Glomerular Filtration Rate Is a Confounder for the Measurement of Soluble Mesothelin in Serum

To the Editor:

The mesothelin gene encodes a 71-kDa precursor protein that is subsequently cleaved into a soluble megakaryocyte potentiating factor and a membrane-bound part, mesothelin, which can be shed as “soluble mesothelin” or “soluble mesothelin-related protein” (SMRP), which can be shed as soluble mesothelin, which can be shed as soluble mesothelin, as low molecular weight proteins have been used as markers of developing mesothelioma. Such renal impairment leads to the accumulation of several similarly sized proteins in the blood [e.g., cystatin C (13 kDa) and β-trace protein (BTP) (23–29 kDa)], and these proteins have been used as markers of the glomerular filtration rate (GFR). Mesothelioma typically occurs in middle-aged men, and the GFR can occasionally decrease in these patients and in individuals at risk of developing mesothelioma. Such renal impairment can cause the accumulation of low molecular weight proteins such as soluble mesothelin, as has previously been reported for a limited number of cases (2). Our aim was to thoroughly investigate the impact of renal function on serum SMRP concentrations in individuals without mesothelin-overexpressing conditions.

We enrolled 66 individuals (49 men and 17 women; median age, 58 years; range, 24–80 years), who were referred for measurement of 51Cr-EDTA clearance to estimate the GFR. We excluded patients with asbestos-related diseases/malignancies, patients with endometrial, ovarian, cervix, lung, breast, pancreatic, or gastrointestinal cancer, and patients with leukemia, because these conditions can overexpress mesothelin (3, 4). The study was approved by the ethics committee of both participating hospitals, and participants gave written informed consent. In addition, we analyzed GFR data from 51 chemotherapy-naïve mesothelioma patients (47 men and 4 women; median age, 63 years; range, 45–79 years) who had undergone treatment at our institution between 2003 and 2008.

We used cystatin C, BTP, and creatinine as serum markers to assess the GFR. The plasma clearance of 51Cr-EDTA was used as a reference standard for the GFR and was measured as previously described (5) with adjustment to a standard body surface area of 1.73 m². Creatinine was measured by a rate-blanked compensated Jaffe method on a Modular P analyzer (Roche Diagnostics). BTP and cystatin C were measured by latex-enhanced nephelometry on a Behring BN II analyzer (Siemens Diagnostics). Serum SMRP was measured with MESOMARK™ ELISA kits (Cisbio/Fujirebio Diagnostics) (4). The GFR of mesothelioma patients was measured with the isotope-dilution mass spectrometry–traceable Modification of Diet in Renal Disease (MDRD) equation.

A Spearman rank analysis showed a significant correlation (P < 0.001) between the GFR and the reciprocal of the concentrations of cystatin C (r = 0.785), BTP (r = 0.770), and creatinine (r = 0.818). The reciprocal of the SMRP concentration was significantly correlated with the GFR (r = 0.494; P < 0.001) and the reciprocals of the concentrations of cystatin C (r = 0.370; P = 0.002), BTP (r = 0.402; P = 0.001), and creatinine (r = 0.462; P < 0.001). The median SMRP concentration was 1.25 nmol/L (range, 0.30–5.28 nmol/L), and the SMRP concentration in 24 of the 66 patients was >1.5 nmol/L, the manufacturer’s cutoff for differentiating healthy controls from mesothelioma patients (4)—a false-positive rate of 36% (Fig. 1).

We then categorized the GFRs of the 66 patients referred for 51Cr-EDTA clearance testing into 5 stages: stage 1, normal [≥90 mL·min⁻¹·(1.73 m²)⁻¹]; stage 2, mild [60–89 mL·min⁻¹·(1.73 m²)⁻¹]; stage 3, moderate [30–59 mL·min⁻¹·(1.73 m²)⁻¹]; stage 4, severely decreased [15–30 mL·min⁻¹·(1.73 m²)⁻¹]; and 5, renal failure (<15 mL·min⁻¹·(1.73 m²)⁻¹]. Falsely increased SMRP concentrations were observed in none of the 11 stage 1 patients, but false positives were observed in 7 (32%) of 22 stage 2 patients, in 10 (40%) of 25 stage 3 patients, in 6 (86%) of 7 stage 4 patients, and in the single stage 5 patient. The mean SMRP concentration of the patients with a nonpathologic GFR was significantly different from that of the patients with a decreased GFR (P < 0.001, ANOVA).

Of the 51 mesothelioma patients, 22 (43%) had a typical renal function, 24 (47%) showed a mildly decreased GFR, and 5 (10%) had a moderately decreased GFR. The majority of the mesothelioma patients thus had a decreased GFR and therefore were susceptible to an accumulation of SMRP in the serum.

Theoretically, the corrected SMRP concentration (SMRP_corr) (in nanomoles per liter) based on a patient’s renal impairment can be derived from the equation for the linear regression of the reciprocal of the SMRP concentration on the GFR for the 66 patients: 1/SMRP = 0.268 L/nmol + 0.01 GFR (r² = 0.255; P < 0.001; Fig. 1). Therefore, the measured SMRP (SMRP_meas) can be corrected for the difference in the patient’s GFR from a reference GFR [120 mL·min⁻¹·(1.73 m²)⁻¹]:

1 Nonstandard abbreviations: SMRP, soluble mesothelin-related protein; GFR, glomerular filtration rate; BTP, β-trace protein; MDRD, Modification of Diet in Renal Disease.
In conclusion, the serum SMRP concentration is significantly correlated with the GFR, which makes the GFR a confounder in the application of the SMRP ELISA kit. Furthermore, the majority of the investigated mesothelioma patients had a decreased GFR. Therefore, caution is advised when interpreting test results in individuals with an impaired renal function, e.g., in screening high-risk populations, because reductions in the GFR can produce falsely increased SMRP concentrations.

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References


