Urinary Proteins and Enzymes as Early Indicators of Renal Dysfunction in Chronic Exposure to Cadmium

Klaus Jung,¹ Mouka Pergande,¹ Hans-Joachim Graubaum,² Läder M. Fels,³ Ulrich Endl,³ and Hilmar Stolte³

We tested the diagnostic sensitivity of various urinary analytes for detecting cadmium-induced nephropathy at an early stage. We investigated 73 healthy persons (control group 1) and individuals exposed to cadmium, either environmentally (n = 36, risk group 2) or occupationally (n = 62, exposed group 3). All data were related to limits of the central 95% reference intervals of the control group. The serum creatinine and ribonuclease values, indicators of the glomerular filtration rate, were not different in the three groups. In the exposed persons (group 3), proximal tubular indicators (low-Mₐ proteins lysozyme, ribonuclease, retinol-binding protein, and α₁-microglobulin) were more often increased than the glomerular indices (higher-Mₐ proteins transferrin, IgG, and albumin). Both the low-Mₐ proteins and tubular enzymes were differently altered in their excretion rates. Alanine aminopeptidase, alkaline phosphatase, and N-acetyl-β-D-glucosaminidase increased even in the risk group 2. α₁-Microglobulin was increased in the exposed persons whose cadmium excretion was <5 μmol/mol creatinine. The combined determination of α₁-microglobulin and N-acetyl-β-D-glucosaminidase exceeded the corresponding upper reference limits in 30% of group 2 and 39% of group 3. We recommend screening for these two analytes to detect cadmium-induced renal dysfunction at an early stage.

The kidney is a critical target organ for induced toxicity from exposure to heavy metals (1). Cadmium has a special importance because long-term occupational or environmental exposure to cadmium often results in renal dysfunction (2–5). Nonferrous smelter workers and workers in the pigment industry and in battery plants are at considerable risk (6). Furthermore, contamination of the environment by cadmium is increasing because of industrial activities, emission from the combustion of fossil fuels and of cadmium-containing wastes, and the growing use of phosphate fertilizers containing trace amounts of cadmium—all of which represents a general risk for the population (7, 8).

Numerous population groups exposed to cadmium have been studied to find reliable biological indicators for detecting the nephrotoxic effect of cadmium (9–16). However, these studies have often not considered the comparative diagnostic potential of the different markers of tubular and (or) glomerular affections. Thus, we measured and compared the brush-border enzymes alanine aminopeptidase, alkaline phosphatase, and γ-glutamyltransferase; the lysosomal enzyme N-acetyl-β-D-glucosaminidase; the low-Mₐ proteins lysozyme, ribonuclease, retinol-binding protein, and α₁-microglobulin as indices of proximal tubular function; the enzyme kallikrein as index of distal tubular function; and the higher-Mₐ proteins transferrin, IgG, and (in part) albumin as indices of a changed glomerular permselectivity.

The aim of this comparative study of various analytes in serum and urine has been to identify the most suitable markers that might be indicative of an early renal dysfunction induced by cadmium exposure. The corresponding analytes could have potential value as indicators of renal function before the kidney is irreversibly injured and, thus, could be suitable as monitoring tools for at-risk persons exposed to cadmium.

Subjects and Methods

Study Subjects

We investigated three groups of subjects with various degrees of exposure to cadmium (Table 1): a control group (group 1) consisting of 73 healthy persons without a known cadmium exposure and living in different areas from the people of the other two groups, a group of 36 persons without occupational exposure to cadmium but working in a plant located ~1.5 km from a battery factory (cadmium-risk group; group 2), and a group of 62 workers exposed to cadmium in the battery factory (cadmium-exposed group; group 3).

The classification of the subjects into these groups was based on the information obtained in a detailed interview related to medical and occupational history and a clinical examination. Control subjects and persons of the risk group had never been occupationally exposed to Cd or other heavy metals. The exposed workers had...
been continually exposed to Cd at the time of examination for at least 1 year. The exposure to cadmium was characterized in terms of the duration of the occupational exposure to the metal, the blood concentration, and urinary excretion of cadmium. Subjects who showed in their clinical examination and medical history nephrological and urological disorders, diabetes mellitus, hypertension, liver and pancreatic disorders, infections in the last 4 weeks, or intake of drugs known to affect renal function were excluded from the respective groups.

