

Lack of association between anemia and renal disease progression in Chinese patients with type 2 diabetes

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Keywords

Anemia, Renal disease progression, Type 2 diabetes mellitus

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J Diabetes Investig 2016; 7: 42–47

doi: 10.1111/jdi.12368

ABSTRACT

Aims/Introduction: Anemia has a close interaction with renal dysfunction in diabetes patients. More proof is still awaited on the relationship between anemia and the progression of renal disease in this population.

Materials and Methods: In the present longitudinal study, 1,645 Chinese type 2 diabetes patients without end-stage renal disease were included in the analysis in Nanjing, China, during January 2006 and December 2012. All patients were managed by staged diabetes management protocol, and clinical parameters were collected at each visit. The end-point of progression of renal disease was evaluated during the follow up. Cox regression analysis was used to estimate the risk of anemia on renal disease progression.

Results: On recruitment, 350 (21.3%) patients had anemia, which was more common among those with older ages, longer diabetes duration, lower estimated glomerular filtration rate or more albuminuria. On median follow up of 49 months (range 28–62 months), 37 patients (2.2%) developed the defined renal end-point. Compared with those without anemia, patients with anemia had a higher risk of renal disease progression. However, multivariate analysis showed that anemia lost its statistical significance once estimated glomerular filtration rate was added into the model. Although the incidence of renal disease progression markedly increased by anemia status in patients of estimated glomerular filtration rate <60 mL/min/1.73 m², anemia was still not an independent risk factor for renal disease progression in this subgroup.

Conclusions: Anemia was a common finding in Chinese type 2 diabetes patients. Anemia was a risk factor for renal disease progression, but lost its significance once baseline renal function was adjusted.

INTRODUCTION

Diabetes mellitus is the worldwide leading cause of chronic kidney disease (CKD). Diabetic nephropathy, one of the major diabetic complications, is the key attributor of end-state kidney disease (ESRD)¹. Besides the traditional risk factors including hypertension, poor glycemic control and levels of proteinuria, some new risk factors for the progression to ESRD, such as anemia, have been identified².

Anemia is common among patients with type 2 diabetes, affecting approximately 15–32% of diabetes patients in popula-

tion-based cohorts, diabetic clinics as well as primary care clinics^{3–5}. Increasing evidence shows that low hemoglobin level contributes to the progression of left-ventricular hypertrophy, heart failure, all-cause and cardiovascular mortality^{6,7}. Similar effects of anemia on the development of nephropathy were also shown^{8,9}. Anemia at baseline was shown as an independent risk factor for ESRD in several groups of high-risk patients including diabetes¹⁰. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, low hemoglobin level at baseline increased the risk of progression of nephropathy in type 2 diabetes patients¹¹. However, correction of anemia failed to show any beneficial effect in alleviating kidney disease progression. Both the Correction of Hemoglobin and

Received 9 January 2015; revised 31 March 2015; accepted 26 April 2015

Outcomes in Renal Insufficiency study and the Anemia Correction in Diabetes study, two large clinical trials examining the effect of raising hemoglobin on the progression of kidney disease, did not show any significant benefit^{12,13}. Most recently, the Trial to Reduce Cardiovascular Events with Aranesp Therapy also reported that treating anemia with darbepoetin alfa in patients with diabetes and CKD conferred no benefit in renal events or ESRD¹⁴. These findings led us to doubt the actual contribution of anemia on CKD progression, especially in diabetes patients.

Anemia has a close interaction with renal dysfunction in diabetes patients. Anemia is common in diabetes patients with nephropathy, and its severity worsens with more advanced stage of CKD and proteinuria². At the same time, low estimated glomerular filtration rate (eGFR) and high urine albumin are two major risk factors for ESRD with strong predictive powers¹⁵. More proof is still awaited on the relationships among anemia, nephropathy and progression of renal disease. Furthermore, most of the studies in this field were carried out in Caucasian populations, whereas epidemiological studies have shown a considerable variation in both anemia and nephropathy in diabetes patients across different ethnicity¹⁶. The prevalence of diabetes is increasing dramatically in China^{17,18}. In the present study, we tried to examine whether anemia is associated with an increased risk of renal disease progression in a cohort of Chinese type 2 diabetes patients. We have also evaluated whether this risk is modified by eGFR.

