

What I tell my patients about **membranous nephropathy**

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Membranous nephropathy (MEM-bruh-nus nuh-FROP-uh-thee) is a condition in which protein leaks into the urine from the kidneys. This can lead to low protein levels in the blood, water retention and sometimes even kidney failure.

Sanjana Gupta and **Neil Ashman** describe this rare condition and its treatment

The most important function of the kidney is to purify blood by removing excess water and waste products, which healthy bodies constantly produce in response to eating, drinking and moving. Each kidney has around 1 million nephrons (see Figure 1) – these are identical functioning units made up of a glomerulus and a long tubule. Blood flows into the glomerulus, a ball of fine blood vessels called capillaries, and then returns to the heart. The glomerulus acts as a filter, allowing water, salts and small molecules to leave the blood and move into the tubule.

Each glomerular filter is made up of an endothelium (cells that line the blood vessels), a membrane, and specialised cells called podocytes that wrap around each tiny blood vessel like a porous mesh (see Figure 2). As blood cells and proteins are too large to pass through this filter, they are retained in the bloodstream. As the filtered fluid flows along the tubule, it is steadily modified by the cells that line the tubule, in order to return important salts to the blood, and allow toxins and waste products to pass out of the body in the urine.

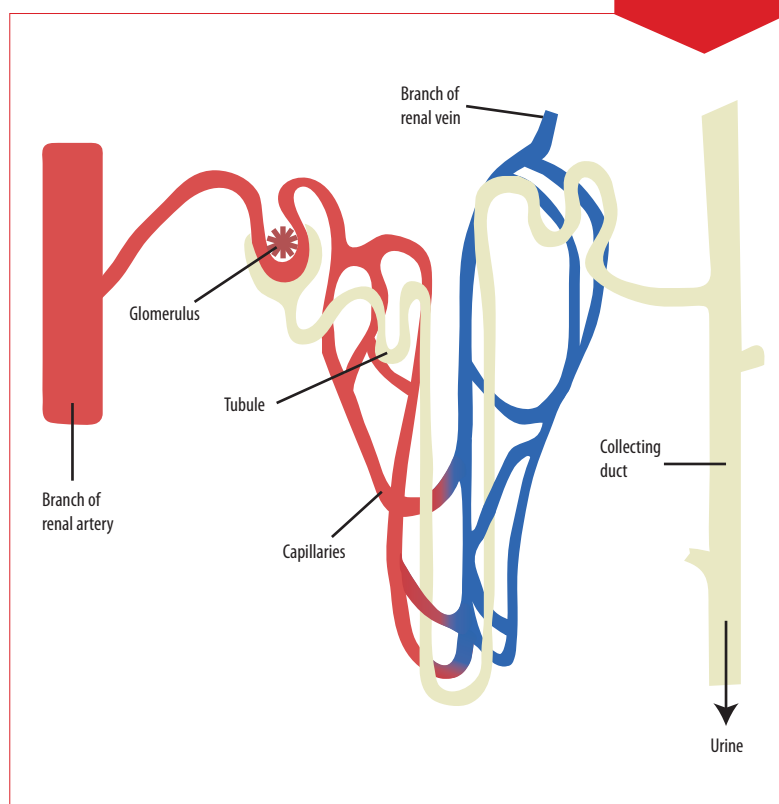
What is abnormal about the glomeruli in membranous nephropathy?

In membranous nephropathy, the membrane within the filtering system, known as the glomerular basement membrane, is thickened. This thickening can be seen under a microscope, and was how the name was originally derived. This thickening of the basement membrane is now known to be due to antibodies, which bind to the glomerular filter. The resulting damage causes the membrane to thicken. Antibodies form part of our immune system and help to fight infection. However, in diseases such as membranous nephropathy, antibodies attack and damage the body's own tissues. These diseases are

