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Renal handling of beta-2-microglobulin in the human neonate

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Renal handling of beta-2-microglobulin in the human neonate. Glomerulotubular balance for beta-2-microglobulin (β_2M) in the human kidney has been reported to occur after 34 weeks conceptional age (CA), and fractional tubular reabsorption of β_2M ($T_{\beta 2M}$) has been suggested as a useful index of renal tubular maturation. To confirm and extend these observations to include still less mature infants, renal handling of β_2M was investigated during timed-urine collections with corresponding blood samples obtained from 57 infants with CA of 26 to 43 weeks and postnatal ages (PNA) 0.2 to 12 days (study 1); 18 infants were studied a second time 5 to 17 days later (study 2). GFR was measured by endogenous creatinine clearance (C_{Cr}). $T_{\beta 2M}$ and fractional reabsorption of sodium (T_{Na}) were calculated. Results indicated that while both increased with CA, $T_{\beta 2M}$ ($r = -0.69$, $P < 0.0001$) and T_{Na} ($r = -0.79$, $P < 0.0001$) varied inversely with fractional urine flow rate (V/C_{Cr}). Moreover, an inverse relationship between changes in $T_{\beta 2M}$ and V/C_{Cr} was observed in the same infant between study 1 and study 2 ($r = -0.47$, $P < 0.05$). These data suggest that the renal handling of β_2M in the human neonate is influenced by physiologic variables that are independent of CA, and thus $T_{\beta 2M}$ may not be a reliable predictor of renal tubular maturation in the human neonate.

Elimination rénale de la béta-2-microglobuline chez le nouveau-né humain. Il a été rapporté que la balance glomérulo-tubulaire pour la béta-2-microglobuline (β_2M) dans le rein humain apparait au bout de 34 semaines d'âge conceptionnel (CA), et il a été suggéré que la réabsorption tubulaire fractionnelle de la β_2M ($T_{\beta 2M}$) est un index utile de maturation tubulaire rénale. Afin de confirmer et d'étendre ces observations en incluant des nouveau-nés encore moins matures, l'élimination rénale de β_2M a été étudiée pendant des recueils d'urines minutés, avec les échantillons sanguins correspondants chez 57 nouveau-nés avec un CA de 26 à 43 semaines et des âges postnataux (PNA) de 0.2 à 12 jours (étude 1); 18 nouveau-nés ont été étudiés dans un second temps, 5 à 17 jours plus tard (étude 2). Le débit de filtration glomérulaire a été mesuré par la clearance de la créatinine endogène (C_{Cr}). $T_{\beta 2M}$ et la réabsorption fractionnelle du sodium (T_{Na}) ont été calculées. Les résultats ont montré que tout en augmentant avec CA, $T_{\beta 2M}$ ($r = -0.69$, $P < 0.0001$) et T_{Na} ($r = -0.79$, $P < 0.0001$) variaient inversement avec le débit fractionnel urinaire (V/C_{Cr}). En outre, une relation inverse entre les modifications de $T_{\beta 2M}$ et les modifications de V/C_{Cr} a été observée chez le même nouveau-né entre l'étude 1 et l'étude 2 ($r = -0.47$, $P < 0.05$). Ces données suggèrent que l'élimination rénale de la β_2M chez le nouveau-né humain est influencée par des variables physiologiques qui sont indépendantes de CA, et donc $T_{\beta 2M}$ pourrait ne pas être un index prédictif fiable de la maturation tubulaire rénale chez le nouveau-né humain.

