, family history of diabetes, ethnicity, increased weight gain in early adulthood and smoking are risk factors for GDM[6–10]. While diagnostic inconsistencies contribute to the variability of the prevalence of GDM, the greater factor is the ethnicity of the population[2]. Indeed, ethnicity is one of the strongest risk factors for GDM. A UK-based study showed that South Asian women were 11 times more likely to develop GDM than white British women[7]. A Norwegian review showed similar results[8].

Summary of current evidence

The prevalence of GDM is increasing[9] in parallel with increasing obesity and prevalence of Type 2 diabetes. An analysis of birth records in New York between 1995 and 2003 showed prevalence rates as low as 3 per cent for non-Hispanic white women, compared with 11.7–21.2 per cent for South Asian women. The highest prevalence rates were seen in Bangladeshi (21.2 per cent) and Pakistani (16.2 per cent) women[11], with comparable rates in indigenous[12,13] and immigrant[11] groups. Not only is GDM much more prevalent in South Asian groups, but it occurs at a lower body mass index[14] and there is also a suggestion that it presents earlier than in white populations[15].

Hyperglycaemia in the second and third trimesters leads to foetal hyperinsulinaemia and placental dysfunction resulting in adverse pregnancy outcomes. These include increased rates of macrosomia, stillbirth, caesarean section, shoulder dystocia, prematurity, admission to neonatal units and perinatal mortality[16–19]. South Asian women are more likely to have small-for-gestational-date infants and pre-term babies[20], but it is unclear whether those with GDM have poorer pregnancy outcomes than white women.

While the risks of GDM are undisputed, it was not until the publication of the Australian Carbohydrate Intolerance Study (ACHOIS)[4] that the benefits of treating 'mild' GDM were shown. ACHOIS included women with a fasting glucose less than 7.8mmol/l or 7.8–11mmol/l after a 75g glucose load, and demonstrated a reduction of severe perinatal complications from 4 per cent to 1 per cent as a result of active treatment with insulin.

More recently the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO)[5], a large multicentred study involving over 25,000 women, demonstrated a continuous relationship between fasting and post-prandial glucose levels and adverse pregnancy outcomes, even within the currently accepted normal range. The fact that HAPO is an observational study, together with the finding that lowering glucose too far can result in small-for-gestational-date infants[21], has resulted in debate as to the clinical implications of the study.

The aim for glucose management during pregnancy is to achieve 'normal' blood glucose concentrations, but the thresholds for treatment and treatment targets are still not agreed. Diet and exercise remain the first line treatments for GDM. Even gentle exercise such as arm exercises while seated can reduce blood glucose levels[22] and insulin usage in overweight women[23].

When lifestyle measures fail, insulin has been the gold standard for the treatment of GDM. However, there is increasing evidence to support the safety and efficacy of glibenclamide and metformin in GDM, and the former also reduces first trimester miscarriage rates in women with polycystic ovarian disease[24,25]. These drugs, particularly metformin are likely to have an increasing role in the management of GDM.

A systematic review documents recurrence rates of GDM of 30–37 per cent in non-Hispanic whites, and 52–69 per cent in ethnic minority groups[26]. Observational studies show that women who are active before and during pregnancy are 76 per cent less likely to develop gestational diabetes, raising the possibility of preventing GDM[27,28] through lifestyle interventions such as those described below.

A history of GDM increases the risk of developing diabetes, with conversion rates varying from 2 to 70 per cent. A large part of the variability is due to differences in the time between presentation with GDM and follow-up[29]. Obesity, age, family history of diabetes, ethnicity and level of glucose intolerance in pregnancy and postnatally have been identified as risk factors for progressing to diabetes. For

example, one US study demonstrated that women with impaired glucose tolerance (IGT) with a history of GDM have a 71 per cent increased risk of developing diabetes than those without a history of GDM[30].

A study in Leicester undertaken four years after the diagnosis of GDM found that South Asian women with GDM were almost twice as likely to develop diabetes as those without (48.6 per cent versus 25 per cent)[31], and similar rates have been shown in South India[32]. In indigenous Sri Lankan women, a history of GDM also increases the risk of polycystic ovarian disease and metabolic syndrome[33].

Several studies have demonstrated that intensive lifestyle interventions resulting in weight loss, or the use of drugs such as metformin reduces the progression of IGT to diabetes[34–36]. One of these studies, the Diabetes Prevention Programme is a multicentred US study involving people with IGT[36]. A subgroup analysis of outcomes in 350 women with a history of GDM[30] showed that metformin or intensive lifestyle interventions halved the incidence of diabetes. While the control group benefited from lifestyle interventions, they did not benefit from the use of metformin. Thus, a history of GDM not only highlights a group at high risk of developing diabetes, but also that the risk is modifiable. The challenge is whether these intensive interventions can be delivered within routine clinical practice.

These studies used western-style lifestyle approaches, which are unlikely to be transferable to all South Asian groups, particularly those from poor socio-economic backgrounds. Qualitative studies have explored the barriers to, and facilitators of, the uptake of lifestyle changes in South Asian people. Healthcare professionals sometimes perceive these groups as regarding obesity as a sign of prosperity, and being fatalistic in their attitudes. A study in Bangladeshi women in London showed that only a minority were fatalistic, and that most perceived a medium build as being healthy[37]. However, a Scottish group demonstrated that Indian and Pakistani people with diabetes were more likely to blame external factors such as migration for their diabetes, whereas white respondents tended to blame themselves and their lifestyle choices[38]. South Asian people with diabetes have been reported to be less likely to take ownership of their condition or work in partnership with healthcare professionals, preferring prescribed treatments to lifestyle changes as treatment options[39,40].

While knowledge was not a barrier to lifestyle changes, Pakistani women were noted to find it hard to apply their knowledge to practical situations[41]. Language and cultural barriers to undertaking western-style exercise have been described in a number of South Asian groups, particularly Bangladeshi and Pakistani people from poor socio-economic backgrounds. These include perceiving going to a gym as an alien concept, and exercise as a standalone entity being completely at odds with the woman's role in the home. Shame and fear of ridicule were recurrent themes. While many accepted the importance of a healthy diet, they perceived straying away from traditional methods of preparing food for guests as impolite[37,39,40].

The findings from qualitative studies such as these may inform the development of culturally appropriate lifestyle intervention strategies to prevent diabetes and gestational diabetes in South Asian women.

Foetal hyperinsulinaemia, as a result of maternal hyperglycaemia, could lead to *in utero* programming, predisposing the baby to obesity and diabetes. In Pima Indians, the offspring of mothers with diabetes show high rates of obesity and diabetes[42]. Studies assessing siblings and the offspring of fathers with diabetes support the conclusion that the effects on offspring are over and above those expected as a result of genetic risk[42,43]. While the effects of GDM are less clear, there is evidence of IGT and increased markers of insulin resistance among offspring of mothers with GDM[44,45], making them a high-risk group for developing diabetes, whose risks could also be potentially modified through lifestyle measures.

Finally, for the women who do develop diabetes, their subsequent pregnancies are not only at risk of the complications outlined above, but also have a three- to four-fold increase in congenital abnormality rate[46]. Effective pre-pregnancy care through optimising glycaemic control, the use of high dose folic acid, and replacing teratogenic drugs with those safe in pregnancy can reduce these risks to a background level[47]. In Derby, while we have increased the percentage of women pre-conceptually (32 per cent in 2002/3 to 73 per cent in 2007/8), 80 per cent of white women were seen, compared with 46 per cent from South Asian backgrounds, creating inequalities in care which clearly need addressing[48]. We particularly struggle to engage those from low socio-economic backgrounds, whose pregnancies are at highest risk.

Gaps in research

While qualitative work has explored the barriers and facilitators to lifestyle interventions in South Asian women, an understanding of the issues relating to pregnancy in general and diabetes and GDM specifically in South Asian women, particularly from poor socio-economic backgrounds is a priority. A range of women should be studied to identify common themes as well as differences between different South Asian groups. The results could be used to inform culturally appropriate interventional strategies specifically targeted to treat and prevent GDM and diabetes, as well as effective pre-pregnancy care for those with pre-gestational diabetes. These would require testing in randomised trials.

HAPO demonstrated a continuous relationship between glucose and adverse outcomes. An analysis of pregnancy outcomes in South Asian women in HAPO would be valuable to ascertain how their risk compares with the group in general.

Research priorities

- developing culturally appropriate interventions specifically targeted at South Asian women
- studies in the role of lifestyle intervention programmes for the prevention and treatment of GDM in this population
- studies developing and assessing the effectiveness of pre-pregnancy care
- further studies in the epidemiology of hyperglycaemia in pregnancy, including relationship between glucose and maternal and foetal outcomes in South Asian women
- studies assessing the effectiveness of intervention programmes for prevention of diabetes in South Asian women in the postnatal period following GDM.

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Chapter 10: Psychological consequences of diabetes

Margaret Stone and Cathy Lloyd

Context

Quality of life is an important consideration in relation to health and wellbeing. In common with other chronic conditions, Type 2 diabetes can have serious psychological consequences for the person affected. These consequences may be related to the condition itself, for example the perceived impact of dietary restrictions on quality of life related to social functioning; or to complications of the condition, such as retinopathy and erectile dysfunction. Three meta-analyses of published studies[1,2,3] have identified an increased prevalence of depression in people with diabetes compared to the background population. However, the direction of causation for this association has not been adequately clarified[4]. Depression in people with diabetes may lead to a reduced capacity to engage effectively in self-management and self-care and can thus lead to poorer outcomes related to increased levels of hyperglycaemia[5]. Diabetes-related anxiety and stress may also impair quality of life and have an impact on self-care behaviours, although the relationship between stress and glucose levels requires further investigation[6].

