

Contribution of sex hormones in the progression of diabetic microvascular diseases

Sex hormones might contribute to the progression of diabetic microvascular diseases. First, prepubertal duration of diabetes is an important determinant for development of diabetic retinopathy and nephropathy. Second, male sex has been reported to be an independent risk factor for diabetic nephropathy, though not as strong as in non-diabetic subjects. Female sex appears to be a protective factor in non-diabetic nephropathy; however, this advantage seems to be lost in diabetes. Third, interventions with the involved sex hormones *in vivo* changed the progression of diabetic nephropathy. In a recent issue of *Diabetologia*, Harjutsalo *et al.*¹ reported the cumulative incidence of end-stage renal disease (ESRD) and proliferative retinopathy in patients with early-onset type 1 diabetes in Finland. They affirmed male sex as a predictor for both nephropathy and retinopathy, whereas such predominance was associated with the age at onset of diabetes. Puberty was shown as the turning point for the development of diabetic nephropathy and retinopathy.

An earlier age at diabetes onset means a longer exposure to the metabolic disorders. However, prepubertal years with diabetes involve a reduced risk or a longer time to development of diabetic nephropathy and retinopathy when compared with the pubertal diabetes duration². End-stage renal disease and severe retinopathy rarely develop before puberty. In addition, increases in albumin excretion rates and glomerular filtration rate or changes in the retinal microvasculature often accelerate during puberty. The initial protective effect of younger age at diagnosis disappears over time. After 15 years of diabetes duration, the risk of developing microalbuminuria is

similar in subjects diagnosed with diabetes before 5 years of age and those diagnosed between 5 and 11 years of age or after the age of 11 years². It is also true in terms of diabetic retinopathy. Although patients diagnosed at a young age have a longer time free of proliferative retinopathy, they are at a higher risk of proliferative retinopathy when compared with those diagnosed in adulthood. The recent prospective studies in Finland¹, Sweden³ and Japan have also confirmed a reduced risk or a delay in development of ESRD and severe retinopathy in both men and women with type 1 diabetes before puberty. All these observations point toward an association between rapid changes of sex hormones during puberty with the development of microvascular complications.

A gender diversity has been found for vascular complications. Male sex has been reported to be a risk factor for development of non-diabetic renal diseases. However, the data are inconsistent in respect to diabetic microvascular disease. Although some observations showed that sex-related difference might not exist in the incidence or progression of renal disease in type 1 diabetes, more evidences still point toward male sex as a risk factor for the development of diabetic nephropathy. As reported by the Pittsburgh Epidemiology of Diabetes Complications Study, the risk for the development of microalbuminuria decreased with the duration of diabetes in women, whereas it steadily increased in men⁴. Female sex was a risk factor for the development of microalbuminuria in patients with prepubertal onset of type 1 diabetes, compared with age-matched male patients under comparable glycemic control during puberty; whereas among adults with type 1 diabetes, the risk is higher for males. These differences in women have been suggested to be related to changes in the hormonal milieu and to a higher degree of insulin resistance in

girls during puberty. Furthermore, Monti *et al.*⁵ reported in their investigation of familial risk factors for microvascular complications associated with type 1 diabetes that the percentage of females showing a second complication is far greater than that of males. These controversial data implied the complexity of the interaction between sex hormones and diabetic microvascular diseases. Aside from the differences in ethics, sample size, study designs and methods of data analysis, age at onset of type 1 diabetes and sex difference are both possible reasons for these conflicting observations. After long-term follow up and stratification by age at onset of diabetes, Harjutsalo *et al.*¹ concluded that the preponderance of male sex in ESRD and proliferative retinopathy was evident at age at onset of 10 years, and became more pronounced thereafter. They strengthen the concept that the critical period of puberty is important to the advanced stage of microvascular disease.

