Low birth weight – is it associated with few and small glomeruli in normal subjects and NIDDM patients?

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Summary These studies were undertaken to ascertain if there is any association between low birth weight, and low kidney weight, few and/or small glomeruli, in kidneys from a control group and a group of non-insulin-dependent diabetic (NIDDM) patients. The background for this study comes from findings suggesting a correlation between low birth weight and the development of NIDDM and high blood pressure. Furthermore, Brenner has postulated that humans born with a low number of glomeruli, thereby having a low glomerular filtration surface area, have a greater tendency to develop high blood pressure. We examined 79 autopsy kidneys, with known weight from normal and NIDDM patients, which had previously been used for studies of glomerular number and volume. In the archives of the Danish midwives we were able to find birth weight for 26 NIDDM patients and an age- and sex-matched sample of 19 control persons. The kidney weight (g) (Control: 137 ± 36 ; NIDDM: 150 ± 38 ; $2p = 0.26$), glomerular number (10^3) (Control:

670 ± 176 ; NIDDM: 673 ± 200 ; $2p = 0.95$), glomerular volume ($10^6 \mu\text{m}^3$) (Control: 6.25 ± 1.48 ; NIDDM: 5.71 ± 1.74 ; $2p = 0.28$) or birth weight (g) (Control: 3577 ± 400 ; NIDDM: 3489 ± 429 ; $2p = 0.49$) were not different between the groups. There was no significant correlation between birth weight and glomerular number (Control: $2p = 0.80$; $r = 0.06$ and NIDDM: $2p = 0.10$; $r = -0.33$), glomerular volume (Control: $2p = 0.43$; $r = 0.19$ and NIDDM: $2p = 0.78$; $r = 0.06$) or kidney weight (Control: $2p = 0.56$; $r = 0.14$ and NIDDM: $2p = 0.81$; $r = 0.05$). Our results on a limited number of subjects in Denmark do not support the hypothesis that there is any association between low birth weight and low kidney weight or low birth weight and few and/or small glomeruli in NIDDM patients. [Diabetologia (1996) 39: 1634–1637]

Keywords Birth weight, diabetes mellitus, glomerulus, kidney, stereology.

In several studies, Barker and others [1–5] have found an association between low birth weight, the development of glucose intolerance and non-insulin-dependent diabetes mellitus (NIDDM) in adult humans. An association has also been found between low birth weight (in combination with a large placenta) and the development of hypertension in adult humans [6, 7], and low birth weight and death from cardiovascular causes [8]. These associations are known as the

“Barker hypothesis”. The association between low birth weight and hypertension has been ascribed to several different changes during fetal life [9], where the focus has been primarily upon maternal glucocorticoids [10, 11]. The development of hypertension might be the result of persistent changes in the secretion of fetal hormones and altered sensitivity of different kinds of tissue to the above-mentioned hormones.

Based on clinical and experimental evidence, Brenner et al. [12] postulated that essential hypertension might be the result of an inborn reduction in the total glomerular filtration surface area, due to a low number of glomeruli and/or small glomeruli (a low filtration surface area per glomerulus). During the human growth phase hypertension may result in

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Abbreviations: NIDDM, Non-insulin dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

Table 1. Clinical characteristics of 19 normal subjects and 26 NIDDM patients

	Control subjects	NIDDM patients	<i>p</i> -value
Sex	8 male/11 female	14 male/12 female	$2p = 0.55$
Age (years)	59 ± 16 [34–87]	63 ± 11 [35–85]	$2p = 0.31$
Kidney weight (g)	137 ± 36 [91–206]	150 ± 38 [82–228]	$2p = 0.26$
Glomerular number (10^3)	670 ± 176 [393–1056]	673 ± 200 [379–1124]	$2p = 0.95$
Mean glomerular volume ($10^6 \mu\text{m}^3$)	6.25 ± 1.48 [3.95–8.97]	5.71 ± 1.74 [2.81–9.18]	$2p = 0.28$
Birth weight (g)	3577 ± 400 [2900–4250]	3489 ± 429 [2750–4500]	$2p = 0.49$

Data are mean $\pm$ SD. Numbers in parentheses indicate range

Fig. 1. No significant correlation ($2p = 0.80$; $r = 0.06$) was seen between birth weight and total glomerular number in 19 control subjects

glomerular capillary hypertension and later on in glomerular sclerosis, which will further reduce the total glomerular filtration surface area, thus perpetuating a vicious cycle [13].

In relation to the kidney in NIDDM patients, the unified hypothesis of Barker and Brenner [9, 13] is that low birth weight caused by poor intrauterine growth could lead to smaller kidneys with fewer and/or smaller glomeruli having a lower renal functional reserve. The purpose of this study was therefore to examine the possibility of a relationship between low birth weight; few and/or small glomeruli and small kidneys in normal (Control) and in NIDDM patients.

Subjects and methods

Subjects. Nearly all the 79 kidneys from autopsies of control and NIDDM subjects have previously been used in our studies for the estimation of glomerular number [14, 15]. Glomerular volume was also estimated in the control subjects. Information about the subject's age, weight, height, sex, known diabetes duration, kidney weight and state of renal function (proteinuria = reagent-strip testing for bromphenol blue reaction; positive: over 0.3 g protein per 1 litre urine) can be found in the same publications. In the Danish midwives' archives we were able to trace the birth weight of 26 NIDDM patients and an age- and sex-matched sample of 19 control subjects. The study was approved by the local Danish ethical committee.