The ability to measure factors associated with quality of life in large samples is most commonly dependent on the use of self-completion questionnaires, and a number of validated diabetes-specific psychological measures are available[7]. However, for populations with specific language and literacy needs, the appropriateness of traditional instruments and methods of administration may be limited[8,9]. For example, the use of self-completion questionnaires remains problematic in sections of the South Asian population where there are high levels of illiteracy or where the main language spoken has no agreed written form[8]. Qualitative methods can be a useful means of identifying and exploring psychological consequences, although they cannot assist with quantifying problems and associations.

Summary of current evidence

The three meta-analyses cited above[1,2,3] did not include any studies specifically considering South Asians with diabetes. A study published since these reviews used the Montgomery and Aasberg depression rating scale to assess depressive symptoms in people newly diagnosed with diabetes compared to a random sample without diabetes in rural Bangladesh[10]. The authors noted higher than expected levels of depression in the background population, but also reported a significant

association between diabetes and depression after adjustment for potential confounding factors.

There is a scarcity of data, however, relating to the psychological wellbeing of migrant South Asians, including those living in the UK. A recently completed study compared the prevalence of diagnosed depression (according to diagnostic coding or prescribing data) in South Asian and white European people registered on a UK hospital diabetes clinic database[11]. The authors identified significantly higher rates of diagnosed depression in white Europeans compared to South Asians, but noted that this disparity may be due to differences between the two ethnic groups in terms of presentation of depressive symptoms or a lack of cultural appropriateness of western methods of identifying depression[12]. These considerations may help to explain the reported lower rates (for South Asians) of consulting and prescribing for mental disorders in UK primary care[13–15].

Some work has been reported in relation to validating South Asian language versions of instruments designed to identify anxiety and depression, for example, the Amritsar Depression Inventory[16] and the Hospital Anxiety and Depression Scale (HADS)[17]. However, published reports of the use of validated self-report instruments to assess anxiety and depression in South Asian people with diabetes are currently lacking. HADS was one of the measures used in a study of Bangladeshi people living in the UK with a range of chronic conditions, including diabetes, but separate findings for diabetes were not presented[18].

Qualitative studies have provided some information about people of South Asian origin regarding the psychological impact of receiving a diagnosis of Type 2 diabetes and of subsequently living with the condition. In one interview study in a population of people predominantly of Indian origin, the most commonly cited cause of diabetes-related anxiety was the perceived difficulty of coping with changes to lifestyle, specifically in terms of diet[19]. The impact of dietary modification on perceived quality of life was also highlighted in a qualitative study involving people of both Pakistani and Indian origin[20], and both these studies[19,20] suggested that cultural perceptions about the importance of family and social patterns of eating contribute to anxiety related to lifestyle modification.

Qualitative studies have also, however, suggested that some cultural perceptions and experiences may have a beneficial influence on levels of anxiety. For example, cultural perceptions related to the causes of diabetes may influence reactions to being diagnosed and readiness to accept the diagnosis. One study has suggested cultural differences in perceptions about personal responsibility for developing the condition, with some South Asians tending to attribute blame to external factors (life circumstances) rather than internal factors (personal lifestyle choices), when compared to their white counterparts[21]. South Asian participants in another study most commonly, though not exclusively, fitted the typology of people who viewed their diagnosis with resignation[19]. Levels of support provided to South Asians with diabetes by the family[19] and by religious leaders[22] have also been suggested as offering a potential mitigating influence relating to anxiety.

Gaps in research

Problems associated with gathering data from people with language and literacy needs have contributed to the shortage of data relating to psychological consequences of diabetes in people of South Asian origin. There is a strong need for further evidence in this field.

Research priorities

- additional qualitative studies aimed at increasing our understanding of cultural differences related to the type and presentation of the psychological consequences of diabetes
- studies designed to identify and evaluate methods of identifying anxiety and depression in South Asian people with diabetes
- studies seeking to quantify cultural differences related to the psychological consequences of diabetes
- intervention studies that acknowledge and address cultural differences related to the psychological consequences of diabetes.

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Chapter 11: Treatment and care of people with diabetes

Wasim Hanif, Vinod Patel and Sudhesh Kumar

Context

The treatment of long-term conditions such as diabetes involves education and understanding of the condition and its consequences, along with concordance with available treatments. This chapter considers the management options for diabetes in South Asians in the following areas: 1) lifestyle modification 2) oral hypoglycaemic agents 3) insulin 4) newer agents such as GLP-1 analogues 5) multifactorial interventions 6) and management of diabetes during special occasions that involve fasting.

Summary of current evidence

Oral hypoglycaemic agents

There is a paucity of studies looking at the effect of specific oral hypoglycaemic agents (OHAs) in South Asians. Most of the data are from large, retrospective studies such as the United Kingdom Prospective Diabetes Study (UKPDS), Action in Diabetes and Vascular Disease and others that involved a small number of people from South Asian communities. There is no data to suggest that the actions of these agents are any different than in other populations. It may be the case that certain agents are better suited to the cultural needs of the population, for example dipeptidyl peptidase-4 (DPP4) inhibitors when people fast during Ramadan[1].

Insulin

Insulin treatment is generally initiated late in South Asians with diabetes, because, it is believed, of patient reluctance to initiate the treatment. In the United Kingdom Asian Diabetes Study (UKADS)[2], even when the link worker delivered care in a culturally sensitive manner, the uptake was low. A number of factors have been cited for this, including traditional fear of needles, social pressures and the inevitability of disease progression. However, these factors have never been studied rigorously. One study showed that insulin glargine caused less hypoglycaemia but no difference in HbA1c when compared to traditional neutral protamine Hagedorn insulins in South Asian people[3]. Certain insulin types, such as human lispro Mix 25, have been shown to be better at lowering HbA1c and lead to fewer incidents of hypoglycaemia during Ramadan[4].

Multifactorial interventions

The Steno-2 study has shown that multifactorial interventions are very effective in reducing macrovascular and microvascular complications in Type 2 diabetes. The UKADS was a cluster randomised control trial of complex multifactorial intervention to improve cardiovascular outcome in primary care setting. The trial involved 21 inner city practices in the UK, which were assigned by simple randomisation to an intervention group of 868 subjects (who received enhanced care, including additional time with a practice nurse and support from a link worker and diabetes specialist nurse) or a control group of 618 subjects who received standard care. Primary outcomes were change in blood pressure, total cholesterol and glycaemic control after two years. There were significant differences in terms of reduction of diastolic blood pressure and mean arterial pressure after adjusting for confounders and clustering. There were no significant differences between the groups for total cholesterol, systolic blood pressure or HbA1c. Economic analysis suggested that the nurse-led intervention was not cost effective.

A number of secular trends affected the results of the UKADS, chief among them being the GMS contract for GPs, which gave financial incentives for improving diabetes care. The diabetes management of the control groups improved. There appeared to be more of a focus of resources on managing patients that were poorly controlled than in getting the patients in the target range. A pilot study of UKADS[5] showed significant improvements in systolic and diastolic blood pressures and total cholesterol between intervention and control groups, while HbA1c remained unaffected.

A number of observational studies[6–8] showed a higher prevalence of diabetes and hypertension in the South Asian population, with poorer management compared to the white population. Although studies have shown improvements in the management of hypertension and lipids over the last few years, control of risk factors is still poor compared to the white population.

Obesity is highly prevalent in the South Asian diaspora and is thought to underlie the high prevalence of other cardiovascular risk factors and diabetes. It is now recognised that we may have underestimated the extent of the problem in the past by using thresholds of body mass index (BMI) and waist size developed from studies in white European individuals. There is an argument for using ethnic-specific cut-offs for treating obesity in South Asians, but as yet there is no evidence of any benefit. Thus, there is a need for more research on the benefits of treating obesity at lower thresholds of BMI and waist size. A similar argument has been made that we should treat blood pressure at lower levels. Again, there is as yet no evidence base for this.

The multifactorial intervention cited above, Steno-2 study, clearly showed that achieving targets such as blood pressure less than 130mm Hg systolic, total cholesterol less than 4mmol/l, low-density lipids (LDL) less than 2mmol/l, high use of statins and ACE inhibitors leads to greater than 50 per cent reduction in rates of all diabetes complication, including specifically an 85 per cent reduction in stroke, 50 per cent reduction in coronary artery bypass graft and an-all cause mortality

reduction of 46 per cent. The retinopathy sub-study of the main UKADS study showed that the prevalence of diabetic retinopathy was higher in South Asians with diabetes in comparison to white populations. The South Asians with diabetes were significantly disadvantaged with respect to multifactorial intervention as summarised below:

- South Asian blood pressure 144/84mm Hg versus 137/74 mm Hg in white populations (p<0001)
- South Asian total cholesterol 4.5mmol/l versus 4.2mmol/l in white populations (p<0001)
- South Asian HbA1c 7.9 per cent versus 7.5 per cent in white populations (p<0001)
- South Asian blood pressure 144mm Hg versus 137mm Hg in white populations (p<0001)
- there was significantly less aspirin, ACE inhibitor and statin use in the South Asian cohort in comparison to the white cohort.