A widely held concept is that development of renal tubular function lags behind glomerular function and that glomerulotubular imbalance with glomerular preponderance characterizes the functional state of the kidney during development [1–4]. Additional support for this hypothesis was provided more recently in studies of newborn infants by Aperia and Broberger [5]. These authors interpreted their findings of lower values for fractional tubular reabsorption of β_2M ($T_{\beta 2M}$) in infants with less than 34 weeks conceptional (gestational + postnatal) age (CA) to represent glomerulotubular imbalance for β_2M while the higher values obtained after 34 weeks CA indicated that glomerulotubular balance for β_2M had been achieved. They concluded that $T_{\beta 2M}$ is a useful predictor of tubular maturation in the human kidney. One disadvantage of their study was the use of mean values of GFR obtained from other infants of similar maturity to calculate individual values of $T_{\beta 2M}$; therefore, the glomerulotubular relationship for an individual infant may not have been represented accurately by the value derived. A second disadvantage to the design of their study was volume loading of infants, a maneuver known to affect the proximal tubular reabsorption of other substances [6–8] and alter glomerulotubular relationships [9, 10]. The results of glucose studies in newborn infants given similar volume loads prior to being studied led Tudvad and Vesterdal [11] to conclude that the function of the renal tubule was relatively less mature than its glomerulus, findings that were later incorporated into the concept of functional glomerulotubular imbalance with glomerular preponderance [3]. Studies in which volume loading of the infants was not done reported ratios of tubular to glomerular function in the infants to be similar to adult values, that is, glomerulotubular balance for glucose in the developing human kidney [12, 13]. In a more recent study, Aperia et al [14] measured GFR in each infant and avoided volume loading but still found lower $T_{\beta 2M}$ for preterm than for more mature infants. However, mean values for $T_{\beta 2M}$ in preterm infants actually decreased from 96.2 to 89.4% during the first week of life and at 3 to 5 weeks $T_{\beta 2M}$ was still lower than for term infants at birth; these changes are difficult to explain on the basis of tubular maturation.

The renal handling of no other substance has been found to predict maturation of tubular function; therefore, confirming such a role for β_2M would seem useful in further clinical studies of renal function during human development. The present study was designed to investigate the renal handling of β_2M in human infants in whom volume loading was avoided, and in whom $T_{\beta 2M}$ was calculated from simultaneous measurement of GFR in each infant.

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Table 1. A summary of data obtained at initial study[a]

CA, *weeks*	26 to 30	31 to 33	34 to 37	38 to 43
N	9	5	13	30
Weight, *g*	966 ± 54	1544 ± 72	1980 ± 112	3053 ± 130
PNA, *days*	1.27 ± 0.22	1.62 ± 0.62	3.79 ± 0.40	4.22 ± 0.45
Hct, %	51.3 ± 2.2	50.0 ± 4.6	48.5 ± 2.1	51.5 ± 1.3
C_{Cr} *ml/min*	0.58 ± 0.13	1.14 ± 2.1	2.39 ± 0.33	4.92 ± 0.43
$P_{\beta 2M}$, *μg/ml*	5.89 ± 0.82	5.07 ± 0.45	3.56 ± 0.26	3.52 ± 0.18
$F_{\beta 2M}$, *μg/min*	2.98 ± 0.43	5.27 ± 1.02	8.04 ± 0.87	17.46 ± 1.87
$U_{\beta 2M}$, *μg/ml*	19.22 ± 3.05	22.12 ± 3.47	6.16 ± 1.61	4.79 ± 0.87
$U_{\beta 2M}$, *μg/mgCr*	182.8 ± 34.2	157.1 ± 29.7	51.8 ± 13.5	38.0 ± 7.3
$F_{\beta 2M}$-$U_{\beta 2M}V$, *μg/min*	2.14 ± 0.43	3.57 ± 1.04	7.23 ± 0.85	16.66 ± 1.84
$T_{\beta 2M}$, %	67.6 ± 6.2	66.5 ± 9.3	89.5 ± 2.6	94.6 ± 1.0
T_{Na}, %	96.0 ± 1.2	98.0 ± 0.8	98.9 ± 0.2	99.7 ± 0.1
V, *ml/min*	0.05 ± 0.01	0.09 ± 0.02	0.14 ± 0.02	0.18 ± 0.02
VC_{Cr}, %	9.44 ± 1.96	8.42 ± 1.72	5.81 ± 0.74	3.97 ± 0.35
P_{Osm}, *mOsm/kg*	293.6 ± 4.4	278.4 ± 0.7	271.9 ± 2.4	269.3 ± 1.4
U_{Osm}, *mOsm/kg*	244.8 ± 20.1	194.0 ± 12.0	121.3 ± 9.3	120.6 ± 7.4

