Appraisal for screening for Glomerulonephritis

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Contents

1. Introduction

This paper reviews screening for Glomerulonephritis against the UK National screening criteria for appraising effectiveness and appropriateness of a screening programme (National Screening Committee 2003).

In February 2002 (Laitner 2002) a brief review concluded that the National Screening Committee should not recommend screening for Glomerulonephritis.

In October 2009 a knowledge update (Coles 2009) was carried out to determine if any further, relevant studies were published between January 2001 and September 2009. A total of 7047 references were identified by the search strategy of which 181 were deemed to be relevant.

Evidence from the initial review by Laitner (2002), relevant papers identified by the Knowledge Update form the basis of this review.

2. Background

Glomerulonephritis (GN) covers a group of conditions in which there is injury to the glomerulus, the filtering unit of the kidney. Nearly all this group of conditions are a subset of a more general umbrella term of Chronic Kidney Disease (CKD). The most common types of CKD are due to diabetes, hypertension and GN (National Collaborating Centre for Chronic Conditions – NCC-CC 2008). CKD was reviewed by the National Screening Committee and it concluded that there was insufficient evidence to support the implementation of a population based screening programme (Heffernan 2008).

It should be clear to the reader throughout this appraisal whether the evidence referenced relates to CKD generally which includes GN or GN as a specific set of conditions.

It may be appropriate for any future appraisal of CKD to include GN as a sub-section of the review.

The context of this appraisal must be seen in the light of the following developments:

1. In 2004 the Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference recommended that all countries should have a targeted screening programme for CKD (Levey *et al* 2007).
2. The Department of Health announced that the NHS would be implementing 'NHS Health Checks' by 2012/13 (Department of Health 2008). This programme will invite all people between the ages of 40-74 for a health check every five years (NHS Health Check Programme, 2009). The objective of this policy is to lead to a higher uptake of primary prevention interventions, reduce the risk of vascular disease and enable earlier detection of kidney disease and diabetes (Department of Health 2008). The NHS Health Check includes a test for hypertension, which is commonly associated with GN and wider CKD (NCC-CC 2008). If hypertension is diagnosed then kidney function will be tested to give an indication if CKD is present (NHS Health Check Programme, 2009). With the

implementation of the national health checks a significant proportion of people identified with CKD will have a diagnosis of GN.

3. The condition

3.1 The condition should be an important health problem

GN can occur as primary glomerular disease or secondary to drugs, infections or tumours (Macanovic & Mathieson 2007). Typically there are no symptoms of the disease and late presentation is common with many patients only becoming aware of the condition in the last stages (Nickolas *et al* 2004). Urinanalysis with a positive result for total protein, albumin or red blood cells in the sample is often the first indication of the condition but renal biopsy is the method to definitively diagnose GN (Macanovic & Mathieson 2007).

GN is commonly a minor illness but may persist for many years. In a small number of cases kidney failure (End Stage Renal Failure) may develop and then renal replacement therapy (RRT) is necessary on an ongoing basis for the patient to remain alive. On 31/12/2008 there were 47,525 people undergoing RRT in the UK of which 16% (7604) had a primary renal diagnosis of GN (Ansell & Feest 2009). Biopsy proven GN remains the most common primary renal diagnosis of all those receiving RRT in the UK. A high but unknown proportion of those cases with 'Uncertain aetiology' includes people with presumed GN who have not had a biopsy to confirm the diagnosis.

Table 1: Percentage distribution of primary renal diagnosis leading to RRT in the UK (prevalence)

Diagnosis	Percentage
Diabetes	14.1
GN	16.0
Pyleonephritis	12.0
Polycystic Kidney disease	9.6
Renal vascular disease	3.5
Hypertension	5.6
Uncertain aetiology-includes presumed GN without renal biopsy)	20.5
Other	14.5
Data not available	4.4

Source: Ansell & Feest 2009

Reported incidences of GN vary depending on renal biopsy policies and in the UK the range is between 17 to 60 per million population (Macanovic & Mathieson 2007). However, there are many more mild cases where a renal biopsy is not carried out and the disease does not progress to the point of kidney failure. Any age group may be affected though some types are particularly common in children.

In the UK 6639 adult patients with CKD started renal replacement therapy (RRT) in 2008 of which 664 (10.5%) had a definite diagnosis of GN (Ansell & Feest 2009).