The above data prevails despite South Asian people having a shorter duration of diabetes and younger age of onset of diabetes. Therefore, there appears to be a significantly lower attainment of quality-of-care standards in terms of clinical and biochemical parameters, even when South Asian and white populations are treated by the same general practice[9]. The reasons for this are not known.

Management of diabetes during Ramadan

In the UK, the size of the Muslim population is estimated to be close to 1.6 million and it constitutes 2.7 per cent of the overall population of UK[10]. While diabetes affects around 4 per cent of the white population, it affects 22 per cent of the Pakistani Muslim population and 27 per cent of the Bangladeshi Muslim population (aged 25–74). The Epidemiology of Diabetes During Ramadan (EPIDIAR) study suggests that 43 per cent of patients with Type 1 diabetes and 79 per cent with Type 2 diabetes fast, sometimes contrary to medical advice[11–13].

Due to a lack of randomised controlled trials, the medical implications of fasting are poorly understood. Most patients with diabetes are asymptomatic, so they do not consider themselves as having an illness and fast during Ramadan without any medical advice. The concern is that fasting in patients with diabetes may lead to hypoglycaemia, hyperglycaemia with or without ketoacidosis, or dehydration. Another concern is the reluctance of patients to take their medication during the fast; therefore, the timing and dosage of antidiabetic agents have to be adjusted for individual patients. The EPIDIAR study showed that fasting in Ramadan led to: the risk of severe hypoglycaemia (defined as hypoglycaemia leading to hospitalisation) increasing 4.7-fold in patients with Type 1 diabetes and 7.5-fold in patients with Type 2 diabetes; and the incidence of severe hyperglycaemia (requiring hospitalisation) increasing fivefold in patients with Type 2 diabetes and threefold in those with

Type 1 diabetes[13]. An international consensus meeting of healthcare professionals and research scholars with an interest in diabetes and Ramadan was held at Morocco in 1995. The aim was to establish guidelines regarding patient groups who should be exempt from fasting. They concluded that the following groups should be exempt:

- people with Type 1 diabetes
- people with Type 2 diabetes with poor control
- people with diabetes with comorbid degenerative diseases
- pregnant women with diabetes
- elderly patients with diabetes.

At the same time, they also concluded that people with diabetes who have stable diabetes should be allowed to fast even if they are on medications such as biguanides or sulphonylureas[12].

A number of studies have looked at the management of diabetes during Ramadan. One looked at the effects of diet, sulphonylureas and repaglinide therapy on clinical and metabolic parameters in people with Type 2 diabetes. They found no differences in body weight, fasting plasma glucose, serum fructosamine, HbA1c or serum cholesterol levels[14]. Another looked at the role of prandial regulators versus glibenclamide. Though serum fructosamine was lower in the repaglinide group, no difference in HbA1c was noted[15]. A further study compared the glycaemic effects of glimepiride, repaglinide and insulin glargine, and found no significant differences in glycaemic control and the incidence of hypoglycaemia[16]. The Ramadan study group compared insulin lispro mix 25 and human insulin 30/70. Results suggested a lower average blood glucose concentration in patients treated with insulin lispro mix 25, with a lower incidence of hypoglycaemia[4].

Gaps in research

There is a paucity of studies on the efficacy and acceptability of various oral hypoglycaemic agents for diabetes in South Asians. There is evidence for poor uptake of insulin therapy and also of the effectiveness of this therapy with respect to varying degrees of obesity, the underlying reasons being unclear. More data are needed from studies with South Asian cohorts. Multifactorial interventions are poorly implemented in the South Asian community. Multifactorial interventions such as the UKADS have shown some benefit in clinical outcomes, but demonstrate the need for alternative approaches to the delivery of care. As studies in Ramadan have shown that a large number of patients fast and are at an increased risk of hypo- and hyperglycaemia, there is a need for studies looking at safe and effective treatment options during Ramadan.

Research priorities

- evidence for benefit of treatment of obesity as defined by lower ethnic-specific cut-off points for BMI and waist
- studies in ethnic differences in the efficacy and adverse effects of various classes of oral hypoglycaemic agents
- studies to examine the reasons for reluctance to initiate insulin therapy early and also the effectiveness of insulin therapy, especially in overweight South Asian patients
- more multifactorial intervention trials to look at better delivery of care and improving care
- more multifactorial intervention trials to look at the effect of treating blood pressure at lower thresholds on the prevention of diabetic renal and eye disease
- research to establish the factors that effect the uptake of evidence-based interventions that reduce morbidity and mortality
- more studies needed on festivals such as Ramadan, in order to improve diabetes management.

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Chapter 12: Cardiovascular disease and peripheral vascular disease

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Context

Type 2 diabetes is growing at epidemic proportions and is associated with a rapidly rising incidence of its debilitating complications, such as coronary heart disease (CHD) and strokes[1]. People of South Asian origin are the largest ethnic minority population in the UK, and the prevalence of diabetes is between four and six times higher, and develops five to ten years earlier, in this population compared to people of white European origin[2–9]. The emergence of evidence-based guidelines on diabetes, CHD and stroke are benefiting Europeans. However, a commensurate decline in the rates of CHD and stroke in the UK South Asian population is seen to a much lower extent[10]. Potential reasons for this are the lack of trials involving South Asian populations[11], and the fact that it may be inappropriate to extrapolate from the current evidence base, which is derived mostly from western populations, to South Asian people. Although it is reasonable to adopt current guidelines and implement them more aggressively, there is an urgent need for more research in the South Asian population[12].

Summary of current evidence

Diabetes and cardiovascular disease

A progressive relationship exists between glucose levels and cardiovascular risk. People with Type 2 diabetes have a two- to fourfold increased risk of cardiovascular disease compared to people without diabetes[2,13]. Furthermore, prevalence of admission hyperglycaemia, including those with newly detected abnormal glucose regulation, is very common in people admitted with acute coronary syndrome (ACS) and is associated with higher mortality[14–16]. CHD is more prevalent in South Asian people, occurs at younger age and carries a 50 per cent higher mortality than in Europeans[17,18]. Much of this excess CHD mortality comes from people with diabetes and, although the reasons for this are not entirely clear, it is thought that it is mediated through insulin resistance and related atherogenic risk factors[19].

The INTERHEART study found higher levels of conventional risk factors present at a younger age to be the likely explanation for occurrence of myocardial infarction at an earlier age in the South Asian population[18]. Diabetes, a high waist-to-hip ratio and a high Apolipoprotein B to Apolipoprotein A1 ratio were found to be the three metabolic risk factors particularly associated with myocardial infarction at a younger

age. Aggressive management of such conventional risk factors is likely to improve CHD risk in South Asians but there is paucity of such studies in this population. Furthermore, there are issues around inequalities in access to standard CHD care, such as use of statins or invasive management using percutaneous intervention or coronary artery bypass grafting[20,21]. The recently published UK Asian Diabetes Study also identified many challenges in achieving more stringent targets in South Asian people[22]. Although blood pressure and lipid targets were achievable, improvements in HbA1c and body mass index were found to be more difficult to achieve in this study. As the authors have suggested, there is a need for exploring additional approaches to change motivation and behaviour through education[22].

Admission hyperglycaemia is one of the factors significantly associated with adverse clinical outcomes in ACS, independent of the severity of ACS and the type of revascularisation strategy used for the treatment. This adverse association is thought to be due to various effects related to the state of hyperglycaemia, including increased oxidative stress, a prothrombotic and proinflammatory environment and microvascular dysfunction[16]. A recent study showed that glucose normalisation after admission was associated with better survival in hyperglycaemic patients hospitalised with acute myocardial infarction[23]. Further work in these areas involving South Asian people is urgently needed.

Heart failure

The increased short- and long-term mortality seen in people with Type 2 diabetes after myocardial infarction is also related to the high incidence of heart failure and is not entirely explained by ventricular remodelling and systolic dysfunction[24]. Asymptomatic left ventricular hypertrophy, diastolic dysfunction and heart failure with normal ejection fraction are common in people with diabetes and impaired glucose regulation (IGR). These are thought to be mediated through insulin resistance and glucose intolerance, and could be playing a significant role in heart failure seen after myocardial infarction[25–27]. With regard to heart failure, the prevalence, prognosis and outcome in different ethnic groups is not well documented. Equitable access to advanced therapies in heart failure such as device therapy and transplantation requires ethnically specific databases that do not currently exist. Also relevant is access to cardiac interventions in South Asian people[28]. There is a paucity of evidence regarding appropriateness of revascularisation in South Asian people with Type 2 diabetes.

Diabetes and stroke

Like CHD, stroke is also more common in the South Asian population, presents at a younger age and has a 40 per cent higher mortality compared to a western population[29–33]. Older age and the presence of atrial fibrillation mainly contribute to the high stroke-related mortality in Europeans[30]. However, studies looking at the

stroke risk factors and mortality in South Asian patients are lacking. A 17-year mortality follow-up of the Southall and Brent Cohort showed diabetes as a strong predictor of stroke mortality in South Asians compared to Europeans[34], and similar findings were seen in studies from the USA and India[31,32].

In another recent study from the UK involving 242 South Asians with ischaemic strokes, hypertension (70.2 per cent) was the most prevalent predictor followed by diabetes (56.2 per cent), while atrial fibrillation was present in only 7.4 per cent of cases and stroke mortality was mainly associated with diabetes[33].

