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Summary:

The qualitative evaluation of proteinuria represents a crucial diagnostic step in clinical practice for the classification of renal diseases according to glomerular, tubulo-interstitial, mixed injury or related to monoclonal gammopathy. Combined with the quantitative evaluation, it also allows an assessment of the disease's severity and prognosis as well as the response to treatment. The development of the urine protein profile (UPP) combines specific urine protein assays on a urine spot analyzing glomerular protein markers such as albumin, transferrin and immunoglobulin G, and tubular markers such as alpha-1microglobulin and retinol binding protein, to generate a detailed quantitative and qualitative proteinuria assessment. This short overview proposes to illustrate the diagnostic and prognostic usefulness of UPP in different common clinical situations.

Key words: proteinuria, glomerular disease, tubulopathy

Proteinuria is a major biomarker of kidney diseases. In physiological conditions, the glomerular filtration barrier is impermeable to plasma proteins with a molecular weight over 60 kD, including albumin, transferrin and immunoglobulin G, whereas low molecular weight proteins (alpha-1 microglobulin, retinol binding protein, free light chains…) freely reach the primary urine formed after the glomerular ultrafiltration and are reabsorbed by the proximal tubule, leading to a final urine protein-creatinine ratio under 20 mg/mmol. The qualitative evaluation of proteinuria represents a crucial diagnostic step in clinical practice for the classification of renal diseases according to glomerular, tubulo-interstitial, mixed injury or related to monoclonal gammopathy. Combined with the quantitative evaluation, it also allows an assessment of the disease's severity and prognosis as well as the response to treatment (1 - 4). Several tools are currently available to evaluate proteinuria (Table 1). Urine dipstick allows a semi quantitative assessment of glomerular proteinuria by the specific detection of albuminuria but it is not informative for tubulo-interstitial proteinuria or for abnormal excretion of monoclonal free light chains (FLC). Total urine protein measurement addresses the quantitative evaluation and albuminuria excretion is informative for the presence of prominent glomerular lesions when urine albumin/protein ratio exceeds 0.6. Specific assays for low molecular weight urine makers are also available in clinical use, including alpha-1-microglobulin, retinol binding protein or bêta-2-microglobulin. Except the detection of urine monoclonal FLC, the usefulness of urine protein electrophoresis (UPEP) remains limited because it only provides semi-quantitative and semi-qualitative information. Several urine biomarker assays have been developed in recent years that specifically address acute kidney injury (AKI) diagnosis and prognosis and for which abundant reports are available (5 – 8). These biomarkers mostly include tubular proteins such as urinary neutrophil gelatinase associated lipocalin, urinary kidney injury molecule-1, urinary liver-type fatty acid binding protein, urinary interleukin-18, urinary cystatin C, and the product of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 (5 - 8). Although their pathophysiological relevance in AKI has been demonstrated, their clinical use remains to be established.

The development of the urine protein profile (UPP) combines specific urine protein assays on a urine spot, analyzing glomerular protein markers such as albumin, transferrin and immunoglobulin G (IgG), and tubular markers such as alpha-1-microglobulin and retinol binding protein, to generate a detailed quantitative and qualitative proteinuria assessment. While FLC are not specifically assessed in UPP, abnormal urine FLC excretion may be suspected, and should be confirmed by urine electrophoresis and/or urine immunofixation (4). The software "MDI Lablink", developed by Regeniter et al., allows a classification of proteinuria integrating these marker proteins (1 - 4). In this mini-review we illustrate the advantages of using the UPP and the software.