Table 2: Percentage distribution of primary renal diagnosis leading to RRT in the UK in 2008 (incident)

Diagnosis	Percentage
Diabetes	21.4
GN	10.5
Pyleonephritis	6.9
Polycystic Kidney disease	6.5
Renal vascular disease	6.1
Hypertension	5.3
Uncertain aetiology-includes presumed GN without renal biopsy)	18.5
Other	13.9
Data not available	10.8

Source: Ansell & Feest 2009

Biopsy proven GN is much more common in those under 65 compared to those over 65 (13.6% vs 7.1%) and the male to female ratio is 2.2 (Ansell & Feest 2009).

The leading renal diagnosis in the prevalent cohort of patients is GN compared to diabetes in the 2008 incident cohort. This reflects the different ages and survival of the patients with different diagnoses. People with GN generally start RRT at an earlier age than those with diabetes and are receiving treatment for a longer period (Ansell & Feest 2009).

The Health Technology Assessment published in 2005 indicated that in 2000 there were approximately 30,000 people receiving RRT at a cost of £600 million pounds which equates to a treatment cost of £20,000 per person per year. In 2008 GN accounted for at least 7604 cases requiring RRT which at £20,000 per person would cost £15.2 million per year.

3.2 The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

There are a number of lifestyle factors that are strongly associated with many types of CKD (diabetes, cardiovascular disease, obesity, hypertension) but with GN immune reactions underlie the condition. Black *et al* (2010) reviewed the data about the natural history of CKD but there was limited detailed information.

In some cases of GN the target immune response is known, for example when GN complicates tumours or infections (Hurtada & Johnson 2005) but in many cases the target is unknown and an autoimmune aetiology is suspected. As with other autoimmune conditions GN is considered to be a result of a combination of genetic susceptibility and environmental factors. The genetic factors are typically genes involved in the control of the immune response whereas the environmental factors may be drugs, chemicals or infections (Macanovic & Mathieson 2007).

Different patterns of abnormality within the glomerulus may be used to define subtypes of glomerular disease. There is a poor understanding of how GN is triggered and subsequently develops with many of these sub-types (Macanovic and Mathieson 2007).

Late diagnosis of GN is a major issue because there may be a long undetected asymptomatic latent phase and significant disease is diagnosed when the patient does present (Macanovic & Mathieson 2007). In contrast one type of GN has a rapid onset and it is unlikely that a screening programme would be able to be effective in detecting these cases.

Minimal-change Nephropathy
Minimal-change nephropathy (MCN) occurs in both children and adults but is most common in children. It sometimes develops secondary to drug use (especially NSAIDs) or malignancy (especially Hodgkins disease and other lymphomas). The idiopathic form is thought to result from an abnormality of T lymphocytes but studies to clarify this mechanism have been inconsistent (Macanovic & Mathieson 2007).

MCN typically presents with heavy proteinura, hypoalbuminaemia and odema.

Focal Segmental Glomerulosclerosis (FSGS)
FSGS is diagnosed when a renal biopsy shows scarring of some glomerli or parts of some glomerli. It is associated with hypertension and extreme obesity (Kincaid-Smith 2004), HIV infection, and may result from a reduction in functioning nephrons (eg: nephrectomy). This has led to the hypothesis that FSGS results from 'overloading' of healthy nephrons. This has been shown in animal studies although there is little evidence that this is the case in humans (Macanovic and Mathieson 2007).

FSGS presents with nephrotic syndrome and may be associated with microscopic haematuria and impaired renal function. The disease often progresses to ESRD despite treatment (Macanovic & Mathieson 2007). About 50% of patients develop ESRD within 10 years.

Membranous nephropathy (MN)
Idiopathic MN may arise from the formation of immune complexes the characteristics of which determine that they are localized in the kidney. This autoimmune response results in damage to the glomerli. MN may be a secondary condition in response to use of NSAIDs, gold, penicillamine and may develop when solid-organ tumors are present (especially breast, colon or bronchus). Infection, hypothyroidism, and SLE may also trigger MN.

MN typically presents with proteinuria, which may be severe enough to cause nephrotic syndrome. The prognosis is dependent on the underlying disease. When a particular drug that has triggered MN is withdrawn remission is likely, whereas MN associated with a malignancy will remain until the tumour is removed. Where there is no underlying cause at least 25% undergo spontaneous remission (Macanovic & Mathieson 2007).