MATERIALS AND METHODS

The present longitudinal study was carried out within the frame of the Staged Diabetes Targeting Management study, which began in 2006 as part of a continuous structured diabetes care program for outpatient diabetes management in Jiangsu Province Official Hospital, aiming to document all the risk factors, medical interventions, complications and clinical outcomes of diabetes patients in the real-world practice. A modified European Implementation of Quality Management in Diabetes Care (DIABCARE) assessment of complications and risk factors¹⁹ was carried out during the first visit when the patient was enrolled into the study. All patients were followed up according to the Staged Diabetes Management protocol adopted from the International Diabetes Center (Minneapolis, MN, USA)²⁰, and the clinical information at each visit was recorded online (www.chinasdtm.com). The study protocol has been approved by the ethical committee, Jiangsu Province Institute of Geriatrics, Nanjing, China. Written informed consent was obtained from all patients at the time of the first assessment to allow use of their data for research purposes.

Data in this analysis were collected from patients recruited in the period between January 2006 and December 2012, and all the follow-up data were censored on 30 June 2013. A total of 2,802 diabetic patients were enrolled into the Staged Diabetes Targeting Management study. After excluding those who had a history of type 1 diabetes, cancer, hematological diseases, CKD

of stage IV and V (eGFR <30 mL/min/1.73 m²) at baseline, or incomplete data for key variables (hemoglobin and serum creatinine), we had the complete data from 1,645 patients for the final analysis.

Simple physical examinations including bodyweight, height and blood pressure measurement were carried out by the diabetes nurses. Body mass index was calculated by dividing weight (kg) by the square of height (m). Blood pressure was measured with a standard mercury manometer after at least 5 min of rest. Details on personal information, disease history and current use of medications were also obtained from all patients through interviews by the nurses.

Blood tests were carried out after an overnight fasting for plasma glucose, lipid profiles, complete blood count, renal/liver functions and glycated hemoglobin (HbA_{1c}). A spot urine specimen was collected for albumin-to-creatinine ratio. Fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and serum creatinine were measured using a Hitachi 7060 automated analyzer (Hitachi Koko Co. Ltd., Hitachinaka City, Japan). HbA_{1c} was measured by Bio-Rad Diamat high-performance liquid chromatography analyzer (Bio-Rad Labs., Brea, CA, USA). Spot urine albumin-to-creatinine ratio was measured with DCA 2000 (Bayer Corp., Elkhart, IN, USA).

Anemia was defined as hemoglobin concentrations <120 g/L in women or <130 g/L in men²¹. Estimated GFR was calculated using the abbreviated Modification of Diet in Renal Disease formula²²: $eGFR = 186 \times (SCR \times 0.011)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female})$, where SCR is serum creatinine expressed as $\mu\text{mol/L}$. Progression of renal disease was defined as: (i) death as a result of diabetes with renal manifestation or renal failure; (ii) permanent need for dialysis or renal transplantation; or (iii) doubling of baseline serum creatinine level. The decline rate of eGFR per year was calculated: $(eGFR \text{ at baseline} - eGFR \text{ at last follow up}) / \text{years of follow up}$.

Statistical analysis was carried out using the SPSS software (version 15.0; SPSS, Chicago, IL, USA). All data are expressed as mean \pm standard deviation, median (interquartile range) or percentage, where appropriate. Rates were compared using the χ^2 -test and means using Student's *t*-test between the two groups with or without anemia at baseline. Variables not normally distributed were analyzed using non-parametric tests (Mann-Whitney *U*-test). Cox hazards regression analysis was used to study the association of anemia and eGFR with renal disease progression. All the variables included for multivariate Cox regression models are described in the Results section.