(1) Technical considerations and interpretations

UPP is performed on a minimal volume (0.5 ml) of unconcentrated urine sample, ideally resulting from the second morning urine. The proteins are measured by immunonephelometry, a specific and analytically very sensitive method that can measure proteins reliably down to 0.3 mg/l. The result is usually available on the day of collection. Urine marker evaluation by UPP is a two-step process: (1) Step 1 : measurement of total protein, urine creatinine, and two protein markers testing either glomerular (albumin) or tubular (alpha-1-microglobulin) dysfunction, respectively, and the urinary dipstick which estimates erythrocyte, white blood cell and nitrite count (2) Step 2 : only performed if albumin to creatinine ratio (ACR) and/or alpha-1-microglobulin to creatinine ratio (A1MCR) are higher than the upper normal limit, respectively > 3 mg/mmol and 2.26 mg/mmol (9 – 10): additional urine protein makers are evaluated to classify abnormal proteinuria. Transferrin confirms the glomerular alteration and IgG is indicative of severe damage of the glomerular filtration barrier. Tubulo-interstitial alterations, suspected by an increase of A1MCR, are further evaluated by retinol binding protein, which is particularly elevated in cases of severe proximal tubular cell dysfunction and when tubulo-interstitial fibrosis is present. UPP results are presented graphically (Fig. 1- Fig.5) with a diagnosis commentary generated by the MDI Lablink software, and an additional graph that show historical results when available.

(2) UPP in the clinical practice

UPP is indicated if a total proteinuria/creatinine ratio over 30 mg/mmol is detected, and/or for the evaluation of patients with a glomerular filtration rate (GFR) decrease below 60 ml/min/1.73m^2 or if the patients are exposed to a specific renal risk, including nephrotoxic or extrarenal conditions such as infection, systemic diseases.

We propose to illustrate the diagnostic and prognostic usefulness of UPP in different common clinical situations

UPP in glomerular diseases

While glomerular diseases are typically characterized by proteinuria composed by more than 60% of albuminuria, additional evaluation of urine IgG and protein tubular makers may be informative for the non-invasive evaluation of glomerular alterations and associated tubulo-interstitial lesions.

Cases 1, 2 and 3 illustrate how UPP anticipate distinct histopathological glomerular defects and associated tubulo-interstitial lesions in patients presenting with oedema and nephrotic syndrome. In addition, UPP provides an important diagnostic and prognosis orientation in patients with nephrotic syndrome and eGFR decrease, to distinguish functional pre renal azotemia to progression of glomerular and tubular lesions.

Case 1 (Fig. 1): A 21-year old woman presented with an idiopathic nephrotic syndrome related to histologically-characterized minimal change disease (MCD) with normal GFR. Protein-creatinine ratio (PCR) at diagnosis was 446 mg/mmol, with ACR and transferrin creatinine ratio at 310 and 27 mg/mmol respectively, while IgG was normal, indicative of glomerular proteinuria of high selectivity. Alpha-1-microglobulin and retinol binding protein were around or below the normal limit. Two weeks after steroids administration, a complete remission was observed with both PCR, ACR below the normal limit at 1 and < 1.6 mg/mmol. In most of the MCD relapse, urine protein profile show selective proteinuria. However, the use of UPP anticipates distinct histopathological glomerular

defects and associated tubulo-interstitial lesions in patients presenting with oedema and nephrotic syndrome in the follow-up. Thus, such a UPP (Fig. 1) during MCD relapse, similar to the UPP at diagnosis may allow avoiding the realization of kidney biopsy since it permits distinguishing a "simple" MCD relapse compared to a progression of glomerular and/or tubular lesions in this context.

In most of the MCD relapse, urine protein profile show selective proteinuria. However, the use of UPP anticipates distinct histopathological glomerular defects and associated tubulo-interstitial lesions in patients presenting with oedema and nephrotic syndrome in the follow-up. In this case, the same UPP during MCD relapse may avoid the need for kidney biopsy by allowing distinguishing between a "simple" MCD relapse and a progression of glomerular and/or and additional tubular lesions before a symptomatology of nephrotic syndrome

Case 2 (Fig. 2): A 23-year old man presented with acute edema and acute kidney injury with GFR decrease. A nephrotic syndrome was detected with protein-creatinine ratio (PCR) of 849 mg/mmol, and non-selective glomerular proteinuria with ACR of 542 mg/mmol, transferrin - creatinine ratio of 57 mg/mmol and an increase of IgG-creatinine ratio of 54 mg/mmol. In addition, alpha-1-microglobulin and retinol binding protein were dramatically increased (Fig. 2). Renal biopsy showed focal and segmental glomerulosclerosis responsible for the massive non selective glomerular proteinuria, but also severe lesions of acute tubular injury that were suspected by the presence of increased urine tubular markers.