Mesangiocapillary GN (MCGN)
MCGN is uncommon and presents with proteinuria, haematuria, hypertension and impaired renal function. There are three subtypes identified via electron microscopy although the clinical presentation is similar. Idiopathic MCGN is difficult to treat.

MCGN may develop as a result of chronic infection (visceral abscesses, infective endocarditis) or cryoglobulinaemia.

It tends to have a progressive course with 50% of patients having chronic renal failure within 10 years (Macanovic & Mathieson 2007).

Focal necrotising GN (FNGN)
FNGN has rapid onset, may be triggered by a number of environmental factors such as exposure to hydrocarbons, smoking and viral or other infections. Severe acute inflammation occurs in the glomerulus and the patient usually presents with acute renal failure, haematuria and proteinuria. It is a medical emergency (Macanovic & Mathieson 2007). It is unlikely a screening programme would be effective at detecting that this type of GN because of the rapidity of onset (within 3 months).

IgA Nephropathy
IgA nephropathy is the most common form of glomerulonephritis worldwide (Macanovic & Mathieson 2007). The prevalence differs widely between geographic areas accounting for 29.2% of biopsied populations in Asia, 12% in Australia, 10.7% in Europe and 5% in North America (Shen et al 2008).

IgAN is relatively rare in the Indian sub-continent and people of African descent (Kiryluk *et al* 2010). Familial IgAN was first reported in the 1970s and studies have shown that 4-10% of patients with IgAN have had a family history of kidney disease (Kiryluk et al 2010). Other studies have reported that urinary abnormalities were detected in over 20% of asymptomatic first degree relatives of people with IgAN (Kiryluk et al 2010). No causal gene has yet been identified and ascertainment of familial forms has been complicated by the need for renal biopsy for a definitive diagnosis of the disease. A study of incident cases in Japan concluded that risk factors associated with an increase in the likelihood of developing IgAN were genetic factors, immune response to upper respiratory infections and nutritional imbalance (Wakai et al 2002). The typical clinical presentation is haematuria, which may be macroscopic. Without proteinuria the prognosis is good, if proteinuria is more than 1g/ 24 hours the risk of ESRD is about 25% (Macanovic & Mathieson 2007). Shen et al (2008) showed that out of 177 cases with early IgAN 28% presented with just haematuria, 16% with just proteinuria and 56% with both. Of the 177 cases 38% had hypertension. A high proportion (up to 40%) of people with early IgAN progressed to chronic renal failure (Shen et al 2008).

3.3 All the cost-effective primary prevention interventions should have been implemented as far as practicable

Some types of GN may be triggered by environmental or lifestyle factors whilst others may occur because of a genetic disposition or develop spontaneously with an unknown aetiology (Macanovic and Mathieson 2007).

General lifestyle advice is to achieve a healthy weight, take exercise and stop smoking. These actions will all reduce the likelihood of developing CKD including some types of GN (National Institute Clinical Excellence - NICE 2008).

The full NICE guidance (2008) recommends that in primary care people should be offered testing for CKD if they have any of the following risk factors:

- Diabetes
- Hypertension (associated with most types of GN)
- Cardiovascular disease
- Structural renal tract disease renal calculi or prostatic hypertrophy
- Multisystem diseases with potential kidney involvement (GN)
- Family history of CKD (associated with some types of GN)
- Opportunistic detection of haematuria or proteinuria (associated with some types of GN)

Additionally in 2008 the Department of Health (2008) announced that the NHS Health Check would be implemented by Primary Care Trusts by 2012/13.

The programme aims to invite all 40-74 year olds for a health check at their GP practice every five years. PCTs may rollout the programme by targeting their high risk most deprived populations first before inviting the whole cohort. The Health Checks will determine:

- Smoking status
- Ethnicity
- Body Mass Index
- Cholesterol test
- Family history of Cardiovascular Disease
- Blood pressure
- Blood glucose testing
- Previous medical history

Using this information a Chronic Kidney Disease risk assessment will be triggered if a persons blood pressure is >140/90mmHg or where the systolic blood pressure is above 140mmHg and/or the dystolic blood pressure is above 90mmHg. It is therefore more likely that people with hypertension associated with GN (such as FSGS) will be identified with the health check than other types of GN such as IgAN where proteinuria rather than hypertension is a primary symptom. Buckalew *et al* (1996) reported a prevalence of 85% of people with a GN diagnosis had hypertension in contrast to Shen *et al* (2008) where only 38% of people with IgA nephropathy had the condition.