Urine and Blood Sampling

Blood samples and urine specimens were collected at the time of examination, generally between 0700 and 1000 h. Informed consent according to the Helsinki Declaration was obtained from all subjects. Blood for cadmium analysis was drawn into Monovettes (Sarstedt KG, Nümbrecht, Germany) containing Na2EDTA and stored at 4 °C; plasma samples obtained after centrifugation (3000 × g, 10 min) were stored at −20 °C. Urine was collected in cadmium-free polyethylene containers (Sarstedt KG). For analyses for retinol-binding protein, IgG, and transferrin, we mixed a urine aliquot of 4 mL with 0.4 mL of a stabilization solution (1 mol/L phosphate buffer, pH 7.6, containing 30 mmol/L NaNO3) and stored it at −20 °C. Another centrifuged urine aliquot was stored at −20 °C for the analyses for total protein, ribonuclease, and lysozyme. Urine specimens for albumin and α1-microglobulin determination were stored without preservative at 4 °C for ≤3 days before analysis. Samples for assays of urine enzyme activities were prepared by gel filtration (17).

Laboratory Analyses

Blood and urine cadmium concentrations were measured by electrothermal graphite-furnace atomic absorption spectrometry (18) with a Model 372 Perkin-Elmer atomic absorption spectrophotometer, equipped with a deuterium background compensator and a HGA 400 atomizer unit (Perkin-Elmer Bodenseewerk, Überlingen, Germany). Creatinine in serum and urine was measured by a kinetic method with use of alkaline picrate (19).

Urine and serum protein constituents were determined as follows: total protein was quantified with a commercial kit based on Coomassie Brilliant Blue (Sigma Co., St. Louis, MO) with human serum albumin (Behring AG, Marburg, Germany) as the calibration material; albumin and α1-microglobulin by single radial immunodiffusion techniques (Behring AG); lysozyme by enzyme immunoassays (20); ribonuclease in serum and urine with poly(C) as substrate (21); transferrin (22), IgG (23), and retinol-binding protein (24) by latex immunoassays.

Enzyme activities, measured at 37 °C and calculated in enzyme units (1 U = 1 μmol of substrate turnover per minute), were related to urinary creatinine (see Calculations) to characterize the enzyme excretion rates. The volume ratio of gel-filtered sample to final reaction volume was 1:11 for alanine aminopeptidase, alkaline phosphatase, and γ-glutamyltransferase activity measurements and 1.3 for N-acetyl-β-D-glucosaminidase activity determination. In the methods used (17, 25), the final concentrations were, per liter: 2 mmol of alanine-4-nitroanilide and 50 mmol of Tris·HCl, pH 7.80, for alanine aminopeptidase; 10 mmol of 4-nitrophenyl phosphate, 0.5 mmol of MgCl2, and 1 mol of diethanolamine, pH 9.80, for alkaline phosphatase; 4 mmol of γ-glutamyl-4-nitroanilide, 101 mmol of glycylglycine, pH 8.20, and 101 mmol of NaCl for γ-glutamyltransferase; and 2 mmol of 4-nitrophenyl-N-acetyl-β-D-glucosaminidase and 100 mmol of citrate, pH 4.40, for N-acetyl-β-D-glucosaminidase. Kallikrein was measured with b-valyl-L-leucyl-L-arginine-4-nitroanilide as substrate (26).

Calculations

Excretions of urinary analytes were related to urinary creatinine to compensate for the influence of urine flow rate on excretion rates (27). Data were given as the ratio of the respective concentration of analyte to creatinine concentration in urine.