Case 3: A 64-year old man was referred for nephrotic syndrome with preserved GFR of 70 ml/min/1.73m^2. UPP at diagnosis showing a non-selective glomerular proteinuria and a renal biopsy established the diagnosis of primary membranous glomerulopathy without tubular alteration or interstitial fibrosis. At 12 months, whereas the PCR was unchanged, UPP profile was modified with an increased urine IgG suggesting a progression of the glomerular disease (GFR= 25 ml/min/1.73m^2), as well as a huge increase of both tubular makers alpha-1-microglobulin and retinol binding protein (4).

A second kidney biopsy indeed demonstrated a progression of the glomerular lesions and the development of chronic tubulointerstitial changes related to the uncontrolled glomerular disease, as suspected by UPP. This highlights the importance of specific tubular and glomerular protein assays since the monitoring of such nephropathy on only protein and albumin assays is not sufficiently informative.

UPP in renal tubulo-interstitial diseases

Non-invasive detection of tubular and/or interstitial renal lesions may be very challenging. Indeed, urine dipstick only detects albumin and UPEP provides little information on low molecular weight proteins. It is important to notice that tubulopathies generally present with low grade proteinuria with PCR below 0.1 g/mmol. The reference range of tubular proteins is very low (retinol binding protein < 0.75 mg/g creatinine (0.08 mmol/l), alpha-1-microglobulin <14 mg/g creatinine (1.58 mmol/l)) and the chemical measurement method of total protein does not detect these proteins adequately. Tubulopathies can be observed with PCR at 0.2 to 0.3 g/mmol. In addition, follow-up evaluation after specific therapeutic intervention must be adequately assessed by specific longitudinal quantitative evaluation of tubular markers.

Case 4 (Fig. 3): This is the case of a patient hospitalized for severe impairment of GFR in the context of systemic sarcoidosis. Total proteinuria was below the limit of detection of the assay method. However the use of UPP in this context showed an increase of the alpha-1-microglobulin with a normal ACR. The realization of the complete UPP thus showed tubulointerstitial proteinuria with normal proteinuria and albuminuria (FIG. 3). Renal biopsy showed severe granulomatous interstitial nephritis. This example focuses on the extended ability of UPP to detect early renal abnormalities when tubular marker proteins are measured. The only alternative for detecting these disorders is invasive renal biopsy. Indeed, acute estimated GFR decrease in sarcoidosis may be related to acute kidney injury induced by acute interstitial nephritis (AIN), or to pre-renal azotemia related to hypercalcemia or both. Diagnostic and therapeutic interventions are quite distinct with kidney

biopsy only required in suspected interstitial inflammation. Tis case illustrates that detection of abnormal increase of retinol binding protein in addition to alpha-1-microglobulin strongly suggests AIN, a diagnosis that may be mistaken by urine PCR within the normal range.

Case 5: A HIV-infected patient, receiving Tenofovir, was referred for severe acute kidney injury with GFR of 10 ml/min/1.73m^2 and PCR= 86 mg/mmol. UPP showed 15 and 22 x fold increase of alpha-1-microglobulin and retinol binding protein, respectively, while ACR was 11 mg/mmol. Tubular proximal toxicity of Tenofovir was suspected and confirmed after the rapid decrease and complete normalization of the both tubular marker, 2 months after drug discontinuation.

UPP in renal complications of monoclonal gammopathy

A wide range of glomerular and tubulo-interstitial alterations may be observed during monoclonal gammopathy, mostly related to the nephrotoxicity of the monoclonal FLC or heavy chain. Myeloma cast nephropathy is the most frequent renal complication in multiple myeloma, related to intratubular precipitation of monoclonal FLC present in large excess in urines, and early diagnosis and therapeutic intervention are required to avoid non-reversible end stage renal disease. When the sum of specific marker proteins is very low compared to the total protein, the sample should be checked for free urinary light chains (Bence Jones protein).

