CHAPTER 8

INSULIN-LIKE GROWTH FACTOR I AND ALTERED RENAL HAEMODYNAMICS IN GROWTH HORMONE DEFICIENCY, ACROMEGALY AND DIABETES MELLITUS

K. Hoogenberg, P.M. ter Wee, A.G. Lieverse, W.J. Sluiter and R.P.F. Dullaart

Growth hormone (GH) influences renal haemodynamics indirectly by enhancing the synthesis of insulin-like growth factor I (IGF-I). In patients with acromegaly increases in glomerular filtration rate (GFR) are well correlated with IGF-I levels. Circulatory GH-levels have also been implicated in the elevated GFR of IDDM patients, but IGF-I levels are often low in these patients. In the present study, we found IGF-I levels to be highly correlated with renal haemodynamics parameters in GH-deficient, acromegalic and healthy subjects, whereas this relationship was not present in normo-hyperfiltering IDDM groups. In contrast, in all groups amino acid stimulated renal function was inversely correlated with baseline renal haemodynamics, indicating similar renal haemodynamic abnormalities in hyperfiltering IDDM and acromegalic patients, despite large differences in plasma IGF-I levels. It is suggested, therefore, that the lack of a relationship between plasma IGF-I and renal function in IDDM does not exclude the role of elevated GH levels in diabetic glomerular hyperfiltration.

Introduction

Evidence has accumulated that glomerular hyperfiltration plays an important role in the development of glomerular damage in experimental diabetes mellitus [1] and possibly in human diabetes as well [2]. An increased glomerular filtration rate (GFR) is also a characteristic feature of acromegaly [3]. Growth hormone (GH) influences renal haemodynamics indirectly by enhancing the synthesis of insulin-like growth factor I (IGF-I), which has a direct stimulatory effect on renal function [4]. Since circulatory levels of GH are frequently elevated in patients with insulin-dependent diabetes mellitus (IDDM), especially during poor metabolic control, it is possible that circulatory GH plays a pathogenetic role in diabetic glomerular hyperfiltration. However, no differences in diurnal GH-profile could be demonstrated between normo- and hyperfiltering diabetic patients [5]. In contrast, recent studies show a positive correlation between GH-releasing hormone-stimulated [6] or exercise-stimulated GH levels [7] and renal haemodynamics in Type 1 diabetes mellitus, independently of metabolic control.

In the present study we therefore investigated the relationship between plasma IGF-I

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1 Departments of Internal Medicine, State University Hospital, Groningen; 2 Free University of Amsterdam, The Netherlands.

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and GFR as well as effective renal plasma flow (ERPF) among GH-deficient, acromegalic, normo- and hyperfiltering IDDM patients and healthy control subjects. As the assessment of renal reserve filtration capacity using amino acids (AA) infusion has been demonstrated to provide insight into the presence of glomerular vasodilation associated with abnormal GH secretion [3,8] and diabetes mellitus [9], the AA-induced changes in renal haemodynamics in these patients were compared.

**Subjects and methods**

The study was approved by the local medical ethics committee and all participants consented to the procedure. Fasting GFR and ERPF were determined simultaneously, using $^{125}$I-iothalamate and $^{131}$I-hippuran, respectively [9]. On the second day, renal reserve filtration capacity was measured as the % increment of GFR and ERPF after 17-hours of amino acids infusion (Vamin-N®, 7% weight/volume, Kabi Vitrum, Limoges, France; infusion rate 83 ml/h). All subjects had an age between 21 and 55 years. Only subjects without hypertension (systolic blood pressure <160 mmHg and diastolic blood pressure <95 mmHg) and without blood pressure lowering or non-steroidal anti-inflammatory medication participated. The IDDM patients did not have clinical proteinuria and had a disease duration of at least 5 years.

The relationships between plasma IGF-I and baseline GFR and ERPF were determined in 8 GH-deficient patients [8], 7 patients with active acromegaly who were studied before and after treatment with the somatostatin analogue octreotide [3], 17 normo- and 9 hyperfiltering Type 1 diabetic patients (GFR >130 ml/min per 1.73m$^2$) and 6 healthy controls. Renal reserve filtration capacity was compared among these GH deficient and acromegalic patients, another 6 normo- and 6 hyperfiltering diabetic patients and 12 healthy controls [9]. Serum GH and plasma IGF-I concentrations were measured by radioimmunoassays. Data are given as mean ±SEM. Correlation coefficients were calculated with linear regression analysis. A $p$-value <0.05 was considered significant.

