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Q1 What led you to pursue a career in medicine, particularly metabolic and cardiometabolic medicine?

To be honest, I had no idea what I wanted to do after school, and medicine was popular amongst Asian families if children were deemed bright enough. So I sort of funnelled into this direction. After medical school and my first year of house jobs, I actually left medicine as I did not enjoy it up to then. Instead, I became an accountant for 6 months. However, a few weeks of auditing brought me to my senses, and I returned to medicine promptly.

I wished I had done cardiology as I miss the chance to use practical skills, but clinical biochemistry was one of the few subjects I really enjoyed at medical school. Therefore, on returning to medicine, I was lucky enough to move into a registrar post in this specialty. Cardiology seemed too high a bar to me as I did not trust my clinical skills at that time. In the early weeks of clinical biochemistry, an older consultant (Alastair Glen) introduced the idea of research by handing me some data on different types of fatty acids measured in thousands of pregnant women. Glen told me to make something of it. It was an amazing spark that led me to completely different ways of thinking. I guess I have never looked back since.

Q2 Which have been the most exciting advances in your field since you began to practise in the 1990s?

Probably statins. My unit led the world's first primary prevention trial of statins, called WOSCOPS, led by the energetic James Shepherd, who gave me my registrar post. This seminal trial, which came soon after the first secondary prevention trial, changed people's way of thinking about cholesterol and heart disease. Now, nearly 30 years later, statins are amongst the most commonly prescribed drugs in medicine. I have also gained much by association with these trials. I still work on some of the data my senior colleagues generated in this trial and the later PROSPER trial (statins trial in elderly patients). In fact, we helped with a recent paper on statin-associated muscle side effects, which was published a few days ago.¹

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Q3 What is the one moment in your career that you are most proud of, and why?

Being awarded the Minkowski Lecture, which I delivered to an audience of nearly 5,000 people in a massive stadium in Lisbon, Portugal, at the opening lecture of the European Association for the Study of Diabetes (EASD) Annual Meeting in 2011. The happiness came as my parents and sister were in attendance, and I do not think they realised I could actually talk comfortably to such big audiences. They were blown over and I could actually see my late, beloved dad crying whilst he was listening to me talk. It was an emotional experience, shared with parents and friends. I only wish I had convinced my wife and kids to come over.

Q4 Throughout your career, you have worked across a number of different disciplines. Could you detail how this cross-collaboration comes to be, and list some of the positives which working with other disciplines brings to both research and practice?

I have been lucky to dip into many disease areas clinically, in research, and by working with close colleagues from different specialities. When one does this, and reads some of the wider literature, it becomes clear there are overlaps in risk factors and complications that one can apply across disciplines. One of my first grants, which I conceived, came from the recognition that high insulin levels in females with polycystic ovary syndrome could be driving their infertility. Therefore, we set up one of the first and largest trials at that time of the diabetes drug metformin, which lowers insulin levels. I owe a great debt of gratitude to Richard Fleming, who helped me run this trial, and Ian Greer, who took my initial ideas and helped mature them into two useful reviews on this topic.^{2,3} Greer told me to submit both these reviews for publication. Amazingly, both were accepted. So, one thing I have learned is to trust your instincts, as you never know what may happen.



Q5 Several of the findings you have made have been implemented into clinical practice. Please detail one or two of these, and let us know how you feel they have improved the healthcare of patients.

I was one of the first to discover that statins may actually increase the risk of developing diabetes. This side effect does not negate the enormous benefits of statins on the prevention of heart disease; however, it does mean people who are at higher risk of diabetes need to be told to also take lifestyle issues seriously. By doing so, they will not only lower their heart disease more on top of the effect of statins, but they will also attenuate any associated risk of developing diabetes coming from starting statins. This information is now in National Institute for Health and Care Excellence (NICE) guidelines.