Case 6: A 73- year old woman was referred for acute kidney injury (GFR=28 ml/min) associated with severe anemia. UPP the day of admission showed PCR at 492 mg/mmol with ACR of 11 mg/mmol, an increase of tubular makers with A1MCR = 14.6 mmol/l and RBPCR = 1.09 mg/mmol (Fig. 4); urine excess of monoclonal FLC was suspected regarding the discrepancy between PCR and albuminuria, confirmed by urine immunofixation and the diagnosis of multiple myeloma was established. Chemotherapy combining dexamethasone, cyclophosphamide and bortezomib was promptly initiated two days after admission, leading to a dramatic decrease of PCR, tubular marker normalization within 4 weeks (Fig. 5) and huge GFR improvement.

In conclusion

UPP presents several advantages. First of all, one of the major advantages is that it integrates tubular biomarkers in its analysis, which are tools that were lacking until their development in clinical practice. Second, the use of several different urinary biomarkers is useful in glomerular disease to evaluate severity of glomerular barrier damage at diagnosis and follow-up; Third, UPP allows us a precise quantification of tubular proteinuria as compared to UPE that only allows a semi quantitative evaluation. Moreover, UPP with complete evaluation available in 2 hours if necessary is less time consuming than UPE in addition to bêta-2-microglobulin, total proteinuria and albuminuria measurements, which is a major consideration in cases of acute kidney injury that usually required rapid etiologic orientation. In addition, the determination of specific urinary proteins measured on a nephelometer makes it easy to integrate this activity into that of a conventional biochemistry laboratory. This makes it possible to avoid the systematic use of electrophoresis of urinary proteins, which requires an additional technical station dedicated to its implementation, for a simple typing of proteinuria outside the suspicion of monoclonal pathology. Thus, UPP represents a non-invasive and suitable diagnostic tool for the diagnostic and prognosis approach of the renal diseases.

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Table I: Proteinuria evaluation tools in clinical practice

	Quantitative	Qualitative		
		Glomerular	Tubulointerstitial	Monoclonal light chain
Dipstick	+/-	+/-		
Total Proteinuria	++			
Albuminuria	++	++		
Urinary protein electrophoresis	+/-	+/-	+/-	++
Urine protein profile	++	++	++	+/-

Figure 1: 21-year old woman presented with a relapse of idiopathic nephrotic syndrome related to histologically-characterized minimal change disease with normal GFR. Results expressed as mg/mmol of creatinine as a graph allowing to appreciate urinary proteins increase compared to usual values.

Figure 2: 23-year old man with nephrotic syndrome presented by acute edema and acute kidney injury with GFR decrease. Results expressed as mg/mmol of creatinine as a graph allowing to appreciate urinary proteins increase compared to usual values.

Figure 3: Patient hospitalized for severe impairment of GFR in the context of systemic sarcoidosis. Results expressed as mg/mmol of creatinine as a graph allowing to appreciate urinary proteins increase compared to usual values.

Figure 4: 73- year old woman with multiple myeloma referred for acute kidney injury (GFR=28 ml/min) associated with severe anemia. Results expressed as mg/mmol of creatinine as a graph allowing to appreciate urinary proteins increase compared to usual values.

Figure 5: 73- year old woman with multiple myeloma after treatment combining dexamethasone, cyclophosphamide and bortezomib within 4 weeks. Results expressed as mg/mmol of creatinine as a graph allowing to appreciate urinary proteins increase compared to usual values.