**Results**

Serum GH levels were higher in the normo- and hyperfiltering IDDM patients than in the control subjects (4.1±1.2 and 5.9±2.9 µg/l vs 0.8±0.2 µg/l, $p<0.001$ for both). In contrast, plasma IGF-I was significantly lower in both IDDM groups as compared to controls (0.37±0.02 and 0.36±0.03 kU/l vs 1.08±0.20 kU/l, $p<0.02$ for both). In the combined groups of GH-deficient, acromegalic and control subjects, positive correlations were observed between plasma IGF-I, GFR ($r=0.87$, $p<0.001$, Figure 1A) and ERPF ($r=0.77$, $p<0.001$, Figure 1B). In the combined IDDM groups, these renal haemodynamics parameters were not related to plasma IGF-I ($r=0.08$ for GFR and $r=0.11$ for ERPF).

AA infusion significantly increased GFR in GH-deficient patients ($p<0.001$), healthy subjects ($p<0.01$), normofiltering IDDM ($p<0.01$) and treated acromegalic patients ($p<0.02$) but not in patients with active acromegaly and hyperfiltering IDDM patients (Figure 2A). ERPF was stimulated in GH-deficient patients ($p<0.001$), healthy subjects ($p<0.05$) and treated acromegalic patients ($p<0.02$), whereas there was no
Figure 1. Relationships of plasma IGF-I with GFR (A) and ERPF (B) in healthy subjects ◇, GH-deficient patients ○, acromegalic patients before ● and after ○ treatment, normofiltering □ and hyperfiltering □ diabetic patients.
Figure 2. Relationships of baseline renal haemodynamics with AA-induced increments in GFR (A) and ERPF (B) in healthy subjects ◇, GH-deficient patients ○, acromegalic patients before ● and after □ treatment, normofiltering □ and hyperfiltering □ diabetic patients.

increase in patients with active acromegaly as well as in normo- and hyperfiltering IDDM
patients (Figure 2B). Taken all groups together, significant inverse relationships could be demonstrated between mean baseline renal haemodynamics and the mean AA-induced responses (GFR: r=-0.95, p<0.005; ERPF: r=-0.90, p<0.02).

Discussion

This study showed that baseline GFR and ERPF are positively related to the plasma level of IGF-I in GH-deficient, acromegalic and control subjects, but not in diabetic patients. Both hyperfiltering diabetic and acromegalic patients had an abolished response to AA infusion. Thus it appears that hyperfiltering IDDM and acromegalic patients share comparable renal haemodynamic abnormalities, despite large differences in plasma IGF-I levels.

The stimulatory effects of IGF-I on renal haemodynamics are ascribed to glomerular vasodilation and a rise in the ultrafiltration coefficient [4]. The enhanced response of GFR and ERPF to AA in GH deficiency, in contrast to acromegaly, supports the notion that IGF-I is an important determinant of these renal haemodynamic parameters. The renal vasodilatory effects of IGF-I could be mediated by nitric oxide, whereas prostaglandins may have a permissive role [4]. These factors are also thought to play a role in the multifactorial process that leads to diabetic glomerular hyperfiltration [10].

Plasma IGF-I was low in the diabetic patients, despite elevated GH levels. This paradox is in accordance with other observations [11], but does not exclude the potential contributory role of abnormalities in the GH-IGF-I-system in diabetic glomerular hyperfiltration. For example, increases in IGF binding protein I facilitate the action of IGF-I on aortic smooth muscle cells [12]. Thus alterations in IGF-I binding proteins in diabetes mellitus may influence its biological activity. Furthermore, augmented accumulation of IGF-I [11] and increased expression of kidney IGF-I receptors [13] have been found in the diabetic kidney, possibly resulting in an enhanced renal haemodynamic effect of IGF-I in the diabetic state. Therefore, the lack of a relationship between plasma IGF-I and renal function in IDDM does not contradict that elevated circulatory GH levels could play a contributory role in diabetic glomerular hyperfiltration. Obviously, further experiments are needed to clarify the impact of abnormalities in the GH-IGF-I-axis on diabetes-related changes in renal function.

References

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