3.4 If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications

More research is needed before genetic testing could be carried out to identify a sub-set of individuals at risk of developing IgAN (Kiryluk 2010).

4. The Test

4.1 There should be a simple, safe, precise and validated screening test

Dipstick analysis
The presence of low levels of protein, albumin or red blood cells may indicate kidney damage. A urine sample checked for protein with a reagent strip has been used to test people for CKD as an initial primary care investigation and for mass population screening (Heidland *et al* 2009, Iseki 2006).

Haematuria may indicate CKD but it may also indicate other tumors, urinary tract infections, stone disease and bleeding from other benign diseases of the urinary tract (NCC-CC 2008). Screening studies indicate that asymptomatic microscopic haematuria in the UK adult male population is 2.5% rising to 22% in men over 60 years of age (Ritchie *et al* 1986). The NCC-CC (2008) reported the results of one study (Chan *et al* 2005) of patients with lupus were the sensitivity of the reagent strips was high (98%) but specificity and PPV was low (53% and 39% respectively). Iseki *et al* 2003 showed that out of 106,177 people screened in Japan for heamaturia 9% had a positive result. Of the 106,177 people screened 420 went on to develop End Stage Renal Failure of which 18.1% had haematuria. Of these 420 people 48.8% (205) had chronic GN. The NCC-CC (2008) concluded haematuria alone would not be sufficient to trigger a referral and that clinicians would need evidence of concurrent proteinuria and/or evidence of decreased glomeruler filtration rate before recommending renal biopsy to confirm kidney damage.

Proteinuria is a strong independant predictor of ESRD in a mass screening setting (Iseki *et al* 2003). In two population studies the prevalence of proteinuria was between 1% and 6%. In one Japanese study of over 100,000 adults the prevalence of dipstick proteinuria was 5% (Iseki *et al* 1996). From a 16 years study of over 5,000 men and women in the Framingham cohort the prevalence of proteinuria was between 1% and 6% depending on age and gender (Kannel *et al* 1984). Rates of definitely significant disease in asymptomatic individuals with proteinuria have been in the range of 0.0% and 1.4% (Woolhander *et al* 1989). Of 420 screened subjects who went on to develop ESRD (205 with GN), 44.3% had proteinuria (Iseki *et al* 2003).

The measurement of protein in urine samples using reagent strips (dipsticks) have been in use for 50 years but have significant limitations. Most reagent strips used in primary care do not detect total protein but only albumin (NCC-CC 2008). The levels, of either protein or albumin, depends on concentrations that may vary depending on urine flow rate, patient dehydration, exercise, infection and extremely alkaline urine leading to false positive results. Conversely false negatives may occur because of excessive hydration (NCC-CC 2008). Gai *et al* (2006) tested 297 patients with different renal diseases, the dipstick test failed to detect pathological proteinuria in 94 people (31.6%).

The 'gold standard' method of urinanalysis is to collect all urine from the patient over a 24 hour period and then test it for protein or albumin. However, this is subject to inaccurate collection, low patient compliance and an expense and time requirement that is difficult to implement routinely (NCC-CC 2008). A rate of protein excretion of $\geq$150mg/24h or albumin excretion of 30-300mg/24h is a positive test result (NCC-CC 2008).

NCC-CC (2008) reviewed the evidence for diagnostic accuracy of reagent strips to detect albuminaria and proteinuria. For albuminaria overall the sensitivity was generally low

ranging from 37%-93%. The specificity was high (93 -98%) whilst the positive predictive value varied between 71-91% for the same cut off point. For proteinuria, Gai *et al* (2006) reported a sensitivity of 49% and specificity of 94% compared to the 24-hour protein excretion.

In contrast Craig *et al* (2002) reported that when the gold standard of a 24-hour urinary excretion of protein of 300 mg or more is used dipstick sensitivity was 90% and a specificity of 67%. It was concluded that as only 30% of those who had a positive dipstick result would also have a positive test using the gold standard 24hr urine excretion, there would be a high proportion of false positives. Of the 30% confirmed positives 13% will be assessed as having a "moderate" to "high risk" of ESRD in the future. This gives an overall positive predictive value (PPV) of about 4% for a positive urine dip test for protein as an assessment of moderate to high risk of ESRD in the future (Craig *et al* 2002).