Patient	**X1, x**
Birth date/Sex/Age	**01/01/1998, W, 21**
Patient ID	
Printed at	21.01.2019 / 11:16
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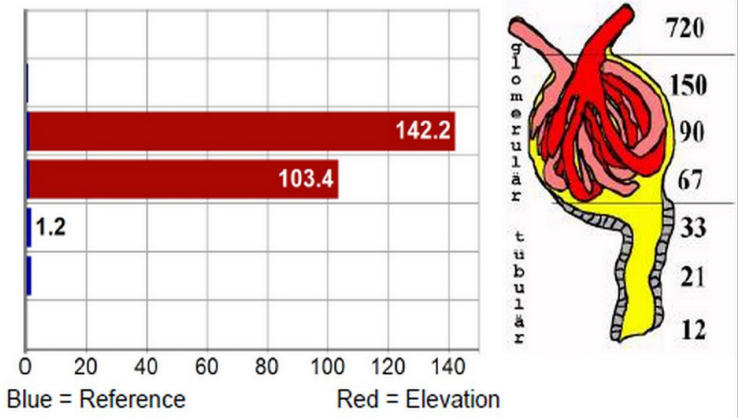
Sample date	21.01.2019 / 11:12	BMI	-- kg / -- cm / --
Sample reception date	21.01.2019 / 11:12		
Sample ID			

Parameters	Value	Classe	Norm
A-2-microglob.	n.d.	p.f.	< 0.23 mg/mmol crea
Immunoglob. G	0.56	norm	< 1.13 mg/mmol crea
Transferrin	27.34	+++++	< 0.19 mg/mmol crea
Albumin	310.44	+++++	< 3.00 mg/mmol crea
A-1-microglob.	2.75	+	< 2.26 mg/mmol crea
Retinolb. protein	<0.05	<sen	< 0.08 mg/mmol crea
ß-2-microglob.	n.d.	p.f.	< 0.11 mg/mmol crea
Total protein	**446.43**	>>>>>	**< 11.31 mg/mmol crea**
Creatinine	7.28	norm	5.7-34 mmol/l

Diagramme: Multiple of upper reference range



Dipstick

Ery	+	Leu	neg	Nitrite	neg

Marker proteins

Sum of marker proteins (mg/mmol crea):	341 (76%)
Rel. elevation of glom. proteins:	93.5 times
Rel. elevation of tub. markers (A1M, RBP):	1.4 times
Ratio of Glom ./Tub. markers:	68.3 times

Patient	Y1, y
Birth date/Sex/Age	01/01/1996, M, 23
Patient ID	
Printed at	21.01.2019 / 12:04
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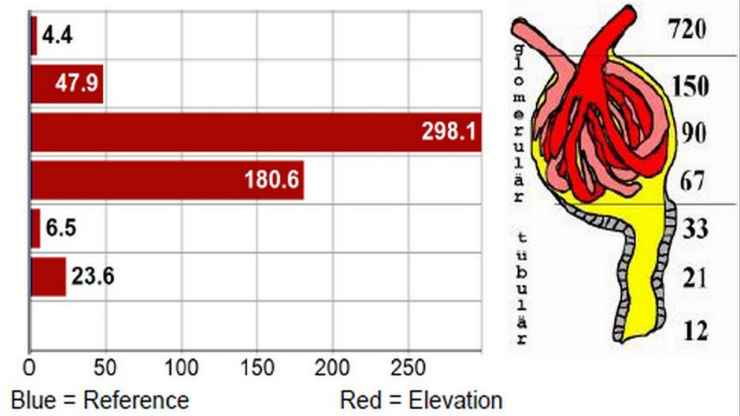
Sample date	01.01.2019 / 00:00	BMI	-- kg / -- cm / --
Sample reception date	21.01.2019 / 12:03		
Sample ID			

Parameters	Value	Classe	Norm
A-2-microglob.	1.00	+	< 0.23 mg/mmol crea
Immunoglob. G	54.22	++++	< 1.13 mg/mmol crea
Transferrin	57.33	+++++	< 0.19 mg/mmol crea
Albumin	542.22	>>>>>	< 3.00 mg/mmol crea
A-1-microglob.	14.67	+++	< 2.26 mg/mmol crea
Retinolb. protein	2.00	++	< 0.08 mg/mmol crea
ß-2-microglob.	n.d.	p.f.	< 0.11 mg/mmol crea
Total protein	**848.89**	>>>>>	**< 11.31 mg/mmol crea**
Creatinine	2.25	-	5.7-34 mmol/l