RESULTS

Of the 1,645 participants, there were 1,055 (64.1%) men and 590 (35.9%) women. Their mean age was 64.2 ± 11.9 years (median 66 years, range 30–89 years). Anemia defined by the World Health Organization was present in 21.3% ($n = 350$) of the whole cohort. Table 1 summarizes the baseline characteristics of patients grouped by anemia status. Compared with those

Table 1 | Baseline characteristics of the 1,645 Chinese type 2 diabetes patients with or anemia

	No anemia (n = 1,295)		Anemia (n = 350)		P-value
	Mean, SD or median or percent	SD or IQR	Mean, SD or median or percent	SD or IQR	
Male (%)†	64.2	–	64.0	–	0.95§
Age (years)	63.0	11.8	68.6	11.1	<0.001
Diabetes duration (years)‡	7.0	8.0	9.0	11.0	<0.001¶
BMI (kg/m ²)	24.7	3.0	24.1	3.5	0.001
Systolic BP (mmHg)	127.5	13.9	129.7	15.0	0.012
Fasting PG (mmol/L)	7.8	3.1	7.4	2.6	0.044
HbA _{1c} (%)	7.8	1.9	7.8	1.9	0.478
Total cholesterol (mmol/L)	4.86	1.30	4.65	1.07	0.008
Triglyceride (mmol/L)	1.82	1.40	1.52	0.94	<0.001
HDL-C (mmol/L)	1.18	0.32	1.18	0.32	0.852
LDL-C (mmol/L)	2.91	0.79	2.76	0.84	0.004
Hemoglobin (g/L)	142.8	11.0	115.4	10.7	<0.001
Male	146.2	9.6	118.2	11.3	<0.001
Female	136.5	10.6	110.5	7.3	<0.001
Hematocrit (L/L)	0.40	0.04	0.34	0.04	<0.001
Red cell count (10 ¹² /L)	4.55	0.44	3.84	0.50	<0.001
eGFR (mL/min/1.73 m ²)	97.9	27.8	89.7	29.5	<0.001
ACR (mg/g)‡	11.3	19.0	15.0	25.6	<0.001¶
ACEI or ARB treatment (%)†	32.9	–	44.6	–	<0.001§

Data were expressed as mean ± standard deviation (SD), †percentage or ‡median and interquartile range. §The χ^2 -test and ¶non-parametric Mann–Whitney *U*-test. ACEI, angiotensin converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; PG, plasma glucose.

without anemia, patients with anemia had a lower eGFR, but higher albuminuria, and a longer duration of diabetes. As expected, the hemoglobin level was notably lower in patients with anemia, both in males and females. There were more older age patients in this group, and they were more likely to be treated with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers.

The median follow up was 49 months (interquartile range 28–62 months). During the follow-up period, 49 patients (2.98%) died, all of them were evaluated for the progression of renal disease using the last available data in the diabetic clinic visits. In total, 37 (2.25%) patients had a doubled serum creatinine compared with their baseline levels, including those nine patients who received long-term renal dialysis. All of these 37

Table 2 | Multivariate Cox regression for renal disease progression by baseline characteristics

	Wald	SEM	HR (95% CI)	P-value
Anemia Crude	7.974	0.340	2.609 (1.341–5.077)	0.005
Adjusted for age, sex	4.583	0.362	2.170 (1.068–4.410)	0.032
Adjusted for age, sex, eGFR	3.297	0.368	1.952 (0.948–4.016)	0.069
Multiple adjusted	2.095	0.393	1.767 (0.817–3.821)	0.148
Diabetic duration (+1 month)	4.830	0.002	1.004 (1.000–1.008)	0.028
eGFR (+1 mL/min/1.73 m ²)	4.582	0.005	1.012 (1.001–1.023)	0.032
HbA _{1c} (+1%)	4.900	0.090	1.221 (1.023–1.457)	0.027