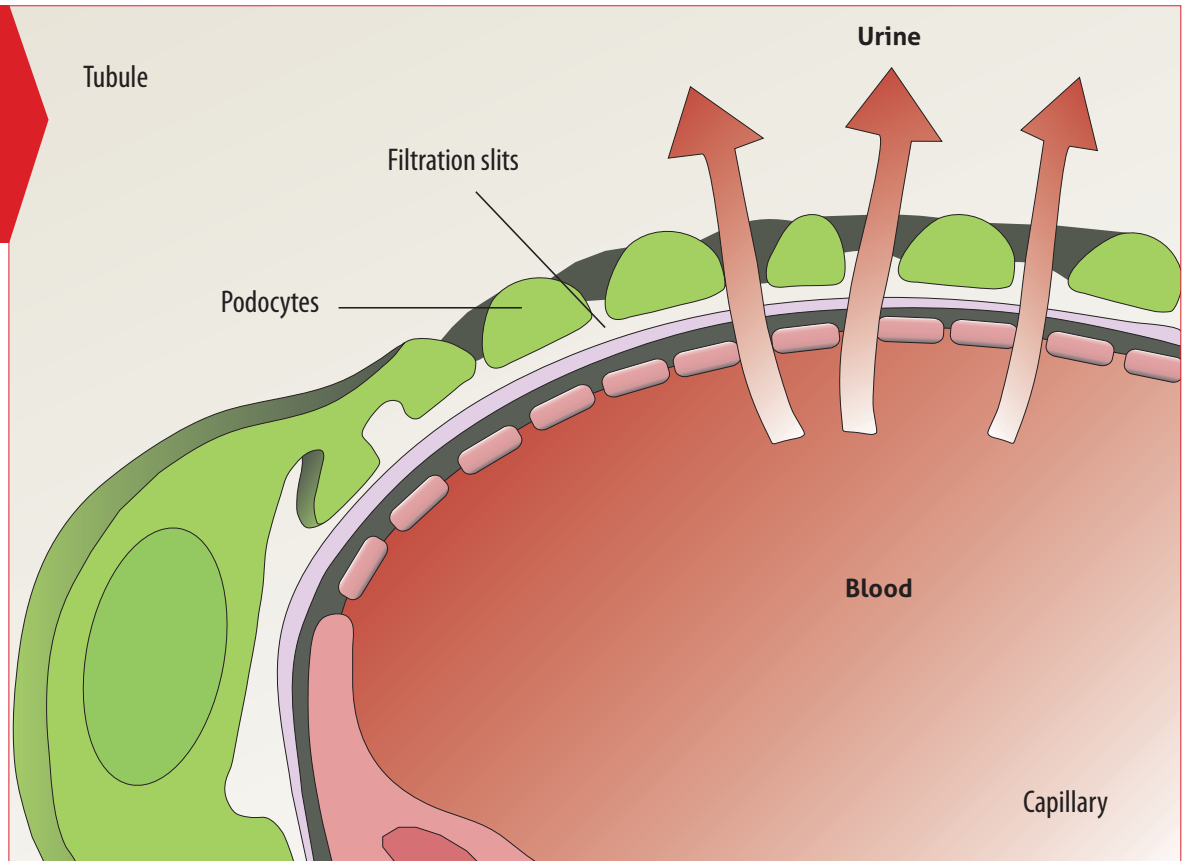
termed autoimmune disorders. We do not know why the immune system produces antibodies against the body's own tissues, but we can now test for the specific antibodies involved in membranous nephropathy in at least 80% of cases.

As the glomerular filter can no longer work normally in membranous nephropathy, larger molecules, such as the protein albumin, appear in the urine, and the level of proteins in the blood falls. Because proteins constantly draw fluid out of the tissues and into the bloodstream, falling blood protein levels (hypoalbuminaemia) mean that fluid starts to collect in the body. These symptoms are called nephrotic syndrome and are usually harmless.

Figure 1. Diagram of a nephron, consisting of a glomerulus (a ball of fine blood vessels) and a long tubule (a tube that contains urine)



■ **Figure 2.** Diagram of a glomerular filter. The capillary is in the middle, covered by the basement membrane and wrapped by podocytes



Is there something that I could have done to prevent this?