Two further studies identified association of metabolic syndrome-related risk factors and high Lipoprotein(a) levels and the Apolipoprotein B to Apolipoprotein AI ratio in South Asian people with ischaemic stroke[35,36]. Healthy relatives of South Asian stroke patients exhibit hyperinsulinaemia, increased insulin resistance and tissue plasminogen activator levels[37]. Further understanding of the pathophysiology, risk factors for, and mortality of, stroke in South Asian people would help develop effective treatment and preventive strategies.

Peripheral vascular disease

Peripheral vascular disease (PVD) is a significant complication of Type 2 diabetes and accounts for a spectrum of manifestations, including intermittent claudication, chronic foot ulcers, acute leg ischaemia and lower extremity amputations. It can be associated with significant morbidity and mortality, higher rates of hospitalisation and reduced quality of life[38]. Furthermore, presence of PVD is considered to be an important marker of associated CHD. Despite this increased risk, there are only a few studies currently looking at diabetes and PVD in the South Asian population.

One UK study of people with diabetes comprising 55 South Asian people (8 cases with lower extremity amputation (LEA) and 47 controls without LEA), and 493 Europeans (164 cases with LEA and 329 controls without LEA), found that South Asian people had about a quarter of the risk of amputation compared with Europeans[39]. This was thought to be related to the lower rate of PVD and neuropathy seen in South Asian patients. Furthermore, the prevalence of PVD was low among South Asian controls compared with Europeans controls.

Another more recent study from the UK reported paradoxically low levels of lower-limb atherosclerosis at any given level of ischaemic heart disease in Indian Asian men compared with European men[40]. These findings were similar to a study from the Indian subcontinent[41]. The findings of a low incidence of PVD in South Asian people is conflicting and, as suggested by the authors of this UK study, further work is needed to look into haemodynamic/structural factors as a possible cause of the disparity between PVD and CHD rates in the South Asian population[40]. The prevalence of PVD is known to rise significantly with age, and its prevalence in South Asian people is likely to rise in future as the numbers of ageing South Asian people grow. There are, therefore, a number of unresolved issues around diabetes and PVD in South Asian people that will need exploring for improved patient care.

Gaps in research

There is a paucity of evidence in many areas related to diabetes and vascular diseases in the South Asian population and further research is urgently needed. Such research should focus on various aspects of atherosclerotic vascular disease, including epidemiology and pathophysiology, acute and preventive therapies and novel ways to optimise the delivery of evidence-based treatments in this difficult-to-reach population.

Research priorities

- epidemiological studies to determine the impact of traditional and novel risk factors, including IGR, insulin resistance and markers of inflammation on CHD and stroke
- studies to assess revascularisation strategies in South Asian people with diabetes and CHD, including the benefits of revascularisation in patients with silent ischaemia but prognostically significant anatomical disease
- prospective trials assessing the effect of pharmacological interventions aimed at achieving lower than current targets for lipids and blood pressure and modifying the novel risk factors on CHD and stroke outcomes in South Asians with diabetes
- large-scale, longitudinal studies to establish the prevalence and prognostic significance of IGR on ventricular structural abnormalities and abnormalities of various biomarkers such as plasma brain natriuretic peptides; and studies of C-reactive protein in patients from South Asian populations admitted with myocardial infarction
- studies to investigate the epidemiology and pathophysiology of PVD in South Asians with diabetes, and longitudinal studies examining their long-term impact on cardiovascular disease outcomes
- investigations to determine the impact of using non-invasive techniques on earlier detection of asymptomatic CHD in people with Type 2 diabetes.

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Chapter 13: Dyslipidaemia

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Context

Primary prevention is the most significant contributor to the decline in coronary heart disease (CHD) at a population level in England over the past two decades. Second only to smoking cessation and tobacco control, treatment of dyslipidaemia for primary prevention is the most significant contributor to the prevention of CHD[1]. For South Asian populations, there are two likely reasons why primary prevention statin treatment has possibly not been as widespread as for the white European population[2]. Firstly, at a policy level, the 'pay for performance' Quality and Outcomes Framework (QOF) threshold of 5mmol/l for total cholesterol, for all individuals, overlooked the different pattern of dyslipidaemia in the UK South Asian population, where total cholesterol levels were often lower, primarily due to lower high-density lipid (HDL) cholesterol levels. Unintentionally discriminatory, this may have widened inequalities in primary prevention.

Essentially, total cholesterol levels were lower in UK South Asian groups towards the end of the last century and would have prevented access to primary prevention statin therapy[3]. Secondly, the absence of evidence for therapeutic interventions relating to dyslipidaemia in South Asian people prevented the development or harmonisation of specific guidelines, targets or thresholds for the management of dyslipidaemia in the South Asian population[4].

Industry-funded research in the field of dyslipidaemia therapy had focused, and continues to do so, on the general and predominantly white European population in developed countries, while the global burden of cardiovascular disease projections illustrate that, by 2025, India alone will harbour almost 40 per cent of the world's cardiovascular disease[5]. Research may, therefore, have been driven by commercial market forces rather than the evidence-base requirements for the world's ethnically diverse populations. The consequence of this oversight of healthcare systems to guide, develop and execute research pertinent to the needs of their own populations has exposed major gaps in research.

Summary of current evidence

It is well established that compared to white Europeans, South Asian people are less likely to meet all three national treatment targets for diabetes (HbA1c, blood pressure and total cholesterol)[6]. Rather than interpret this as a disparity or inequality in care, we must first examine the validity of treatment targets being identical for all

ethnic groups. Some experts have proposed that these three treatment targets should be lower in South Asian groups to compensate for the more premature, aggressive and prevalent impact of diabetes in South Asian populations. Moreover, a recently launched cardiovascular disease prevention study in the West Midlands[7] advocates screening for diabetes from the age of 30 years in South Asians, and 40 years in white European people. Commensurate with this approach in screening, in the USA, the Coronary Artery Disease Among Asian Indians Research Foundation advocates much more aggressive targets for dyslipidaemia management in the South Asian than for the white population[8]. While these more aggressive treatment approaches appear to be unopposed, the paucity of evidence to support expert opinion is apparent. The South Asian Health Foundation first published a consensus statement on dyslipidaemia treatment in South Asians in 2005, which was updated in 2008[4], highlighting the lack of evidence; yet remarkably little, if anything, has changed since then in the field of dyslipidaemia.

Lipid abnormalities are more prevalent among South Asian people. In the INTERHEART study, many more native South Asians than individuals from other countries had an elevated Apolipoprotein B100 to Apolipoprotein A-I ratio (43.8 per cent against 31.8 per cent). Moreover, there has been a substantial change in lipid profiles on the subcontinent over the past two decades. While the mean total cholesterol in the USA has decreased from 6.2 mM to 5.2 mM in the last decade of the 20th century, in urban India the average cholesterol level increased from 4.1 to 5.2 mM, a rise that was accompanied by a threefold increase in coronary artery disease (CAD)[9]. With migration, lipid profiles have become more adverse for the South Asian diaspora, illustrating rising total cholesterol and falling HDL cholesterol with migration[10].

The classic lipid profile in South Asian individuals is widely acknowledged to be one of low HDL cholesterol, high triglycerices and higher Lipoprotein(a)[11]. Total cholesterol used for cardiovascular risk prediction, in the absence of HDL cholesterol, underestimates risk in the South Asian population. Mean population HDL cholesterol is 1.3mmol/l in the UK. For Bangladeshis, Indians and Pakistanis, the corresponding values are 1.1, 1.3 and 1.1mmol/l respectively, so HDL cholesterol is significantly lower than in the general population in two out of three South Asian groups. In line with the above evidence, the total cholesterol to HDL ratio has been shown to be a better predictor for CAD than total cholesterol alone[12].

Raising HDL cholesterol and lowering triglycerides

There is plentiful evidence from epidemiology linking low HDL cholesterol to greater risk for vascular events[13]. Low HDL cholesterol levels are also associated with restenosis after percutaneous coronary interventions[14] and also a predictor of poor outcome following coronary artery bypass grafts[15]. However, the evidence base linking changes in HDL cholesterol to outcomes is actually relatively weak. A recent systematic review and meta-regression analysis showed no associated treatment-

induced change in HDL cholesterol and risk ratios for CHD deaths, CHD events or total deaths[16]. Part of the reasons for this may reflect the limited choice of drugs available to significantly increase HDL cholesterol. Despite this, the authors of the latter article concluded that, on the basis of the available evidence, reduction in low-density lipoprotein (LDL) cholesterol should be the primary goal for lipid-modifying interventions. Moreover, the outcome trials evidence base for fibrates, commonly used to tackle a high triglyceride to low HDL cholesterol pattern, is also relatively weak, as recently summarised[17]. Indeed, although fibrates may lessen the risk for non-fatal myocardial infarction, overall mortality rates are not lowered, and their use is associated with a significant increase in non-cardiovascular mortality and a tendency to greater overall mortality[18].

LDL cholesterol

There is a clear and consistent evidence base emanating from multiple trials of the benefit of statins for primary and secondary prevention of vascular disease[17]. In terms of therapeutic intervention, although there are no direct trials in South Asian people, there is no reason to believe that lowering LDL cholesterol would not provide at least equivalent benefit in this population, including those with Type 2 diabetes, who, experts suggest, would derive an even greater absolute risk reduction from LDL reduction than patients without diabetes[19]. The data from the INTERHEART study demonstrating higher Apolipoprotein B to Apolipoprotein A-I ratios in South Asian people strongly suggests that the abnormal lipid profile for this group contributes significantly to the excess vascular risk in this ethnic group. There is also evidence that statins have the desired clinical benefit in other ethnic groups[20] outside of the white European population. The use of statins in primary prevention of cardiovascular disease in South Asians would therefore appear appropriate but the question of the target value has not been determined.