Only anemia and statistically significant variables were presented in the table. Other variables included in the model were: age (year), sex (male vs female), body mass index (kg/m²), systolic blood pressure (mmHg), low-density lipoprotein cholesterol level (mmol/L) and use of angiotensin converting enzyme inhibitor or angiotensin II receptor blocker. CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; SEM, standard error of the mean.

patients met the definition of renal disease progression as described above, 14 (4.00%) in the group with anemia and 23 (1.78%) in the group without anemia. Incidence of renal disease progression was strongly associated with both anemia ($P < 0.013$) and renal function ($P < 0.001$). There were obvious additive effects of anemia and worsening renal function on renal disease progression. The incidence of renal disease progression in patients with eGFR more than 90 mL/min/1.73 m² and without anemia was 1.5%. However, it was 21.4% in those patients with anemia and eGFR less than 60 mL/min/1.73 m² at baseline ($P < 0.001$).

Multivariate cox regression analysis showed that baseline anemia was a strong predictor of renal disease progression (Table 2, line 1). As illustrated, anemia was associated with a high risk of renal disease progression even after adjustment for age and sex (Table 2, line 2). However, when eGFR was included for the analysis, anemia lost its significance (Table 2, line 3 and 4). Anemia was also removed from the model after adjustment for traditional predictors for ESRD, such as age, systolic blood pressure, eGFR and blood glucose level. In the final multiple adjusted model, diabetes duration, eGFR and HbA_{1c} were independent predictors of renal disease progression (Table 2, line 5, 6 and 7).

Based on anemia being strongly associated with renal dysfunction in diabetes patients, interaction analysis between anemia and eGFR was carried out in subgroups divided by eGFR ≥ 90 mL/min/1.73 m², $90 > \text{eGFR} \geq 60$ mL/min/1.73 m² or $60 > \text{eGFR} \geq 30$ mL/min/1.73 m². As shown in Table 3, HR of baseline anemia was significantly higher in patients with CKD 3 (eGFR < 60 mL/min/1.73 m²) compared with the rest of the diabetic patients (hazard ratio 4.816 vs 0.034 and 1.876,

Table 3 | Hazard ratio of baseline anemia for renal disease progression

eGFR	n	Crude HR	P-value (95% CI)	Multiple adjusted HR†	P-value (95% CI)†
All	1,644	2.609 (1.341–5.077)	0.005	1.767 (0.817–3.821)	0.148
≥90 mL/min/1.73 m ²	688	1.876 (0.594–5.922)	0.283	1.202 (0.226–6.388)	0.829
60–90 mL/min/1.73 m ²	576	0.034 (0.001–144.1)	0.428	0.001 (0.000–3464)	0.969
<60 mL/min/1.73 m ²	112	4.816 (1.457–15.91)	0.010	1.609 (0.244–10.63)	0.621

†Multiple adjusted for age, sex, diabetic duration, body mass index, glycated hemoglobin, low-density lipoprotein cholesterol level, systolic blood pressure, estimated glomerular filtration rate (eGFR) and use of angiotensin converting enzyme inhibitor or angiotensin II receptor blocker. CI, confidence interval; HR, hazard ratio.

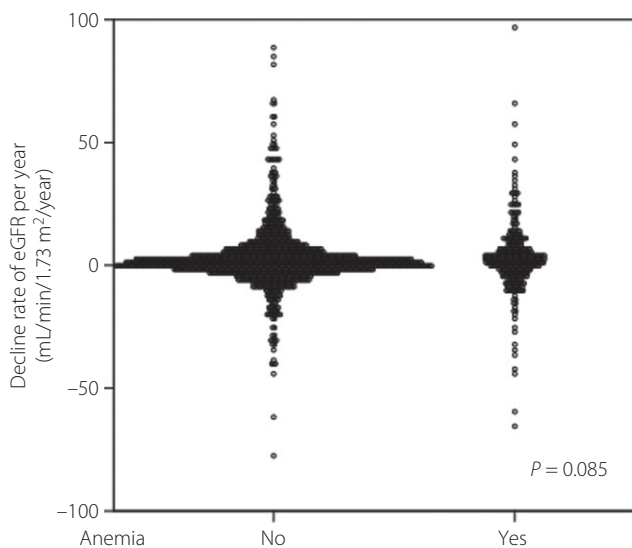


Figure 1 | Distribution of the decline rate of estimated glomerular filtration rate (eGFR) in patients with or without anemia. Differences between groups were compared by non-parametric Mann–Whitney *U*-test.

