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> **In the Western world, around one in three people in the general population has some degree of steatosis**

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Q1 MASLD is rapidly becoming one of the leading causes of chronic liver disease worldwide. Which trends in patient presentation or disease progression are you currently seeing most often in clinical practice?

The main trend is exactly what we have all been discussing over recent years: MASLD is becoming increasingly prevalent. We already know that, in the Western world, around one in three people in the general population has some degree of steatosis, largely driven by the obesity epidemic.

What we are seeing clinically is growing awareness of MASLD as a disease entity, alongside increasing prevalence. We also increasingly recognise it as a cofactor in many other liver diseases. Patients may present with a classical liver condition, but concurrent metabolic dysfunction and steatosis significantly affect outcomes as well.

One of the major challenges remains identifying which patients actually require referral from primary care. If one-third of the population has steatosis, we clearly cannot refer everybody. The difficulty lies in identifying those patients at highest risk of progressing to fibrosis, cirrhosis, and liver-related complications.

There is still considerable uncertainty within primary care regarding whom to refer, when referral is appropriate, and how to stratify high-risk candidates. We now have several non-invasive tools that can help, which is extremely valuable, but there is still a very large pool of patients who require assessment before determining whether specialist hepatology input is needed.

From a transplant hepatology perspective, we are also seeing a much more complex patient population. Patients increasingly present with multiple comorbidities that we did not routinely encounter previously, which means hepatologists also need broader expertise in managing metabolic and cardiovascular complications, both before and after transplant.

Another important point is that, as with many chronic liver diseases, MASLD often presents late. Patients frequently only seek medical attention once they develop complications of cirrhosis, such as jaundice, ascites or other advanced manifestations.

Do you think there are still major barriers to early detection and referral?

We actually have very strong guidelines now. A major multidisciplinary guideline was recently developed involving not only hepatology societies, but also endocrinology and obesity societies, reflecting the fact that MASLD is truly a multisystem disease.

The issue is less about a lack of guidance and more about identifying the right patients. Again, if one in three people in the community has steatosis, the key challenge is finding those individuals at genuine risk of progression to advanced liver disease. That is where the real struggle lies.

There are also important differences between healthcare systems. In some parts of the world, primary care infrastructure is less well established, meaning patients may not even know they have diabetes, hypertension, or other metabolic risk factors.

Screening is another major topic of discussion. We recently saw important data from the large international Liverscreen consortium, which evaluated risk factors, prevalence, and disease progression across multiple countries and healthcare systems. These types of studies are helping us move towards more formalised screening strategies.

However, before implementing a true screening programme, several things need to be in place. First, you need to identify not simply the disease itself, but the patients at highest risk of clinically significant disease. Second, you must have something meaningful to offer once the disease is detected.

To use an analogy, there is little value in screening for lung cancer if no treatment options exist. Until recently, we did not have approved therapies specifically targeting MASLD and metabolic dysfunction-associated steatohepatitis. Only within the past few years have treatment options started to emerge.

What we have largely been doing so far is case finding: identifying higher-risk patients within the community who may benefit from referral to hepatology clinics. I think formal screening pathways will continue to evolve as therapeutic options expand.

> **One of the greatest long-term challenges is balancing immunosuppression**

Q2 Liver transplantation remains one of the most complex areas of medicine. What are the greatest challenges in long-term transplant management?

Liver transplantation is uniquely complex, both anatomically and physiologically. Unlike kidney disease, for example, we do not have an equivalent of dialysis for liver failure. We cannot simply place patients on a machine indefinitely while awaiting transplantation.

One of the greatest long-term challenges is balancing immunosuppression. On one hand, immunosuppression is essential to prevent graft rejection and preserve the transplanted liver. On the other hand, these therapies come with substantial risks, including infection, diabetes, obesity, kidney disease, metabolic syndrome, and malignancy.

The risk of malignancy in transplant recipients is several times higher than in the general population. Interestingly, when we examine causes of death following transplantation, many are no longer liver related. Cardiovascular disease, stroke, and cancer are major contributors. In part, these complications are consequences of the treatments we use.

Another major challenge is organ shortage, which has existed for as long as transplantation itself. Despite substantial efforts to increase organ donation rates and expand living donation programmes, globally we still only provide transplantation to a small proportion of potentially eligible patients.

At the same time, the donor pool itself is changing. The general population is ageing and becoming increasingly affected by obesity and metabolic disease. As a result, donor organs are also increasingly affected by steatosis and other comorbidities.

We therefore face a difficult balance: increasing the number of usable organs often means accepting higher-risk or poorer-quality grafts while if we wait only for ideal organs, more patients would die waiting.