For secondary prevention, whether diabetes is present or not, there is no debate about the benefits of statin therapy. For primary prevention in a person with non-diabetic hyperglycaemia, treatment of dyslipidaemia is based upon the calculation of overall cardiovascular risk[21], and in a patient with diabetes treatment is based upon an assessment of absolute risk of a coronary event and adverse lipid profile (defined as total cholesterol 5mmol/l or, LDL-C 3.0mmol/l or, triglycerides 2.3mmol/l)[22]. Many advocate prescribing statins to all patients with Type 2 diabetes, since only age would guide the exact timing of intervention with primary prevention statins in this group. The Heart Protection Study[23] and the Collaborative Atorvastatin Diabetes Study[24] support statin use for primary prevention in people with diabetes, regardless of baseline total cholesterol, a position broadly supported by the Joint British Societies (JBS2) guidelines. As South Asians with diabetes have greater absolute vascular risk compared to white Europeans with diabetes[25], a case for statin therapy in all South Asian people with diabetes could be made, although it must be remembered that statins are contraindicated in pregnancy, and that many South Asian women with diabetes will still be of a reproductive age.

Lipid-lowering therapy in South Asian people

In the future, those planning large research studies relating to therapeutic interventions should usefully include greater representation from ethnic subgroups. Currently, the evidence base from studies undertaken in predominantly white European populations must be generalised and assumed to be applicable to all sections of the general population. While this approach appears to be satisfactory in most areas of therapeutic intervention, as diabetes and cardiovascular disease are disproportionately more common in the South Asian population, there is a strong argument for specific endpoint studies to address a number of unanswered questions.

A number of studies have addressed statin efficacy in South Asian people. For example, the Investigation of Rosuvastatin in South Asian Subjects study of rosuvastatin 10mg and 20mg, and atorvastatin 10mg and 20mg, concluded that 'statin therapy was well tolerated and effective in decreasing LDL cholesterol in people of South-Asian origin, with the 10- and 20mg doses of rosuvastatin and atorvastatin allowing most patients to reach recommended LDL cholesterol goals' over a six-week period of treatment[26]. The ongoing trial of ezetimibe[27] will aim to provide further evidence in this area.

Patterns of prescribing over time

Even without lower thresholds for intervention in South Asian people, there was evidence from the early 1990s that this population suffered from inequalities in access to statin therapy[2]. Whether this inequality exists today, following the QOF and the paradigm shift towards prevention of disease, requires ongoing evaluation. A report from 2005[28,29] suggests that the inequalities gap in prescribing statins has lessened. On the Indian subcontinent, studies suggest that treatment of dyslipidaemia in diabetes is poor[30].

Gaps in research

The relative efficacy of statins in South Asians may be different from that in white Europeans, and pharmacokinetic and pharmacodynamic data might differ in ethnic groups leading to a potential increase in dose-related adverse events in this population. Such data could also be potentially obtained from ongoing data collections in primary practice databases or the General Practice Research Database. There is a lack of data on appropriate treatment targets in South Asian people with diabetes. It would be useful to determine whether individual participant data from all primary and secondary endpoint statin trials could identify sufficient numbers of South Asians in these trials for a powered subgroup analysis. Primary prevention risk algorithms incorporating ethnicity have been developed but require independent validation[31].

Research priorities

- statin efficacy studies in South Asian people to evaluate pharmacokinetic and pharmacodynamic properties
- studies to determine pattern of lipid-lowering management of South Asians with and without diabetes as compared to white Europeans
- multicentre study to evaluate outcomes of intensive versus conventional statin therapy
- newer HDL cholesterol-raising treatments are being developed and clinical endpoint trials would usefully include South Asian individuals, given their lower HDL cholesterol levels and greater vascular risk; the same is true for newer formulations of nicotinic acid
- appropriate risk algorithms incorporating ethnicity, and interventional studies using these algorithms, are a key priority for primary prevention of cardiovascular disease.

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Chapter 14: Diabetic nephropathy

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Context

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in western countries[1]. Prevalence, rates of progression and mortality associated with diabetic nephropathy vary significantly between ethnic groups[2]. Although there have been significant improvements in our understanding of the pathogenesis and management of this complex disorder in recent years, the reasons for the differences between ethnic groups remain poorly understood.

Diabetic nephropathy is a progressive condition with varying degrees of proteinuria and gradual decline in renal function[3]. Microalbuminuria (defined as Albumin Excretion Rates of 20 to 200µg/min) is the earliest detectable evidence of renal injury[4]. Rates above these are considered 'overt proteinuria'. Microalbuminuria is potentially reversible and may be associated with normal renal function. Studies in white populations estimate progression from microalbuminuria to overt proteinuria as 30 per cent over 10 years. Once overt proteinuria occurs, there is often a progressive decline in renal function leading on to ESRD requiring renal replacement therapy. It also greatly increases the risk of cardiovascular disease.

Summary of current evidence

Microalbuminuria

The prevalence of microalbuminuria in South Asians has been compared with other ethnic groups in many cross-sectional studies[5–7]. Most of these have compared South Asians with European populations. In contrast, there have been relatively fewer studies from native South Asian countries, though the Microalbuminuria Prevalence Study (MAPS) study did suggest a range of microalbuminuria from 27.4 per cent in Pakistan to 36 per cent in South India[8]. Despite the differences in methodology, sizes of cohorts and the definitions of microalbuminuria used, the overall prevalence of microalbuminuria in South Asians is estimated to be between 25 per cent and 40 per cent. Comparison of the prevalence of microalbuminuria in South Asian and white European patients with Type 2 diabetes living in the UK showed rates of 40 per cent versus 33 per cent for men, and 33 per cent versus 19 per cent for women[5]. Studies from Southern India also report similarly higher levels of microalbuminuria. The overall prevalence of microalbuminuria in a study from South India, was around 36 per cent; further, microalbuminuria was present in nearly a quarter of those with newly diagnosed diabetes[9]. In the Chennai Urban Rural Epidemiology Study, the prevalence of microalbuminuria was 27 per cent[10]. Similarly, higher rates of

microalbuminuria in people of South Asian origin have been reported in studies from other countries[11,12]. Not all studies, however, have reported higher prevalence. In the United Kingdom Prospective Diabetes Study (UKPDS), no differences in the prevalence of microalbuminuria were observed between ethnic groups and another study also reported similar prevalence. These differences may have arisen due to the fact that the subjects in the UKPDS were newly diagnosed while other studies have included subjects with longer duration of diabetes.

Increasing age, duration of diabetes, smoking and hypertension are recognised risk factors for microalbuminuria[9,13]. The increased susceptibility of South Asians, however, appears to be independent of these risk factors. In a study comparing the prevalence of microalbuminuria in Europeans and different subgroups of South Asians, significantly higher levels of urinary albumin excretion were observed in South Asians independent of their age and the presence of diabetes or hypertension[13]. Moreover, the relationship between blood pressure and microalbuminuria may be different in South Asians. Data from the pilot study of the UK Asian Diabetes Study suggest that microalbuminuria may be detectable in South Asians even when the blood pressures are within 'normal' limits[7]. Apart from being a marker of nephropathy, microalbuminuria is an independent risk factor for cardiovascular disease[14], and the higher prevalence of microalbuminuria in South Asians is consistent with the excess cardiovascular risk observed in this population.

Overt proteinuria and ESRD

Epidemiological studies suggest that approximately one-third of subjects with microalbuminuria progress to overt nephropathy over 10 years. A variety of studies, including the Third National Health and Nutrition, DEMAND and MAPs study all suggest a two- to threefold higher prevalence of overt nephropathy in South Asians[8,15,16]. Glomerular function (GFR) declines at a rate of 2 to 20ml/min/year thereafter, eventually resulting in ESRD[4]. Progression rates may vary from individual to individual, however, and between ethnic groups. In a study in Surinamese South Asian migrants to the Netherlands, it was found that the loss of GFR was 1.45 times higher in South Asians compared to that in the Europeans[6]. A more recent study in the UK examined the relationship between ethnicity and chronic kidney disease (CKD) and found that South Asians were more likely to have severe disease (CKD stages 4 and 5) than their white European counterparts, suggesting a faster progression of renal disease[17]. Not all studies support this, however[18], and although it is generally believed that progression rates are faster in South Asians, the paucity of long-term studies makes this difficult to verify.

The risk of cardiovascular disease and death from cardiovascular causes increases with the degree of proteinuria[3]. In the UKPDS, the risk of cardiovascular death was 2 per cent in those with microalbuminuria, 3.5 per cent in those with proteinuria and 12.1 per cent in those receiving renal replacement therapy (RRT). Cardiovascular risk is significantly higher in South Asians, and the presence of renal disease may further exacerbate this.