Despite the limitations of the dipstick method it is commonly used for mass screening programmes as the first line test because it is simple inexpensive and can be used in a range of community settings (Boulware *et al* 2003). Urinanalysis has been accepted for use by the population in Japan to test annually for CKD as part of the mass screening programme that has been in place since 1973 (Imai *et al* 2007).

Albumin and total protein creatinine ratio

Other methods of detecting proteinuria involve calculating the protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) from a single urine sample. Creatinine, a byproduct of muscle metabolism, is normally excreted into the urine on a consistent basis. Its level in the urine is relatively stable. Since the concentration (or dilution) of urine varies throughout the day, this property of creatinine allows its measurement to be used as a corrective factor in urine samples (NCC-CC 2008).

Both ACR and PCR have been shown to correlate with the 24 hour albumin or protein excretion rate (NCC-CC 2008, Antunes *et al* 2008, Gai *et al* 2006, Craig *et al* 2002). These ratios are calculated by measuring albumin or protein (mg per dL) and dividing by the level of creatinine (g. per dL). In contrast to the urine dipstick test a urine sample needs to be tested in the laboratory to obtain a result. NCC-CC (2008) reported from unpublished data that a PCR with cut off of 98mg/mmol was found to give a sensitivity of 95% and specificity of 83%. For ACR with a threshold of 16.5mg/mmol was found to give the same sensitivity and specificity of 70%.

Glomerular filtration rate

The Glomerular Filtration Rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons and is the best index of overall kidney function. The gold standard method for estimating GFR (eGFR) requires the measurement of a filtration marker such as inulin. Accurate testing is expensive and time consuming. However, a cheaper and easier, although less accurate, method involves the measurement of serum creatinine. In order to improve the accuracy of GFR estimation an equation can be used that corrects for the factors which adversely influence the serum creatinine result. NICE guidance (2008) recommended that where eGFR is measured using serum creatinine the 4-variable MDRD equation should be used. This is in line with the UK CKD guidelines and the UK consensus conference (Taal 2007, Archibald *et al* 2008).

4.2 Current use of tests

CKD testing in the NHS Health Check programme
Guidance for the NHS Health Check programme indicates that following a raised systolic or diastolic measurement of blood pressure that a serum creatinine test should be used to calculate the Glomerular filtration rate (eGFR) to assess the level of kidney function. Where the eGFR is below 60ml/min/1.73m^2 the management and assessment for chronic kidney disease is required in line with NICE guidance (2008).

If eGFR is above 60ml/min/1.73m^2 no further assessment is needed unless the individual is diagnosed with hypertension or diabetes mellitus then their risk of kidney disease will be monitored as part of the management of their condition.

Guidance on CKD testing in routine clinical practice
The NICE (2008) recommended that the dipstick test is not used to identify proteinuria in routine clinical practice unless it can detect albumin at low concentrations and the result is expressed as ACR. ACR should be used as the preferred measure as this has greater sensitivity than PCR for low levels of proteinuria although PCR is acceptable. Currently ACR is predominantly used for identifying proteinuria in patients with diabetes whereas PCR is used for all other patients. UK guidelines currently reflect this difference in the tests used for different groups of patients (Taal 2007, Archibald *et al* 2008).

4.3 The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

A dipstick result of (1+) for proteinuria would indicate a positive result and indicate further testing was required (NICE 2008). A dipstick test result of 1+ would be a positive test result for heamaturia (NICE 2008). When ACR is used to identify proteinuria a result between 30mg/mmol and 70mg/mmol should be confirmed by a subsequent early morning sample. If ACR is above 70mg/mmol then repeat testing is not required (NICE 2008). When eGFR is reported as >60ml/min/1.73m^2 in a person not previously tested the test should be repeated within two weeks with an allowance of + or - 5% to account for biological and analytical variability. A drop of 20% in serum creatinine between tests indicates a significant reduction in renal function (NCC-CC 2008).