Diagramme: Multiple of upper reference range



Dipstick

Ery	2+	Leu	neg	Nitrite	neg

Marker proteins

Sum of marker proteins (mg/mmol crea):	668 (79%)
Rel. elevation of glom. proteins:	195.2 times
Rel. elevation of tub. markers (A1M, RBP):	13.5 times
Ratio of Glom ./Tub. markers:	14.5 times

Patient	Y2, y
Birth date/Sex/Age	01/01/1957, M, 62
Patient ID	
Printed at	21.01.2019 / 18:40
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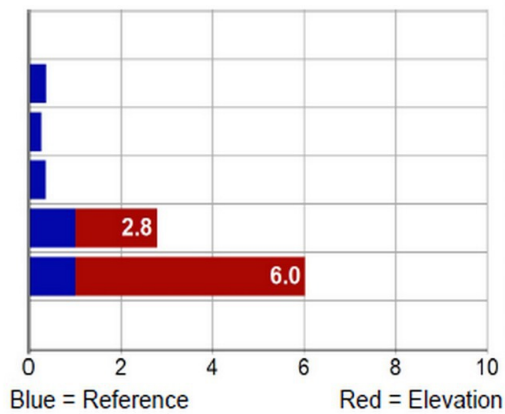
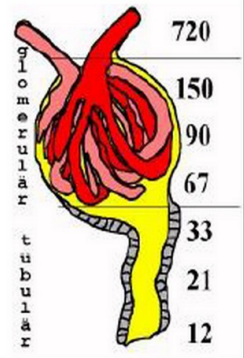
Sample date	01.01.2019 / 00:00
Sample reception date	01.01.2019 / 00:00
Sample ID	
BMI	-- kg / -- cm / --

Parameters	Value	Classe	Norm
A-2-microglob.	n.d.	p.f.	< 0.23 mg/mmol crea
Immunoglob. G	0.40	norm	< 1.13 mg/mmol crea
Transferrin	<0.11	<sen	< 0.19 mg/mmol crea
Albumin	1.04	norm	< 3.00 mg/mmol crea
A-1-microglob.	6.28	++	< 2.26 mg/mmol crea
Retinolb. protein	0.51	+	< 0.08 mg/mmol crea
ß-2-microglob.	n.d.	p.f.	< 0.11 mg/mmol crea
Total protein	**<4.52**	**<sen**	**< 11.31 mg/mmol crea**
Creatinine	7.49	norm	5.7-34 mmol/l

Diagramme: Multiple of upper reference range





Dipstick

Ery	neg	Leu	neg	Nitrite	neg

Marker proteins

Sum of marker proteins (mg/mmol crea):	8 (- %)
Rel. elevation of glom. proteins:	1.0 times
Rel. elevation of tub. markers (A1M, RBP):	4.2 times
Ratio of Glom ./Tub. markers:	0.2 times

Patient	**X2, x**
Birth date/Sex/Age	**01/01/1946, W, 73**
Patient ID	
Printed at	21.01.2019 / 18:45
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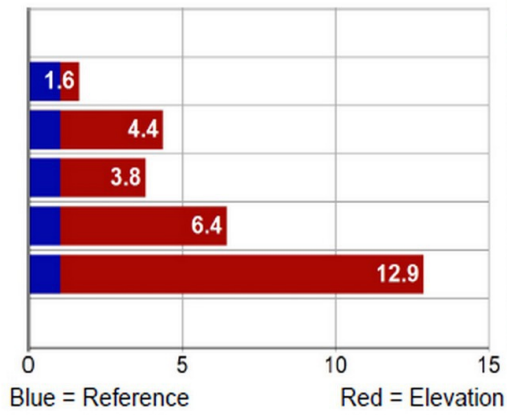
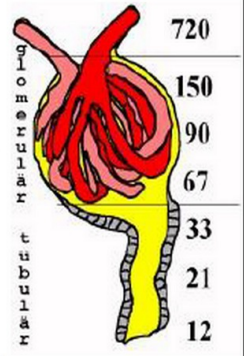
Sample date	31.12.2018 / 00:00
Sample reception date	31.12.2018 / 00:00
Sample ID	
BMI	-- kg / -- cm / --