Currently, there are no prevalence data based on ethnicity for diabetes and CKD. An increased demand for RRT in South Asians, however, has been observed in recent years[19]. A report from the UK Renal Registry suggests that nearly 18 per cent of the population receiving renal replacement therapy were from ethnic minorities[17]. There are, however, no studies in South Asians to examine the effect of renal disease on mortality. Thus, there appears to be a reduction in the rate of acceptance of South Asians onto renal replacement programmes, and indeed there is a longer delay in enrolment to such programmes for South Asians compared to white populations. Given the high prevalence of diabetes in South Asians, it is reasonable to assume that the number of South Asians needing renal replacement therapy would at least be proportionate to the prevalence of diabetes, if not higher. Ethnicity data is clearly needed to understand the prevalence of ESRD and plan the necessary resources to meet the needs of this population.

Risk factors and management

Diabetic nephropathy can be regarded as a potentially reversible complication, and the ability to detect the disease in early stages has made it possible to intervene and alter the natural course of the disease[4]. Age, duration of diabetes, glycaemic control, blood pressure and smoking are considered major risk factors for nephropathy. Effective management of nephropathy requires an effective screening strategy combined with aggressive management of risk factors[20]. Currently, there are no ethnic-specific screening strategies, and ethnicity as a risk factor is not universally recognised. The role of annual screening for microalbuminuria is also not clear. Given the relatively high risk of nephropathy and cardiovascular disease, annual screening may be appropriate in South Asians.

There is substantial evidence to suggest that both tight glycaemic and blood pressure control can reverse or slow the progression of renal disease. Epidemiological studies have shown that tight glycaemic control decreases the risk of progression from normoalbuminuria to microalbuminuria[21]. The role of glycaemic control after the onset of overt proteinuria, however, is less certain. Similarly, tight blood pressure control has been shown to reduce significantly the risk of progression to microalbuminuria[22]. Although blood pressure control in itself is important, certain classes of agents such as ACE inhibitors and angiotensin receptor blockers (ARBs) may have additional protective effects independent of their effect on blood pressure[3]. Tight blood pressure control has been shown to be beneficial even after the onset of overt proteinuria and is known to decrease the rate of fall in GFR. Presently, there are no randomised controlled trials involving South Asians to examine the benefits of glycaemic control and blood pressure. However, the UKPDS and more recently the Action in Diabetes and Vascular Disease study[23], which included patients of South Asian origin, have shown that the benefits are similar regardless of ethnicity. Similarly, there is no evidence to suggest that the renoprotective agents such as ACE inhibitors or ARBs are less effective in South

Asians. The available data do suggest that in South Asian patients with established proteinuria, treatment with agents of the ARB group do reduce the rate of progression to ESRD[24]. What must be remembered, though, is that the thresholds for treatments may vary between ethnic groups, and that more studies involving South Asians are required to establish ethnic-specific targets.

A significant proportion of patients with proteinuria may have non-diabetic renal disease. In one UK study, a high prevalence of non-diabetic kidney disease such as idiopathic interstitial nephritis was reported in South Asians presenting for RRT[25]. Such studies, however, have not been replicated. As the prognosis and management of these conditions may be considerably different, it is essential to establish the correct diagnosis.

Gaps in research

Large gaps remain in our understanding of diabetic nephropathy in South Asians, especially when compared with white population groups, in relation to:

- Epidemiology – the incidence and prevalence of diabetic renal disease remain unclear, especially in relation to South Asians originating from different geographical regions. This lack of clarity applies to all stages of renal impairment.
- Exploration of differences in possible pathogenetic mechanisms for the development of diabetic renal impairment.
- Different responses to possible interventions. These include interventions early in the spectrum of diabetic renal impairment, as well as responses to RRT, such as graft survival.

The increased awareness of the risk of nephropathy and cardiovascular disease in the South Asian population has generated a lot of interest among healthcare professionals in recent years. The role of ethnicity in disease causation, however, remains unclear and is further hampered by the lack of adequate clinical trials in this population. Nephropathy is a major complication of diabetes and is also potentially reversible. Despite this, our knowledge of this condition in South Asians is limited to a few cross-sectional studies. Investigations into the causes that lead to this excess risk, and strategies to effectively manage these patients, are clearly needed to reduce the morbidity and mortality associated with this condition.

Research priorities

- benefits of early screening – including non-diabetic hyperglycaemic states such as impaired fasting glycaemia and impaired glucose tolerance
- larger cohort studies to establish the epidemiology of diabetic nephropathy in South Asians, especially to evaluate progression rates of varying levels of albuminuria and decline in renal function; such studies to provide an insight into possible pathogenetic differences among differing populations
- interventions to establish ethnic-specific treatment targets for risk factors such as glycaemia and blood pressure in South Asians with varying degrees of renal impairment, in an attempt to reduce the rate of progression and ultimately reduce the prevalence of ESRD
- cardiovascular risk and survival in patients with ESRD
- prevalence of non-diabetic kidney disease in South Asian patients with diabetes.

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Chapter 15: Diabetic retinopathy

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Context

Duration of diabetes, age at onset of diagnosis, poor glycaemic control, elevated blood pressure and dyslipidaemia are the major risk factors for the development of diabetic retinopathy[1]. Therapeutic intervention can potentially reduce risk through improvements in glycaemic control and blood pressure[2,3], supporting behaviour change such as healthy eating and increasing physical activity, and through use of agents that improve lipid profiles[4].

Studies have confirmed that the prevalence of visual loss and impairment is higher in South Asians who have diabetes in the UK[4,5] but the exact contribution of diabetic retinopathy compared to other ocular conditions is unclear.

Summary of current evidence

There remains conflicting evidence with regard to the epidemiology of diabetic retinopathy in South Asians[6,10]. A recent large study in the UK[1] from the UK Asian Diabetes Study group confirms that the prevalence of retinopathy and sight-threatening retinopathy is greater (diabetic retinopathy 45 per cent among South Asians compared to 37 per cent among white Europeans; sight-threatening retinopathy 16 per cent among South Asians compared to 12 per cent among white Europeans) in a community-based population sample. Early age of onset (53 versus 59 years), duration of diabetes (7.6 versus 8.8 years), poorer glycaemic control (HbA1c: 7.9 versus 7.5 per cent), poorer blood pressure (144 versus 137mm Hg) and poorer lipid control (cholesterol: 4.5 versus 4.2mmol/l) are the major risk factors, and are a more likely explanation for the increased prevalence than genetic differences[1]. Most of these risk factors are potentially amenable to improvement but improving glycaemic control remains a substantial challenge in South Asian communities[11,12]. These findings have been confirmed in other recent studies in the UK in South Asians[7,8].

The UK Prospective Diabetes Study (UKPDS) showed a similar prevalence of retinopathy at diagnosis and trial entry in its South Asian and African Caribbean groups compared to its white European group[10]. In contrast, other studies have confirmed that South Asians were 1.5 times more likely to have laser treatment for diabetic retinopathy[6,10].

A consistent finding in studies on the microvascular complications of diabetes is that the duration of diabetes and age at onset together with glycaemic control are strong

and well-established risk factors in the development of retinopathy[2]. All studies confirm that South Asians develop metabolic conditions and diabetes at a younger age[7–12]. The differential risk of retinopathy between South Asians and white Europeans is largely observed in those with diabetes duration of less than 10 years[1]. This highlights the need for screening and earlier diagnosis of diabetes in South Asian populations. It suggests that the pathogenesis of diabetic retinopathy in these groups may be more aggressive than in white Europeans. More recent studies[1,7,8] have found a higher prevalence of retinopathy than was observed in the UKPDS, reflecting the longer duration of diabetes and a greater risk-factor profile[1,2,10]. Studies from the USA have reported retinopathy prevalence of up to 40 per cent, with significant variation between ethnicity-defined groups[13,14].

The prevalence of diabetic retinopathy reported from large-scale studies of South Asians in India is lower than in white European populations (17 per cent versus 37 per cent). These studies confirm that earlier age, duration of diabetes, male gender and elevated HbA1c are risk factors within the indigenous population[8,9]. Systolic blood pressure in younger South Asians in India was much lower than that reported in studies in South Asians who have moved to the UK (115 versus 135mm Hg)[8,9]. An increase in blood pressure from the adoption of a more westernised lifestyle is proposed as the causal link to explain these changes[1,9]. This hypothesis clearly needs more research, with studies comparing populations and their migration, and its effect not only on the migrant group but subsequent generations.

Genetic differences between racial groups may contribute to increased risk and prevalence of diabetic retinopathy. However, those studies across the world that have reported their findings have been either too small or have used common analysis of too many genetically distinct subgroups to provide sufficient evidence for definitive conclusions. It seems likely, though, that genetic contributions are relatively small when compared to those of the modifiable risk factors[8,9,15].

Putting together all the evidence, it seems likely that effective screening for diabetic retinopathy carried out through systematic programmes, and linked to intensive blood glucose and blood pressure control (international targets for HbA1c and systolic blood pressure less than 125/75mm Hg)[16], should help to reduce the incidence of visual impairment and blindness in ethnic community groups across the world.

Specific new treatments for treating diabetic retinopathy, such as angiotensin receptor blockers or fenofibrate, have not fully lived up to their promise or the resources invested in them, so the challenge remains to provide trials showing that medical treatments have a place in management beyond the imperative of risk-factor control. For ethnic groups, where the risk factors and glycaemic control are particularly challenging, we await studies on the possible value of fenofibrate or high-dose thiamine (vitamin B1) and novel agents that act to reduce the impact of the metabolic effects of glucose and pressure on retinal cells.