4.4 The test should be acceptable to the population

Changes in urine composition have been used for centuries in many parts of the world as a method for diagnosing diseases and for over one hundred years urine has been chemically tested for protein (Tighe 2004). In 1956 the first dipstick test, Clinistix, was marketed for use in primary and secondary care (Tighe 2004). The test is non-invasive and although it has been in widespread use historically and geographically no studies could be identified which considered whether urine testing was acceptable. Additionally no evidence could be found about whether the test or subsequent investigations of abnormal results would cause any physical, psychological or social harm. Testing by dipstick or by deriving ACR from a urine sample has successfully been used in many studies (NCC-CC 2008) and in the Japanese mass screening programme (Imai *et al* 2007).

4.5 There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

The current NICE guidance outlines further diagnostic investigations once a positive result has been identified (NICE 2008).

4.6 If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

There are currently no mutations that can be tested.

5. Treatment

5.1 There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

There is some evidence that treatment for hypertension and proteinuria with ACE Inhibitors and immunosuppressive drugs can delay progression of GN to end stage renal disease (NICE 2008, Ballardie 2004, Laville & Alamartine 2004, Kidney Disease Outcomes Quality Initiative, 2004) although grade 1 evidence is very limited and all the authors recommend that further studies are necessary. Bargman (1999), Burgess (1999), Lindal (1999) Levin (1999) and Muirhead (1999) each proposed evidence based treatment strategies for the different types of GN as has the guideline published by the Singapore Ministry of Health (2007).

Black *et al* (2010) reviewed evidence about early referral to specialist nephrology care and determined that this would provide a patient with access to an array of investigations, treatments and dietary advice. This would aim to slow the progression of CKD and enable preparation for planned RRT when necessary. The evidence for this was limited and only seven studies and no randomised controlled trials relevant to assessing clinical effectiveness of early referral strategies were identified. Black *et al* (2010) suggested that this should be a major focus for research.

5.2 There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

There are agreed policies on the treatment of glomerulonephritis (NICE 2008, DOH 2010) which can decrease the progression of GN toward ESRD.

Evidence based recommendations for the treatment of GN are available (NICE 2008, Singapore Ministry of Health 2007). Once a person has been diagnosed with GN management of the condition should include some or all of the following:

- Lifestyle change to lower blood pressure and cardiovascular disease risk (eg: stop smoking, lose weight, take more exercise)
- Immunosuppressive therapies (eg: use of prednisolene, alkylating agents and Cyclosporin A)
- Monitoring of haematuria and proteinuria regularly
- Management of blood pressure (eg: with ACE inhibitors)
- Use of antithrombotics (eg: dipyridamole)
- Dietary supplements and exclusions (eg: reduced salt intake)
- Intravenous immunoglobulin
- Plasma exchange

5.3 Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

NICE (2008) sets out the current guidance for the clinical management of the condition. However it is not clear if this is optimized in all health care providers. Black *et al* (2010) identified the need for prospective randomized controlled trials to assess the clinical effectiveness of early referral and management strategies on the progress of CKD as there was only limited evidence of benefit.

6. The Screening Programme

6.1 There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

No evidence was identified from high quality Randomised Controlled Trials that a mass population screening programme for GN in the UK would be effective in reducing mortality or morbidity.

6.2 Screening strategies in other countries

Japan's screening programme
In the early 1970's kidney disease screening was implemented for all workers and school age children using urinanlysis targeting GN (Imai *et al* 2007). In 1983 the programme was expanded to a community based screening programme for those 40 years of age or over. This was still based on urinalysis but in 1992 an additional *serum* creatinine measurement was included for all those tested who were 40 years or older. Prevalence of proteinuria was 4.1% and in a 6 yr follow up study new proteinuria developed in 0.4% -0.9% of all Japanese men (Iseki *et al* 2003). Wakai *et al* (2004) showed that the incidence of ESRD from GN in men was 96.3 per 1 million population in 1995/6 which decreased to 84.0 pmp in 1999/2000. Similarly in women there was a reduction from 52.7 pmp to 46.1 pmp for the same time periods. In comparison in the US, Wirta *et al* (2008), showed an incidence proven biopsy rate of 17.6 pmp for GN.