For statistical calculations we used nonparametric methods of the statistical package Statgraphics, version 5.01 (Statistical Graphics Corp., Rockville, MD). Differ-

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**Table 1. Characteristics of the Groups Studied**

<table>
<thead>
<tr>
<th>Strength</th>
<th>Group 1, controls</th>
<th>Group 2, risk group</th>
<th>Group 3, exposed group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. and sex</td>
<td>29 F; 44 M</td>
<td>14 F; 22 M</td>
<td>39 F; 23 M</td>
</tr>
<tr>
<td>Age, years</td>
<td>32 (22–77)*</td>
<td>39 (23–62)*</td>
<td>37 (23–74)*</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>80 (50–100)</td>
<td>85 (70–100)</td>
<td>80 (70–100)</td>
</tr>
<tr>
<td>Diahostic</td>
<td>125 (95–160)</td>
<td>135 (110–160)</td>
<td>120 (105–160)</td>
</tr>
<tr>
<td>Duration of exposure, years</td>
<td>15* (1–37)</td>
<td>15* (1–37)</td>
<td>15* (1–37)</td>
</tr>
<tr>
<td>Urine cadmium, μmol/mol creatinine</td>
<td>0.86 (0.21–5.17)</td>
<td>5.43* (1.03–30.8)</td>
<td>9.79* (1.10–108)</td>
</tr>
<tr>
<td>Blood cadmium, nmol/L</td>
<td>8.89 (3.56–17.8)</td>
<td>75.6* (17.8–142)</td>
<td>107* (8.89–472)</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>80 (59–97)</td>
<td>82 (64–97)</td>
<td>82 (62–138)</td>
</tr>
<tr>
<td>Serum ribonuclease, kU/L</td>
<td>20.5 (11.3–24.5)</td>
<td>19.6 (12.5–35.5)</td>
<td>18.5 (8.0–34.8)</td>
</tr>
</tbody>
</table>

* Median (and range).  
* For this group, duration of residence time in the area.  
* Significantly higher than controls by at least P < 0.01 (Mann–Whitney U-test).
ences between groups were tested with the Mann-Whitney U-test after transformation of data, as explained in Results. Associations between variables were assessed with Spearman's rank correlation coefficient. The central 95% reference intervals for the analytes in the control group were calculated according to the recommendations of the International Federation of Clinical Chemistry for nonparametric procedures (29), taking into account sex-related differences if necessary. P < 0.05 was considered statistically significant.

Results

Characteristics of the Groups

Table 1 lists characteristics of the groups investigated in this study. Blood concentration and urine excretion of cadmium in groups 2 and 3 were clearly higher than in the control subjects.

In the control group, 23 persons were smokers and 49 were nonsmokers. Group 2 included 13 smokers and 21 nonsmokers (and 2 persons without information), and group 3 consisted of 28 smokers and 31 nonsmokers (and 3 persons without information). The blood concentration and urine excretion of cadmium did not statistically differ between smokers and nonsmokers within the corresponding group studied.

Glomerular Filtration Rate

The serum creatinine concentrations and serum ribonuclease values, indicators of the glomerular filtration rate (29) and global kidney function, were not different in the three groups (Table 1). There was no significant correlation of these serum analytes to the duration of exposure, the blood concentration, or the excretion of cadmium.

Relationship between Excretion of Proteins and Enzymes and Exposure to Cadmium

Figure 1 shows the relationships between the three exposure criteria (blood concentration of cadmium, urine excretion of cadmium, and exposure duration) in the exposed group (group 3). The cadmium excretion was significantly correlated to exposure time and blood cadmium concentration, whereas blood cadmium concentration was not correlated to the exposure time.

Table 2 lists the relationships of these exposure criteria to the excretions of the various urinary analytes. There were numerous significant correlations between the exposure characteristics and the excretion rates of proteins and enzymes.

Reference Limits for Excretion Data

To compare the excretion data of the three groups, one must consider that the reference values for the urine analytes investigated are partly dependent on age and sex (30, 31). In this study, the age of the control group was slightly lower than that of group 2 but was not different from group 3; however, the number of men and women differed among the groups. Many of the urine analytes in the control group were significantly dependent on sex (U-test according to Mann-Whitney; P < 0.05). When these differences were statistically significant, we calculated separate upper limits of the central 95% reference intervals for women and men according to the nonparametric procedure (28). The reference limits used in this study are summarized in Table 3.