Screening for diabetic retinopathy and, potentially, screening the South Asian populations in the UK for diabetes may hold the key to establishing earlier intervention in the pathogenesis of diabetic retinopathy and effectively slowing the disease process. While screening for diabetic retinopathy in the developed world is becoming more effective and systematic, the coverage rates and uptake among ethnic minority groups in inner city areas are much lower than among their white European counterparts[4].

Gaps in research

While consensus appears to have grown that there is an increased prevalence of microvascular complications, including retinopathy, in South Asians with diabetes, this needs confirmation in larger studies. Areas with large numbers of this ethnic group, such as Coventry, Birmingham, Bradford and parts of London, seem appropriate for comparative studies[1,7,8]. Studies need to compare South Asians with diabetes with the other major ethnic group in the UK: the Black African and Caribbean groups who are reported to have a higher prevalence of retinopathy, largely attributable to higher blood pressure, a situation also described in African Americans.

There is a suggestion that the pathogenesis of diabetic retinopathy in South Asians may be more aggressive than in white Europeans – an area that needs further research. There is also a need to investigate the relationship between conventional risk factors and risk of retinopathy, and for interventional studies to investigate appropriate target thresholds to determine if the case for a lower threshold is supported by evidence. The coverage rates and uptake of screening among ethnic minority groups in inner city areas are much lower than those for comparable white Europeans, and ways of increasing awareness and improving healthcare strategies to reach these groups need to be researched.

Research priorities

- the epidemiology of retinopathy and the relationship of risk factors for retinopathy in the different South Asian communities in the UK
- the barriers to screening for retinopathy and methods for enhancing uptake in culturally and socio-economically diverse South Asian communities
- the feasibility and benefits of aiming for lower thresholds for blood pressure control in South Asian patients with retinopathy
- differences in pathogenesis and pattern of retinopathy and the relationship to other non-diabetic eye diseases.

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Chapter 16: Bariatric surgery

Shahrad Taheri and Sudhesh Kumar

Context

Finding cures for both Type 1 and Type 2 diabetes is a tantalising prospect that has captured the imagination of people with diabetes and diabetes healthcare professionals. It also drives a significant amount of the diabetes-related research carried out today[1,2]. Among people with Type 1 diabetes, islet-cell transplantation has offered hope to those few eligible for the procedure, while developments in stem cell biology hold out the promise of one day bringing about a remission of diabetes[3]. While the ageing process increases the risk of developing Type 2 diabetes, there are interventions that can prevent the onset of the condition or halt its progress.

Among people with diabetes in the South Asian community who have diabetes, the greatest proportion by far has Type 2 diabetes. The proportion of South Asian people with diabetes who are classified as extremely obese has also increased dramatically in recent years. For these individuals, bariatric surgery has emerged as a viable option for producing a remission of diabetes.

Summary of current evidence

Bariatric surgery for extreme obesity is becoming more common worldwide. The lack of effective medical management and the positive outcomes observed with the surgery have driven demand[4]. Bariatric procedures have also improved over the years. Previous surgical attempts included: jaw-wiring (which proved to be ineffective); jejuno-ileal bypass, which was effective in weight loss but resulted in significant morbidity and mortality; and the vertical-banded gastroplasty, which resulted in weight regain). Current procedures can be divided into the purely restrictive: laparoscopic adjustable gastric banding; and a combination of the restrictive and the malabsorptive, eg the Roux-en-Y gastric bypass. Other less commonly performed operations include: biliopancreatic diversion/duodenal switch (BPD/DS), which can result in significant malabsorption; and sleeve gastrectomy, which is increasingly used in patients with a very high body mass index (BMI) as a standalone procedure or as a procedure to be later converted into a BPD.

Bariatric operations were once considered to be extreme operations associated with increased morbidity and mortality. However, the use of laparoscopic surgery, greater training in bariatric surgery, improvements in band technology and high volume centres (comprising multidisciplinary assessment and support) have made these operations much safer: mortality is approximately 0.25 per cent from the gastric

band and 1 per cent from the gastric bypass[5]. Procedures vary in the UK and worldwide. The relative safety, the ease with which the procedure can be carried out and good outcomes have made this a popular choice in recent years.

A meta-analysis of 22,094 patients has revealed significant weight loss with bariatric surgery and a resolution of diabetes in 76.8 per cent of patients, of dyslipidaemia in 70 per cent, and of hypertension in 61.7 per cent[5]. Weight loss after surgery is more likely to be maintained long term. Importantly, recent data show a mortality reduction with weight loss after surgery[6]. Current guidance for bariatric surgery originated in, and differs very little from, the US National Institute of Health consensus statement of 1991. The National Institute for Health and Clinical Excellence (NICE) has recognised the role of bariatric surgery and has provided guidance for patient selection for surgery[7]. Previously, surgery was recommended for adults with a BMI of 40kg/m^2 or more, or 35kg/m^2 with comorbidities. NICE now also recommends surgery as a first-line option for adults with BMI 50kg/m^2 in whom surgery is considered appropriate, instead of lifestyle interventions or drug treatment.

Several studies have shown resolution/remission of diabetes with bariatric procedures[4,8], but the mechanisms for this have yet to be identified. The majority of studies have shown a superior resolution of diabetes with the gastric bypass and BPD/DS[5]. Remission of diabetes occurs in about 80 per cent of patients with the gastric bypass and in 57 per cent following gastric banding. These operations result in greater weight loss and maintenance than the gastric band operation. There is less evidence for resolution of diabetes with sleeve gastrectomy, but a recent study showed weight loss and resolution of metabolic syndrome results comparable to those of the gastric bypass operation. The improvements in blood glucose that have been observed with gastric bypass appear to be independent of, and earlier than, weight loss, suggesting alterations in neurohormonal mechanisms regulating glucose homeostasis.

Gaps in research

Because of the success of bariatric surgery in the remission of diabetes, it may be hypothesised that it is effective as a treatment for diabetes at lower BMI[9]; however, there are currently no credible studies to support this. The use of BMI as the measure for selection for bariatric surgery has also been questioned, since it is visceral obesity that increases the risk of diabetes and subsequent cardiovascular disease. Also, current BMI cut-offs do not cater adequately for ethnic groups such as South Asians who have visceral obesity and diabetes at much lower BMI levels[10,11]. There are no studies that have examined the efficacy of bariatric surgery in the remission of diabetes in South Asians. Also, the acceptability and impact of these procedures have not been assessed in this group. The whole area of lower thresholds for diagnosis and treatment of obesity in South Asians requires more research. In terms

of diagnosis, more research is required in the South Asian diaspora. A consensus statement from India has argued recently for lower thresholds for treatment, including bariatric surgery[9]. There is, however, inadequate evidence to support this statement and the balance of risks and benefits at lower BMI thresholds need to be studied.

Research priorities

- epidemiology of relationship between BMI and waist size to diabetes in the South Asian diaspora in longitudinal cohort studies
- studies to investigate the benefits and risks associated with bariatric surgery, particularly laparoscopic gastric banding and other bariatric procedures at lower thresholds of BMI in South Asian people with diabetes; more data on long-term effects are needed and can be achieved by establishing a cohort
- studies investigating acceptability and effect on perceived quality of life in patients who require this procedure and the effect of surgery on these parameters.

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Appendix 1: Search methods

Jo Brodie

Context

After discussion between Diabetes UK and the South Asian Health Foundation, we approached potential writing group authors for each of the chapters. In addition to the literature searches that the authors undertook during the writing process, each writing group was provided with the results of a basic Medline search on their topic area.

Literature reviews

This basic search was the same for all chapters, with the addition of topic-specific keywords and Medical Subject Headings (MeSH) terms, as outlined below, for each chapter. The basic search was intended to provide a reasonably wide overview rather than narrowing the focus at an early stage.

The following simple search was performed using the Ovid Medline database covering literature published between 1996 and the present day:

1. (Bangladeshi or Bangladeshis).mp.
2. (South Asian or South Asians).mp.
3. (Pakistani or Pakistanis).mp.
4. Asian Continental Ancestry Group/cl, eh, px, ge, sn [Classification, Ethnology, Psychology, Genetics, Statistics & Numerical Data]
5. japanese.mp.
6. chinese.mp.
7. (korean or koreans).mp.
8. 5 or 6 or 7
9. 4 not 8
10. 1 or 2 or 3 or 9

For most of the literature searches, the following additional search strings were used. However, for some of the searches on diabetic complications, MeSH terms were also used, eg ‘diabetic nephropathy’ as well as ‘diabetes’ plus ‘nephropathy’:

11. diabetes.mp. or exp *Diabetes Mellitus/
12. 10 and 11

For each chapter, additional search strings were added as follows:

1. Participation in research

13. research.mp. or Biomedical Research/or Research Subjects/or Behavioral Research/or Research/or Qualitative Research/or Health Services Research/or Research Design/
14. clinical trial.mp. or exp Clinical Trial/
15. exp Randomized Controlled Trials as Topic/or RCT.mp.
16. 13 or 15 or 14
17. 16 and 12

2. Epidemiology

13. Epidemiology/or epidemiology.mp.
14. Prevalence/or epidemiological.mp.
15. incidence.mp. or Incidence/
16. 13 or 15 or 14
17. 16 and 12

3. Genetics

(a)
13. exp Genetics, Medical/or genetics.mp. or exp Genetics/
14. genetic$.mp.
15. 13 or 14
16. 12 and 15