IgAN is by far the most common form of GN and accounted for 47.4% of people with primary GN who underwent renal biopsy in Japan (Research Group on Chronic Renal

disease, 1999). Specific treatments for IgAN such as steroids and ACE inhibitors that have been developed over the last 10 years may have improved the prognosis of the condition so it is difficult to assess improvements due to the screening programme and those due to improved treatment (Imai *et al* 2007). As the prevalence of GN has decreased there has been an increase in diabetes (Imai *et al* 2007) which is now the leading cause of ESRD in Japan. It has been suggested that a new kidney disease screening programme targeted at people with diabetes, hypertension and metabolic syndrome may be required. In order to reduce costs the Japanese health administration removed the serum creatinine test from the list of mandatory screening tests (Imai *et al* 2007). Some cases of GN will be identified by targeted screening and the cost effectiveness of CKD screening will be improved but it is likely that a proportion of GN cases that would have been identified by the original programme will not be diagnosed if the targeted approach is implemented (Imai *et al* 2007).

Norway Study

A study by Hallan *et al* (2006) invited everyone 20 years or older to participate in a general health survey in a county in Norway. Between 1995 and 1997, 65,604 (70.6%) people participated in the survey which included an extensive questionnaire and analysis of serum creatinine. A total of 3069 (4.7%) people had chronic kidney disease indicating that 21 people would need to be screened to identify one case. If screening was restricted to those with hypertension, diabetes or those who were over 55 then 93.2% of patients with CKD would be identified with the number needed to screen dropping to 8.7. Screening only people with previously known diabetes or hypertension would identify one case for every 6 people screened but only 44.2% of all cases would be detected. During the eight year follow up only 38 of the 3069 people with CKD progressed to ESRD and the risk was especially low in people without hypertension, or diabetes, in women and those aged under 70. They concluded that screening people with hypertension, diabetes and those over 50 was the most effective strategy to detect patients with CKD. This was based on the premise that serum creatinine measurements would be taken to estimate GFR.

Screening for Proteinuria in US adults

Boulware *et al* (2003) carried out a cost-effectiveness analysis of screening for CKD and looked at a number of elements including screening those who had hypertension and diabetes and those who had neither condition (which would include a significant proportion of people with GN). For those without diabetes or hypertension it was not cost effective to carry out annual screening until age 60 whereas for those with hypertension screening was cost effective from age 30. They concluded that 'early detection of urine protein to slow progression of chronic kidney disease and decrease mortality is not cost-effective unless selectively directed to high risk groups (those with diabetes, hypertension and older persons).' Jaar *et al* (2008) and Powe & Boulware (2009) reviewed the principles of screening as they apply to CKD testing in the adult population of the US. They concluded that the majority of Wilson and Jungner (1968) criteria could be met and that a population based screening programme should be implemented in certain high risk groups (those with hypertension, diabetes and those in older age groups). This was based on the premise that urine protein would be measured.

7. Conclusion

There has been a strong focus on early identification of CKD including GN over the past few years however there are still significant aspects of the condition and its management with little robust evidence to indicate that a screening programme would be effective.

Evidence from screening programmes and studies from around the world indicate that a general population based screening programme to afford the early detection of CKD which includes GN is not cost or clinically effective (Boulware et al 2003, Powe & Boulware 2009, Hallan *et al* 2006). International guidance recommends that a targeted screening programme aimed at people with diabetes, hypertension and cardiovascular disease should be implemented with the use of a urine test for proteinurua and a blood test for creatinine to estimate GFR (Levey *et al* 2007).

There have been no randomised controlled trials assessing the effectiveness of a screening programme in reducing the mortality and morbidity from GN. The treatments for GN show some effectiveness but the evidence is limited and more effective treatments need to be developed and tested. There is no direct evidence of acceptability of the test or follow up investigations to the UK population.

The current position in the UK is that NICE (2008) have recommended that case finding for wider CKD and GN in primary care should be optimized however it is not clear how effective that will be in identifying significant numbers of cases. The NHS Health Check is in the process of being implemented which will through it's monitoring of hypertension also identify a proportion of GN cases. The targeting of CKD detection through screening for diabetes, hypertension and CVD will not pick up the proportion of people with GN who present only with proteinuria or haematuria.

Data from the NHS Health Check should be used to assess how effective the programme is in identifying different types of CKD including GN. This will help to inform further reviews. If the NHS Health Check is considered to be the best way to identify people with CKD and GN then further reviews should consider whether a more specific test of kidney function should be used rather than hypertension.

It is recommended that when the screening policy for CKD and GN are next updated that they are combined in one review.

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