No. In the majority of cases, we do not yet understand what causes abnormal antibody production. This is called idiopathic, as it is not connected to an understood disease. In some cases, it is possible to identify an underlying condition that has caused the membranous nephropathy, but this is less common. These cases are called secondary membranous nephropathy. Common causes of secondary membranous nephropathy are other autoimmune conditions such as systemic lupus erythematosus, viral infections such as hepatitis, medications such as gold and penicillamine, and cancer.

Who gets membranous nephropathy?

Membranous nephropathy is rare. It usually affects adults aged between 40 and 70 years. It is very uncommon in children and affects men more frequently than women. Membranous nephropathy affects ten people in every million, which means that approximately 650 new cases are diagnosed in the UK each year.

What symptoms should I expect?

Most people first notice swelling, called oedema, due to excess fluid collecting in the tissues. This can be mild to begin with; you may only notice swelling around your eyes, as fluid accumulates where the skin is thinnest. However, fluid may also gather in the feet, ankles or abdomen. You may also notice

that your urine becomes frothy, which is caused by protein in the urine (proteinuria). For most people with membranous nephropathy, oedema and proteinuria are normally the first symptoms. Other symptoms include high blood pressure, tiredness, a poor appetite, whitening of the nails and symptoms related to an underlying condition.

What investigations should I expect?

Your GP will carry out blood and urine tests to determine whether protein is present in the urine with low protein levels in the blood. The urine test is carried out using a dipstick similar to that used for urine infections, and which changes colour when protein is present in the urine. Following these tests, you will be referred to a kidney specialist (nephrologist), to test your kidney function, check for the antibody that causes membranous nephropathy, and measure the amount of protein that is leaking into the urine. The nephrologist may also arrange for a kidney ultrasound and biopsy.

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What is the prognosis?

In a third of people with membranous nephropathy, the proteinuria will get better on its own over the course of a year. In a further third, kidney failure may develop, which, if not treated, will lead to permanent damage and may result in the need for dialysis. Your nephrologist will help you to understand whether it is right to wait to see if the condition resolves spontaneously (watchful waiting), or if you will need treatment. Any treatment deemed necessary may begin immediately or after a period of watchful waiting. There are a number of risk factors that can help identify those who are at most at risk of kidney failure and, therefore, require early treatment. Risk factors include heavy losses of protein in the urine, abnormal kidney function, high blood pressure, scarring seen on the kidney biopsy under the microscope, and high levels of antibody in the bloodstream. Membranous nephropathy tends to recur, so even if successfully treated the disease can come back.

What treatment will I need?

While everyone with membranous nephropathy will receive tablets to control the symptoms, those individuals with specific risk factors will need specialised treatment. A period of waiting to see if your body will get rid of the antibody is usual. If this happens, your kidneys will get better as a result. In secondary membranous nephropathy, treatment of the underlying cause often solves the problem.

Dietary and lifestyle changes

There are a number of dietary and lifestyle changes that you can make, including:

- Stopping smoking. This can help reduce proteinuria
- Avoiding over-the-counter anti-inflammatory medications for pain. These can cause kidney function to become abnormal and may interact with other drugs that you are taking
- Eating a healthy balanced diet. You should avoid high fat foods that increase cholesterol levels, reduce salt intake to help control blood pressure and continue with a normal protein intake
- Regular exercise. This improves the strength of muscles and bones.

Drug treatment

All patients with membranous nephropathy are usually offered an angiotensin converting enzyme (ACE) inhibitor. This drug lowers blood pressure and the pressure inside the kidneys, which may prevent scarring, and reduces the amount of protein leaking into the urine. ACE inhibitors also appear to help the condition resolve spontaneously in some patients.

If your blood pressure is raised, this can be treated with antihypertensives. The ACE inhibitor may be

enough on its own, but if it is not, you will also be prescribed another antihypertensive drug. It is very important to eat as little salt as possible, to help control blood pressure.

Diuretics, which promote the production of urine, will remove more salt and water from the bloodstream in the urine. This should help the fluid in your tissues move back into the bloodstream.

One of the many proteins lost in the urine carries vitamin D, which is important for bone strength. Some doctors will, therefore, prescribe vitamin D tablets. Proteins that prevent blood clotting are also lost, which may increase the risk of blood clots forming in your legs and lungs. If the risk of blood clot formation is high, your doctor may recommend blood-thinning medication (anticoagulants).