The precise mechanism by which puberty influences the progression of microvascular disease is not well understood. The imbalance between sex hormones was shown as one of the mechanisms during the progression of diabetic nephropathy (Figure 1). The growth hormone–insulin-like growth factor-I axis has been reported to be a major contributing factor during puberty for sex differences in nephropathy and retinopathy. However, the disturbances of sex hormone levels are likely to be involved throughout the progression of diabetes and diabetic complications. Increased testosterone levels have been observed in diabetic girls with microalbuminuria and in males with diabetic proliferative retinopathy. The development of albuminuria in men with type 1 diabetes is associated with reduced testosterone levels, whereas progression of ESRD is associated with increased levels of both free testosterone and estradiol. Testosterone

*Corresponding author, Weiping Jia
Tel: +86-21-64369181-8922 Fax: +86-21-64368031
E-mail address: wpjia@sjtu.edu.cn
Received 26 September 2011; revised 6 October 2011;
accepted 6 October 2011

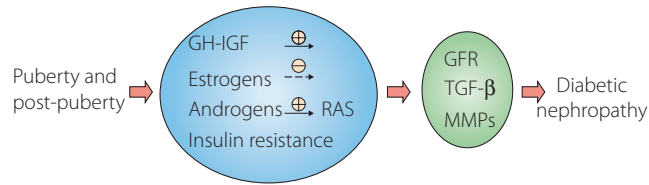


Figure 1 | Sex hormones and diabetic nephropathy. (⊕) Increase, (⊖) decrease. GFR, glomerular filtration rate; GH, growth hormone; IGF, insulin-like growth factor; MMP, matrix metalloproteinases; TGF, transforming growth factor.

has been shown to be an activator for the renin–angiotensin system. Under comparable declines of blood pressure, only females showed a reduction in glomerular filtration rate after angiotensin-converting enzyme inhibition treatment. Administration of testosterone led to tubulointerstitial kidney damage, along with increased expression of transforming growth factor- β (TGF- β) in prepubertal male streptozotocin (STZ)-induced diabetic rats; whereas treatment with 17 β -estradiol (E2) reduced albuminuria, glomerulosclerosis and tubulointerstitial fibrosis through reducing the expression of TGF- β and increasing matrix metalloproteinases (MMP). The Finnish Diabetic Nephropathy (FinnDi-ane) Study also showed that the influence of sex steroids is likely to be of importance in human disease. Further studies are needed to examine the physiological significance of sex steroids, as no confirmed evidence has been shown in humans as it has in animal models.

Accumulating evidence suggests that the relative imbalance between testosterone and estradiol plays an important role in the onset of diabetes and related microvascular diseases, rather than the absolute levels. Diabetes reduces female sex-mediated protection against progression of renal disease, but the mechanisms responsible for this loss of protection are unknown. The precise mechanism of sex hormones in the pathophysiology of diabetic-related disease is a rising issue and sex-specific therapeutic interventions should be developed to examine the correlation between sex hormones and the progression of diabetic microangiopathy.

Weiping Jia*

Department of Endocrinology and Metabolism, Shanghai Jiaotong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Diabetes Institute, Shanghai, China

REFERENCES

1. Harjutsalo V, Maric C, Forsblom C, *et al.* Sex-related differences in the long-term risk of microvascular complications by age at onset of type 1 diabetes. *Diabetologia* 2011; 54: 1992–1999.
2. Amin R, Widmer B, Prevost AT, *et al.* Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. *BMJ* 2008; 336: 697–701.
3. Mollsten A, Svensson M, Waernbaum I, *et al.* Cumulative risk, age at onset, and sex-specific differences for developing end-stage renal disease in young patients with type 1 diabetes: a nationwide population-based cohort study. *Diabetes* 2010; 59: 1803–1808.
4. Orchard TJ, Dorman JS, Maser RE, *et al.* Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990; 39: 1116–1124.
5. Monti MC, Lonsdale JT, Montomoli C, *et al.* Familial risk factors for microvascular complications and differential male-female risk in a large cohort of American families with type 1 diabetes. *J Clin Endocrinol Metab* 2007; 92: 4650–4655.