# Supplementary Material: The Source and Pathophysiologic Significance of Excreted Cadmium

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### 1. Demonstration that $E_x/C_{cr} = [x]_u[cr]_p/[cr]_u$.

Let $V_u$ = urine flow rate, units of volume/time;
$E_x$ = urinary excretion rate of substance *x*, units of mass/time;
$[x]_u$ = urinary concentration of substance *x*, units of mass/volume;
$E_{cr}$ = urinary excretion rate of creatinine, units of mass/time;
$[cr]_p$ = plasma concentration of creatinine, units of mass/volume;
$[cr]_u$ = urine concentration of creatinine, units of mass/volume;
$C_{cr}$ = renal creatinine clearance (an approximation of GFR) = $E_{cr}/[cr]_p$, units of volume/time;
$E_x/C_{cr}$ = amount of *x* excreted per volume of filtrate, units of mass/volume.
$E_x/C_{cr} = [x]_uV_u/([cr]_uV_u/[cr]_p)$; cancelling $V_u$ and rearranging,
$E_x/C_{cr} = [x]_u[cr]_p/[cr]_u$.

### 2. Demonstration that $E_{Cd}/C_{cr}$ is Unaffected by Muscle Mass

Let
(a) $V_u$ = urine flow rate
(b) $E_{Cd} = [Cd]_uV_u$;
(c) $E_{cr} = [cr]_uV_u$; and
(d) $C_{cr} = E_{cr}/[cr]_p = [cr]_uV_u/[cr]_p$.

$E_{cr}$ is directly related to muscle mass [60]. According to equation (d), at a given $C_{cr}$, $E_{cr}$ and $[cr]_p$ rise or fall by the same factor.

If $E_{Cd}$ is normalized to $E_{cr}$, then $E_{Cd}/E_{cr} = [Cd]_uV_u/[cr]_uV_u$. Since $E_{cr}$ is directly related to muscle mass, $E_{Cd}/E_{cr}$ is inversely related to muscle mass at any $E_{Cd}$. The same is true of $[Cd]_u/[cr]_u$ after cancellation of $V_u$ in the numerator and denominator.

If $E_{Cd}$ is normalized to $C_{cr}$, then $E_{Cd}/C_{cr}$, *i.e.*, $[Cd]_uV_u/[cr]_uV_u/[cr]_p$, is unaffected by muscle mass because *at a given* $C_{cr}$ = $(E_{cr}/[cr]_p)$, $E_{cr}$ and $[cr]_p$ rise or fall by the same factor as muscle mass varies. This fact remains true after simplification of the complex fraction to yield $E_{Cd}/C_{cr} = [Cd]_u[cr]_p/[cr]_u$.

### 3. Demonstration that $E_{\beta 2MG}$ May Rise because of Increased Endogenous Production

Let $I_{\beta 2MG}$ = influx of β2MG from endogenous sources into plasma;
$[\beta 2MG]_p$ = plasma concentration of β2MG, mg/L;
$F_{\beta 2MG}$ = rate of glomerular filtration of β2MG, mg/d;
$E_{\beta 2MG}$ = urinary excretion rate of β2MG, mg/d;
$TD_{\beta 2MG}$ = rate of tubular degradation of β2MG, mg/d;
GFR = glomerular filtration rate, L/d.
Assume that $F_{\beta 2MG} = GFR[\beta 2MG]_p = E_{\beta 2MG} + TD_{\beta 2MG}$.

Assume an equilibrium between $I_{\beta 2MG}$ and $F_{\beta 2MG}$, and assume stable GFR. If $I_{\beta 2MG}$ rises, so do $[\beta 2MG]_p$ and $F_{\beta 2MG}$. If $TD_{\beta 2MG}$ remains stable, $E_{\beta 2MG}$ must rise if $F_{\beta 2MG}$ rises. Thus $E_{\beta 2MG}$ may rise even though $TD_{\beta 2MG}$ has not fallen.

### 4. Demonstration that $E_{\beta 2MG}$ Rises if GFR Falls

From item 3, $F_{\beta 2MG} = GFR[\beta 2MG]_p = E_{\beta 2MG} + TD_{\beta 2MG}$. Dividing the equation on the right by GFR, $[\beta 2MG]_p = E_{\beta 2MG}/GFR + TD_{\beta 2MG}/GFR$.

Assume that $I_{\beta 2MG}$ and thus $F_{\beta 2MG}$ remain stable. Since $F_{\beta 2MG} = GFR[\beta_2MG]_P$, $[\beta_2MG]_P$ must rise reciprocally if GFR falls. Assume that $TD_{\beta 2MG}/GFR$ remains stable as GFR falls. If GFR has fallen, $TD_{\beta 2MG}$ must also fall. Since $F_{\beta 2MG}$ is constant and $F_{\beta 2MG} = E_{\beta 2MG} + TD_{\beta 2MG}$, $E_{\beta 2MG}$ must rise.