Stereology. Being a design-based stereological sampling method independent of tissue deformational changes, the fractionator principle was used to estimate the number of glomeruli [16]. In short, a known fraction of the whole kidney cortex was systematically sampled at random. In this sample the

number of glomeruli was counted with physical disectors [17]. The total number of glomeruli in each kidney was then the number of counted glomeruli in the kidney fraction, multiplied by the inverse sampling fraction:

$$N(\text{glom}) = N(\text{glom/fraction}) \cdot (\text{sampling fraction})^{-1}$$

For the estimation of mean glomerular volume, which is dependent on tissue deformational changes, disector-sampling and point-counting were used, to estimate the number density and volume density of glomeruli in the cortex, respectively. The mean glomerular volume was calculated as:

$$v(\text{glom}) = \frac{Vv(\text{glom/cor})}{Nv(\text{glom/cor})}$$

Statistical analysis

The comparison between mean values and the sex between the groups was analysed by the Student's *t*-test and Fisher's exact test, respectively, with a level of significance of 5%. For the analysis of any relationship between birth weight and glomerular number, glomerular volume and kidney weight, linear regression analysis was used with a level of significance of 5%.

Results

The main results are displayed in Table 1. There was no difference of the age, sex, kidney weight, glomerular number, glomerular volume or birth weight between the groups. There was no significant correlation between birth weight; and glomerular number (Control: $2p = 0.80$; $r = 0.06$, [Fig. 1] and NIDDM: $2p = 0.10$; $r = -0.33$, [Fig. 2]), glomerular volume (Control: $2p = 0.43$; $r = 0.19$, [Fig. 3] and NIDDM: $2p = 0.78$; $r = 0.06$, [Fig. 4]) or kidney weight (Control: $2p = 0.56$; $r = 0.14$, [Fig. 5] and NIDDM: $2p = 0.81$; $r = 0.05$, [Fig. 6]). Three NIDDM patients with birth weights of 3750, 4000 and 4000 g, had proteinuria.

Discussion

One of the elements in the "Barker hypothesis" [1–5] is that babies with a low birth weight have a greater tendency to develop NIDDM. Our results do not support this hypothesis. Brenner et al.'s original hypothesis [12], that development of essential hypertension in humans is induced by an inborn low number of glomeruli and/or small glomeruli, is difficult to support or challenge with the results of this study because we

Fig. 2. No significant correlation ($2p = 0.10$; $r = -0.33$) was seen between birth weight and total glomerular number in 26 NIDDM patients

Fig. 5. No significant correlation ($2p = 0.56$; $r = 0.14$) was seen between birth weight and kidney weight in 19 control subjects

Fig. 3. No significant correlation ($2p = 0.43$; $r = 0.19$) was seen between birth weight and mean glomerular volume in 19 control subjects

Fig. 4. No significant correlation ($2p = 0.78$; $r = 0.06$) was seen between birth weight and mean glomerular volume in 26 NIDDM patients

do not have any exact data on blood pressure from these autopsy subjects.

The unification of Brenner and Barker's hypotheses, with regard to kidneys [9], has had support from five studies: 1) 23 young women with scarred kidneys but stable renal function who weighed more at birth than 17 similar patients with progressive renal failure [18]. 2) Birth weights correlated with the gradients of reciprocal serum creatinine regression lines in 12 patients with idiopathic membranous nephropathy

[19]. 3) In 45 patients with IDDM for more than 20 years, those without proteinuria had a greater birth weight than those with microalbuminuria or proteinuria [20]. 4) Infants with low birth weight below the 10th percentile had a lower kidney weight and a reduced number of glomeruli per optical field covering the entire height of the cortex, than infants with a normal birth weight [21]. 5) Eight type II intrauterine-growth-retarded infants with birth weights below the 10th centile for the accurately determined gestational age, had 65 % of the number of glomeruli when compared with seven infants with birth weights above the 10th centile [22].

In contrast to these studies, our findings do not show any correlation between low birth weight, few and/or small glomeruli or low kidney weight. In relation to the four parameters no difference was seen between the control and NIDDM subjects. It is therefore difficult to support the unification of Brenner and Barker's hypotheses with regard to NIDDM kidneys. It has recently been shown that low birth weight is not a risk factor for the development of diabetic nephropathy in IDDM patients [23]. It is, however, important to emphasise that the number of subjects included in the above-mentioned studies (including our own) is limited.

The percentage of Danish babies born in 1953 weighing less than 2500 g was 5.4 % (unpublished observations, Danmarks Statistik). Previous publications [21, 22] which have included infants with significantly smaller birth weights than in our study, have found less glomeruli in infants with low birth weight (less than 10th centile i.e. $< \sim 2750$ g) compared to infants with a normal birth weight. This low birth weight may explain the discrepancy between our and their results. Our sample is probably a reasonably random sample of Danish control and NIDDM subjects as previously discussed [14], despite the fact that we only ascertained birth weight for 26 of 39 NIDDM patients. Birth weight is probably not influenced by a selection bias, however glomerular number in NIDDM patients may be influenced by

Fig. 6. No significant correlation ($2p = 0.81$; $r = 0.05$) was seen between birth weight and kidney weight in 26 NIDDM patients

age, duration of diabetes, severity of diabetic nephropathy etc. Our control subjects and NIDDM patients did not have a different glomerular number, glomeruli are not generated after birth and it is highly unlikely that NIDDM patients are born with more glomeruli. It is therefore questionable if the “survival effect” would introduce any significant selection bias of glomerular number in NIDDM patients.

In conclusion, previous data suggest that very low birth weight may be associated with small kidneys and few and/or small glomeruli. Our data suggest that in normal subjects and in NIDDM patients this association is of very limited importance in a population where so few people have a very low birth weight. Thus, the hypothesis that low birth weight in a population of humans should have a significant effect on the development of NIDDM and smaller kidneys with few and/or small glomeruli seems relatively unimportant. It cannot, however, be excluded that infants with very low birth weight (< 2750 g) may have fewer and/or smaller glomeruli.

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