For further statistical calculation and comparisons between groups, we related all data of the individuals in the groups to these limits by calculating the ratios of the
original values to the respective reference limits. Although the number of women and men differed in the respective groups, the use of these transformed data allowed the inclusion of all persons of the respective groups for testing differences of excretion patterns between the groups. We applied this evaluation protocol instead of the method of matching groups according to sex, because a further necessary classification with regard to the duration of exposure and to cadmium excretion again resulted in subdivided groups not uniformly constituted by sex. In the following results, the statistical significances indicated in Figures 2-4 between the groups were calculated by means of these transformed data. However, to get a better idea of actual excretion rates, we present in the figures the medians and the upper and lower quartiles of the original data.

Excretion Rates in Each Group

The behavior of the three types of analytes investigated, the high-\(M_r\) proteins, low-\(M_r\) proteins, and enzymes, is presented in Figures 2-4. In these Figures, the group of occupationally exposed persons (group 3) was additionally subdivided into two groups according to the exposure duration (21 persons with <5 years of exposure and 41 persons with >5 years of exposure) and the amount of cadmium excretion (15 persons with cadmium excretion <5 \(\mu\text{mol/mol creatinine}\) and 47 persons with >5 \(\mu\text{mol/mol creatinine}\)). Groups 2 and 3 and the subgroups of group 3 were compared with the control group. In addition, we reclassified the subjects of groups 2 and 3 by means of their excretion rates of proteins and enzymes in relation to the limits of the control group (Table 4). Thus, we could compare percentages of abnormal values of different analytes within and between groups 2 and 3. This approach allowed a better assessment of diagnostic validity of the different markers. In general, these data support the results demonstrated in the Figures. The following findings were evident from the data in Figures 2-4 and Table 4:

- In the first cluster of total protein and the high-\(M_r\) proteins (Figure 2, Table 4), the excretion rates of total protein and albumin were increased only in the group of occupationally exposed workers. In comparison with the control group, the risk group excreted less albumin.

- The proximal tubular markers (low-\(M_r\) proteins, enzymes) were more often increased than were the glomerular indicators (IgG, transferrin, albumin) (Figures 2-4, Table 4).

- Both the low-\(M_r\) proteins and the proximal tubular enzymes as tubular function indicators were differently altered in their excretion rates. For example, whereas lysozyme (Figure 3B) and \(\gamma\)-glutamyltransferase (Figure 4D) did not increase in either the risk group or the exposed group, the two brush-border enzymes alanine aminopeptidase (Figure 4B) and alkaline phosphatase (Figure 4C) as well as the lysosomal enzyme \(N\)-acetyl-\(\beta\)-D-glucosaminidase (Figure 4A) and retinol-binding protein were increased even in the risk group.

- The distal tubular indicator kalikrein was not changed in groups 2 and 3 in comparison with the control group; in the subgroup of subjects exposed >5 years, however, a distinct decrease was observed (Figure 4E).

- In the subgroup of subjects exposed to cadmium <5 years, excretion rates of all analytes studied were not different from those of the control group (Figures 2-4). Except for albumin and \(\alpha_1\)-microglobulin, a similar behavior was observed in exposed subjects with cadmium excretions of <5 \(\mu\text{mol/mol creatinine}\).

- Both \(\alpha_1\)-microglobulin and \(N\)-acetyl-\(\beta\)-D-glu-
Fig. 2. Total protein (A), albumin (B), transferrin (C), and IgG (D) in urine of the groups investigated
C, control group; R, risk group; E, exposed group. The exposed group was subdivided with regard to the exposure time (21 persons exposed <5 years; 41 persons >5 years) and to the cadmium excretion (15 persons <5 µmol/mol creatinine; 47 persons >5 µmol/mol creatinine). The columns represent the medians, the bars the upper and lower quartiles. Significantly higher or lower than controls (by Mann-Whitney U-test): * P <0.05; ** P <0.01; *** P <0.001.