$P < 0.001$), but anemia failed to predict renal disease progression in all three subgroups in a full adjusted regression model. Consistent with the aforementioned results, there was no difference between the decline rate of eGFR per year between patients with or without anemia, as shown by non-parameter Mann–Whitney *U*-test (Figure 1). In addition, the decline rate of eGFR was not correlated with hemoglobin level in both males ($r = -0.028$, $P = 0.400$) and females ($r = -0.086$, $P = 0.060$).

DISCUSSION

This single-center longitudinal study described the rate of anemia, and the association between anemia and renal disease progression in a clinic-based cohort of Chinese type 2 diabetes patients. More than 20% of the study populations were found to have anemia, and these patients had a higher risk of renal disease progression defined as ESRD or doubling of baseline serum creatinine, than those with normal hemoglobin. However, anemia had a significant interaction with baseline eGFR,

and seemed to lose its significance as an independent risk factor for renal disease progression after adjusting for eGFR. Only HbA_{1c}, eGFR and diabetes duration at baseline independently predicted renal disease progression in the present study.

Anemia has shown to be a predictor for ESRD or renal disease progression in most^{9,10,23}, but not all, studies²⁴. In the Multiple Risk Factor Intervention Trial involving middle-aged men without significant kidney disease, there was no association between baseline hematocrit and development of ESRD after a follow up of 25 years²⁴. Bansal *et al.* also found that anemia was associated with an increased risk for a doubling of serum creatinine in subjects with baseline CKD, but not in those without CKD²⁵. In addition, Rossing *et al.* also reported that baseline hemoglobin did not correlate to the subsequent decline rate of eGFR²⁶. In diabetes patients, although many studies showed that anemia was an independent risk factor for ESRD or renal disease progression, few of them^{9,10,23} analyzed the interaction between anemia and eGFR.

The present data showed that baseline anemia was a risk factor for renal disease progression, but lost its significance after adjustment for eGFR. This was probably because of the strong interaction between anemia and eGFR in our population. Impaired renal function is an independent predictor for renal disease progression, and it is closely associated with anemia. As anemia often develops as a consequence of CKD, those patients with lower eGFR are likely to have lower hemoglobin concentrations and have higher risks to reach the definition of renal disease progression. Thus, low hemoglobin could provide some information on the severity of CKD, but anemia itself does not have a strong direct effect on the development of CKD. In fact, the rates of decline in eGFR were not different between patients with or without anemia in the present study. This might explain why anemia seems to be a risk factor for renal disease progression only when the baseline eGFR is not adjusted for. Similarly, Waldum *et al.* found that baseline anemia is not a predictor of all-cause mortality in outpatients with severe renal dysfunction²⁷. However, it is also possible that there are other confounding factors, such as erythropoietic stress²⁸, existing in these patients. As we had no information on erythropoietin in the present study, this possibility remains to be established.

Anemia was a common finding in the present study, affecting approximately 21.3% of the diabetic patients in this popula-

tion. Given most patients in this study were with normal or near normal renal function, it is not known why these patients had a high risk of anemia. In a cross-sectional survey, the prevalence of anemia was also found to be high in diabetic patients, even in those with preserved renal function⁵, and the authors discussed the possibilities that some factors, such as iron stores, albuminuria and hyperglycemia, could contribute to anemia in diabetes⁵. Similar factors might also contribute to the high rate of anemia in this cohort of diabetic patients. In addition, some previous studies have shown a correlation between polyneuropathy and development of anemia in diabetes²⁹. Because the average diabetes duration of the patients in the present study is more than 7 years, the potential diabetic neuropathy of these patients could also account for the high incidence of anemia, especially in those patients with preserved renal function.