(b)
11. genetics.mp. or Genetics/or Genetics, Population/or Genetics, Medical/
12. Genes/or genes.mp.
13. gene.mp.
14. 11 or 12 or 13
15. 10 and 14
16. UK.in.
17. Diabetes Mellitus, Type 1/or diabetes.mp. or Diabetes, Gestational/or Diabetes Complications/or Diabetes Mellitus, Type 2/or Diabetes Mellitus/
18. 15 and 17
19. 16 and 18

4. Cultural aspects

13. culture.mp. or exp Culture/
14. behav$.mp.
15. exp Behavior/or behavior.mp.
16. lifestyle.mp. or exp Life Style/
17. life style.mp.
18. 13 or 14 or 15 or 16 or 17
19. 18 and 12

5. Screening for diabetes and non-diabetic hyperglycaemia

13. screening.mp. or Mass Screening/
14. 13 and 12
15. ogtt.mp. or Glucose Tolerance Test/
16. (oral glucose tolerance test or oral glucose test).mp.
17. 16 or 15
18. 17 and 12
19. 18 or 14

6. Prevention of Type 2 diabetes

13. prevention.mp.
14. prevention of diabetes.mp.
15. Life style.mp. or Life Style/
16. lifestyle.mp.
17. Diabetes Mellitus, Type 2/pc [Prevention & Control]
18. 17 and 12
19. 16 or 13 or 15 or 14
20. 19 and 12
21. 18 or 20

7. Self-management and education

(a) Self-management

13. self-management.mp. or exp *Self Care/
14. 13 and 12

(b) Education

13. education.mp. or exp *Patient Education Handout/or exp *Health Education/or exp *Education/or exp *Patient Education as Topic/
14. exp *Health Knowledge, Attitudes, Practice/or structured education.mp.
15. educational intervention.mp.
16. 13 or 15 or 14
17. 16 and 12

8. Childhood and adolescent Type 2 diabetes

13. child.mp. or Child/
14. children.mp.
15. paediatric.mp. or Pediatrics/or Adolescent/
16. (pediatric or young person or young people).mp.
17. 15 or 16 or 14 or 13
18. 17 and 12

9. Gestational diabetes

(a)
13. pregnancy.mp. or exp *Pregnancy/
14. gestational diabetes.mp. or exp *Diabetes, Gestational/
15. (pregnant or trimester).mp.
16. fetal development.mp. or exp *Fetal Development/
17. foetal development.mp. or exp *"Embryonic and Fetal Development"/
18. exp *Pregnancy Complications/
19. IUGR.mp. or exp *Fetal Growth Retardation/
20. exp *Perinatal Mortality/
21. 17 or 20 or 15 or 14 or 18 or 13 or 16 or 19
22. 21 and 12

(b)
13. gestational diabetes.mp. or exp *Diabetes, Gestational/
14. exp *Women/
15. Female/
16. 13 or 15 or 14
17. limit 16 to humans
18. 17 and 12
19. UK.in.
20. 18 and 19

10. Psychological consequences of diabetes

(a)
13. Psychology/or psychology.mp.
14. psychological.mp.
15. psychosocial.mp.
16. diabetes coping.mp.
17. (diabetes behavior or diabetes behaviour).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18. coping with diabetes.mp.
19. 18 or 16 or 13 or 17 or 15 or 14
20. 19 and 12

(b)
13. qualitative research.mp. or exp Qualitative Research/
14. Attitude to Health/or qualitative data.mp.
15. exp Interview, Psychological/or exp Interview/or interview$.mp.
16. 13 or 15 or 14
17. 16 and 12

11. Treatment and care of people with diabetes

13. treatment.mp.
14. Thrombolytic Therapy/or Drug Therapy/or Diet Therapy/or Nutrition Therapy/or Drug Therapy, Combination/or Tissue Therapy/or therapy.mp. or Exercise Therapy/or Negative-Pressure Wound Therapy/
15. therapeutics/or bariatrics/or behavior control/or drug therapy/or patient care/
16. 13 or 15 or 14
17. 16 and 12

12. Cardiovascular disease

(a)

13. Cardiovascular Diseases/th, nu, dh, px, me, rh, hi, eh, pa, di, pc, cl, ep, ge, mo, et, dt, co, pp, su [Therapy, Nursing, Diet Therapy, Psychology, Metabolism, Rehabilitation, History, Ethnology, Pathology, Diagnosis, Prevention & Control, Classification, Epidemiology, Genetics, Mortality, Etiology, Drug Therapy, Complications, Physiopathology, Surgery]
14. Peripheral Vascular Diseases/th, mo, di, px, nu, rh, ep, pa, pc, dt, eh, et, dh, cl, pp, me, su, co [Therapy, Mortality, Diagnosis, Psychology, Nursing, Rehabilitation, Epidemiology, Pathology, Prevention & Control, Drug Therapy, Ethnology, Etiology, Diet Therapy, Classification, Physiopathology, Metabolism, Surgery, Complications]
15. Coronary Disease/th, nu, dh, px, me, rh, eh, pa, di, pc, cl, ep, mo, et, dt, co, pp, su [Therapy, Nursing, Diet Therapy, Psychology, Metabolism, Rehabilitation, Ethnology, Pathology, Diagnosis, Prevention & Control, Classification, Epidemiology, Mortality, Etiology, Drug Therapy, Complications, Physiopathology, Surgery]
16. Intermittent Claudication/eh, pp, dt, pc, mo, me, px, th, dh, rh, su, cl, et, pa, co, nu, ep, di [Ethnology, Physiopathology, Drug Therapy, Prevention & Control, Mortality, Metabolism, Psychology, Therapy, Diet Therapy, Rehabilitation, Surgery, Classification, Etiology, Pathology, Complications, Nursing, Epidemiology, Diagnosis]
17. stenosis.mp. or Constriction, Pathologic/
18. CVD.mp.
19. embolism.mp.
20. (thrombus or thrombosis or ischemia or ischaemia).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
21. 17 or 20 or 15 or 14 or 18 or 13 or 16 or 19
22. 21 and 12

(b)

13. (stroke or ischaemic or ischemic or ischaemia or ischemia or cerebrovascular).mp.
14. exp Stroke/
15. 13 or 14
16. 12 and 15

13. Dyslipidaemia

13. (lipid or lipids or fat or fats or cholesterol or LDL or HDL or triglyceride or triglycerides or triacylglycerol or triacylglycerols).mp.
14. blood fats.mp.
15. exp Hyperlipidemias/or exp Cholesterol/or exp Cholesterol, LDL/or blood lipids.mp. or exp Triglycerides/
16. 13 or 15 or 14
17. 16 and 12

14. Diabetic nephropathy

(a)
11. exp Diabetic Nephropathies/
12. diabetic nephropathy.mp.
13. nephropathy.mp.
14. 11 or 12 or 13
15. 10 and 14

(b)
13. (kidney or kidneys or renal).mp.
14. nephropathy.mp.
15. diabetic nephropathy.mp. or exp Diabetic Nephropathies/
16. 13 or 15 or 14
17. 16 and 12

15. Diabetic retinopathy

(a)
13. retinopathy.mp.
14. exp Diabetic Retinopathy/
15. 13 or 14
16. 12 and 15

(b)
11. diabetic retinopathy.mp. or exp *Diabetic Retinopathy/
12. 10 and 11

16. Bariatric surgery

13. bariatric.mp. or exp *Bariatrics/
14. roux-en-y.mp. or exp *Anastomosis, Roux-en-Y/
15. exp *Gastroplasty/or gastric band.mp.
16. gastric banding.mp. or exp Gastric Bypass/
17. 16 or 13 or 15 or 14
18. 17 and 12
19. 17 and 2
20. 10 and 17
21. 1 and 17
22. 17 and ethnic$.mp.[†]

[†] This additional search string was added, as the previous search had returned zero results.

Currently funded research

In addition to the published literature already available, searches were undertaken, using clinical trials repositories and other databases, to find current diabetes research with subjects of South Asian origin. The results of the search outputs can be found at http://diabetes.org.uk/southasianreport or at http://sahf.org.uk and the databases used are listed below.

Canadian Institutes of Health Research (CIHR)

Homepage: http://www.cihr-irsc.gc.ca/e/826.html
Search page: http://webapps.cihr-irsc.gc.ca/funding/Search?p_language=E&p_version=CIHR

ClinicalTrials.gov

Homepage: http://www.clinicaltrials.gov
Search page: http://www.clinicaltrials.gov/ct2/search

Computer Retrieval of Information on Scientific Projects (CRISP)

http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen

Current Controlled Trials

Homepage: http://www.controlled-trials.com/
Search page: http://www.controlled-trials.com/mrct/

Diabetes UK

http://www.diabetes.org.uk/Research/Funded_research/

MRC Research portfolio

http://www.mrc.ac.uk/ResearchPortfolio/index.htm

National Institute for Health Research (NIHR)

http://www.nihr-ccf.org.uk/site/commissionedprojects/default.cfm?subcat=viewprogrammes

National Prevention Research Initiative (NPRI)

http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003446

UK Clinical Research Network – diabetes portfolio

http://public.ukcrn.org.uk/search/Portfolio.aspx?Level1=3

Useful web resources

During preparation of the manuscript, a variety of web resources of general interest were bookmarked using Delicious, the shared bookmarking website. The full list can be browsed at http://delicious/sahf

The charity for people with diabetes
Macleod House, 10 Parkway, London NW1 7AA
Telephone 020 7424 1000 **Fax** 020 7424 1001
Email info@diabetes.org.uk **Website** www.diabetes.org.uk

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