Parameters	**Value**	**Classe**	**Norm**
A-2-microglob.	n.d.	p.f.	< 0.23 mg/mmol crea
Immunoglob. G	1.83	+	< 1.13 mg/mmol crea
Transferrin	0.84	+	< 0.19 mg/mmol crea
Albumin	11.39	++	< 3.00 mg/mmol crea
A-1-microglob.	14.56	+++	< 2.26 mg/mmol crea
Retinolb. protein	1.09	+	< 0.08 mg/mmol crea
ß-2-microglob.	n.d.	p.f.	< 0.11 mg/mmol crea
Total protein	**491.91**	>>>>>	**< 11.31 mg/mmol crea**
Creatinine	3.09	(-)	5.7-34 mmol/l

Diagramme: Multiple of upper reference range





Dipstick

Ery	+	Leu	neg	Nitrite	neg

Marker proteins

Sum of marker proteins (mg/mmol crea):	29 (6%)
Rel. elevation of glom. proteins:	3.7 times
Rel. elevation of tub. markers (A1M, RBP):	9.4 times
Ratio of Glom./Tub. markers:	0.4 times

Patient	**X2, x**
Birth date/Sex/Age	**01/01/1946, W, 73**
Patient ID	
Printed at	21.01.2019 / 18:50
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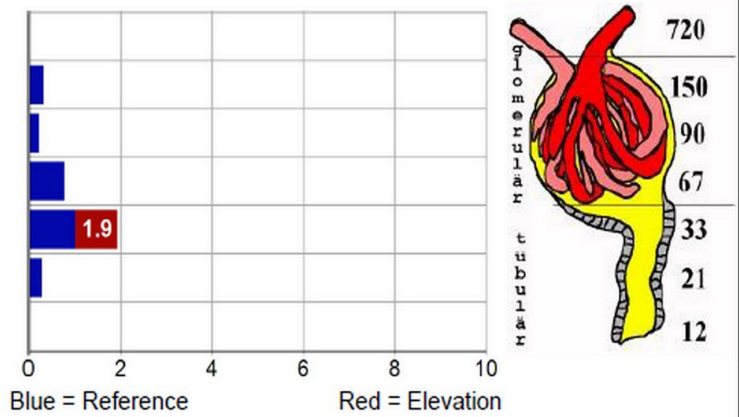
Sample date	01.01.2019 / 00:00
Sample reception date	01.01.2019 / 00:00
Sample ID	
BMI	-- kg / -- cm / --

Parameters	**Value**	**Classe**	**Norm**
A-2-microglob.	n.d.	p.f.	< 0.23 mg/mmol crea
Immunoglob. G	0.35	norm	< 1.13 mg/mmol crea
Transferrin	<0.11	<sen	< 0.19 mg/mmol crea
Albumin	2.27	norm	< 3.00 mg/mmol crea
A-1-microglob.	4.35	+	< 2.26 mg/mmol crea
Retinolb. protein	<0.05	<sen	< 0.08 mg/mmol crea
ß-2-microglob.	n.d.	p.f.	< 0.11 mg/mmol crea
Total protein	**31.22**	**+**	**< 11.31 mg/mmol crea**
Creatinine	12.17	norm	5.7-34 mmol/l

Diagramme: Multiple of upper reference range



Dipstick

Ery	neg	Leu	neg	Nitrite	neg

Marker proteins

Sum of marker proteins (mg/mmol crea):	7 (23%)
Rel. elevation of glom. proteins:	1.0 times
Rel. elevation of tub. markers (A1M, RBP):	1.9 times
Ratio of Glom./Tub. markers:	0.5 times