Abbreviations: CA, conceptional age; PNA, postnatal age; Hct, hematocrit; C_{Cr}, creatinine clearance; $P_{\beta 2M}$, plasma beta-2-microglobulin concentration; $F_{\beta 2M}$, filtered beta-2-microglobulin; $U_{\beta 2M}$, urine beta-2-microglobulin; $U_{\beta 2M}V$, urinary excretion rate of beta-2-microglobulin; $F_{\beta 2M}$-$U_{\beta 2M}V$, reabsorption of beta-2-microglobulin; $T_{\beta 2M}$, fractional reabsorption of beta-2-microglobulin; T_{Na}, fractional reabsorption of sodium; V, urine flow rate; V/C_{Cr}, fractional urine flow rate; P_{osm}, plasma osmolality; mOsm, milliosmoles; U_{osm}, urine osmolality.

[a] Results are mean ± SE.

Methods

Fifty-seven neonates were studied at a mean postnatal age of 3.4 ± 0.3 days (range, 0.2 to 12 days, study 1). Mean gestational age [15] of the infants was 36.0 ± 0.6 weeks (range, 26 to 42 weeks), and mean birth weight was 2395 ± 132 g (range, 710 to 4310 g). To observe changes in renal function with postnatal age in individual infants that could not be attributed primarily to maturation of the kidney, 18 infants were studied again 3.7 days later at a mean postnatal age of 7.9 ± 0.8 days (range, 5 to 17 days, study 2) when mean CA was 38.9 ± 0.6 weeks (range, 34 to 43 weeks).

Infants were studied in the Special Care or Normal Newborn Nursery, Parkland Memorial Hospital, Dallas, Texas. During the study period, infants were nursed while on a radiant warmer bed, or in an isolette or bassinet, depending on the orders of the physician caring for the infant. More mature infants were begun on formula feedings during the first 4 to 6 hr after birth and feedings were given ad lib every 3 to 4 hr with a weight loss of approximately 5 to 10% over the first week of life. Less mature infants were given gavage feedings or intravenous fluids beginning at 65 to 80 ml/kg/day and adjusted to permit gradual weight loss of approximately 10% over the first week of life. For the purpose of the study, no alteration was made in the intravenous fluid or feeding schedule, as ordered by the infant's physician. All infants were clinically stable at the time of study, and none received bolus administration of intravenous fluid or blood products. The technique of timed-urine collections employed in this study has been described elsewhere [13]. After the urine collection was started, 3 ml of blood were obtained from an indwelling umbilical artery catheter or by heel-stick, placed in chilled tubes, and immediately centrifuged. If urine pH was less than 6.0, an aliquot of urine to be used for β_2M determination was alkalinized to pH greater than 6 by the addition of sodium hydroxide. This was necessary in 12 (16%) specimens. Urine and serum were frozen promptly and analyzed later for creatinine [13], sodium (flame spectrophotometry), osmolality (freezing point depression), and β_2M (RIA, Pharmacia Diagnostics, Uppsala, Sweden). The renal clearance of a substance was calculated according to the standard formula (urinary concentration of the substance times urinary flow rate)/plasma concentration of the substance and fractional reabsorption as 1− (the clearance of the substance/clearance of creatinine). Filtered β_2M ($F_{\beta 2M}$) was calculated as the product of plasma β_2M ($P_{\beta 2M}$). GFR was estimated by clearance of creatinine (C_{Cr}). Intra-assay variability for β_2M determinations was 5.3% in our laboratory compared with the manufacturer's results of 6.4%.