It should be pointed out that the present study had several limitations. First, just 1645 patients from the original database were included in the analysis. Many patients were excluded because of lack of availability of serum creatinine and full blood count data. This situation reflects the shortage of our database establishment. Although the outpatient management system in China, in general, is still relatively immature, we are keen to make efforts to improve our skills and experience in managing the Staged Diabetes Management protocol²⁰. Second, given the limited number of events, it might be difficult to definitely answer the question of whether anemia is associated with an increased risk of renal disease progression. More renal complications are expected to occur with a longer follow-up time. Nevertheless, the sample size and the event rates that occurred in the present study should be statistically sufficient for the analysis. Third, the cohort could contain patients who are more health conscious and pay better adherence to treatments. Indeed, relatively good blood pressure (Table 1), as well as relative low incidence of ESRD during the follow-up period was observed in this cohort. Fourth, patients receiving erythropoiesis-stimulating agents (ESA) are probably included in this population, but we did not have the information. However, we believe that the usage rate of ESA should be low in our population, because ESA is mostly prescribed to patients with ESRD in China. In the current study, the baseline hemoglobin level of patients with anemia was 115.4 g/L, which is within the target level recommended by recent studies¹⁴. This might be caused by anemia being defined as hemoglobin concentrations less than 120 g/L in women or 130 g/L in men in the present study. In addition, ESA-related clinical trials failed to show beneficial effects on renal disease progression as aforementioned. Thus, use of ESA might have little effect on the present results. Last, but not least, the present study was carried out in a single urban hospital in an ethnically homogenous Chinese population. Our results might not be representative of the entire type 2 diabetic patient population. More large-scale prospective studies should be carried out to confirm our findings.

In summary, our data showed that anemia was a common finding in Chinese patients with diabetes, particularly in those

with albuminuria or renal impairment. Anemia was a risk factor for progression of renal diseases. However, when eGFR was included into the multivariate analysis, anemia was no longer an independent predictor of renal disease progression. The present study provided new information to the understanding of the association between anemia, diabetes and renal disease progression. More studies are required to elucidate the association among these three conditions.

ACKNOWLEDGMENTS

This research was supported by grants BK2010089 from the Department of Science and Technology of Jiangsu Province and 71373132 from National Natural Science Foundation of China. The authors thank Dr Gary TC Ko of the Chinese University of Hong Kong for his help with preparing the manuscript.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

- Ritz E, Rychlik I, Locatelli F, *et al.* End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. *Am J Kidney Dis* 1999; 34: 795–808.
- Mehdi U, Toto RD. Anemia, diabetes, and chronic kidney disease. *Diabetes Care* 2009; 32: 1320–1326.
- Goldhaber A, Ness-Abramof R, Ellis MH. Prevalence of anemia among unselected adults with diabetes mellitus and normal serum creatinine levels. *Endocr Pract* 2009; 15: 714–719.
- Jones SC, Smith D, Nag S, *et al.* Prevalence and nature of anaemia in a prospective, population-based sample of people with diabetes: teesside anaemia in diabetes (TAD) study. *Diabet Med* 2010; 27: 655–659.
- Thomas MC, MacIsaac RJ, Tsalamandris C, *et al.* Unrecognized anemia in patients with diabetes: a cross-sectional survey. *Diabetes Care* 2003; 26: 1164–1169.
- Zoppini G, Targher G, Chonchol M, *et al.* Anaemia, independent of chronic kidney disease, predicts all-cause and cardiovascular mortality in type 2 diabetic patients. *Atherosclerosis* 2010; 210: 575–580.
- Tong PC, Kong AP, So WY, *et al.* Hematocrit, independent of chronic kidney disease, predicts adverse cardiovascular outcomes in chinese patients with type 2 diabetes. *Diabetes Care* 2006; 29: 2439–2444.
- Hsu CY, Iribarren C, McCulloch CE, *et al.* Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009; 169: 342–350.
- Babazono T, Hanai K, Suzuki K, *et al.* Lower haemoglobin level and subsequent decline in kidney function in type 2 diabetic adults without clinical albuminuria. *Diabetologia* 2006; 49: 1387–1393.
- Yang XL, So WY, Kong AP, *et al.* End-stage renal disease risk equations for Hong Kong Chinese patients with type 2 diabetes: Hong Kong Diabetes Registry. *Diabetologia* 2006; 49: 2299–2308.