I have also helped discover that excess liver fat may be linked to diabetes. My paper on diabetes that looked at liver function tests was noted by Roy Taylor around 2008.⁴ Approximately 10 years later, Taylor and Lean invited me to help on the design and execution of the DiRECT trial, which proved that early Type 2 diabetes can be reversed in the vast majority of patients with sizeable weight loss, a finding with profound clinical implications, now used in the National Health Service (NHS), as well as research implications. We have since repeated this type of intervention in South Asians with results to come soon.

Q6 The COVID-19 pandemic has impacted healthcare worldwide. How has it affected your practice, and have you noticed any correlations between the disease and the prevalence of different metabolic conditions?

COVID-19 impacted people with diabetes much more than those living with a prior heart attack. We now know risk factors such as excess weight, higher blood pressure, higher sugar levels, or poor kidney function are all risk factors for worse COVID-19 outcomes.

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There are also many indirect effects of the pandemic, such as a reduction in physical functioning of many people through weight gain and lower levels of activity. This likely means that even more people have been pushed into chronic disease, or that their diseases have progressed more rapidly. New data emerging all the time tells us this, including the ever-increasing numbers attending emergency departments throughout the country.

We need a lifestyle revolution in the UK, but this requires careful planning and investment. I am worried that if we do not do this, more and more people will live with multiple chronic conditions, putting ever increasing pressure on the NHS and its doctors, nurses, and allied health staff.

Q7 Are there any metabolic conditions which you feel have a lack of awareness?

If we include conditions that obesity is a risk factor for, then many conditions are relevant. This includes diseases such as hypertension, heart failure, psoriasis, fatty liver disease, gout, sleep apnoea, many types of cancer, lung disease, and the vast majority of reproductive health outcomes, to name but a few. So, the list is incredibly long, which is why we must be much more focused on tackling and preventing obesity.

Q8 Which new technologies and recent breakthroughs do you expect will make a real difference in your field in the near future?

I think we are getting progressively better at helping people make positive lifestyle changes; however, more can be done. The old way of just telling people to lose weight does not work and people need much simpler advice on exactly what changes they can make and how to make them. I am working hard on this. In terms of medicines, we are at the beginning of a new generation of weight loss drugs based on the class of drugs called glucagon-like peptide 1 receptor agonists. I like to think of them as chemical appetite suppressants, although they are more complex than that. Even so, some of the newer drugs linked to this class can now help people lose 15–20% of their body weight, which is a major breakthrough. This means people of 100 kg can lose up to 20 kg or nearly 7 units of BMI with these drugs. The implications of such weight loss could be enormous and several

major trials due to report over the next 5 years should confirm the types of gains that could be achieved with this class. If these results go to plan, then such drugs could improve the lives of many patients. However, the cost of these new drugs is high; therefore, health authorities will have to work out who gets them initially. Over time, costs should reduce, and more patients could benefit. Of course, I would prefer we prevented obesity rather than having to treat people once they have excess adiposity. However, with so many now living with obesity, we cannot deny there is great need out there.

Q9 As an educator, where do you feel your focus will lie in the coming years?

As you can see from my preceding responses, it will be improving lifestyle education across the board so that it is no longer ignored but rather becomes the norm, so that all health professionals are able to give rapid, consistent, and evidence-based advice on the range of measures (tools) available to help people improve their diets, activity levels, or sleep habits. Of course, the food industry needs to help too. Hopefully, we can develop partnerships whereby healthier foods become the norm whilst companies still make profits, even if such profits are less than they were in the past with the selling of less healthy foods. There has to be some give and take for all parties.

Q10 What advice would you give to someone hoping to start a career focused on metabolic medicine?

Metabolic medicine opens the potential to work in many different areas and to engage in many types of research. I would try to gain exposure to many different types of clinics so that you become comfortable treating several diseases. This will allow better research but also, as more and more people have multiple conditions, familiarisation with different but linked diseases, enabling better and more efficient care to be delivered. In fact, we need many more doctors working across linked disciplines to improve care. If we can achieve this, more doctors will appreciate the common links between conditions and that some common solutions are available to prevent, delay, or slow many diseases. My personal preoccupation is better weight management across the life course of many chronic diseases. I am working hard, as are many others, to champion this as a major goal for the NHS and wider society.

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