The protocol for this study was approved by the Institutional Review Board, The University of Texas Health Science Center at Dallas, Dallas, Texas, and informed, written parental consent was obtained for all patients prior to study. Statistical analysis of the data was performed by the Medical Computing Resources Center and the Department of Medical Computer Science, The University of Texas Health Science Center at Dallas. Comparison of variables was accomplished by the use of linear regression analysis with application of the 95% level of confidence interval to the correlation coefficients obtained and by comparison of paired values in serial studies of the same infant by the dependent *t* test. Data are presented as the mean ± SEM.

Results

Study 1 (N = 57). A summary of clinical and laboratory data, arbitrarily grouped for CA, is given in Table 1. Birth weight of the infants increased with CA ($r = 0.87$, $P < 0.0001$). The mean ± SEM percent change in body weight between birth and the time of initial study was −2.5 ± 0.6%; the change in weight did not vary significantly with CA ($r = 0.04$, $P = 0.8$) or fluid intake ($r = 0.23$, $P = 0.1$).

C_{Cr} increased with CA ($r = 0.75$, $P < 0.0001$, Fig. 1), but the relationship appeared nonlinear. When a polynomial regression was calculated ($C_{Cr} = 0.039\ CA^2 - 2.27\ CA + 33.66$; $r = 0.81$, $P < 0.0001$) the coefficient of CA^2 was significantly different from

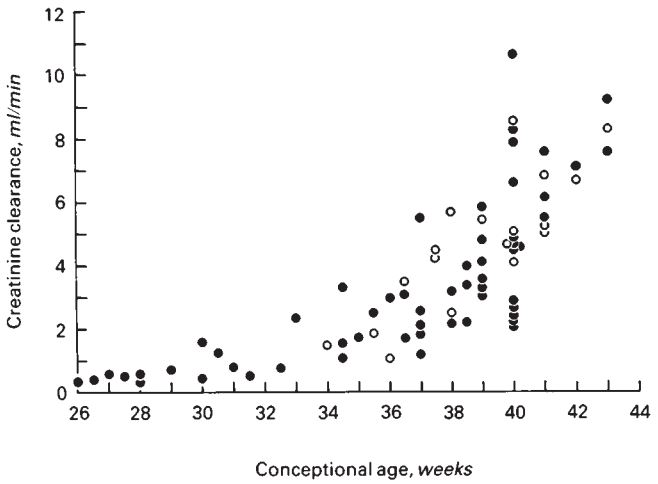

Fig. 1. *Creatinine clearance* (C_{Cr}) *is compared with conceptional age of infants in study 1* (●) *and in study 2* (○). Regression analysis of the data revealed a nonlinear relationship expressed best as an exponential equation in both studies 1 and 2.

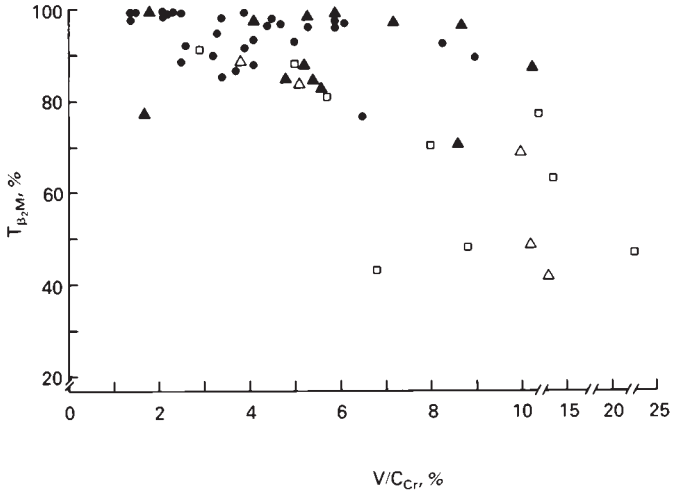

Fig. 2. *A comparison of fractional urine flow* (V/C_{Cr}) *with fractional tubular reabsorption of* β_2M ($T_{\beta 2M}$) *for infants with conceptional ages 26 to 43 weeks in study 1* (y = −0.03x + 1.03; N = 57, r = −0.69, P < 0.0001). The *symbols* correspond to the conceptional age group (weeks) of the infant: □, 26 to 30; △, 31 to 33; ▲, 34 to 37; ●, 38 to 43.