As protein levels in the blood fall, the liver increases protein production to compensate. As some of these proteins carry fats, including cholesterol, your cholesterol levels will rise. To protect your blood vessels and heart, you will be offered a statin, which reduces the production of cholesterol.

Immunosuppression

Some patients will need specific treatment with immunosuppressants to reduce antibody production. Many doctors will begin with steroids, which are chemicals that are also found naturally within the body. As a medicine, steroids are used at high doses so that they are effective, and are normally used in combination with other drugs. The side effects of steroids include bone thinning, diabetes and weight gain.

A treatment called the Ponticelli regimen is the closest treatment to a cure for membranous nephropathy currently available. The Ponticelli

Key points

- Membranous nephropathy is a rare condition that causes protein leakage from the kidneys.
- Most cases of membranous nephropathy occur when the body's immune system incorrectly attacks the kidney filters.
- The condition behaves differently in different people. It can improve spontaneously in some, or in severe cases, can cause kidney failure.
- Treatment does not always cure membranous nephropathy; it may recur despite treatment.
- You may be asked to participate in research so that we can further understand the condition and how best to treat it.

regimen is a combination of the chemotherapy drug cyclophosphamide and steroids, given as either a daily tablet or through a vein (intravenous) at regular intervals. Side effects of the Ponticelli regimen include serious infections and a small risk of infertility and cancer.

Other drugs, such as tacrolimus or cyclosporin, may also be used instead of the Ponticelli regimen. The duration of treatment is longer and the risk of the disease recurring is increased once the medication is stopped. The side effects of these medications include infections, diabetes and high blood pressure.

Are there any additional complications?

People with membranous nephropathy are at increased risk of infection, as the proteins that fight infection are lost in the urine. This risk is much higher if you are treated with immunosuppressants, as these further diminish the body's ability to fight infections. You can obtain specific and detailed information on the side effects of each drug you are taking from your doctor.

Medical research

As membranous nephropathy is a rare disease, there is a significant amount of research ongoing, to help fully understand the causes, what can prevent the condition and how best to treat it. Research is also underway to find new and alternative medications. However, the use of these medications is currently limited to clinical trials.

In the UK, you may be asked to consider participating in research. This may involve collecting extra blood or urine samples, entering clinical data about your disease into a national register or trying a new treatment. If you are suitable for a research trial, your doctor will discuss this with you in detail. Whether or not you participate in a trial will not affect your treatment in any way ■

Declaration of interest

The authors declare that there is no conflict of interest.

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Patients who talk to patients

It is well known that, when kidney patients wish to learn more about their condition, they first turn to a renal consultant or nurse. Following this, they frequently compare experiences with other patients. Only if these avenues are unavailable, do they turn to medical information leaflets, videos, books and websites. Frequently, when it comes to issues concerning kidney disease, the last person that renal patients trust is their own GP.

The National Kidney Federation (NKF) Helpline lies between the authoritative medical advice of trained renal medical staff, and the non-medical advice needed by many kidney patients. The NKF Helpline service has worked well for 16 years, offering invaluable help and guidance on many aspects surrounding kidney disease. However, it is now becoming increasingly involved in social media, in order to correct well intentioned, but misleading, information that circulates faster than a wildfire.

These days, many people use Facebook, Twitter and other such forums to build a network of contacts. Many seem willing to share the most private and personal information publicly, as if they are having a chat with a friend. Renal medicine is no different; there are numerous kidney patient groups, Facebook pages and Twitter accounts, exchanging what can only be described as pseudo medical advice. While in the majority of cases, the information imparted is correct and helpful, particularly to new patients, information is made public without any checks, by people with no medical knowledge or training. This is potentially very dangerous and NKF fears for the safety of unsuspecting kidney patients who have listened to bad advice shared on social media.

Many attempts have been made to control medical websites and ensure quality. However, previous attempts have failed, as regulation or monitoring efforts are too slow to react to the spread of information on the Internet. Compared to traditional websites, social media is a much larger problem; social networking is instant and information can reach thousands of people within seconds. Something must be done ■

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