What are the recurrence rates of primary liver disease following transplantation?

It depends heavily on the underlying disease. Autoimmune liver diseases such as autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis generally recur in approximately 10–20% of cases, depending on the type and cohort studied.

Historically, hepatitis C recurrence after transplantation was almost universal, but thankfully that has changed dramatically with modern antiviral therapies. Hepatitis B recurrence risk is also now relatively low because of effective suppression strategies.

We are now increasingly seeing recurrence of MASLD and steatosis following transplantation, as well as *de novo* steatosis developing post-

transplant. Immunosuppressive therapies themselves often contribute to weight gain and worsening metabolic health.

Q3 There is increasing discussion around expanding donor criteria. What developments are currently shaping this area?

One major area is increasing use of donation after circulatory death (DCD). In many countries, such as the Netherlands and the UK, DCD transplantation now represents a substantial proportion of liver transplants.

These grafts do come with increased risks, particularly biliary complications related to ischaemia reperfusion injury, which can result in development of difficult-to-treat strictures in the biliary tree. However, many healthcare systems simply could not meet transplant demand without DCD organs.

The good news is that this increasing gap between the need for high quality donor organs on the one hand and its availability on the other, has fuelled technological innovations to generate more donors or find ways to better utilise the current donor pool.

One of these innovations is machine perfusion, which has undergone a very rapid evolution from conception to implementation and is now common clinical practice in many countries. With machine perfusion, we are now able to mitigate some of the ischaemia reperfusion injury to the graft as well have created a tool to test the viability of the organ before implantation. This has revolutionised the field, and its potential use continues to be explored further as we move forward.

As a rule, as a transplant community, we are constantly exploring whether organs previously considered unsuitable might still safely benefit selected patients.

Q4 In your experience, what misconceptions do clinicians still have about advanced liver disease or transplant candidacy?

Outside hepatology, one persistent misconception remains: many people still assume all liver disease is alcohol-related, which is clearly inaccurate and often harmful for patients.

Within transplantation specifically, the field has evolved enormously over the past 10–15 years, with major expansion of indications and reconsideration of previous contraindications.

For example, non-liver malignancy was historically viewed as a major contraindication, often requiring a 5-year cancer-free interval before transplantation could even be considered. We now have far more nuanced guidance depending on tumour type and prognosis.

Similarly, older age, obesity, sarcopenia, and frailty were once considered near-absolute contraindications. Today, many centres transplant selected patients well into their 70s, provided they remain biologically fit. High BMI alone is no longer an

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automatic exclusion either, and some centres have adopted to offer such patients a combined simultaneous bariatric gastric sleeve during the liver transplantation.

The problem is that clinicians outside transplant centres may still apply outdated assumptions and therefore be reluctant to refer patients for assessment. In reality, every patient presenting with decompensated cirrhosis should prompt the responsible physician to at least once consider a liver transplantation, even if only through discussion with a transplant centre.

Unfortunately, we still see many patients referred either too late or not at all. Ideally, referral should occur while patients remain relatively fit and before severe sarcopenia or advanced frailty develops, because outcomes are significantly better at that stage.

Q5 Looking ahead, which advances in transplantology are most likely to move into routine clinical practice over the next 5–10 years?

Machine perfusion is one of the most exciting developments and is rapidly becoming standard of care, particularly for higher-risk donor organs such as DCD grafts.

Different perfusion strategies, including normothermic and hypothermic perfusion, are being refined, and over the coming years we will better understand which approaches are optimal for specific donor and recipient scenarios.

An especially important aspect is viability testing. Rather than relying purely on visual assessment of a donor liver, machine perfusion allows us to objectively evaluate organ function prior to transplantation.

Longer-duration perfusion also creates opportunities for therapeutic intervention. Studies are already exploring 'defattening' therapies delivered directly to steatotic donor livers while on the pump, with the aim of improving graft quality before transplantation. These developments could substantially expand treatment options in the future.

Beyond this, bioengineering and xenotransplantation are developing rapidly. While we are unlikely to see scalable bioartificial organs within the next 5 years, these technologies are advancing our understanding and may eventually transform the field.

We are also beginning to explore the concept of using xenografts, such as pig livers, extracorporeally as biological support devices, somewhat analogous to dialysis systems.

Ultimately, these innovations are urgently needed. As MASLD continues to rise globally, transplant waiting lists will continue to grow. We must both expand organ utilisation by innovation and at the same time to our best to improve donation systems.

Spain provides an excellent example of this. Their success has not simply been legislative; it reflects optimisation of the entire donation system and a societal and medical mindset in which organ donation is viewed as the norm rather than the exception. There is a great deal that other countries can learn from that approach.

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