zero ($P < 0.0005$) indicating that a linear fit was insufficient to describe the relationship between CA and C_{Cr}. The best description of C_{Cr} as a function of CA was an exponential equation (ln C_{Cr} = 0.18 CA − 5.86; r = 0.90, $P < 0.0001$).

$P_{\beta 2M}$ decreased with increasing CA (r = −0.57, $P < 0.0001$). $F_{\beta 2M}$ increased with C_{Cr} (r = 0.88, $P < 0.0001$), and with CA (r = 0.65, $P < 0.0001$) but did not vary with $P_{\beta 2M}$ (r = −0.06, P = 0.7). The urinary excretion of β_2M ($U_{\beta 2M/mgCr}$) varied inversely with CA (r = −0.69, $P < 0.0001$), and absolute tubular reabsorption of β_2M ($F_{\beta 2M} - U_{\beta 2M}V$) increased with CA (r = 0.67, $P < 0.0001$) and with $F_{\beta 2M}$ (r = 0.99, $P < 0.0001$). $T_{\beta 2M}$ also increased with CA (r = 0.70, $P < 0.0001$) and $F_{\beta 2M}$ (r = 0.47, $P < 0.001$).

Urine flow rate (V) varied directly (r = 0.56, $P < 0.0001$), but fractional urine flow rate (V/C_{Cr}) varied inversely (r = −0.59, $P < 0.0001$) with CA. Urinary excretion of β_2M/mgCr was directly correlated with V/C_{Cr} (r = 0.76, $P < 0.0001$) and, as demonstrated in Figure 2, $T_{\beta 2M}$ for all infants, irrespective of CA, was related inversely to V/C_{Cr} (r = −0.69, $P < 0.0001$). Although this relationship appears to be nonlinear, when a polynomial regression was calculated, the coefficient of $(V/C_{Cr})^2$ was not significantly different from zero (P = 0.58) indicating that the addition of a quadratic term does not improve the description of the relationship between V/C_{Cr} and $T_{\beta 2M}$. There was a significant difference between the slopes of the regression lines for those infants less than or equal to 33 weeks CA compared with those greater than or equal to 34 weeks CA ($P < 0.001$). However, a significant inverse relationship between $T_{\beta 2M}$ and V/C_{Cr} was observed within each of the CA categories (≤ 33, r = −0.64, $P < 0.05$; ≥ 34, r = −0.34, $P < 0.05$). If a comparison of this same relationship was made in infants of all CA whose V/C_{Cr} were greater than 5% (N = 27), an inverse correlation was again noted (r = −0.59, $P < 0.001$); however, when V/C_{Cr} was less than or equal to 5% (N = 30), no statistically significant relationship was observed (r = −0.26, P = 0.17), and neither the slopes (−0.01 vs. −0.01) nor the intercepts (0.95 vs. 0.98), of the regression lines were different between infants less than or equal to 33 weeks and those greater than or equal to 34 weeks CA.

Fractional tubular reabsorption of sodium (T_{Na}) varied directly with CA (r = 0.63, $P < 0.0001$) and $T_{\beta 2M}$ (r = 0.58, $P < 0.0001$), but varied inversely with V/C_{Cr} (r = −0.79, $P < 0.0001$).