11. Keane WF, Brenner BM, de Zeeuw D, *et al.* The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. *Kidney Int* 2003; 63: 1499–1507.
12. Singh AK, Szczech L, Tang KL, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355: 2085–2098.
13. Ritz E, Laville M, Bilous RW, *et al.* Target level for hemoglobin correction in patients with diabetes and CKD: primary results of the Anemia Correction in Diabetes (ACORD) Study. *Am J Kidney Dis* 2007; 49: 194–207.
14. Pfeffer MA, Burdmann EA, Chen CY, *et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; 361: 2019–2032.
15. Hallan SI, Ritz E, Lydersen S, *et al.* Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009; 20: 1069–1077.
16. Ahmed AT, Go AS, Warton EM, *et al.* Ethnic differences in anemia among patients with diabetes mellitus: the Diabetes Study of Northern California (DISTANCE). *Am J Hematol* 2010; 85: 57–61.
17. Yang W, Lu J, Weng J, *et al.* Prevalence of diabetes among men and women in China. *N Engl J Med* 2010; 362: 1090–1101.
18. Xu Y, Wang L, He J, *et al.* Prevalence and control of diabetes in Chinese adults. *JAMA* 2013; 310: 948–959.
19. Kong AP, Yang X, Ko GT, *et al.* Effects of treatment targets on subsequent cardiovascular events in Chinese patients with type 2 diabetes. *Diabetes Care* 2007; 30: 953–959.
20. Mazze RS, Etzwiler DD, Strock E, *et al.* Staged diabetes management. Toward an integrated model of diabetes care. *Diabetes Care* 1994; 17(Suppl. 1): 56–66.
21. Nutritional a. Report of a WHO group of experts. *World Health Organ Tech Rep Ser* 1972; 503: 1–29.
22. Stevens LA, Coresh J, Greene T, *et al.* Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354: 2473–2483.
23. Mohanram A, Zhang Z, Shahinfar S, *et al.* Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. *Kidney Int* 2004; 66: 1131–1138.
24. Ishani A, Grandits GA, Grimm RH, *et al.* Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol* 2006; 17: 1444–1452.
25. Bansal N, Tighiouart H, Weiner D, *et al.* Anemia as a risk factor for kidney function decline in individuals with heart failure. *Am J Cardiol* 2007; 99: 1137–1142.
26. Rossing K, Christensen PK, Hovind P, *et al.* Progression of nephropathy in type 2 diabetic patients. *Kidney Int* 2004; 66: 1596–1605.
27. Waldum B, Westheim AS, Sandvik L, *et al.* Baseline anemia is not a predictor of all-cause mortality in outpatients with advanced heart failure or severe renal dysfunction. Results from the Norwegian Heart Failure Registry. *J Am Coll Cardiol* 2012; 59: 371–378.
28. Singh DK, Winocour P, Farrington K. Erythropoietic stress and anemia in diabetes mellitus. *Nat Rev Endocrinol* 2009; 5: 204–210.
29. Bosman DR, Osborne CA, Marsden JT, *et al.* Erythropoietin response to hypoxia in patients with diabetic autonomic neuropathy and non-diabetic chronic renal failure. *Diabet Med* 2002; 19: 65–69.