Fig. 3. Low-M, proteins in urine of the groups investigated
Symbols and other explanations as in Fig. 2.
N-Acetylglucosaminidase (U/mmol crea)  

Alkaline phosphatase (U/mmol crea)  

Gamma-Glutamyltransferase (U/mmol crea)  

Kallikrein (U/mol crea)  

Fig. 4. Excretion of urinary enzymes in the groups investigated  
Symbols and other explanations as in Fig. 2  

Discussion  
Cadmium blood concentration is suggested as a useful indicator of the recent cadmium exposure, whereas urinary cadmium reflects the cadmium body burden and the concentration in the kidney (6). There are great variations in the published data on cadmium reference ranges, because biological factors as age, sex, smoking habits, diurnal and infradian rhythms; preanalytical problems such as the collection and preparation of samples; and analytical reasons such as the selected analytical technique may essentially influence the results (6, 32). In nonsmokers without occupational exposure to cadmium, the blood content of cadmium is generally <10 nmol/L and the urine cadmium is <2 µmol/mol creatinine (6, 9). The cadmium values in blood and urine are usually higher in smokers than in nonsmokers (6). In recent studies in healthy nonexposed subjects, the upper 95th percentile value for blood concentrations was 24 nmol/L and for urinary excretion of cadmium was 2–4 µmol/mol creatinine (9, 13, 32–35). The mean cadmium values measured in our controls (Table 1) were below these limits; however, we did not find differences between smokers and nonsmokers. Subjects of groups 2 and 3 showed an unequivocal exposure to cadmium. When we first decided to perform this study, we planned to investigate in addition to our target group of occupationally cadmium-exposed per-
Table 4. Percentages of Urinary Proteins and Enzymes in Cadmium-Exposed Groups Exceeding the Limits of the 95% Central Reference Intervals of the Controls

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Group 2 (Risk group)</th>
<th>Group 3 (Exposed group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>6</td>
<td>15b, c</td>
</tr>
<tr>
<td>Albumin</td>
<td>6</td>
<td>11b</td>
</tr>
<tr>
<td>IgG</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Transferrin</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>β1-Microglobulin</td>
<td>22b</td>
<td>32b</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>6</td>
<td>11b</td>
</tr>
<tr>
<td>Retinol-binding protein</td>
<td>11b, c</td>
<td>23b, c</td>
</tr>
<tr>
<td>Ribonuclease</td>
<td>11b, c</td>
<td>20b</td>
</tr>
<tr>
<td>N-Acetyl-β-D-glucosaminidase</td>
<td>20b</td>
<td>18b</td>
</tr>
<tr>
<td>Alanine aminopeptidase</td>
<td>3</td>
<td>13b, c</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>6</td>
<td>23b, c</td>
</tr>
<tr>
<td>γ-Glutamyltransferase</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Kallikrein</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

* Limits as indicated in Table 3, taking into account sex-related differences if necessary.

b, c Percentages of increased values significantly different b from control group or c between group 2 and group 3, proved by chi-square test (at least \( P < 0.05 \)).

sons (group 3) a group of persons working nearby the cadmium factory (group 2). We had intended to use that group as the control group; however, their blood and urine concentrations of cadmium were clearly higher than in subjects not living in that region (group 1) (Table 1). The increased values in blood and urine in group 2 indicated both recent and chronic cadmium exposure. Therefore, it was suggested that those subjects were environmentally exposed to cadmium because of the pollution from the nearby battery factory. We established that group as the additional risk group. The evaluation of data from this group offers a valuable opportunity to assess the diagnostic validity of our selected analytes as early indicators of cadmium-induced nephropathy in a general population at risk.

Recently, the critical concentration of cadmium that induces nephropathy has been discussed (12, 13, 36, 37). Because "nephropathy" is not a clear-cut clinical entity, obviously its diagnosis depends on its definition. In our study we defined values outside the central 95% reference intervals of the controls (Table 3) as pathological and considered these values to be indices of nephropathy. This approach allowed us to compare the diagnostic sensitivity of various analytes in one study. Thus, we could define which renal markers indicated cadmium-induced renal alterations at an early stage.