Study 2 (N = 18). A summary of results in infants studied serially is shown in Table 2. The only statistically significant difference in the infants between studies was for PNA. The exponential equation describing the relationship between C_{Cr} and CA in study 2 (ln C_{Cr} = 0.17 CA − 5.41; r = 0.73, $P < 0.001$) was not different than the one observed in study 1. $T_{\beta 2M}$ varied directly with CA (r = 0.50, $P < 0.05$) and inversely with V/C_{Cr} (r = −0.84, $P < 0.0001$). As shown in Figure 3, the change in $T_{\beta 2M}$ for an individual infant between studies 1 and 2 varied inversely with the change in V/C_{Cr} (r = −0.47, $P < 0.05$). There was a similar inverse correlation between the changes in V/C_{Cr} and $F_{\beta 2M} - U_{\beta 2M}V$ (r = −0.48, $P < 0.05$).

Discussion

In the human fetus, renal development progresses to the metanephric stage with evidence for glomerular filtration and tubular function prior to the 14th week from conception [16, 17]. Between 24 and 34 weeks from conception, GFR measured in newborn infants at birth and during postnatal life does not increase significantly with CA; however, after 34 weeks, when nephrogenesis is completed in the human kidney [18], an accelerated increase in GFR is observed [13, 19]. As shown in Figure 1, the present data on C_{Cr} support the concept that a CA of 34 weeks is an important period in renal functional development.

Beta-2-microglobulin is a low molecular weight protein found on the cell membrane of all nucleated mammalian cells [20]. In the normal adult kidney, β_2M is freely filtered by the glomerulus, but little is excreted in the urine because most is reabsorbed in the proximal tubule where it is metabolized by tubular cells

Table 2. Study 2. Comparison of data obtained on sequential studies

Study	1	2	P^a
CA, *weeks*	33 to 43	34 to 43	
N	18	18	
Weight, *g*	2710 ± 206	2724 ± 201	NS
PNA, *days*	4.23 ± 0.50	7.87 ± 0.79	<0.001
Hct, *%*	51.3 ± 2.0	48.8 ± 1.8	NS
C_{Cr}, *ml/min*	41.6 ± 0.58	4.72 ± 0.50	NS
$P_{\beta 2M}$, *μg/ml*	3.57 ± 0.21	3.83 ± 0.23	NS
$F_{\beta 2M}$, *μg/min*	14.71 ± 2.30	17.14 ± 1.64	NS
$U_{\beta 2M}$, *μg/ml*	6.98 ± 1.37	6.02 ± 1.29	NS
$U_{\beta 2M}$, *μg/mgCr*	57.3 ± 10.1	63.2 ± 15.5	NS
$F_{\beta 2M}$-$U_{\beta 2M}V$, *μg/min*	13.65 ± 2.26	16.09 ± 1.64	NS
$T_{\beta 2M}$, *%*	91.1 ± 1.7	91.5 ± 2.5	NS
T_{Na}, *%*	99.4 ± 0.1	99.5 ± 0.1	NS
V, *ml/min*	0.18 ± 0.02	0.20 ± 0.02	NS
VC_{Cr}, *%*	5.04 ± 0.51	4.59 ± 0.56	NS
P_{Osm}, *mOsm/kg*	270.4 ± 1.6	271.7 ± 2.4	NS
U_{Osm}, *mOsm/kg*	120.2 ± 10.2	122.2 ± 10.0	NS

Abbreviations are the same as those used in Table 1.
[a] Paired *t* test was used; NS = $P \geq 0.05$.

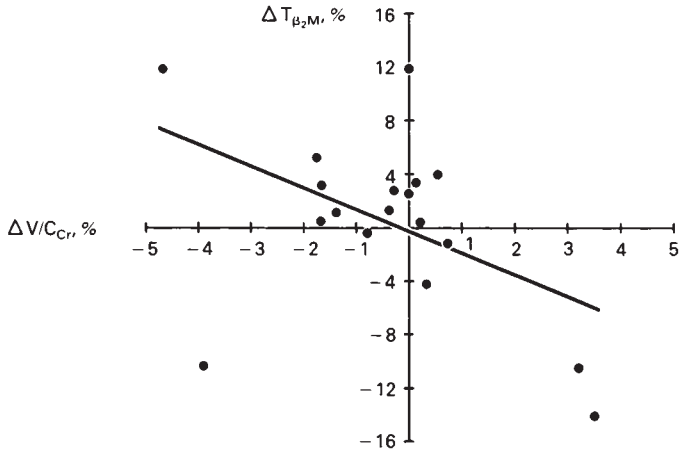

Fig. 3. *Change in fractional urine flow rate* (Δ V/C_{Cr}) *in infants studied serially compared to change in tubular reabsorption of* β_2M (Δ $T_{\beta 2M}$) (y = 1.6x − 0.31; *N* = 18, r = −0.47, $P < 0.05$).

[21–23]. There is also evidence in the canine kidney that extraction of β_2M exceeds glomerular filtration although the site of uptake remains speculative [24]. Increased urinary excretion of β_2M in the adult is used to detect renal tubular injury [25, 26]. Previous reports of the human neonate have suggested that β_2M concentrations in plasma [27], urine [28], and amniotic fluid [28, 29] vary inversely with gestational age. Aperia and Broberger [5] reported that glomerulotubular imbalance for β_2M during development exists prior to 34 weeks CA; however, the validity of such a conclusion must be reconsidered in light of the experimental design which included volume loading of the infants prior to study, a maneuver which alters the proximal tubular reabsorption of substances such as glucose [9, 10], sodium [8], phosphate [6], and bicarbonate [7, 30, 31]. In a subsequent report by Aperia et al [14] volume loading was avoided, and the findings confirmed the authors' original interpretation of glomerulotubular imbalance for β_2M in infants with CA less than 35 weeks. What they failed to explain, however, was the decrease in $T_{\beta 2M}$ in preterm infants between 1 and 2 and 4 to 6 days of life from 96.2 to 89.4% and the failure of preterm infants to increase $T_{\beta 2M}$ further by 3 to 5 weeks of life to values similar to those observed at birth in full-term infants (98.6%). Therefore, an alternate interpretation of their data, which supports the present study, is that factors in addition to tubular maturation appear to influence the renal handling of β_2M in the neonatal kidney.

Recent studies of renal function during development demonstrate that glomerulotubular balance obtains for a variety of substances even in very immature mammals [10, 12, 13]. It now appears likely that previous functional data, both in animal and human studies, which led to the widely held concept of glomerulotubular imbalance with glomerular preponderance were influenced by factors critical to the experimental design, for example, volume loading [10, 11]. Although the volume of fluid intake varied among infants in the present study, fluid intake did not correlate significantly with either V/C_{Cr} or change in body weight. In infants studied serially, body weights, hematocrits, and plasma osmolalities did not change significantly between studies. Furthermore, if glomerulotubular imbalance does obtain for β_2M in the kidney of low birth weight infants then, as $F_{\beta 2M}$ increases, the urinary excretion rate ($U_{\beta 2M}V$) should also increase; in the present study, this did not occur and $F_{\beta 2M} - U_{\beta 2M}V$ increased pari passu with increased filtered load (r = 0.99, $P < 0.0001$). Thus, these data do not support the hypothesis that glomerulotubular imbalance for β_2M exists in the human kidney during development.