Whether one or more of the analytes studied by us indicate irreversible damage to the kidney cannot be answered. However, the predictive value of these markers is important. Long-term observations have shown that tubular dysfunction characterized by increased excretion of β2-microglobulin is irreversible, even when it is minor (38). However, experimental studies in rabbits showed that mild cadmium-induced health effects, indicated by aminoaciduria and proteinuria, could be overcome in a short period after cessation of cadmium exposure (39). Low-Mr proteinuria appears when the cadmium excretion is ~10 μmol/mol creatinine and has been suggested to predict a further decline of glomerular filtration rate (38, 40, 41). These conclusions are based on results of studies with β2-microglobulin. Because the reliable determination of β2-microglobulin is impaired by the limited stability of this protein in urine (42), we did not evaluate its excretion. However, as our results show, other tubular indicators such as α1-microglobulin and enzymes of the proximal tubulus apparatus also sensitively react to cadmium exposure. Mueller et al. (13) found that some workers with cadmium excretion rates <10 μmol/mol creatinine, the recommended upper limit of the World Health Organization (43), already had increased excretions of alanine aminopeptidase. They concluded that these guidelines should be interpreted cautiously. Similar results have recently been reported with metallothionein or N-acetyl-β-D-glucosaminidase, suggesting that the currently recommended biological exposure thresholds should be lowered (13, 36, 37, 44). These recommendations were supported by our data when we subdivided group 3 with regard to the excretion of cadmium and the duration of exposure. For example, the α1-microglobulin (Figure 3A) was already increased in the subjects excreting cadmium at <5 μmol/mol creatinine. The diagnostic usefulness of this tubular protein was also evidenced by Tohyama et al. (45). In addition, excretion rates of α1-microglobulin (Figure 3A) and N-acetyl-β-D-glucosaminidase, alanine aminopeptidase, and alkaline phosphatase (Figure 4, A–C) were increased in group 2, in which 26 of 36 subjects had cadmium excretions <10 μmol/mol creatinine.

Our comparative study of various indicators representative for renal damage at different localizations confirms data that cadmium first of all induces changes in the proximal tubular apparatus (3). The tubular indicators—the low-Mr proteins and tubular enzymes—were more often increased than were the typical glomerular indicators, e.g., IgG or transferrin. Kallikrein, a typical distal nephron indicator (15, 46), was decreased only in the subgroup exposed to cadmium >5 years.

The observed excretion patterns may be interpreted as reflections of ultrastructural alterations. Atrophy and degeneration as well as regeneration and recovery occur simultaneously in proximal tubules of kidneys exposed to cadmium (47, 48). Consequently, tubular impairment causes low-Mr proteinuria and increased excretion of tubular enzymes (9). However, the changed pattern of proteinuria and enzymuria was not uniform, thereby demonstrating different processes. Increased low-Mr proteinuria results from impaired reabsorptive-catabolic function of the tubular cells, whereas enzyme excretion rates in urine are increased either by the higher release from damaged cells or by the intensified release because of enzyme induction during regenerative processes (49). In addition, the various low-Mr proteins are processed by the kidney in a variety of ways, and the enzymes studied show different localiza-
tions and linkages on the brush-border membrane (49–51). Thus, the different behaviors of proteins and enzymes are not astonishing. Moreover, glomeruli are also affected by cadmium, showing fibrous thickening of the Bowman’s capsule (47); however, tubular damage is seen before that of glomeruli (48). It has been suggested that chronic cadmium exposure induces disturbances in the metabolism of sialic acid and causes the loss of glomerular barrier function, which is associated with glomerular-type proteinuria (52). The ultrastructural changes correspond to intrarenal distribution of cadmium, which is predominantly found in the cytosol of the tubular epithelium (48). However, little is known of the molecular mechanisms of cadmium in the kidney. Recently, the inhibition of DNA synthesis and stimulation of lipid peroxidation by cadmium have been discussed as essential processes (53, 54).

From the practical point of view, we recommend the combined determination of N-acetyl-β-D-glucosaminidase and α-L-microglobulin as screening indicators for early detection of renal dysfunction induced by cadmium. In addition to their diagnostic sensitivity, these two analytes are sufficiently stable in urine and can be measured simply, without expensive sample preparation and sophisticated techniques (42, 55).

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Mitane

Workers

Tech

Health-based

retinol

Kidney

Reduced

lar

Stability

Oversteyns

Patienten.

Cadmiumauscheidung

bei

vierengesunden

und

nierenkranken


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