The results of this study suggest further that $T_{\beta 2M}$, as well as T_{Na}, while related directly to CA, may be influenced greatly by physiologic variables such as those which affect V/C_{Cr}. The increased V/C_{Cr} observed in the smaller, more immature babies may be related to the increased proportion of body weight present as body water. Extracellular fluid volume is 60% of body weight in the fetus at 20 weeks and decreases to 40% in the infant born at term, a value which is still twice that of the adult [32]. The need to excrete this excess extracellular fluid may be a primary factor in the observed higher values of V/C_{Cr} in the youngest infants. Although $T_{\beta 2M}$ and T_{Na} both varied inversely with V/C_{Cr}, the disparity between actual values calculated for our youngest infants, 68% for $T_{\beta 2M}$ versus 96% for T_{Na}, can be explained in part by the avid tubular reabsorption of sodium in the neonatal kidney that occurs distal to the site of β_2M reabsorption. Values for the fraction of filtered sodium that is reabsorbed proximally in kidneys of neonatal guinea pigs [33] and puppies [34], before and during saline loading, are comparable to values for $T_{\beta 2M}$ in our youngest infants.

It is unlikely that V/C_{Cr} is a marker for tubular maturity per se since there was considerable variation in V/C_{Cr} among and within the conceptional age groups and also because an inverse relationship was noted between changes in V/C_{Cr} and changes in $T_{\beta 2M}$ in the same infants over a mean period of 3.7 days, an interval probably too brief for significant tubular maturation to occur. Furthermore, $T_{\beta 2M}$ in some infants actually decreased over that period of time. This decrease was associated with an increase in V/C_{Cr}. This observation is supported by the finding of Hall et al [24] that the fractional excretion of water and fractional excretion of β_2M varied directly in the adult canine kidney. Nevertheless, it should be noted that our data do not

discount the importance of other factors in the renal handling of β_2M, especially the influence of epithelial maturation.

In light of our observation that $T_{\beta 2M}$ varied inversely with V/C_{Cr}, it might be expected that the infants studied by Aperia and Broberger [5] would have had lower $T_{\beta 2M}$ values than infants of comparable CA in our study. On the contrary, consistently higher values for $T_{\beta 2M}$ were found in each CA group in their study population, and the difference was greatest for those with mean CA 32 weeks (87.2 vs. 66.5%). One explanation for these differences might have been the underestimation of urinary concentration of β_2M. In this case, urinary excretion rates ($U_{\beta 2M}V$) would be falsely low and $T_{\beta 2M}$ overestimated; $U_{\beta 2M}V$ values reported by Aperia and Broberger [5] were between 10 to 50% of those found in the present study. Urinary concentrations for β_2M obtained in our infants agree with other published data [27, 35] and were confirmed in duplicate samples submitted to another laboratory. Dissimilar $P_{\beta 2M}$ between the two studies is another possible explanation for the different results since overestimation of $P_{\beta 2M}$ would have led to higher calculated values for $T_{\beta 2M}$. Aperia and Broberger reported that $P_{\beta 2M}$ varied directly with CA. Our observations as well as those of other investigators [27, 36] suggest that $P_{\beta 2M}$ and CA vary inversely. Furthermore, mean $P_{\beta 2M}$ for our term infants (3.52 μg/ml) agrees closely with results of the recent study by van Oort, Monnens, and van Munster [37] in which mean $P_{\beta 2M}$ for term infants was 3.54 μg/ml. In their first study, Aperia and Broberger [5] used mean values of GFR obtained from infants in other studies to calculate $T_{\beta 2M}$; the variability in results introduced by this maneuver makes interpretation of $T_{\beta 2M}$ for an individual infant more difficult. In their recent study [14], which confirmed their previous findings, the variable of GFR was eliminated; however, actual values for $P_{\beta 2M}$ and $U_{\beta 2M}V$ in the infants were not given by the authors for comparison.

In summary, this study supports further our previous observation of a nonlinear relationship between C_{Cr} and CA which is characterized by an accelerated increase in C_{Cr} around 34 weeks after conception. Moreover, additional data regarding plasma and urinary concentrations of β_2M in human infants during postnatal development are provided by the study. Finally, the results of this study suggest that $T_{\beta 2M}$ might be influenced by factors other than CA, as reflected by changes in V/C_{Cr}; thus, $T_{\beta 2M}$ may not be a reliable predictor of renal tubular maturation in the human neonate.

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